SUPRAMOLECULAR CHEMISTRY OF FUNCTIONALIZED TERPYRIDINES

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ii
ABSTRACT

Highly ordered, regularly repeating molecular architectures, constructed via self-assembly techniques, have gained importance over the last three decades due to their potential utilitarian applications. A key construction strategy has relied on the synthesis of specific building blocks capable of forming “higher-ordered” stable structures that have useful properties that can be used as molecular and supramolecular devices. To this end, mono and bis(terpyridine) ligands have been widely used because of their well-known photochemical and electronic properties, as well as their ability to facilitate directed, metal-mediated self-assembly. However, limited accessibility to unsymmetrically functionalized terpyridines has restricted their potential use in the construction of more complex infrastructures. For this purpose, methyl-, methoxy-carbonyl- and cyano-substitution patterns on the 4,4''-positions of 4'-arylterpyridine were chosen since these functionalities afforded simple routes to a variety of useful substituted building blocks for higher-ordered supramacromolecular architectures. Single crystal X-ray studies of these terpyridines revealed that molecules of the diester terpyridine (approximately coplanar) are stacked by the overlap of the central pyridine rings in consecutive layers with mean interplanar distances of 3.4 Å (π – π interactions) in the solid state. Moreover, functionalized bis(terpyridine) ligands were achieved via the Kröhnke method and Pd(0) coupling strategy using either 1,3-toluenylbisboronic acid or 1,3-diethynyltoluene with meta- or para-I or Br-phenylterpyridines.
A dinuclear tetracationic Fe(II) complex was prepared via metal-directed self-assembly. The chair-like molecular architecture was primarily characterized by X-ray crystallography, mass spectroscopy (ESI-MS), as well as $^1$H NMR, UV-vis, and CV experiments. Crystal packing of this metallomacrocycle revealed that it formed channels that encapsulated water and MeCN. The low temperature $^1$H NMR studies suggested that tpy-Fe-tpy moieties in the dimer were interlocked and resembled a spur gear relationship. Surprisingly, dinuclear and trinuclear metallomacrocycles were formed when 1,3-bis(2,2';6',2''-terpyridine-4'-phen-3-ylethynyl)toluene was treated with equimolar amount of Ru(II) that was confirmed by MALDI-TOF mass and NMR spectroscopy.

The construction of a heteronuclear (Ru$_4$Fe$_2$) hexameric metallomacrocycle with methyl- and carbonyl-functionalized bis(terpyridyl) moieties was achieved by Pd(0) coupling strategy for potential solar cell applications and supramolecular aggregation of the resulting hexamers through $H$-bonding. Carboxylic acid functionalized mono- and dinuclear homo- and heteroleptic Ru(II) precursors were also prepared for the same purposes. The single crystal X-ray structure of a homoleptic Ru(II) complex with tetra-ethoxycarbonyl and di(iodo) groups revealed short iodo-carbonyl interactions.
DEDICATION

I dedicate this work to my wonderful parents, Omer and Ayse Eryazici, and my lovely wife, Paula Eryazici, who provided and supported me all these years.
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Firstly, I want to thank Dr. Newkome for his infinite patience with me and his teachings about research and chemistry. I am very thankful for his guidance that lead me to learn to think outside the box. I am just hoping that I have learned a little bit of his endless knowledge and experience in science and research. I also thank Dr. Moorefield for his help in the lab. I thank Dr. Wang for his expertise on growing single crystal and Dr. Durmus and Dr. Panzner for their effort in crystal structure analysis. I also thank all my colleagues who I have worked with six years for their academic discussions.

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TABLE OF CONTENTS

LIST OF TABLES ...................................................................................................................... xi

LIST OF FIGURES .................................................................................................................. xii

LIST OF SCHEMES ................................................................................................................. xxv

CHAPTERS

I SYNTHESIS OF TERPYRIDINES, THEIR SUPRAMOLECULAR CONSTRUCTS AND BIOLOGICAL APPLICATIONS BASED ON THEIR SQUARE PLANAR COMPLEXES ............................................. 1

1.1 Introduction ......................................................................................................................... 1

1.2 2,2':6',2"-Terpyridine Synthesis and Functionalization Strategies ............................... 4

1.2.1 Ring Assembly Methods .................................................................................................. 4

1.2.1.1 Kröhnke method ........................................................................................................ 4

1.2.1.2 Potts Method .............................................................................................................. 6

1.2.1.3 Jameson Method .................................................................................................... 7

1.2.1.4 Adrian Method ....................................................................................................... 8

1.2.1.5 Sauer Method ......................................................................................................... 9

1.2.2 Cross-Coupling Methods .............................................................................................. 10

1.3 Square Planer Terpyridine Transition Metal Complexes ............................................. 11

1.3.1 Chemistry and Properties ........................................................................................... 12

1.3.1.1 Synthesis ............................................................................................................... 12
1.3.1.2 Characterization.................................................................18
1.3.1.3 Single Crystal X-ray Structures and Their Molecular Packing......21
1.3.1.4 Dimerization and Its Constant (K_D)...........................................27
1.3.1.5 Photophysical Properties....................................................27
1.3.1.6 Electrochemical Properties.................................................33
1.3.1.7 Fluxionality......................................................................34
1.3.2 Mononuclear Terpyridine Complexes........................................38
  1.3.2.1 Luminescent Pt-Terpyridine Complexes.................................38
  1.3.2.2 Molecular Packing and Induced Self-assembly..........................41
  1.3.2.3 Molecular Sensors and Switches..........................................47
  1.3.2.4 Photocatalytic Activities..................................................58
  1.3.2.5 Miscellaneous Applications..............................................65
1.3.3 Metallo-Supramolecular Terpyridine Architectures........................71
  1.3.3.1 Dyads and Triads...........................................................72
  1.3.3.2 Supramolecular Self-Assemblies..........................................88
  1.3.3.3 Molecular Recognition by Host-Guest Interaction.....................92
  1.3.3.4 Multimetallic Peptide Scaffolds.........................................99
1.3.4 Biological Activities.............................................................102
  1.3.4.1 DNA Intercalation............................................................102
    1.3.4.1.1 UV-vis Spectroscopy Analysis and Binding Modes.............103
    1.3.4.1.2 Viscosity and Thermal Denaturation..............................107
    1.3.4.1.3 Induced Circular Dichroism........................................109
    1.3.4.1.4 Competitive Fluorescence Spectroscopy.........................110

1.3.4.1.5 Closed Circular DNA.................................112
1.3.4.1.6 Stereochemical Changes in DNA......................113
1.3.4.1.7 Site Specific Intercalation..............................115
1.3.4.1.8 Other Mononuclear Intercalators......................117
1.3.4.1.9 Multinuclear Intercalators.............................120
1.3.4.2 Covalent Binding to Biomolecules........................126
1.3.4.3 Labeling Biomolecules..................................132
1.3.4.4 Cytotoxicity.............................................138
  1.3.4.4.1 Chemotherapeutic Agents..........................139
  1.3.4.4.2 Radiotherapeutic agents............................148
1.4 Conclusion....................................................149

II SYNTHESIS AND SINGLE CRYSTAL X-RAY
CHARACTERIZATION OF 4,4''- FUNCTIONALIZED
4'-(4-R-PHENYL)-2,2':6',2''-TERPYRIDINES.........................150

  2.1 Introduction.............................................150
  2.2 Results and Discussion................................152
  2.3 Conclusion.............................................165
  2.4 Experimental Section....................................166

III MISCELLANEOUS BY-PRODUCTS OF KRÖHNKE TERPYRIDINE SYNTHESIS.................................182

  3.1 Introduction.............................................182
  3.2 Results and Discussion................................183
  3.3 Conclusion.............................................187
  3.4 Experimental Section....................................187
IV  DESIGN, CHARACTERIZATION AND X-RAY STRUCTURE OF AN INTERLOCKED DINUCLEAR CHAIR-LIKE METALLOMACROCYCLE .................................................................................................. 191

4.1  Introduction ........................................................................................................ 191

4.2  Results and Discussion ...................................................................................... 193

4.3  Conclusion ........................................................................................................... 199

4.4  Experimental Section ......................................................................................... 199

V  ONE POT SELF ASSEMBLY OF DI- AND TRI-NUCLEAR METALLOMACROCYLES AND THEIR MALDI-TOF ANALYSIS .............................................................. 204

5.1  Introduction ........................................................................................................ 204

5.2  Results and Discussion ...................................................................................... 206

5.3  Conclusion ........................................................................................................... 213

5.4  Experimental Section ......................................................................................... 214

VI  CONSTRUCTION OF A HEXANUCLEAR MACROCYCLE BY A COUPLING STRATEGY FROM 4,4''-FUNCTIONALIZED BIS (TERPYRIDINES) .............................................................. 220

6.1  Introduction ........................................................................................................ 220

6.2  Results and Discussion ...................................................................................... 223

6.3  Conclusion ........................................................................................................... 237

6.4  Experimental Section ......................................................................................... 237

VII  SUMMARY ........................................................................................................... 256

REFERENCES ............................................................................................................ 258
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>CV data of complexes 199-202 in DCM^{162,221}</td>
</tr>
<tr>
<td>1.2</td>
<td>Host-guest interactions and their stoichiometry</td>
</tr>
<tr>
<td>1.3</td>
<td>The DNA binding constants ($K_b$) of intercalators 274-287 and their effect in melting temperature ($\Delta T$) of ct-DNA</td>
</tr>
<tr>
<td>1.4</td>
<td>Binding parameters of intercalator 274 with DNAs of varying G-C contents in a 50 mM Tris.HCl buffer with 0.1 M NaCl at pH 7.5</td>
</tr>
<tr>
<td>1.5</td>
<td>Binding parameters of mono- and bisintercalators to ct-DNA^{73,239}</td>
</tr>
<tr>
<td>1.6</td>
<td>Positions of accessible amino acids which are reactive with [Pt(tpy)(Cl)]$^+$ and exposed on the surface of cytochrome c proteins</td>
</tr>
<tr>
<td>1.7</td>
<td>Products obtained from reactions between cytochrome c proteins and [Pt(tpy)(Cl)]$^+$ in 0.1 M acetate buffer at pH 5.0, separated by cation-exchange chromatography^{77,78}</td>
</tr>
<tr>
<td>1.8</td>
<td>IC$_{50}$ values ($\mu$M, 4-days) for the <em>in vitro</em> growth inhibition of human ovarian cell lines by mono- and dinuclear Pt-terpyridine complexes^{80}</td>
</tr>
<tr>
<td>1.9</td>
<td>IC$_{50}$ values ($\mu$M) of carborane containing mono- and dinuclear Pt complexes 288-291 and 314-317 against selected cancer cell lines^{257,259}</td>
</tr>
<tr>
<td>1.10</td>
<td>Percent inhibition of selected complexes <em>in vitro</em> against parasites^{85}</td>
</tr>
<tr>
<td>1.11</td>
<td>IC$_{50}$ ($\mu$M) values of 363 and 182 against glioblastoma cell lines^{81}</td>
</tr>
<tr>
<td>1.12</td>
<td>IC$_{50}$ ($\mu$M) values of 292, 294-296, 298, 299 and cisplatin against various human carcinoma cells and normal 293 cells^{31}</td>
</tr>
<tr>
<td>2.1</td>
<td>Crystallographic and structure data</td>
</tr>
</tbody>
</table>
### LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Structure of 2,2':6',2''-terpyridine</td>
</tr>
<tr>
<td>1.2</td>
<td>$^1$H NMR of (A) terpyridine and (B) [Pt(tpy)(Cl)]$^+$ in DMSO-d$_6$. (Reprinted with permission from ref 99. Copyright 2001 Elsevier)</td>
</tr>
<tr>
<td>1.3</td>
<td>The UV-vis spectra of (A) [Pt(tpy)(Me)][BPh$<em>4$] in MeCN at 25 °C. In the inset: the straight line represents the theoretical concentration dependence of absorbance at 313 nm with $\varepsilon</em>{313} = 12780$ M$^{-1}$cm$^{-1}$ according to Beer's law, and the line connected with open squares represents the experimental result (Reprinted with permission from ref 131. Copyright 2000 Elsevier), (B) [Pt(4'-Phe-tpy)(Cl)][SbF$_6$] in MeCN at 25 °C (Reprinted with permission from ref 102. Copyright 1999 The Royal Society of Chemistry)</td>
</tr>
<tr>
<td>1.4</td>
<td>Crystal structures of (A) [Pt(4'-Phe-tpy)(Cl)]$^+$ (Reprinted with permission from ref 102. Copyright 1999 The Royal Society of Chemistry) and (B) [Pt(tpy)(Cl)]$^+$ (Reprinted with permission from ref 99. Copyright 2001 Elsevier)</td>
</tr>
<tr>
<td>1.5</td>
<td>Crystal structure of (A) [Pd(tpy)(pyr)]$^{2+}$ (Reprinted with permission from ref 123. Copyright 2004 Elsevier) and (B) [Au(4'-MeS-tpy)(Cl)]$^{2+}$ (Reprinted with permission from ref 116. Copyright 1999 The Royal Society of Chemistry)</td>
</tr>
<tr>
<td>1.6</td>
<td>Molecular packing of (A) [Pd(tpy)(O-Ph-Me$_2$)]$^+$ (Reprinted with permission from ref 125. Copyright 2003 Elsevier) and (B) [Pd(tpy)(1-Me-cytosine-N$_3$)]$^{2+}$ (Reprinted with permission from ref 127. Copyright 1999 The Royal Society of Chemistry)</td>
</tr>
<tr>
<td>1.7</td>
<td>Linear chain packing of (A) [Pt(4'-(o-Ph)tpy)(Cl)][SbF$_6$] (Reprinted with permission from ref 103. Copyright 2002 The Royal Society of Chemistry) and (B) [Pd(4'-[Ph(CH$_2$)$_2$O]tpy)(Cl)]$^+$ (Reprinted with permission from ref 118. Copyright 2001 Elsevier)</td>
</tr>
</tbody>
</table>
1.8 Crystal molecular packing of (A) [Au(tpy)(Cl)]_2[AuCl_2][AuCl_4] (Reprinted with permission from ref 115. Copyright 1983 American Chemical Society) and (B) [Au(tpy)(OH)][ClO_4] (Reprinted with permission from ref 117. Copyright 1999 The Royal Society of Chemistry)……………………………………………..…24

1.9 Stacking of [Pt(4'-Ph-tpy)(Cl)][BF_4]-MeCN (Reprinted with permission from ref 102. Copyright 1999 The Royal Society of Chemistry)………………..25

1.10 X-ray crystal packing diagrams of (A) [Pt(tpy)(Cl)][ClO_4] dimer (Reprinted with permission from ref 92. Copyright 1995 American Chemical Society) and (B) [Pt(tpy)(Cl)][Pt(DMSO)(Cl)_3] dimer (Reprinted with permission from ref 99. Copyright 2001 Elsevier)……….25

1.11 Crystal packing of [Pt(tpy)(MeCN)][(SbF_6)_2] (Reprinted with permission from ref 101. Copyright 1997 American Chemical Society)……….26

1.12. (A) Corrected emission spectra of [Pt(tpy)(R)]^+ (R = [a] OH, [b] OMe, and [c] NCS), (Reprinted with permission from ref 112. Copyright 1994 American Chemical Society) (B) Concentration dependence (mM) of emission spectrum of [Pt(tpy)(Cl)][PF_6] in EtOH:MeOH:DMF (5:5:1) at 77 K (547 nm excitation) (a) 0.003, (b) 0.072, (c) 0.15 (Reprinted with permission from ref 92. Copyright 1995 American Chemical Society)…………………………………28

1.13 Solid state emission of [Pt(4'-Ph-tpy)(Cl)][BF_4] (A) yellow and (B) red form recorded at 40 K intervals over the range of (a) 80 K to (b) 280 K upon excitation at 340 nm. (Reprinted with permission from ref 102. Copyright 1999 The Royal Society of Chemistry)……………..…30

1.14 Selected luminescent Pt(II) terpyridine complexes 35-50 in DCM, MeCN or DMF solutions at 25 ºC 94, 107-109, 136, 137 .........................31

1.15 Energy level diagrams of Pt(II) complexes with either (A) [Cl] 66 or (B) [CN] 138, 139 as co-ligand, k_r and k_n as radiative and nonradiative decay, respectively…………………………………………………..32

1.16 Cyclic voltammogram of complex 51 in MeCN with 0.1M n-Bu_4NPF_6. (Reprinted with permission from ref 141. Copyright 2004 American Chemical Society)………………………………………………………..33

1.17 Interconverting structures of cis-[M(tpy)(C_6F_3)_2] complexes as a result of the 1,4-metallotropic fluxional shift via a ‘tick-tock’ twist mechanism 144 …………………………………………..34

xiii
1.18 $^1$H NMR spectrum (aromatic region) of complex 54 in (CDCl$_2$)$_2$ at 313 K (Reprinted with permission from ref 148. Copyright 1998 The Royal Society of Chemistry) ........................................36

1.19 Proposed solution rotamers for complexes 52 and 53$^{144,150}$..................................36

1.20 $^1$H NMR and fluxional process of complex 55 (Reprinted with permission from ref 151. Copyright 1996 American Chemical Society) ...............37

1.21 Fluxional process in complexes 55-57 occurred via (A) an oscillatory or a ‘tick-tock’ twist and (B) a classical $\eta^3$-$\eta^1$-$\eta^3$ mechanisms$^{152}$ ...............37

1.22 Luminescent Pt(II) terpyridine complexes 58-72 with alkynyl moieties$^{67,114,153}$ .................................................................................................39

1.23 Structures of aryl-modified and fused terpyridine complexes 73-75$^{155-157}$........40

1.24 Quaterpyridine-based structures of complexes 76 and 77. $^{158}$ The twisting motion in 77 is limited.................................................................41

1.25 Single crystal structure of (A) H-bonded dimer 78, (Reprinted with permission from ref 143. Copyright 2006 The Chemical Society of Japan) and (B) 79, (Reprinted with permission from ref 159. Copyright 2003 The Royal Society of Chemistry) .........................42

1.26 Molecular stacking of (A) linear chain-like [Pt(8-QNS)$_2$][Pt(tpy)(Cl)$_2$][(ClO$_4$)$_2$] (Reprinted with permission from ref 161. Copyright 2003 Elsevier) and (B) mononuclear bis-terpyridine complex 80$^{162}$ .................................................................43

1.27 Crystal packing diagrams of (A) 82 and (B) 86. (Reprinted with permission from ref 163. Copyright 2006 American Chemical Society) ..........44

1.28 (A) Structure of 58 and 88-90, (B) UV-vis spectra of (a) 88, (b) 88 + PAA + TBAH, (c) 58, (d) 58 + PAA + TBAH, and (C) aggregation of Pt(II) complexes. (Reprinted with permission from ref 164. Copyright 2005 Wiley-VCH) ..................................................45

1.29 CD spectrum of (A) 90 $\mu$M of poly(dT)$_{25}$ (a) and its binding with 30 $\mu$M of complexes 90 (b) and 88 (c), (B) 90 $\mu$M of poly(dC)$_{25}$ (a) and its binding with 30 $\mu$M and 45 $\mu$M of complex 90 (b and c) and 30 $\mu$M of complex 88 (d), (C) 30 $\mu$M of complex 90 binding to 90 $\mu$M of poly(L-aspartate) (a) and poly(L-aspartate) (b) in 5 mM Tris-HCl buffer with 10 mM NaCl at pH = 7.5. (Reprinted with permission from ref 165. Copyright 2006 National Academy of Sciences, U.S.A.) .........................46

xv
1.30 Perspective view of complex cation of 88 in (A) dark-green form is an extended linear chain packing and (B) in red form is in a dimeric zigzag arrangement. (Reprinted with permission from ref 167. Copyright 2002 American Chemical Society)

1.31 (A) Solution of 88 (1.47 × 10⁻⁴ M) in MeCN/Et₂O mixture displaying color changes upon increasing Et₂O composition (from left to right): 64, 68, 72, 74, 76, 78, 80%, and (B) absorption and (C) emission spectra of those solutions. Darker blue solutions exhibit stronger emission. (Reprinted with permission from ref 167. Copyright 2002 American Chemical Society)

1.32 (A) H-bonded dimer, (B) zigzag stacking of orange form, and (C) nearly linear packing of red form of complex 91. (Reprinted with permission from ref 68. Copyright 2004 American Chemical Society)

1.33 (A) Solid state emission of 58 acquired from cycling through exposure and removal of MeOH in air multiple times. (B) Luminescence of 58 observed by eye in the presence and absence of MeOH. (Reprinted with permission from ref 68. Copyright 2004 American Chemical Society)

1.34 Chemical structures of pH sensitive complexes 72 and 92-97

1.35 (A) Solution of 94 (1.8 × 10⁻⁴ M) in MeCN with various concentrations of p-toluenesulfonic acid (from left to right): 0, 0.11, 0.16, 0.18, 0.22, 0.27, 0.33, and 44 mM, displaying dramatic color changes, and (B) absorption and (C) emission spectra of those solutions. (Reprinted with permission from ref 169. Copyright 2005 American Chemical Society)

1.36 Proton induced deactivation of LLCT in complexes 72 and 92-94

1.37 Changes in absorption of complex 96 (1.47 × 10⁻⁵ M) upon addition of various concentration of [HBF₄] in MeCN. (A) [HBF₄]: 0-1.47 × 10⁻⁵ M, (B) [HBF₄]: 1.47-4.4 × 10⁻⁵ M. (Reprinted with permission from ref 171. Copyright 2007 Wiley-VCH)

1.38 Chemical structures of ion binding complexes 98-102

1.39 (A) Solution of 98 (2.2 × 10⁻⁴ M) in MeCN with variety of metal ions (from left to right): no metal, Li⁺, Na⁺, Mg²⁺, Ca²⁺, Cd²⁺, and Zn²⁺, (B) changes in absorption of 98 upon addition of various concentrations of Cd²⁺ (Both reprinted with permission from ref 69. Copyright 2005 The Royal Society of Chemistry), and (C) Ca²⁺ (Reprinted with permission from ref 170. Copyright 2004 Wiley-VCH)
1.40 (A) Changes in absorption of $^{99}$ with various concentrations of $^{99}C^{2+}$ and (B) changes in emission of $^{99}$ with various concentrations of $^{99}M^{2+}$. (Reprinted with permission from ref 69. Copyright 2005 The Royal Society of Chemistry)..........................................................56

1.41 (A) Chemical structures of azobenzene containing $^{108}$ and $^{109}$, (B) changes in absorption of $^{109}$ in DMF ($4.2 \times 10^{-5}$ M) upon irradiation at 366 nm light for 25 min, and (C) changes in emission of $^{108}$ in EtOH-MeOH-DMF = 5:5:1 (v/v) at 77 K upon irradiation with 366 nm light for 8 min. (Reprinted with permission from ref 174. Copyright 2002 American Chemical Society)………………………….58

1.42 Chemical structures of photosensitizers $^{110}$ and $^{111}$175................................59

1.43 (A) Chemical structures of Nafion membranes and (B) their two-phase cluster network model176....................................................................................60

1.44 EPR spectrum of nitroxide radical generated of $O_2$ saturated TMP/MeOH solution, where $^{110}$-incorporated Nafion was immersed (A) in the dark and (B) after the sample was irradiated for 100 s. (Reprinted with permission from ref 175. Copyright 2003 American Chemical Society).........................................................60

1.45 Chemical structures of optical limiting complexes $^{127}$-$^{130}$153,187 ................65

1.46 (A) Transient absorption difference spectra of complex $^{66}$ in Ar degassed MeCN solution at 25 °C following 355 nm excitation with 160 ns time increments, (Reprinted with permission from ref 153. Copyright 2005 American Chemical Society and (B) optical limiting of complexes $^{127}$ (b), $^{128}$ (a), $^{129}$ (c) and $^{130}$ (d) in a 2 mm cell for 532 nm, 4.2 ns laser pulses with linear transmission of the solutions as 70%, (Reprinted with permission from ref 187. Copyright 2006 American Chemical Society).................66

1.47 Structures of complexes $^{131}$-$^{138}$ and single crystal structure of $^{136}$96.............67

1.48 (A) Cyclic voltammogram of complex $^{139}$ and (B) possible oxidation process from square planar Pt(II) containing $^{139}$ to octahedral Pt(IV) $^{140}$. (Reprinted with permission from ref 191. Copyright 2003 American Chemical Society).....................................................68

1.49 (A) Single crystal packing and (B) UV-vis spectra with concentration of $5 \times 10^{-5}$ M in DCM at 25 °C of [Pt(t-Bu$_3$-tpy)(OH)][TCNQ] $^{141}$. (Reprinted with permission from ref 192. Copyright 2006 American Chemical Society)..............................69
1.50 Chemical structures of 142-155\textsuperscript{193,194} ...............................................................70

1.51 Dinuclear Pt(II) complexes 156-164 with rigid linkers\textsuperscript{24,193,195-198} .................................73

1.52 Single crystal X-ray structures of (A) 123 (n = 4) (Reprinted with permission from ref 195. Copyright 2003 Wiley-VCH) and (B) 124 (Reprinted with permission from ref 196. Copyright 2004 American Chemical Society).................................................................74

1.53 (A) Effect of various metal ions (5.0 × 10^{-5} M) on emission intensities of 161 and (B) emission spectra of calixcrown 161 with K\textsuperscript{+} ion. (Reprinted with permission from ref 24. Copyright 2006 American Chemical Society).............................................................................75

1.54 Chemical structures of dinuclear complexes 165-169 with flexible linkers and their aggregation/deaggregation behavior (bottom right corner, Reprinted with permission from ref 202. Copyright 2006 Wiley-VCH)..........................................................................................76

1.55 (A) High-temperature \textsuperscript{1}H NMR of 168 in DMSO-d\textsubscript{6}, S\textsubscript{1}-S\textsubscript{3} represents H\textsubscript{2}O, DMSO and MeCN solvents, respectively, (B) changes in absorption of 168 upon heating from −40 to 80 °C, and (C) changes in emission of 169 upon heating from 5 to 75 °C. (Reprinted with permission from ref 202. Copyright 2006 Wiley-VCH)..........................................................77

1.56 Structures of dinuclear 170-181 with short intramolecular distances between metal centers (Pt-Pt and Pd-Pd) and terpyridine moieties\textsuperscript{93,125,127,203-210} ...........................................................................................................78

1.57 Crystal structures of trinuclear 170 in its two different diastereomers. (Reprinted with permission of ref 210. Copyright 1980 American Chemical Society)..........................................................................................78

1.58 Single crystal structures of (A) 179 (Reprinted with permission from ref 125. Copyright 2003 Elsevier), (B) 175, (Reprinted with permission from ref 206. Copyright 2001 The Royal Society of Chemistry) and (C) 177 (Reprinted with permission from ref 127. Copyright 1999 The Royal Society of Chemistry)........................................................................79

1.59 Crystal structure of (A) molecular clip-like 178 (red form) and packing of its (B) red form and (C) dark form. (Reprinted with permission from ref 208. Copyright 2006 The Royal Society of Chemistry)......80
1.60 Structures of 185-187 and single crystal X-ray structure of 187
(Reprinted with permission from ref 143. Copyright 2006
The Chemical Society of Japan) .......................................................... 81

1.61 Dinuclear molecular clefts 190-197129,211-220 ........................................ 82

1.62 (A) Single crystal structure and (B) schematic representation
of interplanar distances and angles of bis-Pt(II) complex 190.
(Reprinted with permission from ref 218. Copyright 2004 Wiley-VCH) ... 83

1.63 (A) Single crystal X-ray structure and (B) schematic representation
of interplanar distances and angles of bis-Pt(II) complex 193. (Reprinted
with permission from ref 219. Copyright 2005 American Chemical Society) .. 83

1.64 Structure of 198 and its molecular crystal packing (Reprinted
with permission from ref 162. Copyright 2004 American Chemical Society) .. 84

1.65 Chemical structures of heteronuclear complexes 199-202162,221 .................. 85

1.66 Structures of hetero-dinuclear complexes 203-208224 .............................. 86

1.67 Chemical structures of dyads 209-214225 ............................................. 87

1.68 Chemical structures of triads 215-217194 ............................................... 88

1.69 Self-assembly of rectangular 218-221 and trigonal prism 222
and 223 shape architectures using molecular clefts 191, 194,
and 197187,129,211,212,214,215,220 .................................................... 89

1.70 Chemical structure of a fully aromatic tetranuclear rectangle 220129,211,212 ....... 90

1.71 Single crystal structure of a tetranuclear Pt(II) molecular rectangle 219
(Reprinted with permission from ref 220. Copyright 2005 Wiley-VCH) ...... 90

1.72 Assembly and crystal structure of hexanuclear Pt(II) acetylene
complex 229 from dinuclear Pt(II) 228 and [Pt(tpy)(MeCN)]2+. (Reprinted with permission from ref 226. Copyright 2002
American Chemical Society) ........................................................... 91

1.73 Chemical structures of guest molecules 230-258129,211-220 ..................... 93

1.74 Single crystal packing diagram of [190][[(230)2]].
(Reprinted with permission from ref 213. Copyright 2002
National Academy of Sciences, U.S.A.) ............................................. 94
1.75 (A) Single crystal X-ray structures of [157][201] (Reprinted with permission from ref 217. Copyright 2004 Elsevier) and (B) [160][198] (Reprinted with permission from ref 216. Copyright 2003 American Chemical Society)………………………………..….95

1.76 (A) Single crystal X-ray structure and (B) packing diagram of the covalently bound host-guest complex 259 and (C) its fluxional behavior. (Reprinted with permission from ref 213. Copyright 2002 National Academy of Sciences, U.S.A.)………………….96

1.77 The mole-ratio of guest/host plotted against $^1$H NMR shifts of host and/or guest protons in order to find the stoichiometry of host-guest complexes. (A) is reprinted with permission from ref 129. Copyright 2003 American Chemical Society; (B) and (C) are reprinted with permission from ref 211. Copyright 2001 Georg Thieme Verlag Stuttgart · New York; (D) is reprinted with permission from ref 214. Copyright 2003 The Royal Society of Chemistry……………..….97

1.78 Schematic diagrams of host-guest interactions of 241 and 242 with 190215……..98

1.79 Chemical structures of metal-containing artificial peptides 266-273228,229 ………101

1.80 Structures of Ethidium Bromide (EthBr) and Pt(II) complexes 274 and 275….103

1.81 UV-vis spectra of 274 upon addition of various amounts of ct-DNA in a 1mM sodium phosphate buffer with 3 mM NaCl ($I = 0.003$) at pH 6.8. In curves A to E, concentration of 274 is 6.97 µM and DNA-P concentrations are (A) 0, (B) 17 µM, (C) 34 µM, (D) 146 µM, and (E) 303 µM. In curves 1 to 5, concentration of 274 is 70.4 µM and DNA concentrations are (1) 0, (2) 97.7 µM, (3) 189 µM, (4) 356 µM, and (5) 700 µM. (Reprinted with permission from ref 71. Copyright 1974 S. J. Lippard)……….104

1.82 (A) Scatchard$^{238}$ plot for 274 in a buffer $I = 0.003$ (Reprinted with permission from ref 71. Copyright 1974 S. J. Lippard) and (B) 275 in a buffer with at $I = 0.01$, binding to calf thymus DNA (Reprinted with permission from ref 73. Copyright 1987 The Biochemical Society)………………….105

1.83 Structures of intercalators 274-287 to ct-DNA$^{71,73,98,113,239,241-244}$ …………………106

1.84 Plot of Log($K_B$) vs. Log([M$^+$]) for 275 and ct-DNA (Reprinted with permission from ref 73. Copyright 1987 The Biochemical Society)……….107
1.85  (A) The specific viscosity with intercalator 274 in 1 mM phosphate buffer with $I = 0.003$ at pH 6.8 (Reprinted with permission from ref 71. Copyright 1974 S. J. Lippard) and (B) their relative counter length ($L/L_0$) in 50 mM Tris-HCl buffer with $I = 0.2$ at pH 7.5 of DNA as a function of $r$ (Bound-[Pt]/[DNA]). (Reprinted with permission from ref 249. Copyright 1979 American Chemical Society)………………………………………………...108

1.86  Thermal denaturation curves of 400 $\mu$M of ct-DNA (A) alone, with (B) 20 $\mu$M of 284, and (C) 281; 85 $\mu$M of ct-DNA (D) alone and with (E) 3.5 $\mu$M of 274 (A, B, and C are reprinted with permission from ref 113. Copyright 1996 Elsevier; D and E are reprinted with permission from ref 71. Copyright 1974 S. J. Lippard)……...109

1.87  CD spectrum of (A) 280 and (B) 279 (50-80 $\mu$M) in the presence of 10 fold excess of DNA at 25 °C (1 mM phosphate buffer with $I = 0.0015$ at pH 7.0). (Reprinted with permission from ref 243. Copyright 1999 American Chemical Society)………………………………….110

1.88  (A) Fluorescence Scatchard plot for binding of EthBr ([EthBr] = 4.9 to 12 $\mu$M) to ct-DNA ([DNA] = 3.5 $\mu$M) in a buffer with $I = 0.2$ at pH 7.5 (line 1) and the presence of an increasing amount of 274, [DNA]/[274] = 4.5 (line 2), 1.8 (line 3), 0.90 (line 4), and 0.45 (line 5) (B) Fluorescence Scatchard plot for binding of EthBr ([EthBr] = 5.2 to 20 $\mu$M) to ct-DNA ([DNA] = 5.8 $\mu$M) in a buffer with $I = 0.1$ at pH 7.5 (line 1) and the presence of an increasing amount of 284, [DNA]/ [284] = 5.2 (line 2), 2.6 (line 3), 1.0 (line 4) and 0.52 (line 5). (Reprinted with permission from ref 71. Copyright 1974 S J. Lippard)…………………………111

1.89  Different topologies of closed circular DNA with several superhelical turns (form I), no superhelical turns (form I$_0$), and nicked (form II). (Reprinted with permission from ref 72. Copyright 1999 American Chemical Society)………………………………….112

1.90  (A) Schematic presentation of double helix B-DNA and (B) neighbor exclusion binding of the intercalator (dark area) to the B-DNA. (Reprinted with permission from ref 254. Copyright 1975 S. J. Lippard)………...113

1.91  Structure of deoxycytidinyl-(3',5')-deoxyguanosine (deoxy-CpG)$^{255}$…………114

1.92  X-ray crystal structure of deoxy-CpG:274 (2:2) looking down the $a$ axis, (Reprinted with permission from ref 255. Copyright 1978 Nature Publishing Group)………………………………………………………114
1.93 A view of X-ray crystal structure of deoxy-CpG: 274 (2:2) looking down the $b$ axis. Top base pairs are drawn in shaded solid black, 274 in the center is stippled while bottom base pair is unshaded (Reprinted with permission from ref 255. Copyright 1978 Nature Publishing Group) ................................................................. 115

1.94 Binding affinity dependence of 274 in DNA possessing various % G-C (Reprinted with permission from ref 246. Copyright 1979 American Chemical Society) ................................................................. 116

1.95 Pt(II) complexes 288-291 modified with carborane moieties for use of boron neuron capture theory (BNCT) agents 256-259 .................................................. 117

1.96 Structures of glycosylated complexes 292-299 prepared as potential antitumor agents 31 ................................................................. 118

1.97 Chemical structures of Au(III)-containing intercalators 300-304 261,262 ............... 119

1.98 Dinuclear intercalators 305-313 prepared by treatment with alkyl and aryl dithiols 73,135,239 ................................................................. 120

1.99 (A) CD spectra and (B) proposed binding modes for bisintercalators 312 and 313 to ct-DNA. (Reprinted with permission from ref 135. Copyright 2003 Elsevier) ...................................................................................... 122

1.100 Structure of bis-Pt(tpy) intercalators 314-317 containing carborane cage 257 ...... 122

1.101 Chemical and crystal structure of Ru(II)-Pt(II) complex 318 (Reprinted with permission from ref 263. Copyright 2004 Wiley-VCH) ............... 123

1.102 Structures of Ir(III)-Pt(II) complexes 319-321 connected through peptide linkers 264,265 ...................................................................................... 124

1.103 Chemical structure of tetrapeptide complex 267 and comparison of its space filled molecular model with 12 bp ds-DNA. (Reprinted with permission from ref 28. Copyright 2005 American Chemical Society) ............... 126

1.104 Substitution reaction of 324 with cysteine forming 325 76 .............................. 128

1.105 Structures of 180, 181, 326, and 327 and crystal structure of 180. (Reprinted with permission from ref 209. Copyright 1990 American Chemical Society) ...................................................................................... 128

1.106 Structures of reactive and unreactive biomolecules towards $[M(tpy)(Cl)]^+$ [$M = Pd(II), Pt(II)$] complexes 74,76-78,209,273,276 .................................................. 129
1.107 Structures of nucleoside containing biomolecules 328-33774,75,77-79,276,277……130

1.108 Single crystal X-ray structures of 338-340 (Reprinted with permission from ref 74, 273. Copyright 2004 and 2002 The Royal Society of Chemistry)………………………………………………………………………………131

1.109 Alternating copolymer of nucleosides adenine and uracil with phosphate and phosphorothioate backbone75……………………………………136

1.110 Structures of the bis-[4'-azidoterpyridine Pt(II)] complexes 341293………………137

1.111 Luminescent labeling of HSA with 51 and 342141……………………………………137

1.112 Structure of estrogen Pt(II) complex 345 and its molecular packing (Reprinted with permission from ref 295. Copyright 2006 Wiley-VCH)……138

1.113 Structure of potential Pt-terpyridine antitumor agents 346-356297………………140

1.114 Structure of mononuclear anti-tumor complexes 357-35980,85,86………………141

1.115 Structure of dinuclear Pt-terpyridine complexes 360 and 36180…………………141

1.116 Structures of 182, 362, and 36381……………………………………………………146

1.117 Volumetric MRI scans on day 15 presenting tumor growth in (A) untreated animals, (B) early therapy with 15 mg/kg of 362 and (B) late therapy with 35 mg/kg of 363. Early therapy, treatment at days 4, 8, and 12 after tumor inoculation; late therapy, treatment at days 9, 11, and 13 after tumor inoculation. The dark arrow indicates the sphenoidal sinus (SS) and the arrow heads delineate the tumor region. (Reprinted with permission from ref 300. Copyright 2007 Elsevier)…………………………………………………………147

2.1 Substituted 2,2':6',2"-terpyridines (5-8)………………………………………………151

2.2 The 2D correlation (COSY) NMR of cyano 5i……………………………………158

2.3 Single crystal X-ray structure of ester 4a…………………………………………159

2.4 Single crystal X-ray structure of cyano 4b…………………………………………162

2.5 Single crystal X-ray structure of ester 4f…………………………………………162

2.6 Single crystal X-ray structure of diester 5a…………………………………………163
2.7 Single crystal X-ray structure of dimethyl 5c.................................163
2.8 Single crystal X-ray structure of methyl ester 5g..............................164
2.9 Single crystal X-ray structure of methyl 5j..................................164
2.10 (a) Stacking of diester 5a in the crystal lattice with distances (Å) between central pyridine rings and (b) the orientation of diester 5a in adjacent planes in the lattice, viewing along c axis. Hydrogen atoms are omitted for clarity..................................................165
3.1 The synthesis of cyclobutane 18 by [2+2]-photodimerization of azachalcone 17 and single crystal X-ray structure of cyclobutane 18............186
4.1 Interlocked systems that resemble three- and four-toothed bevel gears........192
4.2 $^1$H NMR spectrum (300 MHz) of the aromatic region of (A) 5[(PF$_6$)$_4$] in CD$_3$CN, (B) 4 in CDCl$_3$. * indicates the CDCl$_3$........195
4.3 The illustration of crystal structure of complex 5; (A) the asymmetric unit, containing a complex dimer, two encapsulated CH$_3$CN molecules (line bar), three water molecules and two partially deprotonated TCBs; (B) molecular packing of crystal 5 (along a axis); water and CH$_3$CN molecules were omitted for clarity...............197
4.4 (A) An ordered packing motif of 5 along with b axis; (B) H-bonding representative (green and red lines) between carboxylic acid and water molecules (along c axis)..............................197
4.5 The variable low temperature $^1$H NMR (400 MHz) of 5[(PF$_6$)$_4$] in CD$_3$CD$_2$OD:CD$_3$CN (2:1).............................................................198
5.1 The self-assembly of metallomacrocycles containing bis(terpyridine) ligand with rigid linkers and formation of polymeric structures$^{373,376,386-389}$ ....205
5.2 The $^1$H NMR spectrum (300 MHz) of the aromatic region of (A) 9[(PF$_6$)$_4$] and (B) 5[(PF$_6$)$_4$] from chapter 4 in CD$_3$CN.........................209
5.3. MALDI-TOF-MS analysis of 9[(PF$_6$)$_4$]..........................................207
5.4 (A) Theoretical and (B) experimental isotope patterns of the [M – 3PF$_6$]$^{3+}$ peak of 9[(PF$_6$)$_4$] in the MALDI-TOF-MS...........211
5.5 MALDI-TOF-MS analysis of 10[(PF$_6$)$_6$]: inset table displays the theoretical and experimental exact mass of the selected peaks..........212
5.6  Molecular modeling of dinuclear 9 and trinuclear 10……………………………213

6.1  Structures of carboxylate functionalized Ru(II)-terpyridine complexes………………..221

6.2  Single crystal X-ray structure of bis(terpyridine) 9……………………………………224

6.3  UV-vis spectra of Fe(II)-terpyridine complexes 25-28 in MeOH at 25 ºC……227

6.4  (A) Single Crystal X-ray structure of 38[(PF6)s] and (B) its space filling model and (C) molecular packing (along c axis); MeCN and PF6 are omitted for clarity……………………………………230

6.5  Molecular packing of crystals of 38 (along b axis); MeCN and PF6 molecules are omitted for clarity……………………………………..230

6.6  UV-vis spectra of Fe(II)-terpyridine complexes 33-39 in MeCN at 25 ºC………………231

6.7  Aromatic region of 1H NMR (300 MHz) of (A) 47[(PF6)12] and (B) 46[(PF6)4] in CD3CN at 25 ºC……………………………………..236
<table>
<thead>
<tr>
<th>Scheme</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Kröhnke oligopyridine synthesis</td>
<td>5</td>
</tr>
<tr>
<td>1.2</td>
<td>Synthesis of 4'-arylterpyridines by a modified Kröhnke method</td>
<td>5</td>
</tr>
<tr>
<td>1.3</td>
<td>Synthesis of 4'-substituted terpyridines by a modified Kröhnke method</td>
<td>6</td>
</tr>
<tr>
<td>1.4</td>
<td>Synthesis of 4'-substituted terpyridines by Potts method</td>
<td>7</td>
</tr>
<tr>
<td>1.5</td>
<td>Synthesis of terpyridines by Jameson method</td>
<td>8</td>
</tr>
<tr>
<td>1.6</td>
<td>Adrian’s high yield (73-93%) synthesis of terpyridines</td>
<td>8</td>
</tr>
<tr>
<td>1.7</td>
<td>Synthesis of substituted terpyridines by Sauer method</td>
<td>9</td>
</tr>
<tr>
<td>1.8</td>
<td>Organometallic coupling procedures for terpyridine synthesis</td>
<td>10</td>
</tr>
<tr>
<td>1.9</td>
<td>Stille cross-coupling terpyridine synthesis</td>
<td>11</td>
</tr>
<tr>
<td>1.10</td>
<td>Synthesis of [Pt(tpy)(Cl)][X]·2H₂O and [Pt(t-Bu₃-tpy)(Cl)][ClO₄]</td>
<td>13</td>
</tr>
<tr>
<td>1.11</td>
<td>Synthesis of [Pt(4'-R(tpy)(Cl)][Cl] and [Pt(4'-R(tpy)(R²)][X]</td>
<td>14</td>
</tr>
<tr>
<td>1.12</td>
<td>Synthesis of [Pt(4'-R(tpy)(Cl)][X]</td>
<td>15</td>
</tr>
<tr>
<td>1.13</td>
<td>Introducing a variety of different R- groups to the Pt(II) terpyridine complex, as co-ligand</td>
<td>16</td>
</tr>
<tr>
<td>1.14</td>
<td>Synthesis of a Pt-alkyne linkage</td>
<td>16</td>
</tr>
<tr>
<td>1.15</td>
<td>Synthesis of [Au(tpy)(Cl)][(X)₂]</td>
<td>17</td>
</tr>
<tr>
<td>1.16</td>
<td>Synthesis of double salts with metallophilic interactions</td>
<td>44</td>
</tr>
<tr>
<td>1.17</td>
<td>Pseudorotaxane and proton-induced interchange of 104 and 105</td>
<td>57</td>
</tr>
<tr>
<td>1.18</td>
<td>Photooxidation of alkenes 112, 115, and 118 by 110/Nafion system</td>
<td>61</td>
</tr>
</tbody>
</table>
1.19  Proposed mechanism for ketone deprotection\textsuperscript{181} .......................................................... 62

1.20  Mechanism for H\textsubscript{2} formation from H\textsubscript{2}O via 66/MV\textsuperscript{2+}/TEOA/colloidal Pt\textsuperscript{19} ......... 64

1.21  Photooxidation of Hantzsch dihydropyridines by Pt(II) complexes\textsuperscript{184} ............. 64

1.22  Formation of crystalline propeller like 184 from dinuclear 182
(Reprinted with permission from ref 206. Copyright 2001 The Royal Society of Chemistry) ............... 81

1.23  Partially aromatic 188 is oxidized to fully aromatic 189 bis-tpy ligand\textsuperscript{129} .......... 82

1.24  Host-guest complex [190][233], as a molecular switch and/or motor\textsuperscript{218} .............. 99

1.25  Formation of cyclic peptides 262-265\textsuperscript{227} .......................................................... 100

1.26  Assembly of hairpin like structure Ln-Pt\textsubscript{2} 323 from 322\textsuperscript{268} ......................... 124

1.27  Acid disassociation constants of cysteine and its reactions with ([Pt(tpy)(H\textsubscript{2}O)]\textsuperscript{2+})\textsuperscript{273} .......................................................... 131

2.1  Preparation of the 4-substituted 2-acetylpyridines and their pyridinium iodide salts: i) H\textsubscript{2}O/CH\textsubscript{2}Cl\textsubscript{2}, AgNO\textsubscript{3}, MeCO\textsubscript{2}H, H\textsubscript{2}SO\textsubscript{4}, (NH\textsubscript{4})\textsubscript{2}S\textsubscript{2}O\textsubscript{8}, 3 h; ii) MeCN, paraldehyde, FeSO\textsubscript{4}·7H\textsubscript{2}O, TFA, \textit{t}-BuOOH, 3 h; iii) I\textsubscript{2}, pyridine, 3 h, N\textsubscript{2} .......................................................... 152

2.2  Preparation of 2'-azachalcones by Claisen-Schmidt aldol condensation: i) MeOH, 1 M NaOH, 1 h; ii) acidic Al\textsubscript{2}O\textsubscript{3}, MW 250 W, 60 °C, 15 min; iii) basic Al\textsubscript{2}O\textsubscript{3}, MW 250 W, THF (2 mL), 15 min ........................................ 153

2.3  Preparation of 4,4'-functionalized 4'-((4-R)-2,2';6',2'-terpyridines by the Kröhnke method: i) MeOH, NH\textsubscript{4}OAc, 8 h; or ii) AcOH, NH\textsubscript{4}OAc, 6 h .......... 154

2.4  Preparation of 4,4'-functionalized 4'-(4-R-phenyl)-2,2';6',2'-terpyridines: i) MeOH, 1 M NaOH, 9 h; ii) AcOH, NH\textsubscript{4}OAc, 8 h .......... 155

2.5  Further 4,4'-functionalization of 4'-(4-R)-2,2';6',2'-terpyridines: i) EtOH, HCl (gas), 8 h; ii) NaBH\textsubscript{4}, EtOH/THF, 10 h; iii) SOCl\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, 24 h .......................................................... 156

3.1  Synthesis of 4'-arylterpyridines by a modified Kröhnke\textsuperscript{44} method ...................... 183

3.2  Proposed mechanism for formation of the green dye 9: i) 1-(2-pyridacetyl)pyridinium iodide, AcOH, NH\textsubscript{4}OAc, 110 °C, 2 h; ii) 1-(2-pyridacetyl)pyridinium iodide, MeOH, NH\textsubscript{4}OAc, 60 °C, 10 h 352 .......... 184
3.3 Formation of condensation by-product 16: i) BH$_3$·THF, THF, 25 °C, 10 h; ii) PCC, DCM, 25 °C, 2 h; iii) NaOH (2 M), EtOH, 25 °C, 9 h………………..185

3.4 Photodimerization of trans-chalcones afforded cyclobutane products ……….186

4.1. Preparation of bis(terpyridine) 4; i) t-BuLi, B(i-OPr)$_3$, THF, – 90 °C, 15 h; ii) NaOH (1 M), MeOH, 25 °C, 3 h; iii) MeOH, 1-(2-pyridacyl)pyridinium iodide, NH$_4$OAc, 70 °C, 7 h; iv) 1, DME, Pd(PPh$_3$)$_4$, K$_2$CO$_3$ (2 M), 85 °C, 12 h, N$_2$…………………..194

4.2. Preparation of crystalline 5[(H$_2$TCB)$_2$]; i) FeCl$_2$·4H$_2$O, MeOH, 70 °C, 8 h, NH$_4$PF$_6$ (1 M); ii) H$_4$TCB, NaOH (1 M), MeCN, 5 days………………..194

5.1 Preparation of bis(terpyridine) 7: i) Me$_3$Si-C≡CH, Pd(PPh$_3$)$_2$Cl$_2$, PPh$_3$, Cul, NEt$_3$, 80 °C, 3 days, Argon; ii) KF, MeOH/THF, 25 °C, 10 h; iii) BH$_3$·THF, THF, 25 °C, 10 h; iv) PCC, DCM, 25 °C, 2 h; v) NaOH (1 M), MeOH, 25 °C, 9 h; vi) AcOH, NH$_4$OAc, 110 °C, 11 h; vii) 2, Pd(PPh$_3$)$_4$, Cul, THF/DIPA, 80 °C, 12 h, Argon…………………..207

5.2 One pot self-assembly of the dinuclear 8[(PF$_6$)$_4$] and 9[(PF$_6$)$_4$] and the trinuclear 10[(PF$_6$)$_6$]: i) FeCl$_2$·4H$_2$O, MeOH, 70 °C, 8 h, NH$_4$PF$_6$ (1 M); ii) RuCl$_3$, N-Ethylmorpholine, MeOH, 70 °C, 12 h, NH$_4$PF$_6$ (1 M)…………………………………………….208

6.1 The construction of hexanuclear metallomacrocycles via either self-assembly or step-wise manner………………..222

6.2 Synthesis of bis(terpyridines) 8 and 9 via Kröhnke method: i) BH$_3$·THF, THF, 25 °C, 10 h; ii) PCC, DCM, 25 °C, 2 h; iii) HTMA, CHCl$_3$, 70 °C, 1 h, N$_2$; iv) AcOH/H$_2$O (1:9), 98 °C, 1 h, N$_2$; v) NaOH (4 M), MeOH, 25 °C, 9 h; vi) AcOH, NH$_4$OAc, 110 °C, 11 h…………………………………………..223

6.3 Synthesis of bis(terpyridines) 14 and 15 and terpyridines 16, 17, 19 and 20 via coupling strategy: i) n-BuLi, Me$_3$SiCl, THF, –78 °C, 6 h, N$_2$; ii) 12 or 13, Pd(PPh$_3$)$_4$, Cul, THF/NEt$_3$, 80 °C, 11 h, Argon; iii) KF, THF/EtOH, 25 °C, 10 h; iv) Me$_3$Si-C≡CH, Pd(PPh$_3$)$_4$, Cul, THF/NEt$_3$, 80 °C, 11 h, Argon; v) (n-Bu)$_4$NF·3H$_2$O, THF, 25 °C, 6 h…………………………………………..225

6.4 Synthesis of mononuclear Fe(II)-complexes 25-28: i) FeCl$_2$·4H$_2$O, MeOH, 60 °C, 8-20 h, then NH$_4$PF$_6$…………………………….226
6.5 Synthesis of mononuclear Ru(II)-complexes 35-41: i) 29 or 13, RuCl₃·3H₂O (> 1 eq.), EtOH/THF, 70 °C, 15 h; ii) 13, or 21, N-ethylmorpholine, EtOH, 70 °C, 10-24 h, then NH₄PF₆; iii) 21 or 30, RuCl₃·3H₂O (0.5 eq.), N-ethylmorpholine, MeOH, 70 °C, 10-20 h; iv) NaOH (1 M), DMF, 60 °C, 12 h, TFA……………...228

6.6 Synthesis of Ru(II) dinuclear 40 and 41 and bis(terpyridine) 43: i) N-ethylmorpholine, EtOH, 70 °C, 24 h, NH₄PF₆; ii) NaOH (1 M), DMF, 60 °C, 12 h, TFA; iii) 17, Pd(PPh₃)₄, CuI, THF/MeCN/NEt₃, 70 °C, 12 h, Argon………………………………………………………………………...234

6.7 Synthesis of Ru(II) dinuclear 44-46 and hexanuclear Ru(II)-Fe(II) 47: i) N-ethylmorpholine, EtOH, 70 °C, 9 h; ii) NaOH (1 M), DMF, 60 °C, 12 h, TFA; iii) 20, Pd(PPh₃)₄, DMF/NEt₃, 70 °C, 48 h, Argon, then NH₄PF₆; iv) FeCl₂·4H₂O, EtOH/Acetone, 60 °C, 20 h, then NH₄PF₆…………………………………………………………...235
CHAPTER I
SYNTHESES OF TERPYRIDINES, THEIR SUPRAMOLECULAR CONSTRUCTS
AND BIOLOGICAL APPLICATIONS BASED ON THEIR SQUARE PLANAR
COMPLEXES*

1.1 Introduction

In the past two centuries, the unprecedented evolution of modern chemistry uncovered from the structure of simple molecules, like urea, to highly complex molecules, such as double helical DNA, therefore transformed biology and medicine fields. In the sequence, new breakthroughs in the technology of computers and electron microscopes have pushed the boundaries of chemistry even further, making it easier for us now to observe and investigate nature at the molecular level. In this climax, science gave birth to a new interdisciplinary field called supramolecular chemistry, which has become an intensively studied area in the last three decades. In 1987, J. -M. Lehn,¹ C. J. Pedersen,² and D. J. Cram³ received the Nobel Prize for their pioneering work. In 1988, J.-M. Lehn defined supramolecular chemistry as “…chemistry of molecular assemblies and of the intermolecular bond,”¹⁰ and he later rephrased it as “supramolecular chemistry aims at developing highly complex chemical systems from components interacting by

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non-covalent intermolecular forces.” Non-covalent forces are mainly based on H-bonding, van der Waals, dipolar, π-π interactions, and metal-ligand coordination. These interactions are generally weaker, with the exception of metal-ligand coordination, and usually reversible when compared to covalent bonds. The DNA structure is nature’s perfect example of a supramolecule, since the base-pairs (adenine, thymine, guanine, cytosine), connected to a phosphate-deoxyribose polymer backbone, self-assemble through H-bonding (A=T, G≡C) to form the double helical DNA. Reversible H-bonding between the base-pairs permits DNA to perform several critical biological tasks in living organisms, such as replication, genetic information storage, transcription, and translation.

In 1959, the famous American physicist Richard P. Feynman gave an inspiring talk; “There’s plenty of room at the bottom,” which in essence pioneered the nano-world. He envisioned the manipulation of matter on a nanoscale, miniaturization of computer parts and developing better electron microscopes, which then became a reality with the development of scanning probe microscopes (e.g. STM and SEM). In a general sense, there are two approaches to reach nanoscale dimension: “top-down” (widely used) and “bottom-up”. Top-down refers to microfabrication of the desired counterparts in a highly complex system by photolithography and etching. Current processes and materials derived from a top-down approach will soon reach their fundamental limits, which will greatly shift the importance of a bottom-up approach, focusing on self-recognition and self-assembly of functional molecules inspired from biological systems. A number of bottom-up techniques have already been scrutinized.
Metal-ligand interactions are a family of important self-assembly strategies used in supramolecular chemistry. To this extend, the development of chelating ligands for transition metals have been of recent increasing interest. In particular, 2,2':6',2''-terpyridine (designated as simple terpyridine or tpy; Figure 1.1) has been utilized extensively as a building block to construct octahedral, square planar or bipyramidal metal complexes with various transition metals leading to highly-ordered supramolecular architectures.

Figure 1.1. Structure of 2,2':6',2''-terpyridine

In 1931, terpyridines were first isolated by Morgan and Burstall\textsuperscript{14} when they heated pyridine and dry FeCl\textsubscript{3} to 340 ºC in an autoclave (50 atm) for 36 hours. Afterwards, addition of Fe(II) ion to a terpyridine solution gave it a purple color denoting the first indication of a metal complex formation. Since then, considerable research has been dedicated to better understand and utilize terpyridine metal complexes with a wide variety of transition metals and lanthanides, in order to capitalize their unique photophysical, electrochemical, magnetic, optical properties and biological activities. Due to these important characteristics, terpyridine metal complexes have exciting potential applications: as dye-sensitized solar cells,\textsuperscript{15-17} photosensitizes,\textsuperscript{18} photocatalysis,\textsuperscript{19-21} luminescent chemosensors,\textsuperscript{22-24} light-emitting diodes (LEDs),\textsuperscript{25,26} homogenous assays,\textsuperscript{27} DNA-binding,\textsuperscript{28} antigene,\textsuperscript{29} anti-tumor\textsuperscript{30,31} and anti-microbial\textsuperscript{32}
agents; magnetic resonance imaging (MRI) contrast agents.\textsuperscript{33,34} Moreover, the self-assembly of terpyridine metal complexes on different surfaces\textsuperscript{35-37} have promising role in the area of nano-molecular devices.\textsuperscript{38-40}

1.2 Terpyridine Synthesis and Functionalization Strategies

The growing interest in tailored terpyridine metal complexes has stimulated the synthesis and functionalization of novel terpyridine constructs. This section will briefly go over the synthetic strategies of terpyridines, since there are limited reviews in the literature.\textsuperscript{41-43} There are basically two synthetic strategies for terpyridine synthesis and functionalization, which are derived from ring-assembly and coupling procedures.

1.2.1 Ring Assembly Methods

Terpyridines are prepared by variety of ring assembly strategies; Kröhnke, Potts, Jameson, Adrian, and Sauer methods.

1.2.1.1 Kröhnke Method

In 1976, Kröhnke\textsuperscript{44} reported the first planned synthesis of oligopyridines. This method utilized a ring-closure procedure of 1,5-diketones 3, which was prepared \textit{in situ} by the Michael addition of \textit{N}-pyridinium salts 1 with enones 2 (Scheme 1.1). This strategy has evident advantages in substituted pyridine synthesis over conventional
routes, e.g. (1) using salts 1 instead of methyl or methylene ketones to synthesize pyridines eliminated the dehydrogenation step that was required to complete the synthesis, since salts 1 have a higher oxidation state than those ketones; (2) synthesis of 2,4,6-substituted pyridines leading to bi-, ter-, and up to septi-pyridines was achieved with diverse functional groups, such as aryl, 2-thienyl, 2-furyl, etc. There are two modified Kröhnke methodologies commonly used to prepare terpyridines.

The first is that of 4'-aryl-terpyridines 6, which were prepared by two routes (Scheme 1.2). In route A, benzaldehydes were reacted with one equivalent of 2-acetylpyridine to form enone 4, which was treated with the iodopyridinium salt of 2-acetylpyridine, NH₄OAc, and AcOH to afford terpyridines. In route B, two equivalents of 2-acetylpyridine were reacted with benzaldehydes to give the 1,5-diketone 5, which was treated with NH₄OAc and AcOH to obtain desired terpyridines.46-48
The second method leads to 4'-substituted terpyridines 8-10, initially reported by Constable and Ward\textsuperscript{49} (Scheme 1.3). Formation of triketone 7 from ethyl 2-picolinate and acetone produced 4'-hydroxyterpyridine (8; the enol tautomer of the 4-terpyridone) by addition of NH\textsubscript{4}OAc. This 4'-hydroxyterpyridine (8) was subsequently functionalized with alkoxy groups, as in 10, by an S\textsubscript{N}2-type nucleophilic substitution with a primary alkyl bromides (Route A) or converted to 4'-chloroterpyridine (9, Route B), which then reacted with any primary alcohols via nucleophilic aromatic substitution to give 4'-terpyridineoxy derivatives 10 (Route C).\textsuperscript{41}

![Scheme 1.3. Synthesis of 4'-substituted terpyridines by a modified Kröhnke\textsuperscript{44} method.](image)

1.2.1.2 Potts Method

In 1982, Potts \textit{et al.}\textsuperscript{50} reported 4'-methylthioterpyridine (13) from the ring-closure of 1,5-enediketones 12 with NH\textsubscript{4}OAc (Scheme 1.4). These enediones were prepared by reaction of the potassium enolate of 2-acetylpyridine with \(\alpha\)-oxoketene dithioacetals 11, which was prepared from 2-acetylpyridine, NaH, CS\textsubscript{2}, and MeI.\textsuperscript{50} Moreover, the introduction of diverse substituents on 4'-methylthioterpyridines was achieved by using
functionalized 2-acetylpyridines and their corresponding potassium enolate salts, e.g. 4-methyl-2-acetylpyridine and its potassium enolate salt led to 4,4''-dimethyl-4'-methylthioterpyridines (Scheme 1.4).  

2.1.3 Jameson Method

In 1991, Jameson and Guise reported an alternate synthetic route for terpyridine (Scheme 1.5), in which N,N-dimethylaminoenone 14 was prepared by the reaction of N,N-dimethylformamide dimethyl acetal with 2-acetylpyridine. Ketone 14 was reacted with potassium enolate of 2-acetylpyridine to give the 1,5-diketone intermediate (not isolated) with loss of dimethylamine. Terpyridine was formed upon ring-closure of 1,5-diketone with NH₄OAc (Scheme 1.5) in a moderate overall yield (47%).
1.2.1.4 Adrian Method

In 1998, Adrian et al. reported a high yield (73-93%) synthesis of terpyridines (Scheme 1.6) starting with treating 2,6-diacetylpyridine with cyclohexylamine to give 2,6-\textit{bis}(\textit{N}-cyclohexylacetimidoyl)pyridine, (Scheme 1.6) which was isolated in quantitative yield. Then, cyclization of Si-protected 3-bromopropylamines with the bis-imine gave the tetrahydropyridines 15, which were reacted with \textit{N}-chlorosuccinimide (NCS) in CCl\textsubscript{4} to afford the tetrachloro adducts 16 and lastly treatment with NaOMe yielded the desired substituted terpyridines 17 (Scheme 1.6).
1.2.1.5 Sauer Method

In 1999, Sauer et al.\textsuperscript{54,55} reported a novel 1,2,4-triazine ring-assembly strategy for desired substituted terpyridines 21, 22, 26, and 27 (Scheme 1.7), in essence a "Click Chemistry" approach\textsuperscript{56} to terpyridine synthesis. In Route A, the regiospecific cyclocondensation of 2-carboxamidrazone-6-R-pyridine 18 (R = H, 2-pyridyl, 2,2'-bi-6-pyridyl) with α-pyridylglyoxal (19) formed 1,2,4-triazine 20, which was then converted to the corresponding substituted terpyridines 21 or 22 via an inverse Diels-Alder reaction with norborna-2,5-diene or ethynyltributyltin (H-C≡C-SnBu\textsubscript{3}), respectively.\textsuperscript{55} Similarly,
in Route B, bis-carboxamidrazones 23 reacted with α-R-glyoxals 24 (R = 2-thiophenyl, 2,2'-bi-5-thiophenyl, 2-pyridyl) to afford bis-triazine 25, which was treated with norborna-2,5-diene or ethynyltributyltin to give substituted terpyridines 26 or 27, respectively.54

1.2.2 Cross-Coupling Methods

Early attempts at terpyridine synthesis using coupling procedures included either an Ullmann synthesis with 2-bromopyridine and 2,6-dibromopyridine with metallic copper or an oxidative route with pyridine and 2,2'-bipyridine with iodine. However, these routes led to < 10% yield.57 More sophisticated organometallic coupling methods were utilized to synthesize terpyridines in more reasonable yields (Scheme 1.8). Kauffmann et al.58 reported the reaction of 6-bromo-2,2'-bipyridine with 2-pyridyllithium (derived from 2-bromopyridine and n-butyllithium), affording terpyridine with an improved but still in a meager 39% yield (Route A in Scheme 1.8). Wakabayashi59 et al.

![Scheme 1.8. Organometallic coupling procedures for terpyridine synthesis.58,59](image)
later increased the yield to 65% for this terpyridine synthesis by coupling 2-pyridyllithium with 6-ethylsulfoxide-2,2'-bipyridine (28), which was obtained from the oxidation of 6-ethylthio-2,2'-bipyridine by magnesium monoperoxyphthalate (Route B, Scheme 1.8).

More recently, modern Pd(0)-catalyzed Stille, Suzuki, and Negishi cross-coupling reactions with their high yield (50-90%) conversions, as well as simple procedures have contributed greatly to the cross-coupling terpyridine synthesis. In particular, the Stille method was applied to the synthesis of terpyridines with a variety of different substitutes. Functionalized terpyridines 31 were obtained in high (90%) yields via either coupling 2,6-dihalopyridines (29) with 2-trialkylstannylpyridines (30) (Route A, Scheme 1.9) or 2,6-bis(trialkylstannyl)pyridines (32) with 2-bromopyridines (33) (Route B, Scheme 1.9).

Scheme 1.9. Stille cross-coupling terpyridine synthesis.64

1.3 Square Planar Terpyridine Transition Metal Complexes

Terpyridines have been utilized to form stable square planar complexes with d⁸-late transition metal ions, such as: Pt(II), Pd(II), and Au(III). The Pt(II) terpyridine complexes, as opposed to Pd(II) and Au(III) ones, have been extensively investigated, since they have unique luminescent properties offering potential applications in
chemosensing for solvents\textsuperscript{68} and metal ions,\textsuperscript{69} photocatalysis\textsuperscript{19,70} and biological activities, such as DNA intercalation\textsuperscript{71-73} and covalent binding to biomolecules\textsuperscript{74-79} with potential applications, as anti-tumor,\textsuperscript{31,80,81} radiotherapy,\textsuperscript{82-84} antiprotozoal agents\textsuperscript{85,86} and protein probes.\textsuperscript{76-78} In turn, Pd(II) terpyridine complexes have been utilized as supramolecular recognition centers\textsuperscript{87} and the Au(III) complexes have been demonstrated to possess anti-tumor\textsuperscript{88} activity.

1.3.1 Chemistry and properties

In this section, synthesis, characterization, single crystal structures, molecular packing, dimerization, fluxionality, photophysical and electrochemical properties of square planar terpyridine transition metal complexes are discussed.

1.3.1.1 Synthesis

In 1934, Morgan and Burstall\textsuperscript{89} initially isolated [Pt(tpy)(Cl)][Cl]\cdot3\text{H}_2\text{O}, as a minor product, from a red aqueous filtrate derived from the reaction of terpyridine with one equivalent K\textsubscript{2}PtCl\textsubscript{4} in H\textsubscript{2}O after refluxing for 6 hours. Unfortunately, the major product of this reaction was the orange-brown precipitate [Pt(tpy)(Cl)]\textsubscript{2}[Pt(Cl)\textsubscript{4}]. Notably, four decades later, when the reaction mixture was refluxed until a clear red solution was realized (20-100 hours), [Pt(tpy)(Cl)][Cl]\cdot3\text{H}_2\text{O} was isolated in 65\% yield and recrystallized from hot H\textsubscript{2}O/EtOH (1:1) affording orange-red needle-like crystals, as the trihydrate, which was subsequently transformed to the dihydrate upon drying \textit{in vacuo}
Counterion exchange of the Cl\(^-\) ion of [Pt(tpy)(Cl)][Cl]·2H\(_2\)O was achieved by its dissolution in water and re-precipitation by the addition of an excess of an appropriate salt (e.g., NaClO\(_4\), NH\(_4\)PF\(_6\), CF\(_3\)SO\(_3\)Na, or CF\(_3\)SO\(_3\)Ag).\(^{92,93}\) Similarly, treatment of \(t\)-Bu\(_3\)-tpy with K\(_2\)PtCl\(_4\) in MeCN/H\(_2\)O generated a clear yellow solution of [Pt(\(t\)-Bu\(_3\)-tpy)(Cl)][Cl], which was filtered into aqueous NaClO\(_4\) to generate [Pt(\(t\)-Bu\(_3\)-tpy)(Cl)][ClO\(_4\)] as a yellow precipitate upon cooling. Its recrystallization by vapor diffusion of Et\(_2\)O into an MeCN solution of the complex afforded yellow crystals in 65% overall yield (Route B).\(^{94}\)

Scheme 1.10. Synthesis of [Pt(tpy)(Cl)][X]·2H\(_2\)O\(^{90-93}\) and [Pt(\(t\)-Bu\(_3\)-tpy)(Cl)][ClO\(_4\)].\(^{94}\)

The treatment of terpyridine ligands (4'-R\(^1\)-tpy; R\(^1\) = H, phenyl, \(p\)-toluoyl) with \(cis\)-[Pt(DMSO)\(_2\)(Cl)\(_2\)]\(^{95-97}\) or \(trans\)-[Pt(DMSO)\(_2\)(R\(^2\))(Cl)]\(^{95,98}\) (R\(^2\) = Me, phenyl) in MeOH\(^{95,98}\) for up to 2 hours at 25 °C or in CHCl\(_3\)\(^{96,97}\) for 24 hours at 25 °C afforded the desired [Pt(4'-R\(^1\)-tpy)(Cl)][Cl] or [Pt(4'-R\(^1\)-tpy)(R\(^2\))][Cl], respectively, (Scheme 1.11) in high overall yield (64-93%). The external Cl\(^-\) counterion in [Pt(4'-R\(^1\)-tpy)(R\(^2\))][Cl] was
easily exchanged by addition of AgNO₃, KPF₆, LiClO₄ or NaB(Ph)₄ (Route C, Scheme 2). However, a terpyridine ligand treated with \textit{cis}-[Pt(DMSO)₂(Cl)₂] in acetone for 12 hours in the dark at 20 °C exclusively formed [Pt(tpy)(Cl)][Pt(DMSO)(Cl)₃], as a red microcrystalline precipitate, which was recrystallized in DMSO (Route A, Scheme 1.11). When this reaction was conducted in refluxing MeOH over 1 hour, [Pt(tpy)(Cl)][X] possessing a mixture of counterions, where X = Cl⁻ and [Pt(DMSO)(Cl)₃]⁻, was generated. It was suggested that [Pt(DMSO)(Cl)₃]⁻ was formed by addition of the Cl⁻ ion to \textit{cis}-[Pt(DMSO)₂(Cl)₂] to give the product + DMSO.

\[ \text{[Pt(DMSO)(Cl)₃]⁻} \text{ + Cl⁻} \rightarrow \text{[Pt(DMSO)(Cl)₃]⁻} + \text{DMSO} \]

Another synthetic approach was developed to afford [Pt(4'-R-tpy)(Cl)][X] (X = SbF₆⁻, BF₄⁻, CF₃SO₃⁻, Scheme 1.12), in which an equimolar amount of AgX was added to a suspension of [Pt(PhCN)₂(Cl)₂] in MeCN, then refluxed for 15 hours to give the neutral [Pt(PhCN)₂(Cl)(X)]; one equivalent of the terpyridine ligand was then added after filtering and refluxed for 16-24 hours affording [Pt(4'-R-tpy)(Cl)][X], as orange-red crystals, in a 70-91% overall yield.
Scheme 1.12. Synthesis of [Pt(4'-R-tpy)(Cl)][X].\textsuperscript{101-105}

Annibale et al.\textsuperscript{100} reported a new synthetic method that gave [Pt(tpy)(Cl)][Cl] in quantitative yield, in which a suspension of [Pt(COD)(Cl)\textsubscript{2}]\textsuperscript{106} (COD = 1,5-cyclooctadiene) with an equivalent amount of terpyridine in MeOH or H\textsubscript{2}O afforded the desired complex after 15 min at 50 °C. It was proposed that the trans-orientation of the coordinated diolefin, and its lability when mono-coordinated to Pt(II), were the rationale for this high yield conversion. A similar method was utilized for the synthesis of Pt(II) complexes with a variety of other terpyridine ligands.\textsuperscript{107-110}

Employing a vapor-extraction apparatus, the co-ligand (Cl) of [Pt(tpy)(Cl)][X] (X = Cl\textsuperscript{-}, SbF\textsubscript{6}\textsuperscript{-}) can be substituted by H\textsubscript{2}O or MeCN. In this process, the continuous extraction of solid [Pt(tpy)(Cl)][X] into refluxing H\textsubscript{2}O or MeCN with an excess of AgX generated a soluble [Pt(tpy)(R\textsubscript{1})][(X)\textsubscript{2}] (R\textsubscript{1} = H\textsubscript{2}O, MeCN) (Route A, Scheme 4).\textsuperscript{101,111}

Moreover, diverse co-ligand functionality, i.e., OH, Br, I, SCN, N\textsubscript{3}, NH\textsubscript{3}, has also been introduced into these Pt(II) complexes (Route B, Scheme 1.13).\textsuperscript{93,112} Such [Pt(tpy)(R\textsubscript{1})][(X)\textsubscript{n}] [R\textsubscript{1} (n) = Cl (1), H\textsubscript{2}O (2), MeCN (2); X = Cl\textsuperscript{-}, SbF\textsubscript{6}\textsuperscript{-}] complexes have been easily converted to other Pt(II)-based terpyridine complexes via simple substitution of labile co-ligands, such as R = Cl, H\textsubscript{2}O, MeCN, with ROH, RSH, and pyridine (Route C, Scheme 1.13).\textsuperscript{91,111-113} Biomolecules containing thiol, imidazole, and guanidine were
also substituted with the Cl co-ligand in these Pt(II) complexes, which will be considered later in the text.

Scheme 1.13. Introducing a variety of different R-groups to the Pt(II) terpyridine complex, as co-ligand.91,93,101,111-113

A series of Pt(II) terpyridine complexes 1, containing alkynyl groups, was prepared by a reaction of [Pt(tpy)(Cl)]⁺ with H-C≡C-R in DMF in the presence of a catalyst (e.g., CuI and NEt₃) at 25 °C (Scheme 1.14) in reasonable yields of ca. 75%.¹¹⁴

Scheme 1.14. Synthesis of a Pt-alkyne linkage.¹¹⁴

An equimolar amount of HAuCl₄ and terpyridine, which was refluxed in H₂O at pH 3-5 for 24 hours, gave the desired [Au(tpy)(Cl)][(Cl)₂] in 80% yield along with traces of [Au(tpy)(Cl)]₂[AuCl₂]₃[AuCl₄] (Route A, Scheme 1.15); whereas at pH 1.9-3, the
protonated terpyridines ([Htpy][H₂tpy][AuCl₄]₃) were isolated after 24 hours in 52% yield along with similar amounts of [Au(tpy)(Cl)]₂[AuCl₂][AuCl₄] (Route B, Scheme 1.15). Further, the [AuCl₄]⁻ salts of the protonated terpyridines at pH 6 afforded the desired [Au(tpy)(Cl)][(Cl)₂] under reflux conditions in 62% yield. To avoid side products, the functionalized terpyridines were subsequently treated with KAuCl₄ and LiPF₆, LiClO₄ or AgCF₃SO₃ to generate the desired [Au(tpy)(Cl)][(X)₂] (X = PF₆⁻, ClO₄⁻ or CF₃SO₃⁻, respectively) in 63-80% yield (Route C, Scheme 1.15). The [Au(tpy)(OH)][(ClO₄)₂] was formed by treating [Au(tpy)(Cl)][(ClO₄)₂] with AgClO₄ in a hot aqueous media. It was suggested that the initially formed [Au(tpy)(H₂O)][(ClO₄)₃] disassociated to give the corresponding hydroxo species, since the Au(III) metal center can act as a strong acid.

![Scheme 1.15. Synthesis of [Au(tpy)(Cl)][(X)₂].](image)

The [Pd(4'-R-tpy)(Cl)][Cl] [R = H, CH₃(CH₂)₂O, Ph(CH₂)₃O] complexes were prepared in 90-93% yield by treatment of terpyridine with diverse Pd(II) sources, such as PdCl₂ either in MeNO₂ or concentrated HCl, cis-[Pd(DMSO)₂Cl₂] in MeOH, and...
[Pd(MeCN)₂Cl₂] in THF. The labile Cl co-ligand of the [Pd(tpy)(Cl)][Cl] complex was subsequently exchanged with various functional groups, such as: H₂O, OH, pyridine, 3,4-dimethylphenol, phenylcyanamides and biomolecules, such as: L-cysteine, glutathione, DL-penicillamine, and 1-Me-cytosine. Furthermore, treatment of terpyridine ligand with [Pd(MeCN)₄][(X)₂] (X = PF₆, BF₄) in MeCN afforded the corresponding [Pd(tpy)(MeCN)][X] complexes, which were later converted to [Pd(tpy)(Cl)][X] by the addition of NH₄Cl or were directly utilized in the construction of metallosupramolecular architectures.

1.3.1.2 Characterization

The Pt-based terpyridine complexes were mainly characterized by NMR spectroscopy, in which [Pt(tpy)(Cl)]⁺ showed down-field shifts for the 4,4''-tpyH (∆δ = 0.51 ppm), 5,5''-tpyH (∆δ = 0.46 ppm), and 6,6''-tpyH (∆δ = 0.20 ppm) (Figure 1.2) relative to the ligand due to the influence of the metal-ligand bond. Similar shifts upon complexation were observed for the Au(II) and Pd(II) terpyridine complexes. The ¹⁹⁵Pt NMR was also used to characterize these Pt(II) terpyridine complexes, each of which revealed a single Pt peak at ca. –3000 ppm.

The UV-vis spectra of [Pt(tpy)(Me)][BPh₄] in MeCN revealed well-resolved peaks at 408 nm (ε = 2300 M⁻¹cm⁻¹), 337 (11950), 325 (10780), 313 (12780), and 270 (31150) (Figure 1.3A). The peaks in the range of 310-340 nm were attributed to a π-π* intraligand (IL) transition of terpyridine; whereas, the peak at 408 nm was assigned to either a dπ-π* transition or “metal-to-ligand charge-transfer” (MLCT) transition.
Similar bands were observed for [Pt(4'-Ph-tpy)(Cl)][SbF₆] (Figure 1.3B)¹⁰² and [Pt(4'-R'1-tpy)(R')⁺ (R¹ = H, Ph; R² = Cl, Me, Ph) in MeCN.⁹⁵ The MLCT peak of these complexes displayed significant red shifts in DCM compared to MeCN due to a net increase of the dipole moment in the MLCT excited state.¹⁰⁷ The UV-vis absorption of [Pt(tpy)(R)]⁺[R (n) = [Cl, Br, I, NCS, OH, OMe, N₃] (1), NH₃ (2)] complexes displayed a similar behavior to that depicted in Figure 1.3.⁹³,¹¹²

![Figure 1.2. ¹H NMR of (A) terpyridine and (B) [Pt(tpy)(Cl)]⁺ in DMSO-d₆. (Reprinted with permission from ref 99. Copyright 2001 Elsevier).](image)

The absorption peaks of [Pt(tpy)(Me)][BPh₄] did not change with increased concentration; however, an increase in the intensity of the absorption displayed a non-linear curve that did not obey Beer’s law (inset in Figure 1.3A).¹³¹ This non-linear behavior was interpreted as an aggregation of complexes through π-π interaction of terpyridine ligands and d(2)-d(2) orbital interactions of the Pt-Pt metals; ¹H NMR data supported this conclusion.⁹⁵ In the case of the terpyridine possessing three bulky t-butyl groups, aggregation of the Pt complexes was circumvented.¹³²
Figure 1.3. The UV-vis spectra of (A) [Pt(tpy)(Me)][BPh₄] in MeCN at 25 °C. In the inset: the straight line represents the theoretical concentration dependence of absorbance at 313 nm with $\varepsilon_{313} = 12780 \text{ M}^{-1}\text{cm}^{-1}$ according to Beer’s law, and the line connected with open squares represents the experimental result (Reprinted with permission from ref 131. Copyright 2000 Elsevier), (B) [Pt(4'-Phe-tpy)(Cl)][SbF₆] in MeCN at 25 °C (Reprinted with permission from ref 102. Copyright 1999 The Royal Society of Chemistry).

Absorption spectra of [Pd(tpy)(Cl)]⁺ showed peaks at 362 nm ($\varepsilon = 8180 \text{ M}^{-1}\text{cm}^{-1}$), 345 (9050), 328 (8670), 279 (23900), 246 (25800), and 205 (57500). Peaks between 200-280 nm were assigned to the $\pi-\pi^*$ IL transitions and the 300-370 nm absorptions to the MLCT bands, which are in agreement with other Pd(II) terpyridine complexes.\textsuperscript{118,126} However, [Au(t-Bu₃tpy)(Cl)]²⁺ did not display any MLCT bands due to electrophilicity of the Au(III) center and the ligand-to-metal charge-transfer (LMCT) absorption that was possibly mixed with the high energy bands below 300 nm. The $\pi-\pi^*$ IL transitions of the [Au(t-Bu₃tpy)(Cl)]²⁺ complex were observed between 310-370 nm with a peak at 349 nm ($\varepsilon = 11430 \text{ M}^{-1}\text{cm}^{-1}$).\textsuperscript{94}
1.3.1.3 Single X-ray Crystal Structures and Their Molecular Packing

Single crystal X-ray structures of [Pt(4'-R-tpy)(Cl)]$^+$ (R = H, Aryl) revealed that the Pt(II) metal center is coplanar relative to the four donor atoms forming an irregular square planar with a deviation$^{92,99,101-103}$ from idealized geometry being evident in N(1)–Pt–N(2) and N(2)–Pt–N(3) possessing angles of 80-82° (Figure 1.4). Since there are d($z^2$)-d($z^2$) orbital interactions between the Pt–Pt metals and possible $\pi$–$\pi$ interactions between the terpyridine moieties in the neighboring coplanar complexes with distances less than 3.8 Å, they were grouped as linear chain,$^{103}$ tetrameric,$^{102}$ dimeric,$^{92,99}$ and monomeric$^{101}$ units along the supramolecular parallel stacks of the coplanar Pt(II) complexes.

Figure 1.4. Crystal structures of (A) [Pt(4'-Phe-tpy)(Cl)]$^+$ (Reprinted with permission from ref 102. Copyright 1999 The Royal Society of Chemistry) and (B) [Pt(tpy)(Cl)]$^+$ (Reprinted with permission from ref 99. Copyright 2001 Elsevier).

The single crystal X-ray structures of [Pd(tpy)(pyr)]$^{2+}$ and [Au(4'-R-tpy)(Cl)]$^{2+}$ (R = H, SMe) revealed a coplanar metal center with a distorted square planar geometry (Figure 1.5).$^{115,116,123}$ Molecular packing of [Pd(tpy)(OPhMe$_2$)]$^+$ revealed a linear chain-like stacking of complexes through $\pi$–$\pi$ interactions of the terpyridine moieties with
interplanar distances of 3.3 – 3.4 Å; the Pd-Pd distance (5.3 Å) ruled out any d(z^2)-d(z^2) orbital interactions (Figure 1.6A). Linear stacking of [Pd(tpy)(1-Me-cytosine-N^3)]^{2+} complex was achieved through H-bonding of 1-Me-cytosine and water. There were neither d(z^2)-d(z^2) orbital nor π–π interactions in the stacks possessing Pd-Pd distances of 7.3 Å (Figure 1.6B).

Figure 1.5. Crystal structure of (A) [Pd(tpy)(pyr)]^{2+} (Reprinted with permission from ref 123. Copyright 2004 Elsevier) and (B) [Au(4'-MeS-tpy)(Cl)]^{2+} (Reprinted with permission from ref 116. Copyright 1999 The Royal Society of Chemistry).

Figure 1.6. Molecular packing of (A) [Pd(tpy)(O-Ph-Me2)]^{+} (Reprinted with permission from ref 125. Copyright 2003 Elsevier) and (B) [Pd(tpy)(1-Me-cytosine-N^3)]^{2+} (Reprinted with permission from ref 127. Copyright 1999 The Royal Society of Chemistry).
The crystal packing of [Pt(4′-(o-Me-Ph)tpy)(Cl)][SbF₆] revealed a linear chain motif with equal spacing (3.368 Å) between the Pt–Pt metals that were stacked on top of each other in a head-to-tail fashion. The torsion angle with respect to Cl(1)–Pt(1)–Pt(2)–Cl(2) was exactly 180° (Figure 1.7A). The cationic Pt(II) complex and SbF₆⁻ counterion formed separate columns stacking parallel to the c-axis. The Pt–Pt–Pt angle was 162° revealing that the neighboring platinum atoms were almost eclipsed when viewed down the stacking axis. The interplanar distance of successive terpyridine moieties (3.33 Å) suggested possible π–π interactions. Another linear, chain-like packing was observed for [Pd(4′-[Ph(CH₂)₃O]-tpy)(Cl)]⁺ (Figure 1.7B) with equal Pd-Pd (3.46 Å) and terpyridine interplanar distances (3.1 Å).

Figure 1.7. Linear chain packing of (A) [Pt(4′-(o-Me-Ph)-tpy)(Cl)][SbF₆] (Reprinted with permission from ref 103. Copyright 2002 The Royal Society of Chemistry) and (B) [Pd(4′-[Ph(CH₂)₃O]tpy)(Cl)]⁺ (Reprinted with permission from ref 118. Copyright 2001 Elsevier).

Molecular packing of [Au(tpy)(Cl)]₂[AuCl₂]₃[AuCl₄] revealed an extended chain-like formation of [AuCl₂]⁻ anions that were situated between [Au(tpy)(Cl)]²⁺ cations with Au(2)-Au(3) and Au(3)-Au(4) distances of 3.3 and 3.1 Å, respectively (Figure 1.8A). Similarly, packing of [Au(tpy)(OH)][ClO₄] revealed a dimeric formation of the [Au(tpy)(OH)]²⁺ cation promoted by H-bonding of the coordinated OH groups to the ClO₄ counterions and weak Au(III)-O⁻ interactions (Figure 1.8B).
The crystal packing of the [Pt(4'-Ph-tpy)(Cl)][BF$_4$] displayed an extended chain of stepped tetramers, which were formed by σ-interaction of d($z^2$)-d($z^2$) orbitals of the Pt–Pt metals.$^{102}$ Each tetramer contains two pairs of independent cations (A, B and A', B'; Figure 1.9), which are related to each other by a center-of-inversion. Stacking within the tetramer was considered to be uniform, since the Pt–Pt distance between independent pairs [Pt(B)-Pt(B') = 3.33 Å] and cation A and B [Pt(A)-Pt(B) = 3.31 Å] is very similar. The overall angle between Pt(A)–Pt(B')–Pt(A') (175°) revealed a column-like stacking of Pt metals inside the tetramer, while the angle between Pt(A')–Pt(B')–Pt(A) (142°) explained the step-like stacking of each tetramer sliding from the edge of the previous molecule with a head-to-tail arrangement.

Figure 1.8. Crystal molecular packing of (A) [Au(tpy)(Cl)]$_2$[AuCl$_2$]$_3$[AuCl$_4$] (Reprinted with permission from ref 115. Copyright 1983 American Chemical Society) and (B) [Au(tpy)(OH)][ClO$_4$] (Reprinted with permission from ref 117. Copyright 1999 The Royal Society of Chemistry).

The crystal packing of [Pt(tpy)(Cl)][X] (X = ClO$_4$,$^-$, CF$_3$SO$_3$,$^-$, [Pt(DMSO)(Cl)$_3$] $^-$) revealed a continuous stack of dimers that formed by a strong Pt–Pt σ-interaction with a distance of 3.33 Å (Figure 1.10).$^{92,93,99}$ Furthermore, stacking of the coplanar [Pt(tpy)(Cl)]$^+$ cations with either ([ClO$_4$]$^-$)$^{92}$ or ([PtCl$_3$(DMSO)]$^-$)$^{99}$ displayed a similar
distance between Pt–Pt dimers of 4.2 Å. The torsion angle of Cl(1)–Pt(1)–Pt(2)–Cl(2) inside the dimers with ClO$_4^-$ and [Pt(DMSO)(Cl)$_3$]$^-$ displayed a staggered, head-to-tail arrangement, respectively. The Pt atoms in the stack showed a zigzag configuration with a Pt(1)–Pt(2)–Pt(1') angle of 143° with ClO$_4^-$ counterion and an almost linear configuration with a Pt(1)–Pt(2)–Pt(1') angle of 167° with the [Pt(DMSO)(Cl)$_3$]$^-$ counterion. A similar dimerization behavior in other Pt(II) and Pd(II) terpyridine complexes has been observed.

Figure 1.9. Stacking of [Pt(4'-Ph-tpy)(Cl)][BF$_4$]·MeCN (Reprinted with permission from ref 102. Copyright 1999 The Royal Society of Chemistry).

Figure 1.10. X-ray crystal packing diagrams of (A) [Pt(tpy)(Cl)][ClO$_4$] dimer (Reprinted with permission from ref 92. Copyright 1995 American Chemical Society) and (B) [Pt(tpy)(Cl)][Pt(DMSO)(Cl)$_3$] dimer (Reprinted with permission from ref 99. Copyright 2001 Elsevier).
The irregular square planar \([\text{Pt}(\text{tpy})(\text{MeCN})][(\text{SbF}_6)_2]\) complex surprisingly did not display any close metal-metal or \(\pi-\pi\) interactions in the crystal lattice.\(^{101}\) Instead, it showed a stacking of parallel sheets consisting of cations and anions (Figure 1.11). The closest distance (4.9 Å) between these sheets implicated that there are not any close range interactions. Furthermore, the \([\text{Pt}(\text{tpy})(\text{MeCN})]^{2+}\) cations form parallel sheets, where each complex is paired with two \(\text{SbF}_6^-\) anions.

![Figure 1.11. Crystal packing of \([\text{Pt}(\text{tpy})(\text{MeCN})][(\text{SbF}_6)_2]\) (Reprinted with permission from ref 101. Copyright 1997 American Chemical Society).](image)

Other than these four most common packing motifs, additional possible packing diagrams of coplanar, Pt-based terpyridine complexes are known, such as the crystal packing of \([\text{Pt}(4'-(\text{o-Cl-Ph})\text{tpy})(\text{Cl})][\text{SbF}_6]\) represented by a structure that is intermediate between linear chain and a stacked dimer due to an alternating close distance (3.37-3.51 Å) between Pt–Pt metal centers in successive layers.\(^{104}\)

The counterion, solvent, and temperature play crucial roles in the formation of supramolecular stacks from Pt(II)-, Pd(II)-, and Au(III)-based terpyridine complexes. These supramolecular stacks possess distinct solid state photophysical properties that will be considered later in this review.
1.3.1.4 Dimerization and Its Constant ($K_D$)

Based on the single crystal X-ray packing and UV-vis spectroscopy analyses, Lippard et al.\textsuperscript{111} suggested that the aggregation of Pt(II) terpyridine complexes would occur in a dimeric formation. The dimerization constants ($K_D$) of [Pt(tpy)(Cl)][Cl] and [Pt(tpy)(SCH\textsubscript{2}CH\textsubscript{2}OH)][NO\textsubscript{3}] were calculated to be $4 \times 10^3$ and $7 \times 10^3$ M\textsuperscript{-1}, respectively, in aqueous 0.1 M NaCl solution. Later, Gray et al.\textsuperscript{92} gave another explanation for the dimerization process by calculating the dimerization constant of [Pt(tpy)(Cl)][ClO\textsubscript{4}], specifically based on either the $\pi$--$\pi$ interaction of the ligands or d-d interaction of the metal centers, as $1.3 \times 10^3$ and $1.0 \times 10^3$ M\textsuperscript{-1}, respectively, in aqueous 0.1 M NaCl solution at 25 °C. Romeo et al.\textsuperscript{131} reported the dimerization constants of [Pt(tpy)(Me)][BPh\textsubscript{4}] in MeCN and water by means of a UV-vis spectroscopy analysis as 180 M\textsuperscript{-1} and $1.0 \times 10^4$ M\textsuperscript{-1}, respectively. The notable difference in $K_D$ was caused by the low dielectric constant of MeCN. Other dimerization constants of mono- and dinuclear Pt(II) complexes have been reported.\textsuperscript{73,135}

1.3.1.5 Photophysical properties

The Pt(II) terpyridine complexes were expected to show luminescent properties, since their planar geometry discourages $D_{2d}$ distortions, thus promoting a radiationless decay. McMillin et al.\textsuperscript{112} reported the first solution emission properties of Pt(II) terpyridine complexes at 25 °C. The [Pt(tpy)(Cl)][Cl] complex did not show any emission at 25 °C due to efficient radiationless decay via its low-lying $^3\text{d-d}$ state;
however, the \([\text{Pt(tpy(R))}^+]\) (R = OH, NCS, OMe) complexes did display broad, structureless emissions at ca. 621, 588, and 654 nm, respectively, in MeCN at 30 °C (Figure 1.12A). The \([\text{Pt(tpy(R))}^+]\) (R = OH, NCS) complexes showed emissions in DCM at 610 and 594 nm, respectively, at 30 °C. These emissions were suggested to arise from the \(3\)MLCT state. Concentrations of the complexes in the solution were kept in the range of 10-500 µM in order to minimize or circumvent dimerization. The \([\text{Pt(tpy(OH))}^+]\) gave the highest excited state lifetime of 2 µs compared to \([\text{Pt(tpy(R))}^+]\) (R = OMe, NCS).

The \([\text{Pt(tpy(Cl)}^+]\) complex showed a highly structured luminescence at ca. 470 nm, assigned to a \(3(\pi^* \rightarrow \pi)\) transition, upon excitation at 366 nm in a dilute (6 µM) glassy solution of butyronitrile at 77 K (Figure 1.12B[a]). Emission behavior of this complex showed a concentration dependence; a narrow, unstructured, low-energy emission band

![Figure 1.12. (A) Corrected emission spectra of \([\text{Pt(tpy(R)}^+]\) (R = [a] OH, [b] OMe, and [c] NCS), (Reprinted with permission from ref 112. Copyright 1994 American Chemical Society) (B) Concentration dependence (mM) of emission spectrum of \([\text{Pt(tpy(Cl)}][\text{PF}_6] \) in EtOH:MeOH:DMF (5:5:1) at 77 K (547 nm excitation) (a) 0.003, (b) 0.072, (c) 0.15 (Reprinted with permission from ref 92. Copyright 1995 American Chemical Society).](image-url)
appeared at ca. 720 nm, which was attributed to triplet metal-to-metal-to-ligand charge-transfer ($^3\text{MMLCT}$) $\pi^* \rightarrow d\sigma^*$ transitions caused by possible dimerization (Figure 1.12B[c]). Other [Pt(tpy)R]$^+$ (R = Br, I, NH$_3$, N$_3$, SCN and CH$_2$NO$_2$) complexes also showed luminescence in a butyronitrile glass at 77 K.$^{93,133}$

Che et al.$^{93}$ observed the first solid state structureless emission from the microcrystalline [Pt(tpy)(Cl)][ClO$_4$] complex at ca. 700 nm at 25 °C. This emission was assigned to a $^3\text{MMLCT}$ transition due to dimer formation of the complex in extended linear stacks, which was observed in the single crystal X-ray structure. Most of the Pt(II) terpyridine complexes displayed strong solid-state emissions at 25 °C and were highly dependent on the counterion, as well as the crystallization solvent. For example, [Pt(tpy)(Cl)][X] (X = ClO$_4^-$, Cl$^-$, and PF$_6^-$) complexes formed deep red, orange, and yellow color crystals, respectively, from aqueous solutions; whereas, the [Pt(tpy)(Cl)][ClO$_4$] complex formed rust-orange crystals from a DMF/Et$_2$O solution.$^{92}$

The [Pt(tpy)(Cl)][X] (X = ClO$_4^-$, Cl$^-$, PF$_6^-$, SbF$_6^-$, and CF$_3$SO$_3^-$) complexes displayed $^3\text{MMLCT}$ emissions in the 630-730 nm range depending on the counterion and crystallization solvent.$^{92,101,133}$ The [Pt(4'-(R-Ph)tpy)(Cl)][X] (R = H, o-OMe, o-CF$_3$; X = BF$_4^-$, SbF$_6^-$) complexes showed solid state luminescence at ca. 630 nm at 25 °C.$^{102,103}$

The [Pt(4'-Ph-tpy)(Cl)][BF$_4$] complex was crystallized in two different crystal packing forms (red and yellow), which determined their solid state emission properties.$^{102}$ The yellow form is in a monomeric environment based on its packing pattern and displayed only triplet intraligand ($^3\text{IL}$) emissions; whereas, the red form packed as dimers and displayed $^3\text{MMLCT}$ emissions (Figure 1.13). Monomeric crystal packing of [Pt(tpy)(MeCN)][(SbF$_6$)$_2$] showed an emission spectrum similar to the yellow form of the
Solid state emissions of all these complexes were observed to be temperature dependent. For example, $^3$MMLCT emission of [Pt(4'-Ph-tpy)(Cl)][BF$_4$] complex (red form) displayed a red shift and an intensity increase in emission upon increasing the temperature causing decreased Pt-Pt packing (Figure 1.13B). The excited state lifetimes of these solids were in the range of 0.1-1 $\mu$s at 25 °C (298 K) and increased up to 14 $\mu$s at 77 K.

Various functional groups were introduced onto the terpyridine ligand with the goal to fine tune the luminescence properties of the resultant Pt(II) terpyridine complexes at 25 °C (Figure 1.14). Trichloro-substituted 35 displayed an ambient temperature luminescence in degassed MeCN at $ca.$ 620 nm that was assigned to the $^3$MLCT with a 1.9 $\mu$s excited state lifetime. Similar long-lived $^3$MLCT transitions at $ca.$ 600 nm for ketonic complexes 36 and 37 were reported with 3.3 and 6.4 $\mu$s excited lifetimes, respectively. It was suggested that greater stabilization of the Pt(II) d($x^2$-$y^2$) orbitals led
to an increase in the energy gap between $^3d$-$d$ and $^3$MLCT, thereby decreasing the radiationless decay.

![Complex structure](image)

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$R = \text{H, Me, Cl, CF}_3$

Figure 1.14. Selected luminescent Pt(II) terpyridine complexes 35-50 in DCM, MeCN or DMF solutions at 25 °C.$^{94,107-109,136,137}$

Complexes 38-40 containing the electron-withdrawing cyano moiety and electron-donating NMe$_2$ and SMe groups exhibited luminescence at 25 °C with excited state lifetimes of 116, 1920, and 146 ns, respectively.$^{107}$ It was proposed that the cyano group in complex 38 activated the $^3$MLCT band by decreasing its energy level and increasing the gap between $^3d$-$d$ and $^3$MLCT; whereas, the NMe$_2$ group in 39 induced the luminescence via mixing the $^3$MLCT and triplet intraligand charge-transfer ($^3$ILCT)
transitions (Figure 1.15A). The cyano group was utilized as co-ligand in complexes 41-44, which exhibited photoluminescence at 25 °C. Photophysical studies of complexes 41-44 revealed that the cyano group, as a co-ligand, deactivated the 3MLCT by increasing its energy level over the 3π-π* of the terpyridine ligand resulting in a weak phosphorescence from 3π-π* band (Figure 1.15B). Complex 43 displayed a remarkable emission, largely based on 3ILCT, with an excited state lifetime of 22 µs and quantum yield of 0.26. Emissions of complexes 38-40 were successfully quenched via exciplex formation with Lewis bases.

Aromatic groups were introduced onto the terpyridine ligand, as in complexes 45-50 (R = H) that were shown to display remarkably long-lived emissions at 25 °C with 0.085, 16.5, 12.1, 21, 64 and 0.6 µs excited lifetimes, respectively, attributed to their orbital parentage excited state that has significant intra-ligand character. Complex 49 showed emissions from 1ILCT, 3ILCT, 3π-π* (pyrene), and 3MLCT. Furthermore, solvents can influence the absorption and emission spectra via their polarity that can effect the MLCT state and/or quenching of the emission. The emission of 50 (R
was affected by the synergic effects of the MLCT, $\pi$(aryl)-p(B) charge-transfer interactions, and electron communication between the Pt(II)-tpy and arylborane moiety; which was confirmed by comparison to the nonemissive complex $\text{50 (R = Me)}$.\textsuperscript{137}

1.3.1.6 Electrochemical properties

The cyclic voltammogram of $\text{51}$ displayed two quasi-reversible reductions at $-0.99$ and $-1.46$ V (vs. SCE) and one irreversible oxidation at $+1.41$ V (Figure 15).\textsuperscript{141} Two successive reductions were assigned to the terpyridine moiety mixed with some Pt(II) character. The irreversible oxidation was attributed to Pt(II) $\rightarrow$ Pt(III). It was suggested that this was caused by a quick decomposition of the unstable Pt(III) metal. Similar assignments have been reported for other Pt(II) terpyridine complexes.\textsuperscript{67,107,109,114} Introducing different chemical groups to the terpyridine ligand did not affect the reduction potentials of the ligand; however, the co-ligand connected to Pt(II) with higher electron-donating ability and aromaticity decreased the oxidation potential of the irreversible Pt(II) $\rightarrow$ Pt(III) reaction.\textsuperscript{67,109,114,141}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure16.png}
\caption{Cyclic voltammogram of complex $\text{51}$ in MeCN with 0.1 M $n$-Bu$_4$NPF$_6$. (Reprinted with permission from 141. Copyright 2004 American Chemical Society).}
\end{figure}
The cyclic voltammogram of [Pt(tpy)(Cl)][PF$_6$] displayed two chemically reversible reductions (−0.74 and −1.30 V), followed by an irreversible process at −2.2 V (vs. AgCl/Ag). The irreversible reduction at −2.2 V became quasi-reversible at −20 °C with −2.1 V. Spectroelectrochemical studies and EPR spectroscopy of [Pt(tpy)(Cl)]$^+$ suggested that the unusual positive reduction potential shifts, when compared to similar Pt(II) complexes, were attributed to stable dimer formation stabilizing the reduced products relative to the monomeric [Pt(tpy)Cl]$^0$. The Pd(II) terpyridine complexes displayed only two irreversible terpyridine reduction.

1.3.1.7 Fluxionality

Square planar cis-[M(tpy)(C$_6$F$_5$)$_2$] [M = Pd(II) and Pt(II)], in which the terpyridine ligand acts as a bidentate chelator, displayed fluxional behavior with the terpyridine oscillating between equivalent bidentate modes described as a ‘tick-tock’ twist mechanism (Figure 1.17). The $^1$H NMR spectra of the Pd(II) 52 and Pt(II) 53 complexes at 0 and 70 °C, respectively, exhibited well-resolved absorptions that were

Figure 1.17. Interconverting structures of cis-[M(tpy)(C$_6$F$_5$)$_2$] complexes as a result of the 1,4-metallotropic fluxional shift via a ‘tick-tock’ twist mechanism.
fully assigned by selective decoupling experiments, thereby proving them to be bidentate terpyridine complexes. Moreover, the ambient temperature $^{19}$F NMR experiments gave well-resolved spectra revealing two different $C_6F_5$ groups. The $^1$H and $^{19}$F NMR studies in the 0-140 °C range for the Pd(II) complex displayed extensive changes characteristic of the previously reported fluxional process associated with bidentate terpyridine complexes using Ru(II), Re(I), Pt(IV), Mo(0), and W(0) metals.$^{145-147}$

New Pt(II) and Pd(II) complexes of 4'-substituted terpyridines were investigated to shed additional light on this mechanism and to give a better understanding to the fluxional process in these complexes.$^{148}$ The $^1$H NMR spectrum of complex 54 revealed two different isomers 54a and 54b, as a result of its fluxional process, with a ratio of 65:35, respectively (Figure 1.18). The $^1$H and $^{19}$F 2D-NMR studies further supported the proposed ‘tick-tock’ twist mechanism.

The energy barriers, as $\Delta G^\ddagger$ values, for the fluxion processes for 52-54 were calculated to be 71, 94, and 100.6 kJ.mol$^{-1}$, respectively, with the aid of high temperature $^1$H and $^{19}$F NMR studies; simpler spectra were observed at higher temperatures further confirming a rapid fluxional process on the NMR timescale.$^{144,148}$

Low temperature $^{19}$F NMR studies of 52-54 displayed splitting of the peaks that was interpreted to the varying rates of rotation of the uncoordinated pyridine ring parallel to the $C_6F_5$ ring and orthogonal to the rest of the terpyridine moiety resulting in two different degenerate rotamers (Figure 1.19).$^{144,148}$ Furthermore, fluxional properties of the Pt(II) complex with a bis-terpyridine ligand was reported.$^{149}$ Fluxional behavior, via an oscillatory process, was observed in the Pd(II) complex with t-Bu$_3$-terpyridine, as a bidentate chelator, and two pentafluorophenyl rings were connected to Pd(II) metal
through a tetrazenido moiety.\textsuperscript{150} Rotation of both C\textsubscript{6}F\textsubscript{5} rings was hindered with an energy barrier of 53.9 kJ\cdot mol\textsuperscript{-1} at 293 K; this agreed with that of complexes \textit{52} (47.0 kJmol\textsuperscript{-1}) and \textit{53} (55.9 kJmol\textsuperscript{-1}).\textsuperscript{144,150}

Figure 1.18. \textsuperscript{1}H NMR spectrum (aromatic region) of complex \textit{54} in (CDCl\textsubscript{2})\textsubscript{2} at 313 K (Reprinted with permission from ref 148. Copyright 1998 The Royal Society of Chemistry).

Figure 1.19. Proposed solution rotamers for complexes \textit{52} and \textit{53}.\textsuperscript{144,150}
Another fluxional process promoted *via* a proposed ‘tick-tock’ twist mechanism in Pd(II) allyl complex 55 was detected by the coalescence of syn and anti allyl peaks into one doublet in the $^1$H NMR in the range of 188-298 K and single crystal X-ray analysis (Figure 1.20 and 1.21A). However, the syn/anti interconversion in 56 and 57 suggested that it occurred *via* a classical $\eta^3$-$\eta^1$-$\eta^3$ mechanism (Figure 1.21B).

Figure 1.20. $^1$H NMR and fluxional process of complex 55 (Reprinted with permission from ref 151. Copyright 1996 American Chemical Society).

Figure 1.21. Fluxional process in complexes 55-57 occurred *via* (A) an oscillatory or a ‘tick-tock’ twist and (B) a classical $\eta^3$-$\eta^1$-$\eta^3$ mechanisms.
The activation barriers ($\Delta G^\ddagger = 44-48$ kJ mol$^{-1}$) for an allyl-to-ring hydrogen exchange in complexes 55-57 were similar to $\Delta G^\ddagger$ of pyridyl hydrogen exchange suggesting that the two fluxional processes are possibly concerted.$^{151,152}$

1.3.2 Mononuclear Terpyridine Complexes

Structure property relationships in square planar terpyridine complexes possessing Pt(II), Pd(II), and Au(III) metals are contingent upon substituents that are introduced to the terpyridine ligand and/or the metal center, as a co-ligand, such as electron-donating and withdrawing, aromatic, $H$-bonding, cyclic, and biomolecules. As a result, novel photophysical, electrochemical, and optical properties can be accessed, thereby promoting new applications in optical limiting, molecular sensing and switches, as well as construction of supramolecular architectures

1.3.2.1 Luminescent Pt-Terpyridine Complexes

A new generation of remarkable photoluminescent Pt(II) terpyridine complexes 58-72 consisting of alkynyl groups, as co-ligands, has been described (Figure 1.22).$^{67,114,153}$ Absorption spectra of these complexes (at concentrations of $10^{-5}$-$10^{-2}$ M) displayed unique MLCT bands mixed with alkyne-to-terpyridine charge transfer (LLCT) bands in the range of 410-480 nm, which were confirmed by computational studies.$^{154}$ Emission spectra of complexes 58-72 revealed $^3$MLCT/$^3$LLCT bands$^{154}$ at ca. 550-670 nm in MeCN or DCM at 25 °C.$^{67,114,153}$ Excited state lifetimes ($\tau$) and quantum yields
(Φ_em) of 58 and 66 were significantly decreased by solvent change from DCM to MeCN revealing a solvent quenching process. The highest τ and Φ_em were observed for 62 and 63 in degassed DCM *i.e.*, 14.6 µs, 0.30 and 10.3 µs, 0.25, respectively; it was postulated that the electron-donating alkynyl ligands increase the energy gap between 3d-d and 3MLCT excited states and, as a result, the radiationless decay of the 3MLCT state, mediated by a low-lying 3d-d state, became less prevalent.114 The Pt(II) acetylene terpyridine complexes containing naphthalene groups, *i.e.*, 64, displayed a similar emission behavior to the parent complex 58 but did not improve its excited state lifetime.105 Even though the acetylene bearing Pt(II) complexes proved to be luminescent at 25 °C, pendant groups and solvent were observed to have a dramatic effect on their excited state lifetimes and quantum efficiencies.

![Figure 1.22. Luminescent Pt(II) terpyridine complexes 58-72 with alkynyl moieties.](image)

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Novel Pt(II) complexes 73-75 with aryl-modified and fused terpyridine ligands have been reported along with their luminescent properties at ambient temperature (Figure 1.23).\textsuperscript{155-157} Complexes based on the architectures of 73 exhibited $^3$MLCT/$^3$LLCT emissions similar to that of alkynyl-containing complexes 58-72; the strongest emission was derived from complex 73 where R = NMe$_2$ ($\Phi_{Em} = 0.11$ and $\tau = 2.4 \mu s$).\textsuperscript{157} All complexes of motif 74 possessing 0-4 methyl groups displayed photoluminescence in the range of 530-670 nm at 25 °C that was assigned to a combination of $^3$ILCT/$^3$MLCT bands.\textsuperscript{155} The quantum yield ($\Phi_{Em}$) and excited state lifetime ($\tau$) of complex 74 dramatically increased from $\Phi_{Em} = 0.0031$ and $\tau = 0.23 \mu s$ (R = H$_4$) to $\Phi_{Em} = 0.055$ and $\tau = 9.3 \mu s$ (R = Me$_4$) in degassed DCM at 25 °C, which was rationalized by MO calculations, thereby unveiling the substituent effect on the HOMO and LUMO energy levels. It was suggested that luminescent complexes 74 and 75 could be useful as spectroscopic probes for biomacromolecules while the architectures of 75 could serve as antitumor agents.\textsuperscript{155,156}

![Figure 1.23](image_url)

Figure 1.23. Structures of aryl-modified and fused terpyridine complexes 73-75.\textsuperscript{155-157}

Two unusually distorted square planar Pt(II) quaterpyridine complexes 76 and 77 were each reported to possess N(1)-Pt-N(4, 1A) angles of 116° (Figure 1.24) and they
both exhibited solid state luminescence at ca. 700 nm with 0.24 $\mu$s excited state lifetimes.\textsuperscript{158} However, complex 77 exhibited a long-lived luminescence in degassed MeCN with an excited lifetime of $\tau = 7.0$ $\mu$s at 25 °C, due to the hindered twisting motion in the ligand.

![Quaterpyridine-based structures of complexes 76 and 77.\textsuperscript{158} The twisting motion in 77 is limited.](image)

1.3.2.2 Molecular Stacking and Induced Self-assembly

Among $N$-heterocyclic thiones, 2,5-dimercapto-1,3,4-thiadiazole (H$_2$dmct) and 2-amino-5-mercapto-1,3,4-thiazolate (Hamct) having five donor atoms in protonated and deprotonated forms can facilitate construction of mono- and multinuclear metal complexes. The Pd(II) complex 78 formed a dimeric structure through NH$_2$--NH $H$-bonding of Hamct, which was established by its single crystal structure (Figure 1.25A).\textsuperscript{143} Moreover, the Pt(II) complex 79 formed a similar dimeric structure through NH--N $H$-bonding of the H$_2$dmct moiety, displayed possible $\pi$-$\pi$ interaction between terpyridines, and did not have a strong Pt-Pt interaction (4.92 Å) (Figure 1.25B).\textsuperscript{159} Complex 79 demonstrated an emission at ca. 620 nm that was attributed to a $^3$LLCT band; whereas, the Pd(II) complex 78 was nonemissive.\textsuperscript{143,159} The cyclic voltammogram of 46 revealed
an oxidation peak at +0.31 V, which was associated with the thiolate-dithio redox process.\textsuperscript{159} It was suggested that these metal complexes might be useful redox reagents, since H\textsubscript{2}dmct and Hamct were utilized as cathode material in high performance lithium batteries.\textsuperscript{160}

![Diagram showing molecular structures](image)

Figure 1.25. Single crystal structure of (A) \(H\)-bonded dimer 78, (Reprinted with permission from ref 143. Copyright 2006 The Chemical Society of Japan) and (B) 79, (Reprinted with permission from ref 159. Copyright 2003 The Royal Society of Chemistry).

The novel linear chain-like structure consisting of one neutral [Pt(8-QNS)\(_2\)] (8-QNS = 8-quinolinethiolate) and two cationic [Pt(tpy)(Cl)]\(^+\) units possess a sandwich-like stacking of alternating strong Pt(II)-Pt(II) (3.35 Å) and weak Pt(II)-S (3.85 Å) interactions, where \(\pi-\pi\) (3.42 Å) interactions were distributed throughout the columnar structure (Figure 1.26A).\textsuperscript{161} This particular structure did not exhibit an emission, since the stacked luminescent [Pt(tpy)Cl]\(^+\) was quenched via charge-transfer to [Pt(8-QNS)\(_2\)].
A unique bis-terpyridine ligand in which two terpyridines were connected through a 2,7-di-tert-butyl-9,9-dimethylxanthene residue was complexed with only one equivalent of Pt(II) metal in order to construct the mononuclear 47, which was assembled as head-to-head columns via intermolecular Pt-Pt (3.42 Å) and π-π (3.69 Å) interactions (Figure 1.26B). In general, the intramolecular distance of 4.0 Å did not appear to contribute to the stacking. The dinuclear complexes of this bis-terpyridine ligand with Pt-Pt and Pt-Ru metals will be considered later in this review.

Figure 1.26. Molecular stacking of (A) linear chain-like [Pt(8-QNS)₂][Pt(tpy)(Cl)]₂ [(ClO₄)₂] (Reprinted with permission from ref 161. Copyright 2003 Elsevier) and (B) mononuclear bis-terpyridine complex 80.

Doerrer et al. reported the synthesis of double salts 81-87 via treatment of [Pt(tpy)(Cl)][Cl] with salts containing Au(III) or Au(I) metals (Scheme 1.16). The products 81-87 were recrystallized in polar organic solvents and displayed an extended linear chain-like structure through ‘metalophilic’ interactions in their crystal packing, forming single-atom-wide wires. For example, the double salts 82 and 86 packed by
means of Pt(II)-Au(I) metal interactions with distances of 3.28 and 3.34 Å, respectively (Figure 1.27). It was proposed that these salts could display interesting solid-state luminescent and conductive properties.

Scheme 1.16. Synthesis of double salts with metallophilic interactions.163

Figure 1.27. Crystal packing diagrams of (A) 82 and (B) 86. (Reprinted with permission from ref 163. Copyright 2006 American Chemical Society).

Yam et al.164 reported that (n-Bu)4NOH (TBAH) deprotonated poly(acrylic acid) (PAA) induced the self-assembly of complexes 58 and 88 via Pt-Pt and π-π interactions, which were supported by unique changes in their absorption and emission spectra (Figure 27). Color changes in solutions of 58 and 88 from yellow to light brown and light-yellow to pink/red, respectively, were attributed to new MMLCT bands appearing at ca. 480/580 and 543 nm, respectively (Figure 1.28). New emission bands for complexes 58 and 88 at ca. 800 nm were assigned to a 3MMLCT luminescence. The maximum intensity for the
absorption and emission spectra of 58 and 88 was obtained with a ratio of 1:3:3 (complex:PAA:TBAH). No color changes were observed for 58 and 88 in only PAA or TBAH and mono-, di-, and tricarboxylic acids with TBAH, which suggested the need for high molecular weight and negatively charged promoters. Complex 89 with bulky t-butyl groups did not aggregate in PAA with TBAH.

![Chemical structures and spectra](image)

Figure 1.28. (A) Structure of 58 and 88-90, (B) UV-vis spectra of (a) 88, (b) 88 + PAA + TBAH, (c) 58, (d) 58 + PAA + TBAH, and (C) aggregation of Pt(II) complexes. (Reprinted with permission from ref 164. Copyright 2005 Wiley-VCH).

Single-stranded nucleic acids, poly(L-glutamate), and poly(L-aspartate), which carry multiple negative charges in aqueous solution at pH = 7.5, were also utilized as templates to self-assemble complexes 88 and 90 that subsequently exhibited new MMLCT absorption and 3MMLCT emissions bands. It was suggested that as the local concentration of the complex increased; the aggregation of these complexes was induced.
by d-d and π-π interactions. Helical self-assembly of 88 and 90 associated with polynucleotides and poly(amino acids) displayed an induced circular dichroism (ICD) in which its shape and intensity depended on the primary and secondary structures of the biopolymers (Figure 1.29). As an exception, aggregation of 90 was only observed at low concentrations with DNA, in that as the concentration of 90 increased the new MMLCT absorption and the emission bands disappeared suggesting that the complex intercalated into DNA instead of electrostatic binding. Supramolecular self-assembly of [Pt(tpy)Me]^+ was also achieved by its electrostatic interaction with α-helical form of poly(L-glutamic acid) at pH = 4.5 as proven by ICD.\textsuperscript{166}

![Figure 1.29](image)

Figure 1.29. CD spectrum of (A) 90 \(\mu\)M of poly(dT)\textsubscript{25} (a) and its binding with 30 \(\mu\)M of complexes 90 (b) and 88 (c), (B) 90 \(\mu\)M of poly(dC)\textsubscript{25} (a) and its binding with 30 \(\mu\)M and 45 \(\mu\)M of complex 90 (b and c) and 30 \(\mu\)M of complex 88 (d), (C) 30 \(\mu\)M of complex 90 binding to 90 \(\mu\)M of poly(L-aspartate) (a) and poly(L-aspartate) (b) in 5 mM Tris·HCl buffer with 10 mM NaCl at pH = 7.5. (Reprinted with permission from ref 165. Copyright 2006 National Academy of Sciences, U.S.A.).

Single crystal packing of complex 88 displayed dimorphism in dark-green and red forms, in which the former was crystallized from the slow diffusion of Et\textsubscript{2}O vapor into MeCN solution of 88 and the later into a diluted acetone solution (Figure 1.30).\textsuperscript{167} The
dark green form of 88 revealed an extended, nearly perfect linear chain-like structure with a Pt-Pt-Pt angle of 179.2° via equally distanced Pt-Pt interactions (3.388 Å) and partial stacking of terpyridine moieties (Figure 1.30A); however, the corresponding red form stacked as dimeric units with alternating Pt-Pt distances of 3.396 and 3.648 Å in a zigzag arrangement with Pt-Pt-Pt angle of 154.3° (Figure 1.30B). The single crystal structure of complex 89 was obtained but it did not show any short-range interactions due to the presence of the bulky t-Bu groups. Dimorphism of [Pt(tpy)(Cl)][Cl], which was crystallized in a yellow colored form from EtOH and a less-stable red form from 1 M HCl, was detected via X-ray powder diffraction.168

Figure 1.30. Perspective view of complex cation of 88 in (A) dark-green form is an extended linear chain packing and (B) in red form is in a dimeric zigzag arrangement. (Reprinted with permission from ref 167. Copyright 2002 American Chemical Society).

1.3.2.3 Molecular Sensors and Switches

Luminescent and colored Pt(II) terpyridine complexes, which are sensitive to their environment, such as: concentration, solvent, acidity, and counter-ions, have been utilized as sensors for pH, ions, and solvents. The reversible responsive behavior of these complexes also suggests their potential use as molecular switches.
Yam et al.\textsuperscript{167} reported remarkable color changes for complex 88 upon increasing the Et\textsubscript{2}O content in either MeCN or acetone (Figure 1.31A). The absorption spectra revealed an intensity drop in the MLCT band at 415 nm and an incidental advancement of a new low energy band at 615 nm, in which the intensity dramatically enhanced upon increasing the Et\textsubscript{2}O composition (Figure 1.31B). Since 88 is insoluble in Et\textsubscript{2}O, it was proposed that it aggregated into oligomeric forms that were confirmed by a new MMLCT absorption band at ca. 600 nm and 3MMLCT emission band at ca. 785 nm (Figure 1.31C). These unique solvatochromic effects via the assembly of 88 can promote applications as adaptable probes of environmental changes.

Figure 1.31. (A) Solution of 88 (1.47 × 10\textsuperscript{-4} M) in MeCN/Et\textsubscript{2}O mixture displaying color changes upon increasing Et\textsubscript{2}O composition (from left to right): 64, 68, 72, 74, 76, 78, 80%, and (B) absorption and (C) emission spectra of those solutions. Darker blue solutions exhibit stronger emission. (Reprinted with permission from ref 167. Copyright 2002 American Chemical Society).

In an elegant work, Eisenberg et al.\textsuperscript{68} reported a nicotinamide Pt(II) terpyridine complex 91, which possesses a reversible vapochromic behavior by changing its color from red to orange and displaying a shift in the emission band to higher energy upon
exposure to MeOH vapors. These two forms of 91, detected in the same single crystal, exhibited a dimeric form via H-bonding of nicotinamide residues (Figure 1.32A); however, they showed different packing arrangements (Figure 1.32B and C). The orange form of 91 revealed molecules of MeOH in the lattice and packed as a chain-like structure with a zigzag conformation of metal centers, in which the Pt-Pt-Pt angle was 126.7°; moreover, molecules of 91 were arranged in a head-to-tail fashion. However, the red form of 91 did not contain any MeOH residues in the lattice and packed as a pseudolinear extended chain structure, in which the Pt-Pt-Pt angle was 171.9° with a head-to-tail orientation. The distances of Pt-Pt metals and terpyridine moieties in the red form being 3.3 and 3.5 Å, respectively, revealing strong d-d and π-π interactions; whereas, the orange form of 91 possessed weak interactions since those distances are more than 3.6 Å.

![Image of complex 91](image)

Figure 1.32. (A) H-bonded dimer, (B) zigzag stacking of orange form, and (C) nearly linear packing of red form of complex 91. (Reprinted with permission from ref 68. Copyright 2004 American Chemical Society).
The red form showed a solid state emission band at 660 nm at 25 °C, which was assigned to the $^3$MMLCT; however, the orange form displayed an emission at 630 nm that was attributed to $^3$MLCT since it had only weak d-d and $\pi$-$\pi$ interactions. The emission band of the red form was at 660 nm, which shifted to higher energy at 630 nm upon exposure to MeOH; whereas upon in vacuo heating, the emission band shifted back to its original position (Figure 1.33A). This reversible vapochromic response cycle was repeated (five times) with no noticeable chemical decomposition of 91. Moreover, complex 91 was immobilized on filter paper and irradiated with long-wave UV light at ambient temperature - color changes from pink to yellow were visually observed in the presence as well as in the absence of MeOH (Figure 1.33B). This notable vapochromic behavior of complex 91 could be utilized as a chemosensor or MeOH-induced molecular switch.

Figure 1.33. (A) Solid state emission of 58 acquired from cycling through exposure and removal of MeOH in air multiple times. (B) Luminescence of 58 observed by eye in the presence and absence of MeOH. (Reprinted with permission from ref 68. Copyright 2004 American Chemical Society).
Yam et al.\textsuperscript{169} reported a remarkable reversible color changes in complexes 92-94 (Figure 1.34) upon consecutive addition of \textit{p}-toluenesulfonic acid and NEt\textsubscript{3} (Figure 1.35A). The absorption spectra of 94 displayed a low energy band at 546 nm that was assigned to the LLCT of amine-containing acetylene moiety-to-terpyridine mixed with some MLCT character and a high energy band at 412 nm that was attributed to MLCT. Upon addition of \textit{p}-toluenesulfonic acid, the intensity of the LLCT band was dramatically decreased and the intensity of the MLCT band was increased with a clear isobestic point at 460 nm indicative of complete conversion of the complexes to their corresponding protonated forms (Figure 1.35B). Moreover, upon protonation of complexes 92-94, a new emission band was observed at \textit{ca.} 600 nm, which was attributed to \textit{3}MLCT band.

![Figure 1.34. Chemical structures of pH sensitive complexes 72 and 92-97.](image)

<table>
<thead>
<tr>
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<th>Number</th>
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<th>(R^2)</th>
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<td>95</td>
<td>NMe\textsubscript{2}</td>
<td>H</td>
</tr>
<tr>
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<td>96</td>
<td>NMe\textsubscript{2}</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>97</td>
<td>NMe\textsubscript{2}</td>
<td>(structure)</td>
</tr>
</tbody>
</table>

\textsuperscript{169-171}
Figure 1.35. (A) Solution of 94 (1.8 × 10⁻⁴ M) in MeCN with various concentrations of p-toluenesulfonic acid (from left to right): 0, 0.11, 0.16, 0.18, 0.22, 0.27, 0.33, and 44 mM, displaying dramatic color changes, and (B) absorption and (C) emission spectra of those solutions. (Reprinted with permission from ref 169. Copyright 2005 American Chemical Society).

Tung et al.¹⁷⁰,¹⁷¹ observed similar reversible absorption and emission behavior for complexes 92-94, as that of complex 72, upon sequential addition of [HBF₄], as a proton source, and NEt₃, as base. It was suggested that the low energy LLCT state was deactivated via protonation, which led to a dominant MLCT absorption in the UV-vis spectra and the formation of the formerly quenched ³MLCT emission band by low energy non-emissive ³LLCT (Figure 1.36). Furthermore, complex 95 containing a -NMe₂ group, which was positioned on the terpyridine moiety instead of the alkynyl co-ligand, as in 72, displayed a new low energy ILCT band from the amino-substituted phenyl to the terpyridine mixed with the MLCT band at 490 nm. Upon addition of acid, the intensity of the ILCT band of 95 was monotonically decreased, leaving a less intense MLCT band at 450 nm; moreover, the formation of a new ³MLCT emission band was also observed.¹⁷¹
Introducing an amino group on both the terpyridine ligand and acetylene co-ligand as in complex 96 promoted a mixed ILCT/LLCT absorption band, which was subsequently deactivated via addition of [HBF₄]. The UV-vis titration spectra of 63 with one equivalent of acid revealed that the LLCT excited state was deactivated, showing a decrease in absorbance at the low energy band $\lambda > 520$ nm with well-defined isobestic points at 445 and 520 nm (Figure 1.37A), then one additional equivalent of the acid deactivated the ILCT excited state, displaying a decrease in absorbance at 490 nm with a well-defined isobestic point at 430 nm and leaving a MLCT band in the range of 380-550 nm (Figure 1.37B). Furthermore, even though the $^3$LLCT and $^3$ILCT states of 96 were not emissive, the fully protonated form of 96 exhibited luminescence from its $^3$MLCT band at 575 nm. Transient absorption spectroscopy of 72, 95, and 96 confirmed the LLCT, ILCT, and MLCT excited states as well as their reversible interconversion to each other under acidic and basic conditions. These studies suggested new promising applications as calorimetric, luminescent pH sensors, and proton-driven molecular switches could be developed by tuning spectroscopic properties of these type of acetylene- and amino-containing Pt(II) terpyridine complexes.
Figure 1.37. Changes in absorption of complex 96 ($1.47 \times 10^{-5}$ M) upon addition of various concentration of $[\text{HBF}_4]$ in MeCN. (A) $[\text{HBF}_4]$: 0-1.47 × 10^{-5}$ M, (B) $[\text{HBF}_4]$: 1.47-4.4 × 10^{-5}$ M. (Reprinted with permission from ref 171. Copyright 2007 Wiley-VCH).

Tung et al.\textsuperscript{171} introduced an azacrown ether to the alkynyl co-ligand and an amino group to the terpyridine ligand, as in complex 97. The UV-vis spectra of 97 revealed an alkyne-based LLCT and aminophenyl-to-terpyridine-based ILCT absorptions, which were deactivated by successive additions of Ca\textsuperscript{2+} cation and $[\text{HBF}_4]$, respectively, showing similar behavior to complex 96.

Yam\textsuperscript{69} and Tung\textsuperscript{170} et al. attached an azacrown ether group to the alkynyl co-ligand of the Pt(II) complex 98 (Figure 1.38) and investigated its ion binding properties. Significant color changes were observed for azacrown 98 upon addition of Li\textsuperscript{+}, Na\textsuperscript{+}, Mg\textsuperscript{2+}, Ca\textsuperscript{2+}, Cd\textsuperscript{2+}, and Zn\textsuperscript{2+} metal ions, depicted in Figure 1.39A.\textsuperscript{69} The absorption spectra of 98 displayed a low energy band at 548 nm, which was assigned to a combination of the LLCT band possessing mixed MLCT character. Upon addition of Cd\textsuperscript{2+} and Ca\textsuperscript{2+} ions, LLCT absorption disappeared and an increased intensity of MLCT was observed (Figure 1.39B and C). It was suggested that ions, bound to the azacrown moiety, decreased its
electron-donating ability and eventually switched the LLCT band of 98 to higher energy where the ion’s charge density played an important role in the switching process. For example, the Li$^+$ ion did not cause complete deactivation of LLCT but rather caused the band to blue shift due to its low charge density. Complex 98 did not show any emission upon ion binding, which was explained by possible ion dissociation caused by the excited Pt(III) center being more electrophilic than Pt(II).$^{170}$ Binding stoichiometry and stability constants of the ions were also reported.

Figure 1.38. Chemical structures of ion binding complexes 98-102.$^{67,69,172,173}$

Figure 1.39. (A) Solution of 98 (2.2 × 10^{-4} M) in MeCN with variety of metal ions (from left to right): no metal, Li$^+$, Na$^+$, Mg$^{2+}$, Ca$^{2+}$, Cd$^{2+}$, and Zn$^{2+}$, (B) changes in absorption of
upon addition of various concentrations of Cd$^{2+}$ (Both reprinted with permission from ref 69. Copyright 2005 The Royal Society of Chemistry), and (C) Ca$^{2+}$ (Reprinted with permission from ref 170. Copyright 2004 Wiley-VCH).

The novel benzo-15-crown-5 demonstrating strong binding affinity towards alkali and earth alkali metal ions was connected to Pt(II) terpyridine complexes 99-102 through variety of bridging co-ligands.$^{67,69,172,173}$ Complex 99, containing an acetylene co-ligand, displayed a low energy LLCT band with some MLCT mixing, which was blue-shifted upon the addition of Ca$^{2+}$ ion (Figure 1.40A).$^{69}$ A new emission band at ca. 650 nm was observed for 99 upon addition of Mg$^{2+}$ ion, which was assigned as $^3$MLCT band that was previously quenched by photoinduced electron transfer from $^3$LLCT (Figure 1.40B). The Li$^+$, Na$^+$, K$^+$, Mg$^{2+}$, Ca$^{2+}$, Cd$^{2+}$, and Zn$^{2+}$ ions were all proven to bind to the benzo-crown moiety of complex 99 by mass, UV-vis, and NMR spectroscopy.$^{67,69}$ The ion binding ability of benzo-crown and azacrown containing Pt(II) complexes offered novel approaches to ion sensors for alkali and earth alkali metals.

Figure 1.40. (A) Changes in absorption of 99 with various concentrations of Ca$^{2+}$ and (B) changes in emission of 99 with various concentrations of Mg$^{2+}$. (Reprinted with permission from ref 69. Copyright 2005 The Royal Society of Chemistry).
Sauvage et al.\textsuperscript{128} reported the preparation of pseudorotaxane 107 \textit{via} threading a string-like molecule 106 through a 35-membered macrocycle 103 that contained a terpyridine moiety with a square planar Pd(II) metal center, as the template (Scheme 1.17). Macrocycle 104 containing 2,6-lutidine, as a co-ligand, was converted to macrocycle 105 containing HNEt\textsubscript{2}, as a co-ligand, in acidic media and \textit{vice versa}. It was proposed that an inter-exchange of the macrocycles by controlling the acidity of the media could open a new avenue to proton-driven molecular machines.

Scheme 1.17. Pseudo rotaxane 107 and proton-induced interchange of 104 and 105.\textsuperscript{128}

Nishihara et al.\textsuperscript{174} reported the azobenzene-conjugated Pt(II) terpyridine complexes 108 and 109 with pyridine and Cl\textsubscript{2}, as co-ligands, respectively (Figure 1.41A). The azobenzene moiety in 108 and 109 was shown to be \textit{trans} in the single crystal structures; isomerization to the \textit{cis} orientation was easily accomplished upon irradiation with visible light. Photoinduced \textit{trans}-to-\textit{cis} isomerization was clearly observed in absorption spectra of 109 by formation of low energy azo n–π* band at 470 nm with two
isobestic points, indicative of complete isomerization (Figure 1.41B). Moreover, a new emission band for 108 was observed at ca. 600 nm at 77 K upon photoirradiation, which confirmed the formation of the cis isomer, since the trans isomer did not show any emission at 77 K. It was proposed that these complexes could be utilized as multifunctional materials, since their emission spectral and trans-cis conformation changes are closely related.

![Chemical structures of azobenzene containing 108 and 109](image)

Figure 1.41. (A) Chemical structures of azobenzene containing 108 and 109, (B) changes in absorption of 109 in DMF (4.2 × 10⁻⁵ M) upon irradiation at 366 nm light for 25 min, and (C) changes in emission of 108 in EtOH-MeOH-DMF = 5:5:1 (v/v) at 77 K upon irradiation with 366 nm light for 8 min. (Reprinted with permission from ref 174. Copyright 2002 American Chemical Society).

1.3.2.4 Photocatalytic Activities

Wu and Tung et al.¹⁷⁵ incorporated a photoluminescent complex 110 (Figure 1.42) into Nafion membrane (Nafion-Na⁺) and utilized this system as a photosensitizer to generate transient singlet oxygen (¹O₂) for the oxidation of alkenes in aqueous or organic...
solutions. The Nafion membrane possesses a perfluorinated backbone and short pendant chains terminated by sulfonic acid groups (Figure 1.43). When Nafion is swollen in H₂O or MeOH, the structure of Nafion resembles that of an inverse micelle. The hydrated R-SO₃⁻ (R = alkyl) headgroups are clustered within in H₂O-containing pockets (ca. 40 Å in diameter) that are interconnected with each other by short channels within the perfluorocarbon matrix. This H₂O-swollen Nafion can incorporate high concentrations of aromatic hydrocarbons and organic dyes; as well, the oxygen concentration in this Nafion is 10 times greater than in organic solvents. Complex 77 was chosen as the photosensitizer, since it can absorb light in the visible region, photochemically generate ¹⁰₂, is positively charged, and contains aromatic ligands, which can easily be incorporated into Nafion membrane via hydrophobic and electrostatic interactions.

Thus, this 77/Nafion system was specifically designed for photooxidation purposes.

\[
\begin{align*}
\text{Pt} & \quad [\text{ClO}_4] \\
R & \quad 110 : R = OMe \\
& \quad 111 : R = Me
\end{align*}
\]

Figure 1.42. Chemical structures of photosensitizers 110 and 111.

The detection of ¹⁰₂ production from the 110/Nafion system was established by its immersion in O₂-saturated MeOH and then the addition of a radical scavenger 2,2,6,6-tetramethylpiperidine (TMP), followed by irradiation (λ > 450 nm) for 100 s. The formation of ¹⁰₂ via energy transfer between molecular O₂ and triplet excited state of 110. Then, the corresponding stable free radical nitroxide (TMPO) product was detected by EPR spectroscopy (Figure 1.44).
Figure 1.43. (A) Chemical structures of Na fion membranes and (B) their two-phase cluster network model.176

![Chemical structures and two-phase cluster network model](image)

Figure 1.44. EPR spectrum of nitroxide radical generated of O₂ saturated TMP/MeOH solution, where 110-incorporated Nafion was immersed (A) in the dark and (B) after the sample was irradiated for 100 s. (Reprinted with permission from ref 175. Copyright 2003 American Chemical Society).

![EPR spectrum](image)

Three substrates 7-dehydrocholesterol (112), α-pinene (115), and cyclopentadiene (118), were oxidized via ¹O₂, generated by the 110/Nafion system in aqueous and organic solutions (Scheme 1.18).175 The cholesterol 112 was converted to 113 in 95% yield along with traces of 114 based on the consumption (20%) of the starting material via 110/Nafion immersed in MeOH. It was suggested that solvent quenching of ¹O₂ caused the low quantum yield, so changing the solvent to CD₃OD and D₂O increased up to 95% the consumption of the starting material. To reduce the cost of the deuterated solvent
used in the process, 110/Nafion system was swollen in the deuterated solvents and the reactions were performed in DCM. As a result, α-pinene (115) was converted to 116 in DCM with D2O-swollen 110/Nafion in 90% yield, based on the consumption of 115, and then treating the peroxo 116 with NaHSO3 afforded alcohol 117. Furthermore, cyclopentadiene (118) underwent [4+2] cycloaddition with \(^1\)O\(_2\), generated by D2O-swollen 110/Nafion in DCM, to give epidioxide 119 with quantitative yield based on the consumption of 118; 119 was readily converted to diol 120 upon addition of thiourea. Advantages of this photocatalyst are that products were easily separated from the reaction mixture and the catalyst can be recycled without any significant loss of activity.

Scheme 1.18. Photooxidation of alkenes 112, 115, and 118 by 110/Nafion system.\(^{175}\)

Wu and Tung et al.\(^{181}\) reported that D2O-swollen 110/Nafion system in oxygen saturated DCM and MeCN successfully removed the oxime protecting groups 121, affording their corresponding carbonyl derivatives 123 in good to excellent yields (57-94%, Scheme 1.19). It was suggested that oxime deprotection occurred through an \(^1\)O\(_2\) mechanism. The oximes 121 underwent [2+2] cycloaddition with \(^1\)O\(_2\) to give the unstable
dioxetane intermediates 122, which decomposed under the reaction condition to give desired 123. The nitrite by-product was detected by using acidic ferrous sulfate. A possible direct electron-transfer mechanism for this deprotection was not possible since none of the oximes used in that study could quench the strong $^3$MLCT-based photoluminescence of 77 at ca. 620 nm in degassed MeCN at 25 °C.

![Scheme 1.19. Proposed mechanism for ketone deprotection.](image)

Wu et al.\textsuperscript{182} reported that the non-emissive Pt(II)-quaterpyridine complex 76 displayed a $^3$IL-based strong photoluminescence upon incorporation to the Nafion membrane (Nafion-Na\textsuperscript{+}) at 25 °C, suggesting that oligomerization of 76 was possible via partial $\pi$-$\pi$ stacking of quaterpyridine ligands. A significant decrease in absorption was observed for 76 upon photoirradiation at 25 °C in aerated MeCN; however, the photochemically unstable 76 when attached to Nafion matrix did not display any change in absorption spectra upon photolysis in MeCN for 10 hours. The 76/Nafion system was utilized as a photosensitizer to generate $^1$O\textsubscript{2}, which oxidized trans-stilbene to PhCHO and trans-1,2-dimethoxystilbene to PhCO\textsubscript{2}Me in quantitative yields.

Abe et al.\textsuperscript{183} reported the electrochemical and photochemical reduction of H\textsuperscript{+} to H\textsubscript{2} via the [Pt(tpy)(Cl)]\textsuperscript{+} complex. In an electrochemical process, the BPG or ITO electrode-coated Nafion membranes, incorporating the [Pt(tpy)(Cl)]\textsuperscript{+}, were analyzed by potentiometric electrolysis at an applied potential of −0.95 V (vs. Ag/AgCl) in H\textsubscript{2}O at pH 5.9; moreover, CV, UV, and XPS studies confirmed the reduction process. In the case of
the photochemical process, a system consisting of (1) [Pt(tpy)(Cl)]^+, as an active catalyst, (2) [Ru(bpy)_3]^{2+}, as sensitizer, (3) methyl viologen (MV^{2+}), as an acceptor and (4) EDTA, as a sacrificial donor, was utilized to reduce H^+ to H_2. Even though the reduction mechanism is not clearly understood, it was suggested that a methyl viologen radical cation (MV^+) was involved in the process, since the reduction potential of H^+/H_2 (–0.54 V vs. Ag/AgCl at pH = 5.9) is slightly lower than MV^{2+}/MV^+ (–0.64 V vs. Ag/AgCl); this radical was observed throughout the reaction.

Eisenberg et al.\textsuperscript{19} reported the photocatalytic generation of H_2 from H_2O using complex 66, as a sensitizer, MV^{2+}, as an acceptor, triethanolamine (TEOA), as a donor, and colloidal Pt (5-7 nm size stabilized by sodium polyacrylate), as a catalyst. Both MV^{2+} and TEOA successfully quenched the strong photoluminescence of 66 at ca. 500-800 nm via oxidative (Scheme 1.20[b]) and reductive (Scheme 1.20[c]) processes, respectively, in degassed MeCN. The degassed solution of 66 with MV^{2+} was colorless after irradiation suggesting the rapid and efficient back-electron-transfer (Scheme 1.20[e]) from MV^+ to MV^{2+} upon quenching. However, when both quenchers were mixed with 66, a deep blue color solution was generated indicating the formation of the methyl viologen radical (MV^+) via reductive quenching (Scheme 1.20[c] and [d]), followed by an oxidative decomposition (Scheme 1.20[g]) of TEOA and another electron-transfer from MV^+, which afforded glycoaldehyde and diethanolamine. Addition of colloidal Pt particles to the 66/ MV^{2+}/TEOA mixture caused an electron transfer from MV^+ to the colloidal catalyst and then, proton reduction at the Pt surface generated H_2 from H_2O at different pHs; the best yield was obtained at pH 7 with extended irradiation times up to 4 hours (Scheme 1.20[h]).
Scheme 1.20. Mechanism for H₂ formation from H₂O via 66/MV²⁺/TEOA/colloidal Pt.¹⁹

Wu and Tung et al.¹⁸⁴ reported a remarkable photocatalytic oxidation of the Hantzsch 1,4-dihydropyridine (DHP) and its 4-alkyl- and 4-aryl- derivatives 124 via the Pt(II) complexes 69, 110, 111, and 126 producing pyridines 125 and H₂ or RH in quantitative yields with high catalytic turnover (Scheme 1.21). Although the mechanism of this photooxidation is not well understood, in a mechanistic study by Schmehl et al.¹⁸⁵ the transient absorption spectroscopy of 67 with various quenchers (NEt₃, N-methylphenothiazine, DHP, etc.) in degassed MeCN gave convincing evidence for the production of an one-electron-reduced Pt(II) intermediate; however, it was previously suggested¹⁸⁴ that DHP behaves as a H-atom donor in its photooxidation.

Scheme 1.21. Photooxidation of Hantzsch dihydropyridines by Pt(II) complexes.¹⁸⁴
1.3.2.5 Miscellaneous Applications

Unique long-lived emissions with high quantum yields of complexes 64-66, 68, 70-72,\textsuperscript{153,186} 110 and 111,\textsuperscript{186} and 127-130 (Figure 1.45)\textsuperscript{153,187} attracted a great deal of interest as optical limiting materials since the structurally analogous Pt-ethynyl\textsuperscript{188-190} complexes displayed such properties. The linear absorption spectrum of these complexes revealed lowest energy MLCT/LLCT band at ca. 560 nm and their transient absorption difference spectrum (\textit{e.g.} Figure 1.46A) exhibited a positive band over 500 nm, suggesting a stronger excited-state absorption than that of the ground state, which can promote a reversible saturable absorption and is beneficial for optical limiting of nanosecond laser pulses.\textsuperscript{153,186,187} To demonstrate this phenomena, nonlinear transmission measurements were conducted at 532 nm using 4.1 ns (fwhm) laser pulses with concentrations of the solution calibrated to achieve the same linear transmission of 70% for complexes 110, 111 and 127-130.\textsuperscript{153,187} Significant deviation from a linear absorption curve for these complexes proved the existence of optical limiting properties in which 130 displayed the strongest optical limiting for nanosecond laser pulses at 532 nm (Figure 1.46B) thus offering it as a promising material for this application.\textsuperscript{187}

![Figure 1.45. Chemical structures of optical limiting complexes 127-130.\textsuperscript{153,187}](image-url)
Figure 1.46. (A) Transient absorption difference spectra of complex 66 in Ar degassed MeCN solution at 25 °C following 355 nm excitation with 160 ns time increments, (Reprinted with permission from ref 153. Copyright 2005 American Chemical Society and (B) optical limiting of complexes 127 (b), 128 (a), 129 (c) and 130 (d) in a 2 mm cell for 532 nm, 4.2 ns laser pulses with linear transmission of the solutions as 70%, (Reprinted with permission from ref 187. Copyright 2006 American Chemical Society).

Eisenberg et al.\textsuperscript{96,97} reported the novel donor-chromophore-like 131, 133, 134 (D-C), chromophore-acceptor-like 132 and 135 (C-A), and donor-chromophore-acceptor-like 136-138 (D-C-A) systems (Figure 1.47), in which the Pt(II) terpyridine complex acted as a chromophore, pyridinium and 4-nitrophenylvinyl acted as acceptors, and trimethoxybenzene, phenothiazine (PTZ), and methoxyphenothiazine (MTZ) acted as donors. Specifically, the D-C-A systems were designed to mimic a photosynthetic reaction center by achieving photoinduced charge separation. Even though the parent complex 66 is luminescent in MeCN solution at 25 °C with a 700 ns excited state lifetime; complexes 131-138 displayed complete reductive quenching of the chromophore $^3$MLCT emission, except for 132 and 135, which were weakly emissive. A single crystal X-ray structure of complex 136 confirmed the distorted square planar
geometry for Pt(II) atom and edge-to-edge D-A separation of 27.95 Å; however, it did not exhibit any short range interactions. Cyclic voltammograms of trimethoxybenzene, PTZ and MTZ containing 131, 133, 134, and 136-138 revealed donor-based oxidations; whereas, pyridinium and nitro-containing 132 and 135-138 displayed acceptor- and terpyridine-based reductions. Transient absorption (TA) spectroscopy of complexes 131-136 revealed that trimethoxybenzene acted as a reductive donor; however, the pyridinium groups failed to perform as an acceptor. Finally, 230 ns long-lived charge separation in D-C-A 137 and 138 was achieved.

![Diagram of complexes](image)

**Figure 1.47.** Structures of complexes 131-138 and single crystal structure of 136.96
A remarkable electrochemical, nearly reversible, two-electron oxidation of a Pt(II) metal center from square planar bis-piperidine containing complex 139 was achieved via an outer-sphere oxidation mechanism giving rise to a possible octahedral Pt(IV)-containing product 140 (Figure 1.48). The CV of bis-piperidine 139 displayed two irreversible reductions at –0.98 to –1.50 V vs. Ag/AgCl, which were assigned to terpyridine reduction and the almost reversible oxidation at 0.4 V, attributed to the Pt(II) → Pt(IV) oxidation. It was suggested that the lone pair electrons of the piperidyl moieties are critical to the stabilization of the octahedral Pt(IV) metal center; this was affirmed by the irreversible oxidation of the protonated analogue of 139 under similar conditions. Moreover, the Pt(II) complexes consisting of either the terpyridyl or piperidine moieties did not yield any similar oxidation process to that of 139.

Figure 1.48. (A) Cyclic voltammogram of complex 139 and (B) possible oxidation process from square planar Pt(II) containing 139 to octahedral Pt(IV) 140. (Reprinted with permission from ref 191. Copyright 2003 American Chemical Society).

Omary et al.192 reported unique black absorbers with continuous UV-vis-NIR absorptions by simply changing the counterion and the co-ligand of the [Pt(t-Bu3-tpy)(Cl)][Cl] to [Pt(t-Bu3-tpy)(R-PhS)][TCNQ] complexes (TCNQ = 7,7,8,8-tetracyanoquinodimethane; R = 4-Me, 4-Cl, 3,4-diMe, and 2,5-diOMe) for possible conducting,
magnetic, and solar cell applications. The crystal structure of 141 revealed short range $\pi$-$\pi$ interactions between Pt(II) cation and TCNQ anion with interplanar distances of 3.5 Å (Figure 1.49A). The singly charged TCNQ$^-$ counterion was reduced to the doubly charged TCNQ$^{2-}$ anion, present in the crystal structure, which was confirmed by a new absorption band at 490 nm (Figure 1.49B). Thus, a charge delocalization was proposed in 141 via the partial oxidation of the Pt(II) cation and reduction of the TCNQ anion. The UV-vis spectra of 141 revealed a MLCT band at ca. 400 nm and TCNQ$^-$ structured absorption in the NIR region. Moreover, the aromatic thiol containing Pt(II) complexes exhibited dramatic red-shifted LLCT absorption bands at ca. 560 nm when compared to MLCT band of 141.

Figure 1.49. (A) Single crystal packing and (B) UV-vis spectra with concentration of 5 × 10$^{-5}$ M in DCM at 25 °C of [Pt(t-Bu$_3$-tpy)(OH)][TCNQ] (141). (Reprinted with permission from ref 192. Copyright 2006 American Chemical Society).

Ziessel et al.$^{193,194}$ reported a new generation of Pt(II) terpyridine complexes 142-155 in which the Pt(II) metal was connected to different aromatic groups via an acetylene bridge (Figure 1.50). A simple and straightforward CuI-catalyzed reaction between
[Pt(R₃-tpy)(Cl)]⁺ (R = H, t-Bu) and the acetylene connected to the aromatic ligands afforded the desired complexes 142-155, except for complex 143, which was prepared by a reaction of trimethylsilyl (TMS)-protected acetylene, attached to boraindacene, with [Pt(tpy)(Cl)]⁺ in the presence of anhydrous K₂CO₃. Solubility problems with 142 and 144 were overcome by either introducing t-Bu groups on the terpyridine moieties or 1,4-di-(n-butoxy)benzene, as a connector. The single crystal X-ray structure of 145 revealed noticeable π-π interactions between different aromatic rings separated by ca. 3.6 Å.¹⁹⁴ The low energy absorption bands of 142-155 were attributed to MLCT and LLCT bands.

Figure 1.50. Chemical structures of 142-155.¹⁹³,¹⁹⁴
Cyclic voltammograms of 147, 151, and 154 exhibited two quasi-reversible reductions in the range from –0.97 to –1.56 V vs. ferrocene (+0.38 V) in DCM, which were assigned to terpyridine reduction that was slightly mixed with some Pt(II) metal character.\textsuperscript{193,194} The Pt(II) complexes 144-147 containing free terpyridines were later coordinated with Fe(II) or Zn(II) forming octahedral complexes in order to construct trinuclear molecular rods; similarly, 148 and 152 attached to free acetylenes were reacted with another [Pt(tpy)Cl]\textsuperscript{+} to form the homonuclear dimetallic Pt-Pt structures.

1.3.3 Metallo-Supramolecular terpyridine architectures

Different multinuclear supramolecular systems were achieved by using square planar Pd(II) and Pt(II) complexes with properly designed mono- and \textit{bis}-terpyridine ligands. Evident $\pi$-$\pi$ interactions between aromatic moieties and d-d orbital interaction between metal centers in these systems promoted interesting solid state packing, remarkable photophysical, and optical properties. Some of the multimetallic complexes were further utilized as molecular building blocks to construct higher-ordered 2- and 3-dimensional supramolecular self-assemblies \textit{e.g.}, rectangles and trigonal prisms. Cavities inside the supramolecular architectures offered possible molecular recognition centers by means of reversible host-guest interactions leading to the construction of molecular switches.
1.3.3.1 Dyads and Triads

Yam et al.\textsuperscript{195} reported luminescent acetylene-containing molecular rods 156 \((n = 1, 2, 4)\) capped with Pt(II) terpyridine complexes (Figure 1.51). The \(t\)-Bu groups were introduced onto the terpyridines to overcome solubility problems. Single crystal structures revealed the Pt-Pt distances in 156, proceeding from the molecular to nanoscale, as 5.16 \((n = 1)\), 7.71 \((n = 2)\), and 12.83 Å \((n = 4,\) Figure 1.52A). The absorption spectra of 156 displayed low energy MLCT bands mixed with some LLCT character and high energy IL \(\pi-\pi^*\) bands attributed to the acetylene and terpyridine ligands. Emission spectra of 156 exhibited a strong luminescence in the range of 550-625 nm in the solid state and solution upon excitation at \(\lambda > 400\) nm; this was assigned to the dominant \(^3\)MLCT mixed with \(^3\)LLCT/\(^3\)IL bands. Ziessel et al.\textsuperscript{193} connected two Pt(II) terpyridine complexes through a linear diacetylene linker, consisting of 2,2'-bipyridine, as in 158 and a 120° juxtaposed diacetylene bridge, attached to the terpyridine 5,5''-position, as in 159 to investigate their energy and electron transfer abilities.

Yam et al.\textsuperscript{196} also utilized 4-acetylenylpyridine, as a connector, which was attached to two Pt(II) terpyridine complexes as in 157. The single crystal X-ray structure of 157 revealed that the Pt-Pt distance was 9.4 Å and did not show any short range interactions due to the bulky \(t\)-Bu groups (Figure 1.52B). The CV of 157 demonstrated four quasi-reversible reduction couples with two at \(ca. -0.82\) to \(-0.93\) and two at \(-1.33\) to \(-1.42\) V vs. SCE, which were attributed to successive one electron reductions of the two terpyridines, since the co-ligand connected to Pt(II) is different.
A luminescent tetranuclear supramolecule 160 was assembled by formation of two Pt-acetylene linkages between two equivalents of a Pt(II)-tpy complex with an n-Bu-carbazole containing core.\textsuperscript{197} Electrochemical, absorption, and emission properties of 160 exhibited similar features to other acetylene containing dinuclear complexes 156-159.\textsuperscript{193,195-197}

![Diagram of supramolecule 160](image)

<table>
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<td>161</td>
<td>MeO\textsubscript{2}O \textsubscript{2}OMe</td>
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Figure 1.51. Dinuclear Pt(II) complexes 156-164 with rigid linkers.\textsuperscript{24,193,195-198}
Yam et al.\textsuperscript{24} reported a unique dinuclear 161 containing alkynylcalix[4]crown-5 ligand. The single crystal X-ray structure did not show any short range interactions; the Pt-Pt metal centers were separated by 8.54 Å due to bulky \textit{t}-Bu groups attached to the terpyridine moieties. Upon excitation at $\lambda > 400$ nm, the calixcrown 161 displayed a weak $^3$MLCT emission mixed with $^3$LLCT band at 738 nm due to possible reductive quenching by photoinduced electron transfer in which the electron-donating calixcrown moiety acted as a quencher. The macrocyclic cavity within the calixcrown was utilized as a molecular recognition center for alkali and alkaline earth metals. Binding of Li$^+$, Na$^+$, K$^+$, Cs$^+$, Ca$^{2+}$, and Mg$^{2+}$ ions was detected with a blue shift of the MLCT band and a well-defined isobestic point in its absorption spectrum. Moreover, a notable increase in emission intensity at ca. 700 nm was observed upon binding of K$^+$ ion, which is favored over the other alkali and alkaline earth metal ions, thereby suggesting a possible application as a luminescent chemosensor (Figure 1.53).

Crutchley et al.\textsuperscript{198} utilized 2,5-dimethyl-$N,N'$-dicyanoquinonediimine dianion (Me$_2$-dicyd$^{2-}$) as a bridge to connect two Pt(II) terpyridines, as in 162 (Figure 1.51). It
was proposed that the Me$_2$-dicyd$^{2-}$ moieties would stack via $\pi-\pi$ interactions and could promote conductivity upon doping similar to related structures.$^{199,200}$ Even though 162 was not crystalline; it could still be doped with iodine to form a radical anion of Me$_2$-dicyd$^{2-}$ and I$_3^-$, which led to its 100 times weaker powder conductivity compared to a crystal conductivity,$^{201}$ as $\sigma = 39 \mu$S cm$^{-1}$ ($x = 1.3$ as in 162·[I$_3^-$]).$^{198}$

Figure 1.53. (A) Effect of various metal ions ($5.0 \times 10^{-5}$ M) on emission intensities of 161 and (B) emission spectra of calixcrown 161 with K$^+$ ion. (Reprinted with permission from ref 24. Copyright 2006 American Chemical Society).

To circumvent the solubility problems, Ziessel et al.$^{193}$ prepared a linear bis-terpyridine ligand with two dodecyloxy chains that was reacted with two equivalents of K$_2$PtCl$_4$ to afford 163, which was later capped by acetylene containing C$_{14}$H$_{29}$ alkyl chain to give desired 164 (Figure 1.51).

Dinuclear Pt(II) bis-terpyridines 165-169, connected through flexible bridges, were reported for their intramolecular self-assembly in solution (Figure 1.54).$^{202}$ The $^1$H NMR of 165 and 166 with short linkers revealed well-defined peaks at 25 °C; however, 167-169 with longer flexible connectors showed poorly resolved broad peaks, which sharpened and shifted downfield upon heating (Figure 1.55A). Absorption spectra of 168 displayed an MMLCT band as a shoulder at 535 nm at –40 °C, which disappeared upon
heating (Figure 1.55B). Upon excitation at $\lambda > 400$ nm, complex 169 exhibited a $^3$MMLCT band at 830 nm at 5 °C that also disappeared upon heating (Figure 1.55C). The Pt-Pt and $\pi-\pi$ interactions were proposed to be the driving force for this particular reversible self-aggregation process.

![Chemical structures of dinuclear complexes 165-169 with flexible linkers and their aggregation/deaggregation behavior (bottom right corner, Reprinted with permission from ref 202. Copyright 2006 Wiley-VCH).](image)

Figure 1.54. Chemical structures of dinuclear complexes 165-169 with flexible linkers and their aggregation/deaggregation behavior (bottom right corner, Reprinted with permission from ref 202. Copyright 2006 Wiley-VCH).
Figure 1.55. (A) High-temperature $^1$H NMR of 168 in DMSO-$d_6$, S$_1$-S$_3$ represents H$_2$O, DMSO and MeCN solvents, respectively, (B) changes in absorption of 168 upon heating from –40 to 80 °C, and (C) changes in emission of 169 upon heating from 5 to 75 °C. (Reprinted with permission from ref 202. Copyright 2006 Wiley-VCH).

Various dinuclear Pt(II) and Pd(II) complexes with short linkers such as: pyrazole in 171,203 diphenylformamidine in 172,203,204 azaindole in 173,203 guanidine in 174,93,205 2-mercaptoimidazole in 175,206 1-methylcytosine in 176 and 177,127 acetamide in 178 and 179,125,207,208 canavanine in 180,209 and arginine 168,203,209 favoring intramolecular interactions between metal centers (d-d) and terpyridine moieties ($\pi$-$\pi$) were reported for their crystal packing and photophysical properties (Figure 1.56). Lippard et. al.210 accidentally discovered 170 from the crystallization of [Pt(tpy)(SCH$_2$CH$_2$NH$_3$)]$^{2+}$ with two-base DNA single strand T-A [deoxymethoxythyminyl-(3',5')-deoxyadenosine]. The trinuclear 170 was crystallized in two diastereomeric structures, which affected an overlap between parallel terpyridines; further, only weak short range (distances > 3.88 Å) interactions were observed between Pt centers and terpyridine moieties (Figure 1.57).
Figure 1.56. Structures of dinuclear 170-181 with short intramolecular distances between metal centers (Pt-Pt and Pd-Pd) and terpyridine moieties.\textsuperscript{93,125,127,203-210}

Figure 1.57. Crystal structures of trinuclear 170 in its two different diastereomers. (Reprinted with permission of ref 210. Copyright 1980 American Chemical Society).

Single crystal X-ray structures of 172 and 174-180 were reported,\textsuperscript{93,125,127,203-209} however, only complexes 175,\textsuperscript{206} 177,\textsuperscript{127} and 179\textsuperscript{125} are depicted in Figure 1.58. These crystal structures revealed that the distances between metal centers in the range of 2.99-
3.23 Å; the terpyridine moieties were found to be parallel to each other with intraplanar
distances in the range of 2.8-3.5 Å. A new low energy MMLCT absorption and $^3$MMLCT
emission bands in solution were observed for these dinuclear complexes, which were
associated with short range intramolecular Pt-Pt and $\pi-\pi$ interactions.93,125,127,203-209

Figure 1.58. Single crystal structures of (A) 179 (Reprinted with permission from ref 125.
Copyright 2003 Elsevier), (B) 175, (Reprinted with permission from ref 206. Copyright
2001 The Royal Society of Chemistry) and (C) 177 (Reprinted with permission from ref

Yam et al.208 prepared the dinuclear complex 178 with an acetamide bridge from a
suspension of [Pt(tpy)(MeCN)] in acetone. Upon slow evaporation of solvent, dark
crystals of 178 were formed, then redissolved in hot acetone and recrystallized to give the
red form of 178 (Figure 1.59A). Single crystal X-ray structure of 178 (red) contained
acetone molecules in the lattice and displayed short intramolecular Pt-Pt and $\pi-\pi$
interactions with distances of 3.12 and 3.48 Å, respectively; it stacked as an extended
linear chain-like structure in head-to-tail fashion with alternating intermolecular Pt-Pt
distances of 3.65 and 4.45 Å (Figure 1.59B). On the other hand, the dark form of 178
exhibited shorter intramolecular Pt-Pt distances of 3.06 Å and stacked as dimers of 178
with intermolecular Pt-Pt distances of 3.26 Å (Figure 1.59C). The solid state emissions of
The dark and red form of 178 displayed $^3$MMLCT emissions at 710 and 690 nm, respectively, at 25 °C. Complex 178 showed a MMLCT absorption at ca. 426-478 and a $^3$MMLCT emission at 600 nm at low concentration. The emission spectra at higher concentrations revealed a new emission band at 790 nm, which was attributed to dimer formation of 178 similar to the dark crystal packing.

![Crystal structure of (A) molecular clip-like 178 (red form) and packing of its (B) red form and (C) dark form.](image)

Figure 1.59. Crystal structure of (A) molecular clip-like 178 (red form) and packing of its (B) red form and (C) dark form. (Reprinted with permission from ref 208. Copyright 2006 The Royal Society of Chemistry).

Lowe et al. prepared a dinuclear complex 182 with a thioacetamine linker, which slowly decomposed in water to form intermediate 183, which take an extra sulfur from a Pt(II) terpyridine moiety of 182 and was converted to a crystalline trinuclear propeller-like complex 184 (Scheme 1.22). Both enantiomeric forms of 184 possessing both right- and left-handed propeller helicity were observed in the crystal structure.
Scheme 1.22. Formation of crystalline propeller like 184 from dinuclear 182 (Reprinted with permission from ref 206. Copyright 2001 The Royal Society of Chemistry).

Sasaki et al.\textsuperscript{143,159} reported dimetallic homonuclear 185 and 186 as well as heteronuclear 187 that were connected through a 2,5-dimercapto-1,3,4-thiadiazole (H\textsubscript{2}dmct) moiety. Single crystal X-ray structures of 185-187 revealed that the terpyridines are parallel with an inversion center in a trans configuration and did not display any inter- or intramolecular short range interactions (Figure 1.60). Dinuclear complexes 185-187 did not show any luminescence and their cyclic voltammograms suggested that there was no metal center interaction.

\textbf{185} : M, M' = Pd(II), Pd(II)  
\textbf{186} : M, M' = Pt(II), Pt(II)  
\textbf{187} : M, M' = Pt(II), Pd(II)

Figure 1.60. Structures of 185-187 and single crystal X-ray structure of 187 (Reprinted with permission from ref \textsuperscript{143}. Copyright 2006 The Chemical Society of Japan).
Bosnich et al.\textsuperscript{129} prepared the bis-terpyridine ligands 188 and 189 connected by partial and full aromatic spacers, respectively (Scheme 1.23). The 3,5-di-tert-butylphenyl group was introduced to the linker to circumvent solubility problems. Two equivalents of Pd(II) and Pt(II) salts were added to bis-terpyridines 188 and 189 in MeCN to form molecular clefts 190-197 consisting of two cofacially separated square planar complexes (Figure 1.61).\textsuperscript{129,211-220} The distance (~7 Å) between two parallel terpyridine moieties was specifically designed to offer potential \( \pi-\pi \) interactions (< 3.5 Å) for planar aromatic molecules, which would intercalate in the cleft to create molecular recognition centers.

Scheme 1.23. Partially aromatic 188 is oxidized to fully aromatic 189 bis-tpy ligand.\textsuperscript{129}

\[
\begin{align*}
&\text{188} \quad \text{DDQ} \quad \text{189} \\
&\left[ (X)_{n} \right] \\
&X = \text{Cl}^{-}, \text{PF}_6^{-}, \text{BF}_4^{-} \\
&190 : M = \text{Pd}(II), L = \text{Cl}, n = 1 \\
&191 : M = \text{Pd}(II), L = \text{MeCN}, n = 2 \\
&192 : M = \text{Pd}(II), L = \text{Pyridine}, n = 2 \\
&193 : M = \text{Pt}(II), L = \text{Cl}, n = 1 \\
&194 : M = \text{Pt}(II), L = \text{Acetone}, n = 2 \\
&195 : M = \text{Pt}(II), L = \text{Pyridine}, n = 2 \\
&196 : L = \text{Cl}, n = 1 \\
&197 : L = \text{MeCN}, n = 2
\end{align*}
\]

Figure 1.61. Dinuclear molecular clefts 190-197.\textsuperscript{129,211-220}

Suitable single crystals of the bis-Pd(II) complex 190 for X-ray analysis were obtained by patiently maintaining the complex in MeCN at \(-20^\circ\text{C for 2 years}\) in a sealed
The crystal packing revealed that two molecules of [tpy-Pd-Cl] interpenetrated through the [tpy-Pd-Cl] moieties. The distances between the interplanes (Figure 1.62A) and Pd-Pd metals were < 3.5 Å; the rationale for packing was the π-π interaction between terpyridines and d-d orbital interaction between Pd-Pd metal centers (Figure 1.62B). The crystal packing of bis-Pt(II) complex 193 (Figure 1.63A), crystallized in DMF, revealed the same interpenetration pattern as 190 with an interplanar distance of < 3.5 Å displaying possible π-π interaction; however, the distances between Pt-Pt metal centers were > 3.8 Å suggesting weaker d-d orbital interactions (Figure 1.63B).

Figure 1.62. (A) Single crystal structure and (B) schematic representation of interplanar distances and angles of bis-Pt(II) complex 190. (Reprinted with permission from ref 218. Copyright 2004 Wiley-VCH).

Figure 1.63. (A) Single crystal X-ray structure and (B) schematic representation of interplanar distances and angles of bis-Pt(II) complex 193. (Reprinted with permission from ref 219. Copyright 2005 American Chemical Society).
Tanaka et al.\textsuperscript{162} reported a dinuclear Pt(II) complex 198, in which the terpyridine moieties were separated by an intraplanar distance of 4.4 Å (Figure 1.64). This distance did not permit 198 to interpenetrate, as in 190 and 193,\textsuperscript{218,219} instead, it stacked as an extended linear chain-like structure with a zigzag configuration of Pt metal centers that displayed only weak intermolecular interactions with distances of 4.2-4.4 Å.\textsuperscript{162} The cyclic voltammogram of 198 displayed concentration-independent reversible redox couples, which were split into two, suggesting possible intramolecular interactions between Pt(II) metal centers.

![Structure of 198 and its molecular crystal packing](image)

Figure 1.64. Structure of 198 and its molecular crystal packing (Reprinted with permission from ref 162. Copyright 2004 American Chemical Society).

Hetero-dimetallic Pt(II)-Ru(II) complexes 199-202, containing 3,5-di-t-butylsemiquinone (SQ) moiety with a radical anion, were reported to possess interesting electrochemical properties (Figure 1.65).\textsuperscript{162,221} Cyclic voltammograms of 199-202 revealed three reversible redox couples assigned to Ru(III)/Ru(II), SQ/catechol and Pt(tpy)/Pt(tpy⁻) that were strongly dependent on the co-ligand connected to metal centers (Table 1.1). The redox properties of 199-202 did not show any electronic interactions between metal centers even in the case of 202 in which metal centers were covalently
connected. Spectroelectrochemical studies of 199-202 displayed a reversible shift between the absorption bands at ca. 600 and 850 nm, which was attributed to Ru(III)-SQ and Ru(II)-SQ bands, respectively. It was suggested that these complexes could be utilized as water-oxidation catalysis like their analogous bis-[Ru(tpy)(OH)(R)] (R = SQ, bipyridine) complexes.222,223

![Chemical structures of heretonuclear complexes 199-202.162,221](image)

Figure 1.65. Chemical structures of heretonuclear complexes 199-202.162,221

Table 1.1. CV data of complexes 199-202 in DCM.162,221

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<tr>
<td>200</td>
<td>+0.64</td>
</tr>
<tr>
<td>201</td>
<td>+0.71</td>
</tr>
<tr>
<td>202</td>
<td>+0.44</td>
</tr>
</tbody>
</table>

Hetero-dinuclear dyads 203-208, containing Pt(II) terpyridine moieties that were connected to porphyrin units through a phenyl-acetylene bridge, displayed photoinduced electron transfers (2-20 ps) from an excited singlet state of porphyrin unit to the Pt(II) complex (Figure 1.66).224 This quenching process of porphyrin fluorescence via ultrafast charge recombination overcame the possible charge separation state of the dyads. Cyclic
voltammograms revealed weak interactions between metal centers. Further, the photophysical studies of 203-208 were conducted via steady-state, time-resolved, and femtosecond transient absorption spectroscopy in DMF in which the rate constants of the electron transfer of the dyads were consistent with Marcus theory. It was suggested that the electron transfer occurred through the conjugated phenyl-acetylene bridge in 203-208.

![Diagram of hetero-dinuclear complexes 203-208](image)

**Figure 1.66. Structures of hetero-dinuclear complexes 203-208.**

Yam et al.\textsuperscript{225} reported heteronuclear molecular rods 209-214, consisting of a Pt(II) terpyridine complex, which was connected to a Re(I) bipyridine moiety via phenyl-acetylene linkers (Figure 1.67). Single crystal X-ray structures of 209 and 211 displayed a distorted square planar geometry for the Pt(II) terpyridine complex and did not show any short range interactions due to the bulky t-butyl groups on terpyridine ligand. Absorption spectra of dyads 209-214 exhibited a low energy band at ca. 404-486 nm, which was attributed to a mixture of MLCT bands of [dπ(Pt) → π*(terpyridine)], [dπ(Re) → π*(bipyridine)], and LLCT band of [π(acetylene) → π*(terpyridine)]; moreover upon excitation λ > 380 nm, intense orange-red emission bands at ca. 570-580 nm were observed for dyads 209-214 with an excited state lifetime of 0.52-0.94 µs in MeCN solutions at 25 °C. Additional electrochemical studies and extended Hückel molecular
orbital (EHMO) calculations revealed that low energy emissions originating from the
$^3\text{MLCT}$ band [$d\pi(\text{Pt}) \rightarrow \pi^*(\text{terpyridine})$] were actually mixed with either LLCT of
[$\pi(\text{acetylene}) \rightarrow \pi^*(\text{terpyridine})$] or unexpectedly metalloligand-to-ligand charge-transfer
of [$\pi(\text{C} \equiv \text{C}-\text{Phe-}\text{C} \equiv \text{C}-\text{[Re]}) \rightarrow \pi^*(\text{terpyridine})$].

![Chemical structures of dyads 209-214.](image)

Figure 1.67. Chemical structures of dyads 209-214.

Ziessel et al.\textsuperscript{194} reported the first octahedral Fe(II) and Zn(II) bis-terpyridine
complexes, which were connected to square planar Pt(II) terpyridine complexes, as triads
215-217 (Figure 1.68). Either $t$-Bu groups introduced on terpyridine in 215 and 216 or
1,4-dialkoxyphenyl acetylene used as a connector in 217 helped to circumvent the
solubility problems. Absorption spectra of triads 215 and 217 displayed a Fe(II)-based
MLCT band at ca. 580 nm and the Pt(II)-based MLCT bands mixed with LLCT band at
car. 425 nm; however, Pt-Zn-Pt complex 216 showed only a Pt(II)-based MLCT band.
Cyclic voltammograms of 215 and 217 revealed successive reductions of four terpyridine
moieties connected to Fe(II) and Pt (II) metals at $-1.27$, $-1.40$ V, and $-0.96$, $-1.54$ V, respectively.
1.3.3.2 Supramolecular Self-assemblies

Bosnich et al.$^{129,211-215}$ utilized the Pd(II) and Pt(II)-based molecular clefts 191, 194, and 197, as molecular building blocks to self-assemble higher ordered supramolecular architectures. Dinuclear Pd(II) complexes 191 and 197, which are kinetically more labile and thermodynamically less stable than their analogous dinuclear Pt(II) complex 194, exclusively formed rectangles 218-221 and trigonal prisms 222 and 223 with linear bidentate 224 and 225, and trigonal tridentate spacers 226 and 227 at 25 °C within hours, respectively (Figure 1.69). The chemical structure of the tetranuclear Pd(II)-based molecular rectangle 220 containing a fully aromatic bis-terpyridine ligand 189 is depicted in Figure 1.70. The dinuclear Pt(II) cleft 194 was able to self-assemble into molecular rectangles 219 and 221 at high reaction temperatures.$^{220}$ The single crystal
X-ray structure of tetranuclear 219 is depicted in Figure 1.71 (hydrogens, counterions, and part of the bis-terpyridine ligand was omitted for clarity).

![Diagram of X-ray structure of tetranuclear 219](image)

<table>
<thead>
<tr>
<th>Number of the Assembly</th>
<th>Shape of the Assembly</th>
<th>Number of the Building Block</th>
<th>Linker (R)</th>
<th>Number of the Linker (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>218</td>
<td>Rectangle</td>
<td>191</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Rectangle</td>
<td>194</td>
<td><img src="image" alt="Linker" /></td>
<td>224</td>
</tr>
<tr>
<td>220</td>
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<td>194</td>
<td><img src="image" alt="Linker" /></td>
<td>225</td>
</tr>
<tr>
<td>222</td>
<td>Trigonal Prism</td>
<td>191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>223</td>
<td>Trigonal Prism</td>
<td>191</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1.69. Self-assembly of rectangular 218-221 and trigonal prism 222 and 223 shape architectures using molecular clefts 191, 194, and 197.87,129,211,212,214,215,220
The rectangular 219 displayed a meso conformation with one spacer in the $R,R$- and the other in the $S,S$-configuration (Figure 1.71). The pair of 4,4'-bipyridyl (224) spacers, used to connect the Pt(II) metals, are buckled and nearly perpendicular to the coplanar Pt-terpyridine moieties, thus almost parallel to each other in the same cleft at a distance of 6.9 Å. The closest distance between two 4,4'-bipyridyl spacers is 1.9 Å allowing appropriate guests to intercalate within the resultant void region. These supramolecular self-assemblies were utilized as molecular recognition centers for small planar molecules to be considered later in this review.

Figure 1.70. Chemical structure of a fully aromatic tetranuclear rectangle 220.

Figure 1.71. Single crystal structure of a tetranuclear Pt(II) molecular rectangle 219 (Reprinted with permission from ref 220. Copyright 2005 Wiley-VCH).

Yam et al. reported a hexanuclear Pt(II) acetylene complex 229, which was assembled via the reaction of the face-to-face dinuclear Pt(II) acetylene complex 228 with four equivalents of [Pt(tpy)(MeCN)]$^{2+}$ (Figure 1.72). The single crystal X-ray
structure of 228 revealed two Pt(II) metals connected through two diphenylphosphine ligands forming an eight membered-ring in a face-to-face arrangement with a distance of 3.28 Å, suggesting a possible Pt-Pt interaction. The single crystal structure of 229 displayed a shorter Pt-Pt core distance (3.18 Å) in the core compared to 228 (3.28 Å), which was attributed to the decreased electron density of the Pt metals in the core upon formation of four peripheral Pt-terpyridine complexes. The two adjacent Pt(II) terpyridine moieties remained parallel with an interplanar distance of 3.67 Å, suggesting possible weak π-π interactions; however, the Pt-Pt distances between these moieties, being 5.08 Å, did not show any Pt-Pt interaction. The hexanuclear 229 showed a low energy absorption band at 416 nm, which was assigned as MLCT. The solution and solid state emissions at 520 and 620 nm, respectively, at 77 K were attributed to ligand-centered phosphorescence and 3MMLCT, respectively.

Figure 1.72. Assembly and crystal structure of hexanuclear Pt(II) acetylene complex 229 from dinuclear Pt(II) 228 and [Pt(tpy)(MeCN)]^{2+}. (Reprinted with permission from ref 226. Copyright 2002 American Chemical Society).
1.3.3.3 Molecular Recognition by Host-Guest Interaction

Bosnich et al.\textsuperscript{129,211-220} investigated the Pd(II)- and Pt(II)-based molecular clefts (190-197), rectangular and trigonal prism shaped (218-223) supramolecular assemblies, as molecular recognition centers for different planar, aromatic, transition metal containing, neutral, positively, and negatively charged molecular guests (230-258, Figure 1.73). Since the bis-terpyridine moieties in those supramolecular architectures are separated by 7 Å, they contain molecular cavities for intercalation of guests by $\pi-\pi$ interactions with aromatic groups and d-d orbital interactions with guest metal centers.\textsuperscript{87} Guests 250-255 did not display any binding properties to hosts 190-197; moreover, yellow solutions of positively charged hosts 190-197 precipitated as red, insoluble materials upon addition of negatively charged guests 256-258 suggesting the formation of host-guest complexes.\textsuperscript{212}

9-Methylantracene (9-MA, 230), as a guest, displayed remarkable binding properties to most of the receptors (Table 1.2).\textsuperscript{129,211,213,214,219} The yellow color of a MeCN solution of cleft 190 turned deep red upon addition of solution of 9-MA. Actual host-guest interactions and stoichiometry of host 190 with guest 230 (1:2) were detected by growing single crystals, which revealed that one 9-MA molecule intercalated between the [tpy-Pd-Cl] moieties by a $\pi-\pi$ interaction proven by an interplanar distance being < 3.5 Å to each side; the other 9-MA molecule lies outside the receptor 190 closely related to [tpy-Pd-Cl] moiety (Figure 1.74).\textsuperscript{129,211,213}

The Pt(II)-, Pd(II)-, and Au(II)-containing square planar complexes 231-238 were utilized as guests, which displayed d-d orbital interaction with the cleft’s metal centers.
For example, single crystal X-ray structures of guests 234 and 231, which intercalated into 190 and 193, respectively, with 1:1 host-guest stoichiometry, revealed that there are d-d orbital and π-π interactions between Pt(II)-based guests and the molecular receptors, since the interplanar and metal-metal distances between hosts and guests are both < 3.3 Å (Figure 1.75).

Figure 1.73. Chemical structures of guest molecules 230-258.
Table 1.2. Host-guest interactions and their stoichiometry.

<table>
<thead>
<tr>
<th>Guest</th>
<th>Host</th>
<th>Host:Guest Stoichiometry</th>
<th>Interplanar Distances (Å)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
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<td>213,219,213</td>
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</tr>
<tr>
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<td>-</td>
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<td></td>
</tr>
<tr>
<td>222</td>
<td>1:6</td>
<td>-</td>
<td>214</td>
<td></td>
</tr>
<tr>
<td>190</td>
<td>1:1</td>
<td>-</td>
<td>213,215,216</td>
<td></td>
</tr>
<tr>
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<td>220</td>
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<td></td>
</tr>
<tr>
<td>221</td>
<td>1:2</td>
<td>-</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>190</td>
<td>1:1</td>
<td>3.21, 3.29</td>
<td>217</td>
<td></td>
</tr>
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</tr>
<tr>
<td>190</td>
<td>1:1</td>
<td>3.24, 3.24</td>
<td>217,218</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1.74. Single crystal packing diagram of [190][(230)_2]. (Reprinted with permission from ref 213. Copyright 2002 National Academy of Sciences, U.S.A.).
Intercalation of 9-MA into the molecular clefts prompted Bosnich et al.\textsuperscript{213} to design receptor 259, which was covalently connected to two 9-MA molecules through a pyridine-2-carboxylate spacer (Figure 1.76A). The single crystal X-ray structure of the covalently bound host-guest complex 259 revealed that one 9-MA molecule intercalates into the cleft and the other one lies on the top of the [tpy-Pd-Cl] moiety; moreover, 259 was stacked on the neighboring molecule to form an extended chain-like structure (Figure 1.76B). Since the guest molecules could fluxionally exchange the binding sites in the cleft, the dynamics of this complex were studied by low temperature $^1$H NMR revealing symmetric, sharp peaks at 16 °C suggesting the rapid exchange of anthracenes between the accessible sites. However, these peaks were broadened upon cooling and separated into two sharp signals of equal intensity at –90 °C, suggesting that fluxional motion in 259 was frozen and statistically equal amounts of isomers were formed (Figure 1.76C).
Figure 1.76. (A) Single crystal X-ray structure and (B) packing diagram of the covalently bound host-guest complex 259 and (C) its fluxional behavior. (Reprinted with permission from ref 213. Copyright 2002 National Academy of Sciences, U.S.A.).

The stoichiometry and intercalation of the host-guest complexes, which did not crystallize, were investigated by their dramatic ¹H NMR shifts of certain protons upon titration of the hosts with different mole equivalents of guests. Then, application of the "mole-ratio" method to the significant ¹H NMR shifts of these protons gave consistent results for the stoichiometry of host-guest complexes with single crystal X-ray structures. For example, two 9-MA guests were found to bind to the host 190 (Figure 1.77A).¹²⁹,²¹¹,²¹³ Four and five 9-MA guests bound to rectangles 220 and 218 respectively (Figure 1.77B and C).²¹¹ Trigonal prismatic shaped assemblies 222 and 223 with short and long tridentate trigonal linkers were able to contain six and seven 9-MA guests,
respectively (Figure 1.77D).\textsuperscript{214} It was suggested that the two larger trigonal linkers 227 in host 223 have enough room between them to accommodate an extra 9-MA.

Figure 1.77. The mole-ratio of guest/host plotted against $^1$H NMR shifts of host and/or guest protons in order to find the stoichiometry of host-guest complexes. (A) is reprinted with permission from ref 129. Copyright 2003 American Chemical Society; (B) and (C) are reprinted with permission from ref 211. Copyright 2001 Georg Thieme Verlag Stuttgart · New York; (D) is reprinted with permission from ref 214. Copyright 2003 The Royal Society of Chemistry.

The guest 243 intercalated into the larger trigonal prismatic supramolecule 223 as detected by $^1$H NMR titration; however no intercalation was observed for guest 243 with the smaller trigonal prism 222.\textsuperscript{214} The rigid, linear 241 and 242, containing two guest molecules connected through a linker, were bound to molecular cleft 190 by 1:1 and 2:1
host-guest ratios, respectively (Figure 1.78). Separation between Pt atoms of guest 241 and 242 was calculated to be 12.2 and 18.8 Å, respectively. It was suggested that electrostatic repulsion of two positively charged molecular clefts 190 was effective at distances < 15 Å, which prevented the second cleft to bind to the shorter guest 241.

![Diagram of host-guest interactions](image)

Figure 1.78. Schematic diagrams of host-guest interactions of 241 and 242 with 190.

Disassociation of host-guest complex <[190][233]> was achieved via protonation of the pyridine ring in guest 233 suggesting that the positively charged host 157 released the charged guest 233 due to electronic repulsion (Scheme 1.24). Remarkable color changes for <[190][233]> from deep red to yellow were observed upon addition of TFA, which was attributed to a disassociation of the guest; moreover the red color was recovered upon addition of NEt₃ indicating the neutralization of guest 220 and its incorporation into the host. It is proposed that proton-driven reversible disassociation of the guest 233 from host 190 can be interpreted, as a molecular switch, or one stroke of a molecular motor; however, it was concluded that this particular process acts more like a switch than a motor, since molecular motors usually require repetitive cycles.
Scheme 1.24. Host-guest complex [190][233], as a molecular switch and/or motor.218

1.3.3.4 Multimetallic Peptide Scaffolds

Tanaka et al.227 reported the liquid phase synthesis of 18- and 24-membered cyclic peptides 262-265 with a repeating unit of [glycine-L-cysteine] (Scheme 1.25). Trinuclear 260 and tetranuclear 262 oligopeptides in which the thiol groups in cysteine were connected to square planar Pt(II) terpyridine complexes were cyclized to give the desired cyclopeptides 262 and 263, respectively, which were subsequently converted to their corresponding cyclopeptides 264 and 265, respectively, by removing the Pt-terpyridine complex. Williams et al.228,229 reported the preparation of multimetallic artificial oligopeptides 266-273 in which peptide backbone, containing pyridine and bipyridine, was utilized as a scaffold to assemble diverse metal complexes (Figure 1.79). These particular oligopeptides, which are analogous to peptide nucleic acids (PNAs), were synthesized to mimic DNA and RNA structures in order to improve their binding abilities to biomacromolecules. Pyridine-substituted oligopeptides with an aminoethyl-glycine backbone of varying length were treated with [Pt(tpy)(Cl)]¹ to give the desired complexes 266-270, which were characterized by UV-vis and ¹H NMR spectroscopy.168 Molecular modeling studies of 266-270 suggested that they probably will form extended
chain-like structures upon increasing the quantity of metal centers tethered to the backbone due electrostatic repulsion between positively charged Pt(tpy) moieties. Electrochemical studies of 266-270 revealed that the [Pt(tpy)(pyr)]$^{2+}$ redox centers are electronically isolated and behave independently.

Scheme 1.25. Formation of cyclic peptides 262-265.$^{227}$
A bipyridine moiety was introduced into the center of a peptide backbone, which was tethered with two Pt(II) terpyridine complexes, then addition of Fe(II), Cu(II), and Zn(II) to this bipyridine-containing oligopeptides promoted the assembly of hetero-multimetallic supramolecular dendrimer-like structures analogous to divergent dendrimer synthesis. Complex 271 displayed two distinct absorptions at ca. 340 and 537 nm, which were attributed to Pt-tpy and Fe-tpy MLCT bands. EPR studies of paramagnetic 272 indicated a lack of interactions between metal centers; this was also observed in electrochemical studies. It was proposed that these transition metal-incorporated oligopeptide nanostructures could be utilized as inorganic “bar codes” and promote new applications as biocompatible pharmacological agents.
1.3.4 Biological Activities

In the following sections, the intercalative and covalent binding modes of square planar Pt(II), Pd(II), and Au(III) terpyridine complexes to DNA and other biomacromolecules will be considered. The initial focus will be on the details for the intercalation of these complexes with DNA and their subsequent effects on the physical and chemical properties of DNA. Utilization of these Pt complexes, as protein tags, as well as the cytotoxic activities of these complexes as anti-tumor, antiprotozoal, and radiotherapy agents will be reviewed.

1.3.4.1 DNA Intercalation

Intercalation of small molecules into DNA by stacking between its base pairs was first suggested by Lerman\textsuperscript{231} to explain high affinity of planar dyes to DNA. Aminoacridine dyes,\textsuperscript{231,232} antimicrobial agents, such as ethidium bromide\textsuperscript{233,234} (Figure 1.80) and antinomycin antibiotics,\textsuperscript{235} were studied as class of planar intercalators. As a result of intercalation of these dyes into DNA, their UV-vis spectra displayed dramatic shifts and they exhibited induced circular dichroism; moreover, they increased the length of DNA, its viscosity and melting temperature, altered the extent of supercoiling in closed circular duplex DNA, and reduced its sedimentation coefficient.\textsuperscript{236,237} With similar goals in mind, Lippard \textit{et al.}\textsuperscript{71,72} suggested that structurally similar planar Pt(II) terpyridine complexes to these planar dyes would also intercalate into DNA. Complex \textbf{274} was chosen over other Pt(II) terpyridine complexes, as an intercalator, in order to eliminate the possible covalent binding of the complex to DNA due to the inert character
of the Pt-S bond in 274 compared to Pt-R bonds in [Pt(tpy)(R)]\(^+\) (R = Cl, O, N) complexes.

![Chemical structures](image)

Figure 1.80. Structures of ethidium bromide (EthBr), and Pt(II) complexes 274 and 275.

Various characterization methods and general experimental criteria were required to confirm the intercalation process, since the terpyridine complexes can covalently bind to DNA bases as well as electrostatically insert into the DNA groove. These requirements were summarized by Barton and Long.\(^{236}\)

1.3.4.1.1 UV-vis Spectroscopy Analysis and Binding Modes

The absorption spectra of 274 with increasing amounts of ct-DNA showed dramatic changes, such as a strong decrease in peak intensity (hypochromocicity) and red shift of the bands at ca. 550 nm with well-defined isobestic points (Figure 1.81).\(^{71}\) These observed shifts were strongly dependent on the concentration of the intercalator and DNA, the buffer solution, and its ionic strength (\(I = [M^+]\): total positive ion concentration). Red shifts of the bands are usually observed for the intercalation binding mode; whereas, the strong hypochromocicity is attributed to an electronic interaction between bound molecules and the DNA.\(^{236}\)
Figure 1.81. UV-vis spectra of 274 upon addition of various amounts of ct-DNA in a 1mM sodium phosphate buffer with 3 mM NaCl ($I = 0.003$) at pH 6.8. In curves A to E, concentration of 274 is 6.97 µM and DNA-P concentrations are (A) 0, (B) 17 µM, (C) 34 µM, (D) 146 µM, and (E) 303 µM. In curves 1 to 5, concentration of 274 is 70.4 µM and DNA concentrations are (1) 0, (2) 97.7 µM, (3) 189 µM, (4) 356 µM, and (5) 700 µM. (Reprinted with permission from ref 71. Copyright 1974 S. J. Lippard).

A classical Scatchard analysis ($r/c$ vs. $r$, $r =$Bound-[Pt]/[DNA], $c =$ Free-[Pt]) of these spectrophotometric titration data at 342 nm upon addition of ct-DNA to 274 and 275 in a low ionic buffers displayed concave upward curves at large $r$ values (Figure 1.82).$^{71,73}$ This behavior is indicative of two different binding modes: a strong intercalative mode and a weaker non-intercalative secondary interaction.$^{239}$ This argument was supported by the analysis of ct-DNA contour length ratio ($L/L_0$) in the presence ($L$) and absence ($L_0$) of 275, where a linear increase in helix extension was observed up to $r \sim 0.2$, followed by a marked decrease in the helix extension suggesting a non-intercalative binding component.
The binding constants ($K_B$) of intercalators 274 and 275 into DNA in low ionic strength buffers estimated by extrapolating the data in the Scatchard$^{238}$ plot to the ordinate axis,$^{71,73}$ since the data did not fit the McGhee-von Hippel$^{240}$ equation. However as the ionic strength of the buffer increased, the secondary non-intercalative interaction of 274 and 275 with ct-DNA was eliminated; eventually, the UV-vis titration data fit the McGhee-von Hippel equation$^{240}$ in order to determine $K_B$, which was summarized in Table 1.3 for various Pt(II) terpyridine intercalators 274-287 (Figure 1.83).$^{73,239,241-243}$

Most of the Pt(II) terpyridine complexes 274-283 bound the DNA exclusively via intercalation; however, [Pt(tpy)(Cl)]$^+$ (284)$^{241}$, [Pd(tpy)(Cl)]$^+$ (287)$^{241}$ and [Pt(tpy)(OH)]$^+$ (286)$^{134}$ were covalently bound to the DNA as well as intercalatively, since they contain -Cl or -OH, as co-ligands. Various other methods (e.g., CD, competitive fluorescence, and ultradialysis experiments) were also utilized to calculate binding modes and constants.
Table 1.3. The DNA binding constants ($K_B$) of intercalators 274-287 and their effect in melting temperature ($\Delta T$) of ct-DNA.

<table>
<thead>
<tr>
<th>Intercalator</th>
<th>$K_B$, M$^{-1}$ (Binding Constants)</th>
<th>$I = [M^+]$</th>
<th>$\Delta T$, ° (ct-DNA)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
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<td>1.2 ± 0.2 × 10$^5$ ($^{a,e}$)</td>
<td>0.003</td>
<td>5.0$^e$</td>
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<tr>
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<td>5.1 ± 0.2 × 10$^5$ ($^{a,e,f}$)</td>
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<td>3.4$^f$</td>
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</tr>
<tr>
<td></td>
<td>3.9 ± 0.3 × 10$^5$ ($^{a,e,f}$)</td>
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<td>2.5$^f$</td>
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<tr>
<td>275</td>
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</tr>
<tr>
<td></td>
<td>4.3 ± 0.2 × 10$^5$ ($^{b,h}$)</td>
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<td>NA</td>
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<tr>
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<td>8.4 ± 0.5 × 10$^5$ ($^{b,h}$)</td>
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<tr>
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<td>NA</td>
<td>241</td>
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<tr>
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<tr>
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<td>281</td>
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<td>1.8 ± 0.5 × 10$^5$ ($^{b,h,k}$)</td>
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<td>9.8 ± 1.3 × 10$^5$ ($^{b,h,k}$)</td>
<td>0.15</td>
<td>NA</td>
<td>244</td>
</tr>
<tr>
<td>284</td>
<td>1.3 ± 0.2 × 10$^5$ ($^{c,f}$)</td>
<td>0.2</td>
<td>5.0$^f$</td>
<td>113,241</td>
</tr>
<tr>
<td>285</td>
<td>NA</td>
<td>0.001</td>
<td>7.8$^e$</td>
<td>98</td>
</tr>
<tr>
<td>286</td>
<td>7.0 ± 0.6 × 10$^5$ ($^{a,j}$)</td>
<td>NA</td>
<td>7.8$^e$</td>
<td>134</td>
</tr>
<tr>
<td>287</td>
<td>1.9 ± 0.2 × 10$^5$ ($^{c,f}$)</td>
<td>0.1</td>
<td>NA</td>
<td>241</td>
</tr>
</tbody>
</table>

$^a$ Calculated by classical Scatchard analysis of UV-vis. 
$^b$ Calculated by McGhee-von Hippel analysis of UV-vis. 
$^c$ Calculated by Scatchard analysis of fluorescence study. 
$^d$ Calculated by analysis of circular dichroism. 
$^e$ 1 mM Phosphate buffer with 3 mM NaCl at pH = 6.8. 
$^f$ 50 mM Tris.HCl buffer with 0.1 M NaCl at pH = 7.5. 
$^g$ 50 mM Tris.HCl buffer with 0.2 M NaCl at pH = 7.5. 
$^h$ 1 mM Phosphate buffer with 0.15 M NaNO$_3$ at pH = 7. 
$^i$ 2 mM Hepes buffer with 0.1 M KF at pH = 7. 
$^j$ 50 mM EPPS buffer at pH = 9. 
$^k$ 45 mM Tris buffer with 1 mM Na$_2$H$_2$EDTA at pH = 7.5.
The linear dependence between logarithmic scale of the observed binding constant ($K_B$) of 275 (Figure 1.84)\textsuperscript{73} to DNA and the ionic strength of the medium ($I = [M^+]$) was explained by polyelectrolyte theory\textsuperscript{245} in the following equation:

$$\text{Log}(K_B) = - \text{Constants} \times \text{Log}([M^+]) + \text{Log}(K_0),$$

where $K_0$ is the binding constant of the intercalator to DNA at 1 M positive ion concentration ($I = 1$). This binding constant was considered to be free of ion concentration effects and calculated by extrapolating the plot of $\text{Log}(K_B)$ versus $\text{Log}([M^+])$ to the ordinate axis. Ion free binding constants ($K_0$) of 274\textsuperscript{246} ($3.5 \times 10^3$ M\textsuperscript{-1}) and 275\textsuperscript{73} ($4.1 \times 10^3$ M\textsuperscript{-1}) were ca. 20 times less than that of EthBr\textsuperscript{246} ($7.4 \times 10^4$ M\textsuperscript{-1}).

![Figure 1.84. Plot of Log($K_B$) vs. Log([M\textsuperscript{+}]) for 275 and ct-DNA (Reprinted with permission from ref 73. Copyright 1987 The Biochemical Society).](image)

1.3.4.1.2 Viscosity and Thermal Denaturation

DNA must partly unwind to accommodate the intercalators. The unwinding of DNA induces an increase in its relative contour length\textsuperscript{239} ($L/L_0$) leading to an eventual stiffening of DNA, which results in an increased viscosity,\textsuperscript{247} e.g., the specific viscosity ($\eta_{sp}$) of a DNA solution increased upon addition of 274 and reached a saturation point at $r$ of 0.23 (Figure 1.85).\textsuperscript{71} The relative counter length of DNA ($L/L_0$) was estimated from
A similar behavior in viscosity and counter length was observed for structurally similar terpyridine-based intercalators to DNA.\textsuperscript{71,73,113,239,243,249} Recently, a Quartz Crystal Resonator (QCR) was invented to determine the binding mode of the molecules to DNA by measuring the increase in its viscosity.\textsuperscript{250}

Figure 1.85. (A) The specific viscosity with intercalator 274 in 1 mM phosphate buffer with \( I = 0.003 \) at pH 6.8 (Reprinted with permission from ref 71. Copyright 1974 S. J. Lippard) and (B) their relative counter length \((L/L_0)\) in 50 mM Tris-HCl buffer with \( I = 0.2 \) at pH 7.5 of DNA as a function of \( r \) (Bound-[Pt]/[DNA]). (Reprinted with permission from ref 249. Copyright 1979 American Chemical Society).

The unwinding of DNA as a result of intercalation also leads to an increase its melting temperature \( (T_m) \), which refers to a transition of the double strand to a single strand DNA by thermally breaking the \( H \)-bonds. This thermal denaturation of DNA is easily monitored by changes in UV-vis absorption at 260 nm. In the case of intercalators 279-281, the complete thermal denaturation of DNA was shown to occur in two steps (Figure 1.86C).\textsuperscript{113,243} It was suggested that a part of the DNA, which was not bound to the Pt intercalator, melted in the first transition, then the part containing the intercalator melted at a higher temperature; however, in the case of 274 and 284 complete denaturation occurred in one-step (Figure 1.86E and B, respectively).\textsuperscript{71,113,243,249}
differences in melting temperature ($\Delta T_m$) of ct-DNA upon the addition of intercalators is summarized in Table 1.3.

![Temperature vs. Relative Absorbance Graph](image)

Figure 1.86. Thermal denaturation curves of 400 $\mu$M of ct-DNA (A) alone, with (B) 20 $\mu$M of 284, and (C) 281; 85 $\mu$M of ct-DNA (D) alone and with (E) 3.5 $\mu$M of 274 (A, B, and C are reprinted with permission from ref 113. Copyright 1996 Elsevier; D and E are reprinted with permission from ref 71. Copyright 1974 S. J. Lippard).

1.3.4.1.3 Induced Circular Dichroism

Other evidence for the intercalation of Pt-terpyridine complexes into DNA is derived from its circular dichroism spectra, which display signals in the range of 300-500 nm caused by an induced circular dichroism.\textsuperscript{71,113,135,243} For example, the CD spectrum of 279 and 280 showed positive bands between 300-400 nm in the presence of ct-DNA (Figure 1.87). Furthermore, Lowe \textit{et al.}\textsuperscript{113} used the CD titration spectra of the intercalator to calculate the binding constant of intercalator 281 to DNA. The initial equilibrium binding constant was calculated to be $2 \times 10^7$ M$^{-1}$ suggesting a binding site of about the size of four base pairs; as the ratio of the Pt complex to DNA increases, a second binding
mode was observed in which $K_B$ was calculated to be $1 \times 10^6 \text{ M}^{-1}$ suggesting a binding site of about the size of two base pairs.

![Figure 1.87](image)

Figure 1.87. CD spectrum of (A) 280 and (B) 279 (50-80 µM) in the presence of 10 fold excess of DNA at 25 °C (1 mM phosphate buffer with $I = 0.0015$ at pH 7.0). (Reprinted with permission from ref 243. Copyright 1999 American Chemical Society).

1.3.4.1.4 Competitive Fluorescence Spectroscopy

The fluorescence Scatchard$^{238}$ plot for the binding of EthBr to DNA in the presence of an increasing amount of Pt-terpyridine-based intercalators displayed two different observations.$^{71,241}$ The Scatchard plot of EthBr and 274 in the presence of DNA (Figure 1.88A) revealed only a competitive inhibition between EthBr and 274, which was characterized by a decrease in the slope caused by the presence of an increasing amount of metal complex with no change in the intercept at the abscissa.$^{71}$ However, the Scatchard$^{238}$ plot of EthBr and 284 in the presence of DNA revealed two different features resulting from a competitive inhibition between EthBr and 284 (line 1, 2, and 3) as well as a noncompetitive inhibition, which is illustrated with a change in both the slope and the intercept in line 4 and 5 ($[\text{DNA}]/[284] < 2$, Figure 1.88B). The competitive
inhibition of EthBr is attributed to intercalation of 274 and 284 and the noncompetitive feature of 284 probably caused by the removal of the labile Cl ion from the intercalator suggesting its covalent binding to the DNA. The binding constants ($K_B$) of 274 and 284 (in the range of [DNA]/[284] > 2) to DNA were calculated via fluorescence competition studies (Table 1.3).$^{71}$ A similar fluorescence competition study revealed that the binding constant of 284 to ct-DNA ($K_B = 4.95 \pm 0.30 \times 10^7$ M$^{-1}$) is 250 times larger than the binding constant of 274 to ct-DNA.$^{113}$

Figure 1.88. (A) Fluorescence Scatchard plot for binding of EthBr ([EthBr] = 4.9 to 12 µM) to ct-DNA ([DNA] = 3.5 µM) in a buffer with $I = 0.2$ at pH 7.5 (line 1) and the presence of an increasing amount of 274, [DNA]/[274] = 4.5 (line 2), 1.8 (line 3), 0.90 (line 4), and 0.45 (line 5) (B) Fluorescence Scatchard plot for binding of EthBr ([EthBr] = 5.2 to 20 µM) to ct-DNA ([DNA] = 5.8 µM) in a buffer with $I = 0.1$ at pH 7.5 (line 1) and the presence of an increasing amount of 284, [DNA]/[284] = 5.2 (line 2), 2.6 (line 3), 1.0 (line 4) and 0.52 (line 5). (Reprinted with permission from ref 71. Copyright 1974 S J. Lippard).
1.3.4.1.5 Closed Circular DNA

Closed circular DNA was utilized to prove the intercalative binding mode of the Pt-terpyridine-based complexes. Different topologies of circular DNA are depicted in Figure 1.89. It was mathematically suggested that the total winding of the strands ($\alpha$) resulting from normal turns ($\beta$) and superhelical turns ($\tau$) must remain constant in the absence of backbone chain scission (nicking) according to $\alpha = \beta + \tau$.\textsuperscript{251} Unwinding of closed circular DNA (form I or I\textsubscript{0}) by the intercalation of 274 was detected by its band sedimentation behavior; however, 274 did not affect the band sedimentation of nicked DNA (form II), which is not subject to the topological constraint;\textsuperscript{71,72,241} a similar behavior was observed for EthBr.\textsuperscript{252} Helix unwinding angles were calculated by viscosity titration of closed circular DNA to be 17.5\textdegree.\textsuperscript{239}

Figure 1.89. Different topologies of closed circular DNA with several superhelical turns (form I), no superhelical turns (form I\textsubscript{0}), and nicked (form II). (Reprinted with permission from ref 72. Copyright 1999 American Chemical Society).
1.3.4.1.6 Stereochemical Changes in DNA

Although intercalation has been proven and is widely accepted as a binding mode for Pt-terpyridine complexes to DNA, stereochemical details of this process are needed to understand the real effect of intercalation on the backbone DNA geometry, especially with regard to the pucker of the deoxyribose ring. To this extent, Carothers suggested a “neighbor exclusion model,” which proposes that every other interbase pair site contains a bound intercalator upon saturation (Figure 1.90). The electron-dense intercalator was utilized as a labeling agent to investigate the X-ray fiber diffraction pattern of calf thymus DNA. Quality X-ray fiber diffraction pictures strongly supported this neighbor exclusion model in which electron-dense Pt atoms are evenly distributed by 10.2 Å throughout the backbone of DNA, in every other interbase pair site.

![Figure 1.90](image)

Figure 1.90. (A) Schematic presentation of double helix B-DNA and (B) neighbor exclusion binding of the intercalator (dark area) to the B-DNA. (Reprinted with permission from ref 254. Copyright 1975 S. J. Lippard).

The single crystal X-ray structure of with two base pair DNA fragments (deoxy-CpG, Figure 1.91) provided a clear picture of how intercalation occurred by modifying the DNA’s backbone conformation. In the crystal lattice, two cations
formed a neutral complex with a dimer of deoxy-CpG, which was formed by three $H$-bonding of paired guanine and cytosine bases, as in the double helical DNA. The complex 274 is intercalated between two base pairs in the DNA fragment, as envisioned down the $a$ axis of the lattice (Figure 1.92). The conformation of deoxyribose at the 3'-end of the DNA fragment possesses a C2' endo pucker, which is the normal pucker conformation found in B-DNA. However, deoxyribose at the 5'-end of the DNA fragment is a C3' endo pucker, which is a modified pucker conformation found generally in double helical RNA and not in B-DNA. This conformational modification of the deoxyribose ring was initially suggested by Lippard et al.254 from X-ray fiber diffraction pattern, 255

Figure 1.91. Structure of deoxycytidinyl-(3',5')-deoxyguanosine (deoxy-CpG).

Figure 1.92. X-ray crystal structure of deoxy-CpG:274 (2:2) looking down the $a$ axis, (Reprinted with permission from ref 255. Copyright 1978 Nature Publishing Group).
model building, and Fourier transform studies. Furthermore, the unwinding angle \((23^\circ)\)\(^{255}\) of a double helical deoxy-CpG dimer with 274 was found to be very similar to the 22.6°\(^{254}\) angle of ct-DNA with 274, as determined by its X-ray fiber diffraction pattern.

The difference in the conformation of the deoxyribose ring in 3'- and 5'-end of the double helical fragment can be clearly seen by looking down the \(b\) axis in Figure 1.93\(^{255}\).

The guanine and cytosine bases displayed extensive \(\pi\)-\(\pi\) interactions with 274; specifically, the O6 of both guanines is positioned virtually above and below the central Pt(II) metal that was separated by 3.4 Å from each oxygen.

![Figure 1.93. A view of X-ray crystal structure of deoxy-CpG:274 (2:2) looking down the \(b\) axis. Top base pairs are drawn in shaded solid black, 274 in the center is stippled while bottom base pair is unshaded (Reprinted with permission from ref 255. Copyright 1978 Nature Publishing Group).](image)

1.3.4.1.7 Site Specific Intercalation

The intercalation of 274 into different DNAs with various guanine-cytosine (G-C) contents was investigated by means of the binding affinity (\(\sigma\)) parameter, which was calculated by the extrapolation of a Scatchard plot to its \(r/c\) axis.\(^{246}\) As well, the relative
binding affinity ($\varepsilon$) was calculated by the ratio of binding affinity of the two different DNAs. Both binding parameters are summarized in Table 1.4. Linear relationships between different G-C content of DNAs and binding affinities ($\sigma$) of 274 (Figure 1.94) revealed its preference to intercalate between the G-C DNA base pair. One of the reasons for this specific binding is the stabilization of Pt(II) metal that can be sandwiched between two guanine O6 atoms, as observed in its crystal structure (Figure 1.93).\textsuperscript{255} Relative binding affinity ($\varepsilon$) of 275 between M. Lysodeikticus (72 % G-C) and Cl. Perfringens DNA (30 % G-C) was calculated to be 2.4 displaying the same behavior compared to 274 ($\varepsilon = 2.62$).\textsuperscript{73,246}

Table 1.4. Binding parameters of intercalator 274 with DNAs of varying G-C contents in a 50 mM Tris·HCl buffer with 0.1 M NaCl at pH 7.5.\textsuperscript{246}

<table>
<thead>
<tr>
<th>DNA</th>
<th>% G-C</th>
<th>$K_p \times 10^4$ (M$^{-1}$)</th>
<th>$\sigma \times 10^4$ (M$^{-1}$)</th>
<th>$K_d \times 10^4$ (M$^{-1}$)</th>
<th>$\varepsilon_a$ (calculated)</th>
<th>$\varepsilon_b$ (observed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl. Perfringens</td>
<td>30</td>
<td>5.9 ± 0.6</td>
<td>0.89</td>
<td>2.2 ± 0.2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>E. Coli</td>
<td>42</td>
<td>8.5 ± 0.4</td>
<td>1.24</td>
<td>3.2 ± 0.2</td>
<td>1.40</td>
<td>1.39</td>
</tr>
<tr>
<td>Calf thymus</td>
<td>51</td>
<td>10 ± 2</td>
<td>1.55</td>
<td>4.2 ± 0.5</td>
<td>1.70</td>
<td>1.71</td>
</tr>
<tr>
<td>M. Luteus</td>
<td>72</td>
<td>10 ± 3</td>
<td>2.34</td>
<td>4.2 ± 0.5</td>
<td>2.40</td>
<td>2.62</td>
</tr>
</tbody>
</table>

*G-C mole fraction of DNA, divided by mole fraction of Cl. Perfringens DNA. $\varepsilon_b$ Binding affinity ($\sigma$) of DNA, divided by binding affinity ($\sigma$) of Cl. Perfringens DNA

Figure 1.94. Binding affinity dependence of 274 in DNA possessing various % G-C (Reprinted with permission from ref 246. Copyright 1979 American Chemical Society).
1.3.4.1.8 Other Mononuclear Intercalators

A new generation of Pt-terpyridine complexes 288-291 that are connected to a 
$^{10}$B-containing carboran$^{256-259}$ cage ($^{10}$B natural abundance is $\sim 20\%$) through a 
monothiolate bridge (Figure 1.95) was synthesized for DNA intercalation opening the 
possibility to its potential application of boron neutron capture therapy (BNCT)$^{260}$ to treat 
cancer cells. The glycerol group was introduced to the carborane cage in 291 in order to 
overcome the solubility problems in aqueous media, which can limit its application.$^{256}$
The UV-vis titration of these complexes with an increasing amount of DNA displayed 
bathochromic shifts and hypochromocity indicative of intercalation;$^{258}$ however, the 
titration data did not fit the Scatchard$^{238}$ plot to calculate binding constants ($K_B$), since 
development from Beer’s law suggested an aggregation of complexes 288-291 at 
concentrations greater than 13 µM.

![Figure 1.95. Pt(II) complexes 288-291 modified with carborane moieties for use of boron 
neutron capture theory (BNCT) agents.$^{256-259}$](image)

Figure 1.95. Pt(II) complexes 288-291 modified with carborane moieties for use of boron 
neutron capture theory (BNCT) agents.$^{256-259}$
Che et al.\textsuperscript{31} reported DNA binding studies of the water-soluble glycosylated acetylide and arylacetylide Pt-tpy complexes 292-299 (Figure 1.96), as possible antitumor drugs and potential luminescent probes via binding to glycosylated biomolecules. The binding constants of 297-299 to ct-DNA were measured to be 4.8 \times 10^5, 3.7 \times 10^5, and 6.9 \times 10^5 M^{-1}, respectively, by Scatchard\textsuperscript{238} plots of absorption spectra. Hypochromic and bathochromic shifts in absorption titration of 297 and 299 with DNA suggested intercalation; moreover, gel mobility shift assay studies for 292 possessing bulky t-butyl groups on terpyridine as well as 298 revealed that 292 binds electrostatically to the DNA minor groove; whereas, 298 binds electrostatically and intercalatively.

![Figure 1.96. Structures of glycosylated complexes 292-299 prepared as potential antitumor agents.\textsuperscript{31}]

The Au(III)-containing complexes 300-304 have been utilized as intercalators to DNA (Figure 1.97). Binding constants of 300 to DNA was calculated to be 5 \times 10^3 M^{-1},
which is lower than for 274.261 Ultradialysis experiments revealed the possible electrostatic binding of the complex 300 to DNA as well as intercalation. Other evidence for intercalation came from an induced circular dichroism of 300 with DNA and an increase for the melting temperature of ct-DNA (ΔTm = 12.4°) in 10 mM NaClO4 buffer with I = 0.001 in the presence of the complex.

<table>
<thead>
<tr>
<th>Number</th>
<th>R</th>
<th>n</th>
<th>Number</th>
<th>R</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>H</td>
<td>2</td>
<td>303</td>
<td>O=S=O</td>
<td>1</td>
</tr>
<tr>
<td>302</td>
<td>phenyl</td>
<td>2</td>
<td>304</td>
<td>PPh3</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 1.97. Chemical structures of Au(III)-containing intercalators 300-304.261,262

Various charged sites and bulky groups were introduced to Au(III)-terpyridine complexes 301-304 in order to investigate their effect on binding properties of these complexes to DNA.262 The intercalation of 301-304 into DNA was proven by hypochromic and bathochromic shifts in UV-vis titration, induced circular dichroism, and competitive fluorescence studies with EthBr. The decreased fluorescence intensity of EthBr with DNA follows the order 301 ≥ 303 > 304 > 302, which revealed that smaller groups on these complexes favored the replacement of EthBr via intercalation; however, the intensity decrease in CD spectral shifts in the presence of increasing amounts of complex following the order of 304 > 301 > 303 > 302, suggesting that increasing charge favored the binding. The UV and CD of 301-304 gave similar results reflecting both steric and electrostatic effects of the chemical groups on binding; whereas, competitive
fluorescence studies mainly illustrated the effect on intercalation. The *in vitro* DNA binding studies of Au(III) complexes were performed by incubating 301 and 304 with human epidermal kidney cells (293T). After 12 hours of incubation, DNA was isolated from the cells and it was determined that the concentration was 207.8 µg mL⁻¹. The ICP-MS analysis revealed that the isolated DNA contained 18.9 and 24.9 ng·mL⁻¹ of 301 and 304, in which one gold ion is present for each 6400 and 4900 nucleotides, respectively.

1.3.4.1.9 Multinuclear Intercalators

Various dinuclear DNA intercalators 305-313 were synthesized by linking two Pt-terpyridine moieties through α,ε-dithiols of the type HS-(CH₂)ₙ-SH (n = 4-10) and a xylyl group (Figure 1.98).⁷³,¹³⁵,²³⁹ Intercalative binding of these complexes was demonstrated by UV-vis bathochromic shifts and hypochromicity, induced circular dichroism, and increased viscosity and melting temperatures for ct-DNA.

![Figure 1.98. Dinuclear intercalators 305-313 prepared by treatment with alkyl and aryl dithiols.](image)

120
Helix-extension parameters for 305-311 were calculated from the plot of relative contour length ($L/L_0$) versus drug/nucleotide (D/P) or binding ratio ($r$). The unwinding angles were determined by viscosity titration measurements with closed circular DNA. Comparison of the helix extension parameters and unwinding angles between monointercalator 275 and bisintercalators 305-311 suggested that 306, 307, and 310 showed mainly bisintercalation; whereas, 309 and 311 displayed a mixture of mono- and bisintercalation (Table 1.5). However, the data from 305 and 311 did not permit a definitive assignment of the binding mode. Binding constants were calculated only for 275, 305, and 307. Relative binding affinity ($\varepsilon$) of bisintercalators revealed that they prefer to bind G-C base pair of DNA with a lower affinity than the monointercalator 275.

The bis-Pt complexes 312 and 313 connected through xylyl group from either the 1,3- or 1,4-positions, respectively, were utilized as a bisintercalator. The CD spectra displayed a normal induced circular dichroism for bisintercalator 313 and its mono analogue 282; however, the CD spectra for 312 displayed a new negative Cotton effect, suggesting that 312 distorted the DNA. The bis-Pt complex 313 was monofunctionally bound to the DNA (Figure 1.99).

Table 1.5. Binding parameters of mono- and bisintercalators to ct-DNA.73,239

<table>
<thead>
<tr>
<th>Intercalator</th>
<th>Helix-Extension Parameter</th>
<th>Increase in contour length ($L/L_0$, Å)</th>
<th>Unwinding angle (°)</th>
<th>Binding Constant $K_B \times 10^4$ (M$^{-1}$)</th>
<th>$\varepsilon$ (observed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>275</td>
<td>0.60</td>
<td>2.0</td>
<td>17.5</td>
<td>0.84</td>
<td>2.4</td>
</tr>
<tr>
<td>305</td>
<td>0.73</td>
<td>2.5</td>
<td>31.1</td>
<td>3.0</td>
<td>1.1</td>
</tr>
<tr>
<td>306</td>
<td>1.12</td>
<td>3.8</td>
<td>31.7</td>
<td>NA</td>
<td>1.4</td>
</tr>
<tr>
<td>307</td>
<td>1.13</td>
<td>3.8</td>
<td>36.0</td>
<td>19</td>
<td>1.3</td>
</tr>
<tr>
<td>308</td>
<td>1.14</td>
<td>3.9</td>
<td>32.0</td>
<td>NA</td>
<td>1.7</td>
</tr>
<tr>
<td>309</td>
<td>0.83</td>
<td>2.8</td>
<td>23.4</td>
<td>NA</td>
<td>1.2</td>
</tr>
<tr>
<td>310</td>
<td>1.13</td>
<td>3.8</td>
<td>25.2</td>
<td>NA</td>
<td>1.4</td>
</tr>
<tr>
<td>311</td>
<td>0.92</td>
<td>3.1</td>
<td>22.9</td>
<td>NA</td>
<td>1.2</td>
</tr>
</tbody>
</table>

* In a 2 mM Hepes/KOH buffer with 0.5 M KF at pH 7.0. * The relative binding affinity of complexes between *M. lysodeikticus* (72% G-C) and *Cl. perfringens* (30% G-C) DNA.
Inspired by the higher affinity of bisintercalators 314-317 compared to their mono-analogues, Rendina *et al.* reported a series of bis-Pt-terpyridine complexes connected through the 1,2-, 1,7-, 1,12-positions of a carborane cage (Figure 1.100). Their DNA binding studies have not yet been reported but *in vitro* cytotoxicity was investigated against L1210 murine leukemia cell line.

Figure 1.100. Structure of bis-Pt(tpy) intercalators 314-317 containing carborane cage.257
Reedijk et al.\textsuperscript{263} reported the first heteronuclear dimetallic complex \textbf{318} containing a pseudo-octahedral Ru(tpy)\textsubscript{2} connected to a square planar Pt(tpy)Cl through flexible diethyleneglycol ether linker, which was crystallized by slow precipitation of the reaction mixture with Et\textsubscript{2}O. The single crystal X-ray structure of \textbf{318} revealed an intermolecular stacking between the Pt-terpyridine moieties despite the bulky Ru(tpy)\textsubscript{2} groups in which Pt metals were infinitely stacked in a head-to-tail fashion with alternating short and long Pt-Pt distances (3.49 and 6.7 Å, Figure 1.101). Covalent binding of the complex to 9-ethylguanine was reported proving that \textbf{318} can intercalate and covalently bind to DNA even when the complex contains a large Ru(tpy)\textsubscript{2} that can electrostatically bind to DNA.

Figure 1.101. Chemical and crystal structure of Ru(II)-Pt(II) complex \textbf{318} (Reprinted with permission from ref 263. Copyright 2004 Wiley-VCH).

Heteronuclear dimetallic complexes \textbf{319-321} containing a planar Pt(II)-terpyridine moiety connected to another planar Ir(III)-dppz moiety through peptide linkers were synthesized as bisintercalators (Figure 1.102).\textsuperscript{264,265} The UV-vis spectra of \textbf{319} with a short peptide linker as well as \textbf{320} and \textbf{321} possessing longer peptide linkers in the presence of DNA revealed that only monointercalation to DNA occurred from the Ir(III)-dppz end, since hypochromic and bathochromic shifts observed at 382 nm corresponded to dppz moiety not the terpyridine.\textsuperscript{264} Binding constants ($K_B$) of \textbf{319} (3.3
\(1.4 \times 10^6 \text{ M}^{-1}\), 320, and 321 \((1.4 \times 10^6 \text{ M}^{-1})\) were calculated by UV-vis titration data at 382 nm, which were fitted in the non-cooperative non-specific binding model by Bard and Thorp. 264,265

\[\text{Figure 1.102. Structures of Ir(III)-Pt(II) complexes 319-321 connected through peptide linkers.}^{264,265}\]

Recently, ligand 322 containing five oxygens and three nitrogens, self-assembled in a hairpin-like multimetallic structure 323 by wrapping itself around a lanthanide metal (Nd, Eu or La) and connecting to two [Pt(tpy)Cl]⁺ from its thiol ends (Scheme 1.26). 268

\[\text{Scheme 1.26. Assembly of hairpin like structure Ln-Pt}_2 \text{ 323 from 322.}^{268}\]

The Nd-Pt₂ complex 323 showed NIR emissions at 1060 and 1340 nm characteristic for Nd(III) ion with an excited state lifetime of 670 ns. Intercalation of Nd-Pt₂ complex 323
to ct-DNA and its binding constant was investigated by linear flow dichroism revealing that the complex *bis*-intercalated into DNA with a binding constant \((K_B)\) of \(9.5 \times 10^6 \text{ M}^{-1}\).

Peptide nucleic acids (PNA), as an analogue of DNA, were designed and functionalized with pyridines, which were later utilized as scaffolds to connect to Pt-terpyridine moieties, *e.g.*, in complexes 266-273.\(^{228,229}\) It was assumed that the four-tethered Pt-terpyridine complexes on the backbone of the peptide chain, as in 267, which resemble nucleic acids on the DNA sugar phosphate backbone, would increase binding affinity of 267. To this extent, a double stranded (ds) DNA fragment with 12 base pairs (bp) was chosen as a model for binding studies (Figure 1.103).\(^{28}\) The oligomeric sequence of 12 bp ds-DNA with 5’-CGT GAC CAG CTG-3’ containing 75% G-C content, was chosen to improve the hybridization efficiency and to circumvent hairpin formation. The binding constants were calculated by isothermal titration microcalorimetry (ITC) revealing that two of the tetrapeptide 267 bound to each 12 bp ds-DNA has a \(K_B\) of \(1.7 \times 10^6 \text{ M}^{-1}\) and 0.67 Pt atoms per base pair. ITC binding studies of 281 with 12 bp ds-DNA revealed a \(K_B\) of \(2.5 \times 10^4 \text{ M}^{-1}\) and 0.16 Pt atoms per base pair, which showed a dramatic increase in binding affinity of tetranuclear 267 to the DNA compared to mononuclear 281. The CD spectra and thermal denaturation experiments of 267 with DNA confirmed the formation of a 2:1 (267:12 bp ds-DNA) adduct by an increase in the \(T_m\) of 12 bs ds-DNA from 60 to 85 °C (\(\Delta T_m = 25 \text{ °C}\))\(^{28}\), which is twice the effect of monointercalators 279-281 on \(T_m\) of ct-DNA (\(\Delta T_m = 12 \text{ °C}\)).\(^{243}\)
1.3.4.2 Covalent Binding to Biomolecules

The intercalation of Pt(II) terpyridine complexes into a DNA offers an aperture route to antitumor drugs - comparable to the well-known cisplatin.\textsuperscript{269-271} The Pt drugs administered by injection or infusion could be reacted with other sulfur-containing biomolecules in the blood to form a stable Pt-S bond prior to reaching the targeted DNA intercalate or covalently react with guanine base in order to interrupt its functions.\textsuperscript{74,272,273}

To shed more light onto the reactivity and mechanism of some of the biomolecules with Pt drugs, many sulfur- and nitrogen-containing amino acids, short peptides, small biomolecules, nucleic acids, ribonucleosides and ribonucleotides were investigated for their covalent binding abilities and kinetics with $[\text{Pt(tpy}(R))]^{n+} \quad [\text{R}(n) = \text{Cl (1), H}_2\text{O (2)}]$. The square planar Pt(II)-based terpyridine complexes were chosen, as model compounds,
because they contain labile leaving groups, such as Cl or H$_2$O, and have a lower pKa ~ 4.5 ([Pt(tpy)(H$_2$O)]$^{2+}$) compared to similar [Pt(NNN)(R)]$^{n+}$ complexes. Site-specific covalent binding of these Pt(II) terpyridine complexes to biological macromolecules can be utilized as labels to investigate primary, secondary, and tertiary structures in these biomolecules. Furthermore, a few examples of Pd(II) and Au(III) terpyridine complexes that were covalently bound to biomolecules are considered here.

Kostic et al. reported that only three chemical moieties in all of the amino acids were able to react with [Pt(tpy)(Cl)]$^+$; they are: the thiol in cysteine, the imidazole in histidine, and the guanidine in arginine. Binding of biomolecules containing these amino acids to [Pt(tpy)(Cl)]$^+$ was characterized by the appearance of new MLCT bands between 300-350 nm in UV-vis, $^1$H and $^{195}$Pt NMR, and mass spectroscopy. Kinetic studies showed that thiol-containing biomolecules (cysteine, glutathione) reacted 300 times faster than imidazole containing histidine, his-his or gly-his-gly under similar conditions. Mixture of glutathione and gly-his-gly (1:1) with [Pt(tpy)(Cl)]$^+$ revealed that the Pt(II) terpyridine moiety was bound exclusively to thiol group in glutathione. It was possible to substitute histidine-bound Pt complex 324 with cysteine leading to complex 325 (Figure 1.104). The [Pd(tpy)(Cl)]$^+$ complex strongly bound to the thiol in cysteine. Reaction kinetics and their rate constants of [Pt(tpy)(Cl)]$^+$ and [Pd(tpy)(Cl)]$^+$ with cysteine, glutathione, and penicillamine were reported. The thiols being smaller nucleophiles and having smaller pKa values than imidazole were much more reactive towards [Pt(tpy)(Cl)]$^+$ than imidazole. Moreover, Lippert et al. suggested that the Pt(II) terpyridine complex can bind to the N$^1$ (major) and N$^3$ (minor) positions of the imidazole moiety in histidine and N-acetylhistidine, which termed linkage isomerism.
Figure 1.104. Substitution reaction of 324 with cysteine forming 325.\(^{76}\)

Guanidine-containing biomolecules (methylguanidine, arginine, \(N\)-acetylarginine; \(pK_a = 13.5, 12.5, 12.5\), respectively) were reacted with [Pt(tpy)(Cl)]\(^+\) under forcing conditions, e.g. as high temperatures and mildly basic or both; canavanine (\(pK_a = 7\)) is the exception in that it reacted with [Pt(tpy)(Cl)]\(^+\) under neutral condition.\(^{209}\) Guanidine-containing biomolecules formed monometallic yellow (326 and 327) or dimetallic red (180 and 181) complexes with [Pt(tpy)(Cl)]\(^+\) (Figure 1.105). The single crystal X-ray structure of 180 revealed that the interplanar distance between Pt-terpyridyl moieties connected through guanidinyl group is 2.8 Å suggesting that the d-d orbital interaction between Pt-Pt metal centers and \(\pi-\pi\) interaction between terpyridine moieties caused the low energy absorption bands.

Figure 1.105. Structures of 180, 181, 326, and 327 and crystal structure of 180. (Reprinted with permission from ref 209. Copyright 1990 American Chemical Society).
The R₂S-containing biomolecules (methionine, L-methionine, N-acetyl-
methionine, N-acetyl-L-methionine, methionine methyl ester, S-methyl-L-cysteine,
cystine, oxidized glutathione, and tetrapeptide Trp-Met-Asp-Phe; Figure 1.106) did not
display any reactivity towards [Pt(tpy)Cl]⁺ or [Pd(tpy)Cl]⁺ even under forcing conditions,
\textit{i.e.}, 100 °C, or using a ten fold excess of the biomolecules.⁷⁷,¹¹⁹

<table>
<thead>
<tr>
<th>Reactive biomolecules with Pt(II) and Pd(II) terpyridine complexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiourea (tu)</td>
</tr>
<tr>
<td>Glutathione (GSH)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unreactive biomolecules with Pt(II) and Pd(II) terpyridine complexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Methylcysteine (MeCys)</td>
</tr>
</tbody>
</table>

Figure 1.106. Structures of reactive and unreactive biomolecules towards [M(tpy)(Cl)]⁺
[M = Pd(II), Pt(II)] complexes.⁷⁴,⁷⁶-⁷⁸,₂⁰⁹,₂⁷₃,₂⁷₆
Studies by van Eldik et al.\textsuperscript{74,273,276} confirmed the dominating reactivity of sulfur-containing biomolecules, such as thiourea, DETDC, thiosulfate, Cys, GSH, and penicillamine over nitrogen-containing nucleosides 328, 329, and 331 (Figure 1.107) towards \([\text{Pt(ppy)}(\text{H}_2\text{O})]^{2+}\) under neutral conditions. Reaction kinetics and rate constants \((k_1)\) of thiourea, Cys, GSH and PCA were investigated under acidic conditions (pH 1) to keep the nucleophiles fully protonated in order to neglect other rate constants, such as \(k_2\), \(k_3\) and \(k_4\) (Scheme 1.27).\textsuperscript{273} Reactivity order of sulfur-containing nucleophiles towards \([\text{Pt(ppy)}(\text{H}_2\text{O})]^{2+}\) was found by comparing their pseudo-first order rate constants \((k_{\text{obsd}}/\text{s}^{-1})\) as DL-penicillamine < L-Cys < GSH < thiourea.\textsuperscript{74,276} The single crystal X-ray structures of thiourea- and cysteine-containing complexes 338 and 339, respectively, proved the basic distorted square planar Pt(II) terpyridine structure (Figure 1.108).\textsuperscript{74}

---

\begin{center}
\textbf{Figure 1.107. Structures of nucleoside containing biomolecules 328-337.}
\end{center}
Scheme 1.27. Acid disassociation constants of cysteine and its reactions with [Pt(tpy)(H₂O)]²⁺.²⁷³

Figure 1.108. Single crystal X-ray structures of 338-340 (Reprinted with permission from ref 74, 273. Copyright 2004 and 2002 The Royal Society of Chemistry).

The guanine-containing nucleosides and nucleotides 328-331 were covalently bound to [Pt(tpy)]²⁺ via N7 position of the guanine base, which was proven by a single crystal X-ray structure 340 (Figure 1.108) in addition to their detailed mass spectroscopy analysis.⁷⁴,⁷⁹ However, adenosine 332 and cytidine 333 were each covalently bound to the [Pt(tpy)]²⁺ complex either mono- or difunctionally from N1, N6 and N3, N4, respectively, which was proven by their ¹H and ¹⁹⁵Pt NMR and mass spectroscopy analysis.⁷⁹,²⁷⁷ Furthermore, the single crystal structures of mono- and dinuclear N-
methylcytosine containing Pt(II) and Pd(II) terpyridine complexes 176 and 177 confirmed that the binding sites were N\(^3\), N\(^4\) positions (Figure 1.58).\(^{127}\) Since the N\(^1\), N\(^6\) and N\(^3\), N\(^4\) positions of adenosine and cytidine, respectively, were engaged in H-bonding in the double stranded DNA, the Pt(II) terpyridine complexes can only covalently bind to the guanine base from its N\(^7\) position. Nucleoside-containing Pt(II) terpyridine complexes were easily displaced by thiol containing biomolecules (thiourea, DEDTC, GSH, Cys, sts), which were stable and could not be replaced by ribonucleotides.\(^{74}\) Lippard et al.\(^{75}\) also introduced a phosphorothioate group to adenosine 335 and uridine 337 observing that these molecules exclusively bind to Pt(II) terpyridine complexes through Pt-S bonding from phosphorothioate moiety rather than from the bases.

Reactivity of coplanar \([\text{Pt(tpy}(R)])[n+]\) complexes with biomolecules was attributed to the \(\pi\)-accepting effect and electronic communication between the pyridine rings of the terpyridine.\(^{278, 279}\)

1.3.4.3 Labeling Biomolecules

Covalent modification of the amino acid side-chain residues has been an important tool for structural, spectroscopic, and mechanistic studies of proteins.\(^{76-78}\) Proteins labeled with transition metals have been utilized for their X-ray crystallography, electron microscopy, NMR relaxation, and EPR spectroscopy experiments.\(^{280, 281}\) Towards this goal, selective reactivity of \([\text{Pt(tpy}(\text{Cl})])[n+]\) towards cysteine, histidine, and arginine among all other amino acids prompted Kostic et al.\(^{77, 78}\) to investigate this Pt(II) complex, as a protein labeling agent. Cytochrome c proteins from horse and tuna heart, candida
krusei and baker’s yeast were chosen for labeling studies, since they contain amino acids such as cysteine, histidine and arginine, which can be easily reacted with \([\text{Pt}(\text{tpy})(\text{Cl})]^+\) complex. Protein structural studies of cytochrome c revealed that the accessible positions of these reactive amino acids were on the outer-sphere of the protein (Table 1.6).\textsuperscript{282-291}

Cytochrome c protein from Bakers’ yeast (iso-1 form)\textsuperscript{290,291} contains all the reactive amino acids (cysteine, histidine and arginine) exposed to the surface of the protein; however, cytochrome c from tuna, horse heart and candida krusei only contain histidine and arginine on the surface.

Table 1.6. Positions of accessible amino acids which are reactive with \([\text{Pt}(\text{tpy})(\text{Cl})]^+\) and exposed on the surface of cytochrome c proteins.

<table>
<thead>
<tr>
<th>Cytochrome c from</th>
<th>Amino acid and its position</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horse heart</td>
<td>His-26, His-33, Arg-91</td>
<td>282</td>
</tr>
<tr>
<td>Tuna heart</td>
<td>His-26, Arg-91</td>
<td>283-288</td>
</tr>
<tr>
<td>\textit{Candida krusei}</td>
<td>His-33, His-39, Arg-91</td>
<td>289</td>
</tr>
<tr>
<td>Bakers’ yeast (iso-1 form)</td>
<td>His-33, His-39, Arg-91, Cys-102</td>
<td>290,291</td>
</tr>
</tbody>
</table>

Cytochrome c proteins were incubated with an equimolar amount of \([\text{Pt}(\text{tpy})\text{Cl})\text{Cl}\) at 25 °C in 0.1 M acetate buffer at pH = 5.0 for 24 h.\textsuperscript{77,78} This procedure allowed only the cysteine and histidine residues to react with \([\text{Pt}(\text{tpy})(\text{Cl})]^+\); however, arginine-91 residues in cytochrome c proteins reacted upon longer incubation time and additional heating in a buffer at pH 7.0. These reactions were terminated by ultrafiltration and the products were separated by cation-exchange chromatography, then characterized by UV-vis, ESI-MS, and $^1$H and $^{195}$Pt NMR spectroscopy. The resulting tagged fractions of the proteins and their yields were summarized in Table 1.7.
Table 1.7. Products obtained from reactions between cytochrome c proteins and [Pt(tpy)(Cl)]\(^+\) in 0.1 M acetate buffer at pH 5.0, separated by cation-exchange chromatography.\(^{77,78}\)

<table>
<thead>
<tr>
<th>Cytochrome c from</th>
<th>Fractions</th>
<th>Binding sites</th>
<th>Number of [Pt(tpy)](^{2+}) tags</th>
<th>Relative yield ± 3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuna heart</td>
<td>1</td>
<td>none</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>His-26</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Horse heart</td>
<td>1</td>
<td>none</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>His-33</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>His-26</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>His-33, His-26</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>1</td>
<td>none</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>His-33</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>His-39</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>His-33, His-39</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Bakers’ yeast (iso-1 form)</td>
<td>1</td>
<td>none</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Cys-102</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>His-33</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>His-39</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Cys-102, His-39</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Cys-102, His-33</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>His-33, His-39</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Cytochrome c protein from horse heart was labeled with [Pt(tpy)(Cl)]\(^+\) mainly at His-33 (50%), which was in the hydrophilic region and the protein’s outer-sphere;\(^{282}\) however, only 5% of the protein was labeled at His-26, which was H-bonded in a hydrophobic pocket of the protein. Further, 10% of cytochrome c from tuna\(^{283-288}\) was labeled, since it has only His-26, which is less reactive than His-33 residue.\(^{77,78}\) The UV-vis spectrum of Pt-tagged cytochrome c from horse revealed two unique bands at 328 and 342 nm corresponding to MLCT bands of [Pt(tpy)(His)]\(^{2+}\), which displayed different
intensity ratios \( \left( \frac{\varepsilon_{342}}{\varepsilon_{328}} \right) \) depending on the position that the Pt was attached; 1.51 for His-33 and 1.15 for His-26. The absorption of the complex bound to the protein is sensitive to its environment suggesting that the \([\text{Pt(tpy)}(\text{Cl})]^+\) tag could be utilized as a protein probe.

Among cytochrome c proteins, only the one from Bakers’ yeast contains a cysteine residue at the 102 position near the carbonyl terminus.\(^{290,291}\) The cysteine residue was expected to react with \([\text{Pt(tpy)}(\text{Cl})]^+\), since it was proven that the thiol-containing biomolecules are much more reactive than \(N\)-containing analogues.\(^{78}\) However, the yeast protein (\(\text{iso}-1\) form) was mainly labeled at the His-33 and His-39 residues not at Cys-102 residue, which is buried in the protein’s hydrophobic region\(^{290,291}\) thus inaccessible for complexation (Table 1.7).\(^{78}\) The \textit{candida krusei} protein,\(^{289}\) an analogue to the yeast protein lacking the free cysteine, was labeled at His-33 (30%) and His-39 (30%).\(^{78}\) The arginine-91 residues, which are barely exposed at the surface in either horse or tuna proteins,\(^{282-288}\) were labeled with 10% yield by \([\text{Pt(tpy)}(\text{Cl})]^+\) under forcing conditions.\(^{76}\) These results have proven that the noninvasive labeling agent, \([\text{Pt(tpy)}(\text{Cl})]^+\), is only attached to reactive groups on the protein’s surface.\(^{78}\) Moreover, UV-vis, \(^1\)H NMR, EPR spectroscopy, and cyclic and pulse voltammetry of the tagged proteins did not display any significant perturbation of the protein’s morphology.\(^{77}\) Kostic \textit{et al.}\(^{292}\) reported that a reversible noninvasive modification of serine proteases enzymes, \(\alpha\)-chymotrypsin and \(\alpha\)-lytic proteases, at their His-57 and His-40 positions in the former and His-57 in the later. Even though labeling the His-57 residue of these enzymes alters their catalytic triad site (Ser-195, His-57, and Asp-102), the platinum-tagged enzymes still possess esterase and amidase activity suggesting that the Pt(II) terpyridine labels for these enzymes are noninvasive.\(^{292}\)
Lippard et al.\textsuperscript{75} reported the exclusive labeling of the alternating copolymer of nucleosides adenine and uracil possessing the phosphorothioate backbone poly(s-A-U) with a Pt(II) terpyridine complex, which was connected to the sulfur of a phosphorothioate group; moreover, there was no evidence of degradation or loss of sulfur from poly(s-A-U) following Pt binding (Figure 1.109). It was proposed that the [Pt(tpy)(R)]\textsuperscript{n+} [R(n) = Cl (1), H\textsubscript{2}O (2)] complexes could be labeling agents for sequencing the nucleic acids by electron microscopy, since Pt complex exclusively reacts with phosphorothioate groups that are incorporated into the RNA or DNA backbone adjacent to a specific base (Figure 108).

\begin{center}
\includegraphics[width=\textwidth]{fig.png}
\end{center}

Figure 1.109. Alternating copolymer of nucleosides adenine and uracil with phosphate and phosphorothioate backbone.\textsuperscript{75}

Lowe et al.\textsuperscript{293} designed the dinuclear Pt-terpyridine complexes 341, (Figure 1.110) which can intercalate into two DNA duplexes in close spacial proximity in order to study the topology of DNA. The azido groups were introduced at 4'-positions of terpyridines to allow the sites-of-intercalation to be photoaffinity labeled and the linker (pyr-R-pyr) is designed to be susceptible to cleavage with thiols and cyanides; a requirement for 2-D electrophoresis to identify the sites of intercalation.
Figure 1.110. Structures of the bis-[4'-azido-terpyridine Pt(II)] complexes 341.

A new generation of luminescent biolabeling agents was designed by introducing reactive isothiocyanate and iodoacetamide groups to the acetylene co-ligand of complexes 51 and 342, respectively (Figure 1.111). Specifically, human serum albumin (HSA), which is the most abundant plasma protein with many physiological functions, was successfully labeled with complex 51 and 342 from its amine and thiol functional residues forming thiourea and thioether linkages, as in 343 and 344, respectively. These Pt(II)-tagged HSAs displayed induced low energy MLCT/LLCT absorption and 3MLCT/3LLCT emission bands at ca. 470 and 630 nm, respectively.

Figure 1.111. Luminescent labeling of HSA with 51 and 342.

Emission bands of the labeled HSAs 343 and 344 were uniquely different than labeling agents 51 and 342, proving successful labeling. The [Au(tpy)(Cl)]^{2+} complex was also
tried as a label for bovine serum albumin (BSA); however, progressive reduction of Au(III) metal center and a complete break down of the complex was observed.\textsuperscript{294}

The estrogen-containing Pt(II) terpyridine complex 345 was elegantly designed to facilitate the cellular delivery of the Pt intercalator to cells with estrogen receptor (Figure 1.112).\textsuperscript{295} The single crystal X-ray structure of 345 revealed an extended chain-like stacking through $\pi-\pi$ and the unusual Pt-$\pi$ packing without any Pt-Pt interactions. This complex was successfully bound to the estrogen receptors in MCF-7 cell lines, human and bovine serum albumins, which are steroid transporting proteins and were covalently attached to guanine base in DNA and 12-base pair DNA fragment. The binding of 345 to these biomolecules was characterized by competitive radiometric binding assay, CD, FTICR, and ESI mass spectroscopy.

![Figure 1.112. Structure of estrogen Pt(II) complex 345 and its molecular packing, (Reprinted with permission from ref 295. Copyright 2006 Wiley-VCH).](image)

1.3.4.4 Cytotoxicity

It is well-known and accepted that Pt(II)-terpyridine complexes can intercalate into the DNA and covalently bind to biomolecules, such as proteins and enzymes. The
intercalation and/or covalent binding of small molecules to the DNA or enzymes induced morphology deformations causing a dysfunction of these biomolecules and eventually leading to cell destruction. Planar dyes such as: dactinomycin, adriamycin, ellipticine, belomycin, and their analogues that can intercalate into DNA were clinically used as antitumor and antiprotozoal drugs. The coplanar Pt(II), Pd(II), and Au(III) terpyridine complexes were investigated in vitro and vivo as antitumor and antiprotozoal drugs.

1.3.4.4.1 Chemotherapeutic Agents

In 1985, McFadyen et al. reported the first cytotoxicity study of various Pt(II) terpyridine complexes 346-356 (Figure 1.113) and [Pt(tpy)(Cl)]\(^+\) against L1210 murine leukemia cells in culture and mice. To determine the cytotoxicity of these complexes, L1210 cells were incubated with these complexes for 2 days at 37 °C and then, cells were counted on a Coulter counter. The IC\(_{50}\) value, which is the concentration required to inhibit the growth of cells by 50%, was determined by plotting cell growth as a percentage of control versus drug concentration. The IC\(_{50}\) values of 346-356 against L1210 lines were in the 4-32 \(\mu\)M range; however, the [Pt(tpy)(Cl)]\(^+\) complex had IC\(_{50}\) of 450 \(\mu\)M against L1210 suggesting the possible covalent binding of this complex to other biomolecules before reaching the DNA. The [Pt(tpy)(Cl)]\(^+\) showed enhanced cytotoxicity against MCF-7 breast cancer epithelial cells (IC\(_{50}\) of 25 \(\mu\)M in vitro) when compared to L1210 but it was not as good as cisplatin, which has a IC\(_{50}\) of 5.6 \(\mu\)M in vitro against MCF-7. The antitumor complex 347 (IC\(_{50}\) of 4 \(\mu\)M in vitro) was investigated in vivo against L1210 in mice; however, it did not show any antitumor activity. Furthermore,
free terpyridine ligands displayed unexpected cytotoxicity with IC\textsubscript{50} of 2 \(\mu\)M against L1210 that was even higher than the corresponding Pt complexes, suggesting that free terpyridine ligand may induce metal-deficient states or form metal complexes in the media that can inhibit cell growth.

![Figure 1.113. Structure of potential Pt-terpyridine antitumor agents 346-356.](image)

Mono- and dinuclear intercalators (275 and 305-311, respectively) with thioalkyl chains displayed in vitro cytotoxicity against L1210 cells with IC\textsubscript{50} values in the range of 4-14 \(\mu\)M suggesting that cytotoxicity is independent of the intercalator character.\textsuperscript{239} Moreover, these complexes produced extensive cell lysis, proposing that they may be only effective on the cell membrane and might not even reach the cell nucleus to intercalate into DNA.

Reports for the high intercalative\textsuperscript{113} binding affinity and covalent binding\textsuperscript{79,277} of the [Pt(tpy)(pyr)]\textsuperscript{2+} complex and its derivatives to DNA prompted Lowe et al. to investigate their cytotoxic properties against parasites\textsuperscript{85} and cancer\textsuperscript{80} cells. Thus, a variety of mononuclear 357-359 (Figure 1.114) and dinuclear 360 and 361 (Figure 1.115) complexes were investigated as antiprotozoal and antitumor agents and their results were compared with conventional cisplatin and carboplatin drugs.
Some of the mono- and dinuclear complexes 358-361 were investigated for their \textit{in vitro} cytotoxicity against five human ovarian carcinoma cell lines, such as: CH1, cisplatin-resistant CH1cis\textsuperscript{R}, deoxorubicin-resistant CH1dox\textsuperscript{R}, A2780, and cisplatin-resistant A2780cis\textsuperscript{R} cell lines; moreover, the SKOV3 cell line was included since it is one of the most resistant to the Pt drugs.\textsuperscript{80} Cells were incubated with Pt drugs for 4 days, and
then the IC$_{50}$ values were calculated (Table 1.8). The most effective complexes against human ovarian carcinoma cells in vitro were proven to be dinuclear Pt complexes with a short and rigid linkers, such as 360 ($R^1 = H$, $R^2 = \text{trans-CH}=$CH and butadiene), which are slightly more effective than cisplatin against cisplatin-resistant lines (CH1cis$^R$ and A2780cis$^R$). The dinuclear complexes 361 with flexible linkers showed relatively low cytotoxicity compared to 360.

Table 1.8. IC$_{50}$ values (µM, 4-days) for the in vitro growth inhibition of human ovarian cell lines by mono- and dinuclear Pt-terpyridine complexes.$^{80}$

<table>
<thead>
<tr>
<th>Complex</th>
<th>CH1</th>
<th>CH1cis$^R$</th>
<th>RF$^a$</th>
<th>CH1dox$^R$</th>
<th>RF$^a$</th>
<th>A2780</th>
<th>A2780cis$^R$</th>
<th>RF$^a$</th>
<th>SKOV3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>0.4</td>
<td>1.2</td>
<td>3.0</td>
<td>0.5</td>
<td>1.2</td>
<td>0.53</td>
<td>8.8</td>
<td>16.6</td>
<td>2.25</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>6.2</td>
<td>14</td>
<td>2.3</td>
<td>6.0</td>
<td>1.0</td>
<td>35</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td></td>
</tr>
<tr>
<td>360 ($R^1 = H$, $R^2 = \text{trans-CH}=$CH)</td>
<td>1.35</td>
<td>0.63</td>
<td>0.46</td>
<td>5.1</td>
<td>3.8</td>
<td>1.6</td>
<td>2.4</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>360 ($R^1 = H$, $R^2 = \text{butadiyne}$)</td>
<td>0.73</td>
<td>0.73</td>
<td>1</td>
<td>0.44</td>
<td>0.6</td>
<td>2</td>
<td>1.8</td>
<td>0.9</td>
<td>1.7</td>
</tr>
<tr>
<td>360 ($R^1 = \text{Cl}$, $R^2 = \text{Phenyl}$)</td>
<td>0.55</td>
<td>0.81</td>
<td>1.5</td>
<td>0.42</td>
<td>0.8</td>
<td>13.5</td>
<td>20.5</td>
<td>1.5</td>
<td>1.7</td>
</tr>
<tr>
<td>357 ($R^1 = H$, $R^2 = \text{4-Br}$)</td>
<td>2.1</td>
<td>2.1</td>
<td>1</td>
<td>0.85</td>
<td>0.41</td>
<td>5.8</td>
<td>6.7</td>
<td>1.16</td>
<td>9.2</td>
</tr>
<tr>
<td>358 ($R^1 = H$, $L = \text{Cl}$)</td>
<td>6.6</td>
<td>6.4</td>
<td>1</td>
<td>3.75</td>
<td>0.6</td>
<td>49</td>
<td>41</td>
<td>0.8</td>
<td>19.5</td>
</tr>
<tr>
<td>357 ($R^1 = \text{NMe[CH$_2$CH$_2$OH]}$, $R^2 = \text{4-Me}$)</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>17.5</td>
<td>40</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td>&gt; 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>361 ($R = H$)</td>
<td>48</td>
<td>42</td>
<td>0.9</td>
<td>40</td>
<td>0.8</td>
<td>19</td>
<td>40</td>
<td>2.1</td>
<td>9.8</td>
</tr>
</tbody>
</table>

$^a$RF is the resistance factor: IC$_{50}$ resistant line/ IC$_{50}$ parent line

Several of the mononuclear complexes showed significant cytotoxicity, such as 359 ($R^1 = H$, $R^2 = \text{4-Br}$), against human ovarian carcinoma cells; however, complexes with bulky and electron-donating substitutes on terpyridine, such as 359 ($R^2 = \text{4-Me}$, $R^2 = \text{NMe[CH$_2$CH$_2$OH]}$), led to a significant loss in their antitumor activities since bulky substituents prevented the intercalation mode.$^{80}$ Further, the [Pt(tpy)$^n$]$(n^+)$ ($R[n] = \text{Cl}$ [1],
H₂O [2], NH₃ [2]) complexes were less cytotoxic than other mononuclear Pt complexes due to its covalent binding affinity towards other biomolecules.

Carborane cage-containing mononuclear 288-291 and dinuclear complexes 314-317 were investigated against L1210 murine leukemia cell line, its cisplatin resistant variant L1210cis⁹, 2008 human ovarian cell line, and its cisplatin resistant variant C13cis⁹. The mononuclear 290 (n = 1) displayed significant in vitro cytotoxicity against these cell lines when compared to cisplatin (Table 1.9). Moreover, 314(n = 3) displayed remarkable cytotoxicity in vitro against L1210 and L1210cis⁹. Low cytotoxicity of other dinuclear complexes and 289 (n = 1) was attributed to their poor solubility in physiological conditions.²⁵⁷,²⁵⁹

Table 1.9. IC₅₀ values (µM) of carborane containing mono- and dinuclear Pt complexes 288-291 and 314-317 against selected cancer cell lines.²⁵⁷,²⁵⁹

<table>
<thead>
<tr>
<th>Complex</th>
<th>L1210</th>
<th>L1210cis⁹</th>
<th>2008</th>
<th>C13cis⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>290 (n = 1)</td>
<td>1.6</td>
<td>0.9</td>
<td>1.7</td>
<td>2.1</td>
</tr>
<tr>
<td>290 (n = 3)</td>
<td>NA</td>
<td>NA</td>
<td>5.3</td>
<td>4.1</td>
</tr>
<tr>
<td>288 (n = 1)</td>
<td>NA</td>
<td>NA</td>
<td>4.6</td>
<td>5.1</td>
</tr>
<tr>
<td>289 (n = 1)</td>
<td>NA</td>
<td>NA</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>314 (n = 3)</td>
<td>0.9</td>
<td>0.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>315 (n = 3)</td>
<td>7.4</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>316 (n = 1)</td>
<td>24.5</td>
<td>5.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>317 (n = 3)</td>
<td>26.5</td>
<td>7.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>cisplatin</td>
<td>0.5</td>
<td>6.9</td>
<td>0.6</td>
<td>10</td>
</tr>
</tbody>
</table>

The antiprotozoal activity of mono- and dinuclear complexes 358-361 was investigated against Leishmania donovani, Typanosoma cruzi and Typanosoma brucei, which are the causes for leishmaniasis, Chaga’s disease and sleeping sickness, respectively, since many planar dyes are active against Typanosoma and Leishmania.
parasites, such as: ethidium bromide, acriflavine, ellipticine, and belomycin. Inhibition percentages of selected complexes against *L. donovani*, *T. cruzi*, and *T. brucei* parasites *in vitro* were summarized in Table 1.10.85

Table 1.10. Percent inhibition of selected complexes *in vitro* against parasites.85

<table>
<thead>
<tr>
<th>Complex</th>
<th><em>L. donovani</em></th>
<th><em>T. cruzi</em></th>
<th><em>T. brucei</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 µM</td>
<td>10 µM</td>
<td>3 µM</td>
</tr>
<tr>
<td>358 (R = H, L = Cl)</td>
<td>1st Gen.</td>
<td>99.1</td>
<td>94.9</td>
</tr>
<tr>
<td>358 (R = H, L = H2O)</td>
<td>1st Gen.</td>
<td>T/100</td>
<td>T/100</td>
</tr>
<tr>
<td>358 (R = H, L = NH3)</td>
<td>1st Gen.</td>
<td>96.1</td>
<td>91.7</td>
</tr>
<tr>
<td>357 (R1 = H, R2 = H)</td>
<td>1st Gen.</td>
<td>99.5</td>
<td>92.2</td>
</tr>
<tr>
<td>357 (R1 = Cl, R2 = 4-Me)</td>
<td>2nd Gen.</td>
<td>93.3</td>
<td>89.5</td>
</tr>
<tr>
<td>357 (R1 = Br, R2 = 4-Me)</td>
<td>2nd Gen.</td>
<td>100</td>
<td>92.8</td>
</tr>
<tr>
<td>358 (R = Cl, L = NH3)</td>
<td>3rd Gen.</td>
<td>T/100</td>
<td>T/100</td>
</tr>
<tr>
<td>358 (R = 4-Br-Phenyl, L = NH3)</td>
<td>3rd Gen.</td>
<td>T/100</td>
<td>T/100</td>
</tr>
</tbody>
</table>

T/100 means the compound was toxic to macrophages, 100% inhibition. T/+ means the compound was toxic to macrophages but parasites still present.

The first generation Pt-terpyridine drugs for parasites revealed that complexes 358 (R = H, L = H2O, NH3) were effective against *L. donovani* and *T. cruzi*; whereas, complexes 358 (R1 = H, R2 = 4-Me and 4-Br) and 357 (R = H, L = NH3) worked better against *T. brucei* (Table 1.10).85 The second generation Pt-terpyridine drugs were more effective than the first generation against these parasites. The complexes 357 (R1 = 4-Me-Ph and 4-Br-Ph, R2 = 4-Me) against *L. donovani*; 357 (R1 = 4-Me-Ph and Cl, R2 = 4-Me)
against T. cruzi; and 357 (R¹ = 4-Me-Ph, Cl and Br, R² = 4-Me) against T. brucei were most effective. The third generation Pt-terpyridine drugs were designed by considering former results and gave the best inhibition percentages in vitro against these parasites; e.g., 358 (R = Cl and 4-Br-Ph, L = NH₃) displayed outstanding antiprotozoal activities. For L. donovani, these complexes were more effective than first and second generation; for T. cruzi, they displayed comparable toxicity, and for T. brucei, they caused complete inhibition at concentrations > 0.003 μM.

Kinetic and spectroscopic studies revealed that complexes 357 and 358 irreversibly bound to Cys-52 residue of typanothione reductase (TR) enzyme from T. cruzi and eventually inhibited its function, which contributed significantly to their antiprotozoal activities besides the intercalation into DNA. In contrast to the parasite enzyme, most Pt-terpyridine complexes reversibly interacted with human glutathione reductase (GR), similar to that of TR. Moreover, an irreversible inhibitor, in which the [Pt(tpy)(SCH₂CH₂OH)]⁺ complex was linked to 9-aminoacridine dye through alkyl chain, displayed same inhibition behavior as in the case of 357 and 358 against T. cruzi TR and human GR.

The human thioredoxin system containing the 12-kDa protein thioredoxin (hTrx) and the selenoenzyme thioredoxin reductase (hTrxR) was involved in thiol-mediated antioxidant defense and redox regulatory processes including transcriptional control, DNA synthesis, and apoptosis; thus supporting cell proliferation. Many tumor cells are known to have increased Trx and TrxR and they can release the TrxR enzyme to stimulate autocrine cell growth. Inhibition of TrxR could selectively induce death of fast growing cancer cells. Lowe et al. reported an effective inhibition of hTrxR enzyme with
complexes 282, 362, and 363 (Figure 1.116) by the reversible competitive or irreversible tight-binding of these complexes to the enzyme. These complexes displayed effective cytotoxicity \textit{in vitro} against glioblastoma cell lines C6, NCH37, NCH82, NCH89, HNO97, and HNO199 with remarkable IC$_{50}$ values (Table 1.11).\textsuperscript{81,300}

![Figure 1.116. Structures of 182, 362, and 363.\textsuperscript{81}](image)

Table 1.11. IC$_{50}$ (µM) values of 363 and 182 against glioblastoma cell lines.\textsuperscript{81}

<table>
<thead>
<tr>
<th>Tumor Cell Line</th>
<th>NCH37</th>
<th>NCH87</th>
<th>NCH89</th>
<th>HNO97</th>
<th>HNO199</th>
<th>C6 $^{300}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC$_{50}$ for 363</td>
<td>10.5</td>
<td>7.4</td>
<td>2.5</td>
<td>5.5</td>
<td>9.2</td>
<td>3.5</td>
</tr>
<tr>
<td>IC$_{50}$ for 182</td>
<td>5.7</td>
<td>3.9</td>
<td>2.5</td>
<td>4.8</td>
<td>6.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

The effects of the potent hTrxR inhibitors 362 and 363 on glioblastoma in rat models were reported.\textsuperscript{300} Triple intravenous application of 25–35 mg/kg of these Pt-terpyridine drugs induced a significant decrease in tumor growth, as determined by MRI (Figure 1.117). The 22% reduction in tumor growth with low dose therapy (15 mg/kg of 362 and 25 mg/kg of 363) as well as 36 and 40% reduction with high dose therapy (25 mg/kg of 362 and 35 mg/kg of 363, respectively) was observed.
Figure 1.117. Volumetric MRI scans on day 15 presenting tumor growth in (A) untreated animals, (B) early therapy with 15 mg/kg of \textbf{362} and (B) late therapy with 35 mg/kg of \textbf{363}. Early therapy, treatment at days 4, 8, and 12 after tumor inoculation; late therapy, treatment at days 9, 11, and 13 after tumor inoculation. The dark arrow indicates the sphenoidal sinus (SS) and the arrow heads delineate the tumor region. (Reprinted with permission from ref 300. Copyright 2007 Elsevier).

Che et al.\textsuperscript{31} reported a new generation of the water-soluble glycosylated acetylide and arylacetylide complexes \textbf{292-299} and their cytotoxicity against five human carcinoma cells (HeLa, HepG2, SF-268, NCI-H460, MCF-7) and normal kidney cells (293), as a model. The IC\textsubscript{50} values of \textbf{292-299} and cisplatin are summarized in Table 1.12. Complexes \textbf{292}, \textbf{294-296}, \textbf{298}, and \textbf{299} showed significant cytotoxicity against these human carcinoma cells and \textbf{292} displayed remarkable cytotoxicity that is ~100 more effective than clinically proven cisplatin drugs. Moreover, \textbf{292} and \textbf{296} have higher cytotoxicity against cancer cells than normal 293 human kidney cells.

Gold(III) complexes \textbf{300-304} displayed cytotoxicity \textit{in vitro} against A2780, cisplatin-resistant A2780cis\textsuperscript{R}, A-549, SGC-7901, HeLa, HCT-116, BEL-7402, HL-60, and P-388 human cancer cells.\textsuperscript{88,262} The IC\textsubscript{50} values of [Au(tpy)(Cl)]\textsuperscript{2+} \textit{in vitro} against A2780 and A2780cis\textsuperscript{R} were calculated to be 0.2 and 0.37 µM, respectively, which were more effective than cisplatin (1.22, 14.16 µM).\textsuperscript{88} The complex \textbf{304} showed the highest
cytotoxicity by inhibiting 80% of the cell growth in A-549, HeLa, and HCT-116 due to its high solubility in physiological conditions; some of the free terpyridine ligands displayed strong cytotoxicity and sometimes even higher than their corresponding Au(III) complexes. 88,262

Table 1.12. IC₅₀ (µM) values of 292, 294-296, 298, 299 and cisplatin against various human carcinoma cells and normal 293 cells. 31

<table>
<thead>
<tr>
<th>Complex</th>
<th>HeLa</th>
<th>HepG2</th>
<th>SF-268</th>
<th>NCI-H460</th>
<th>MCF-7</th>
<th>Cell-293</th>
</tr>
</thead>
<tbody>
<tr>
<td>292</td>
<td>0.1</td>
<td>0.1</td>
<td>0.06</td>
<td>0.1</td>
<td>0.08</td>
<td>0.5</td>
</tr>
<tr>
<td>294</td>
<td>2.0</td>
<td>1.7</td>
<td>1.3</td>
<td>2.8</td>
<td>1.9</td>
<td>10.5</td>
</tr>
<tr>
<td>295</td>
<td>0.09</td>
<td>0.1</td>
<td>0.08</td>
<td>0.1</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>296</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.9</td>
</tr>
<tr>
<td>298</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>299</td>
<td>2.7</td>
<td>3.0</td>
<td>2.1</td>
<td>2.5</td>
<td>3.4</td>
<td>4.6</td>
</tr>
<tr>
<td>cisplatin</td>
<td>11.6</td>
<td>20.6</td>
<td>15.6</td>
<td>25.1</td>
<td>19.1</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>

1.3.4.4.2 Radiotherapeutic Agents

Biomolecules can be damaged by the photoabsorption of X-rays, which were specifically designed to ionize the molecules by forming Auger electrons. 301 The Auger process, which generates electrons and a charged-center from electron-emitting radionuclides, such as: ¹²⁵I, ¹³¹I and ³²P, can induce cleavage of chemical bonds in their neighborhood by direct ionization or charge recombination. 83 This process, which can cause cell death in vivo, single strand breaks (SSBs) and double strand breaks (DSBs) of DNA in vitro, was applied as radiotherapy to kill leukemia and thyroid tumors.

Le Sech et al. 82 introduced heavy Pt(II) atoms to circular plasmid DNA by intercalation and/or covalent binding of the [Pt(tpy)(Cl)]⁺ to allow their use of energetic
X-rays (soft $\gamma$-rays, 11 KeV) on DNA. It was suggested that the absorption of photons from soft $\gamma$-rays (11 KeV) in $L_{III}$ inner shell of Pt atom, which was bound to circular plasmid DNA (dry sample), induced SSBs and DSBs of the DNA. This process was detected by florescence spectroscopy after submitting the sample to agarose gel electrophoresis. Later, SSBs and DSBs of the DNA, which contained $[\text{Pt(tpy)}(\text{Cl})]^+$, were spectroscopically enhanced by tuning the experimental procedures. The Pt-bound circular DNA that irradiated by X-ray in aqueous solution increased SSBs and DSBs due to formation of free radicals from water, which could be a possible application to hadrontherapy. Moreover, fast He$^{2+}$ ion irradiation of circular plasmid DNA, which contained $[\text{Pt(tpy)}(\text{Cl})]^+$, caused the SSBs and DSBs of the DNA displaying similar results to that of X-ray irradiation.

1.4 Conclusion

The reversible metal d-d orbital interactions and terpyridine $\pi$-$\pi$ interactions continue to generate new avenues to self-assemble supramolecular structures that can be utilized as molecular switches and sensors via either their host-guest interactions or photo- and electrochemical responses. Since square planar Pt(II), Pd(II), and Au(III) terpyridine complexes show promise as medical probes their potential as anti-tumor and antiprotozoal agents, and protein probes will continue to be evaluated. Thus, as an active and growing area of interest, terpyridine-based chemistry seems destined to garner continued interest on the physical, biological, medical, and supramolecular as well as yet to be envisioned areas.
CHAPTER II

SYNTHESIS AND SINGLE CRYSTAL X-RAY CHARACTERIZATION OF 4,4''-FUNCTIONALIZED 4'-(4-R-PHENYL)-2,2':6',2''-TERPYRIDINES†

2.1 Introduction

Over the past decade, the coordination and supramolecular chemistry associated with 2,2':6',2''-terpyridines has been studied intensely. However, limited accessibility to unsymmetrically functionalized terpyridines has restricted their potential use in the construction of more complex infrastructures. Since their metal complexes have been shown to possess interesting novel luminescent properties, their potential applications as chemosensors and fluorescent immunoassay agents, as well as their use in catalysis and dye-sensitized solar cells could be expanded if new polyfunctional motifs were available.

Substituted 2,2':6',2''-terpyridines have been synthesized via their N-oxide, and 1,2,4-triazine analogues (Sauer method), the Kröhnke, Potts, and Jameson methods, and modern Pd-mediated cross-coupling procedures; further chemical modifications of substituents have also been reported. The two-step Kröhnke synthesis, using modified 2'-azachalcones and pyridinium iodide salts of

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2-acetylpyridines, facilitates the potential to create unsymmetrical and symmetrical mono and di-substituted 4'-phenyl-2,2':6',2''-terpyridines; however, few examples of these procedures are found in the literature.330-332

Herein, the first microwave-assisted, solid-state aldol condensation procedure for the preparation of –CO2Me and –CN substituted 2'-azachalcones and the facile synthesis of new mono- and di-substituted 4'-(4-R-phenyl)terpyridines (5a-m; Figure 2.1) via the two-step Kröhnke44 method are discussed. Different methyl-, methyl ester- and cyano-substitution patterns on the 4,4''-positions of 4'R-phenylterpyridine were initially chosen since these functionalities afforded simple routes to a variety of useful substituted building blocks for higher-ordered supramacromolecular architectures. The poor solubility of methyl ester groups in 5a and 5m was improved by converting to ethyl ester groups, as in 6a and 6b. Those methyl ester groups in 5g and 5k were reduced to alcohol groups, as in 7a and 7b, and the alcohol groups in 7b were transformed to CH2Cl groups, as in 8. The single crystal X-ray structures of 2'-azachalcones 4a, 4b, 4f and terpyridines 5a, 5c, 5g, 5j, and crystal packing of diester 5a are also presented.

<table>
<thead>
<tr>
<th></th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Br</td>
<td>CO2Me</td>
<td>CO2Me</td>
<td>5j</td>
<td>Br</td>
<td>Me</td>
</tr>
<tr>
<td>5b</td>
<td>Br</td>
<td>CN</td>
<td>CN</td>
<td>5k</td>
<td>OMe</td>
<td>CO2Me</td>
</tr>
<tr>
<td>5c</td>
<td>Br</td>
<td>Me</td>
<td>Me</td>
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<td>H</td>
<td>H</td>
<td>5m</td>
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<td>Br</td>
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<td>6b</td>
<td>I</td>
<td>CO2Et</td>
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<td>Br</td>
<td>CO2Me</td>
<td>H</td>
<td>7a</td>
<td>Br</td>
<td>CH2OH</td>
</tr>
<tr>
<td>5h</td>
<td>Br</td>
<td>CN</td>
<td>Me</td>
<td>7b</td>
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</tr>
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<td>5i</td>
<td>Br</td>
<td>CN</td>
<td>H</td>
<td>8</td>
<td>OMe</td>
<td>CH2Cl</td>
</tr>
</tbody>
</table>

Figure 2.1. Substituted 2,2':6',2''-terpyridines (5-8).
2.2 Results and Discussion

The 4-substituted 2-acetylypyridines (2a-c) were prepared via a radical carbonylation at the 2 position of 1a-c with 38-66% yields (Scheme 1). The low yields were a result of the by-products that formed via 2,6- and 2,5-diacetyl radical carbonylations on pyridine 1a-c. The initial well-known pyridinium iodide salts of 2-acetylpyridines (3a, 3c, and 3d; Scheme 2.1) were prepared according to literature procedures; whereas, the salt of 2-acetyl-4-cyanopyridine (3b) was prepared by the addition of 2b to dry pyridine and iodine to give (85%) the new pyridinium iodide salt (3b) of 2-acetyl-4-cyanopyridine. Support for the structure of salt 3b included appearance of peaks at 6.58 (COCH$_2$) and 66.4 (COCH$_2$) ppm in the $^1$H and $^{13}$C NMR, respectively, and an upfield shift of the COCH$_2$-pyridine resonance (198.1 → 190 ppm, $^{13}$C NMR) that agreed with that of similar conversions in the literature; a peak at $m/z = 224.0836$ [M – I]$^+$ in the HRMS spectrum also confirmed the transformation.

![Scheme 2.1](image_url)

Scheme 2.1. Preparation of the 4-substituted 2-acetylpyridines and their pyridinium iodide salts: i) H$_2$O/CH$_2$Cl$_2$, AgNO$_3$, MeCOCO$_2$H, H$_2$SO$_4$, (NH$_4$)$_2$S$_2$O$_8$, 3 h; ii) MeCN, paraldehyde, FeSO$_4$·7H$_2$O, TFA, t-BuOOH, 3 h; iii) I$_2$, pyridine, 3 h, N$_2$. 

152
The 4-R-2'-azachalcones (4a-f; Scheme 2.2) were prepared by a Claisen-Schmidt aldol condensation. Synthesis of the ester- and cyano-substituted 2'-azachalcones 4a, 4b, 4e, and 4f was achieved using microwave irradiation with little or no solvent in the presence of either acidic or basic Al₂O₃ as a catalyst and solid support.³³²,³³⁶ These protocols were employed instead of using NaOH due to potential side reactions, e.g., saponification. The reaction mixture of 4-R-benzaldehyde (R = Br, I, OMe) and ester 2a was heated to 60 °C; whereas, the cyano 2b was dissolved in a small amount (1-2 mL) of THF to obtain homogenous mixtures, then the addition of Al₂O₃ and microwave irradiation at 250 W for 15 minutes afforded (31-56%) the desired azachalcones 4a, 4b, 4e, and 4f.³³⁷,³³⁸ Methyl substituted 2'-azachalcone 4c was prepared by NaOH-promoted aldol condensation similar to the literature procedure for 4-bromo-2'-azachalcone (4d).³³⁹

Scheme 2.2. Preparation of 2'-azachalcones by Claisen-Schmidt aldol condensation: i) MeOH, 1 M NaOH, 1 h; ii) acidic Al₂O₃, MW 250 W, 60 °C, 15 min; iii) basic Al₂O₃, MW 250 W, THF (2 mL), 15 min.

Azachalcones 4a-f were characterized (¹H NMR) by the two doublets (7.78 – 8.24 ppm) assigned to COCHₐ=CHₖ with large coupling constants (Jₐₖ = 15.9 – 16.2 Hz) indicative of the trans double bond and a single carbonyl (¹³C NMR) resonance for such constructs in the range of 187.5 to 189.7 ppm.³³⁹ Spectral assignment of 4d agreed with
the literature assignments. \(^{43}\) HRMS spectra further confirmed the 4-R-2'-azachalcone structures with peaks at \(m/z = 367.9899\) \([M + Na]^+\) (4a), \(m/z = 334.9812\) \([M + Na]^+\) (4b), and \(m/z = 323.9992\) \([M + Na]^+\) (4c); \(m/z = 320.0891\) \([M + Na]^+\) (4e); and \(m/z = 415.9786\) \([M + Na]^+\) (4f); NaI was used in the positive ion mode.

The pyridinium iodide salts of the modified 2-acetylpyridines 3a-d were then reacted via Michael-type addition with the functionalized 4-R-2'-azachalcones 4a-f (R = Br, I, OMe) followed by ring-closure of the resulting diketone using ammonium acetate in either AcOH or MeOH to afford (33-73\%) the desired unsymmetric and symmetric 4'- (4-R-phenyl)-2,2';6',2''-terpyridines (5a-m; Scheme 2.3). Most of the reactions proceeded with higher yield in MeOH than AcOH due to potential side reactions of the substituents in an acidic and high temperature environment.

\[
\begin{align*}
4a: & \quad \text{Br} & \quad \text{CO}_2\text{Me} \\
4b: & \quad \text{Br} & \quad \text{CN} \\
4c: & \quad \text{Br} & \quad \text{Me} \\
4d: & \quad \text{Br} & \quad \text{H} \\
4e: & \quad \text{OMe} & \quad \text{CO}_2\text{Me} \\
4f: & \quad \text{I} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\begin{align*}
3a: & \quad R^3 = \text{CO}_2\text{Me} \\
3b: & \quad R^3 = \text{CN} \\
3c: & \quad R^3 = \text{Me} \\
3d: & \quad R^3 = \text{H}
\end{align*}
\]

\[
\begin{align*}
5a: & \quad \text{Br} & \quad \text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} & \quad (51\%) \\
5b: & \quad \text{Br} & \quad \text{CN} & \quad \text{CN} & \quad (48\%) \\
5c: & \quad \text{Br} & \quad \text{CO}_2\text{Me} & \quad \text{CN} & \quad (38\%) \\
5d: & \quad \text{Br} & \quad \text{CO}_2\text{Me} & \quad \text{Me} & \quad (39\%) \\
5e: & \quad \text{Br} & \quad \text{CO}_2\text{Me} & \quad \text{H} & \quad (37\%) \\
5f: & \quad \text{Br} & \quad \text{CN} & \quad \text{Me} & \quad (41\%) \\
5g: & \quad \text{Br} & \quad \text{CN} & \quad \text{H} & \quad (58\%) \\
5h: & \quad \text{Br} & \quad \text{Me} & \quad \text{H} & \quad (72\%) \\
5i: & \quad \text{OMe} & \quad \text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} & \quad (35\%) \\
5j: & \quad \text{I} & \quad \text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} & \quad (40\%)
\end{align*}
\]

Scheme 2.3. Preparation of 4,4''-functionalized 4'- (4-R)-2,2';6',2''-terpyridines by the Kröhnke method: i) MeOH, NH\(_4\)OAc, 8 h; or ii) AcOH, NH\(_4\)OAc, 6 h.

154
The dimethyl substituted terpyridines 5c and 5l were also prepared in an alternative route by addition of 2 equivalents of 4-methyl-2-acetylpyridine to 4-R-benzaldehyde (R = Br, OMe) in the presence of NaOH, forming diketone intermediates, which were not isolated. The ring closure of this intermediate was achieved via NH₄OAc in AcOH to give desired dimethyl terpyridines 5c and 5l with 35% and 38% yields, respectively (Scheme 2.4). A similar procedure was also utilized for the synthesis of 4'- (4-bromophenyl)-terpyridine (5d) with 55% yield (Scheme 2.4).

![Scheme 2.4. Preparation of 4,4''-functionalized 4'-(4-R-phenyl)-2,2';6',2''-terpyridines: i) MeOH, 1 M NaOH, 9 h; ii) AcOH, NH₄OAc, 8 h.](image)

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<tr>
<th>R¹</th>
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<th>Yield</th>
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<tr>
<td>5c: Br</td>
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<tr>
<td>5d: Br</td>
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<td>55%</td>
</tr>
<tr>
<td>5l: OMe</td>
<td>Me</td>
<td>38%</td>
</tr>
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</table>

Scheme 2.4. Preparation of 4,4''-functionalized 4'-(4-R-phenyl)-2,2';6',2''-terpyridines: i) MeOH, 1 M NaOH, 9 h; ii) AcOH, NH₄OAc, 8 h.

The poor solubility of dimethyl ester terpyridines 5a and 5m in common solvents (CHCl₃, CH₂Cl₂, THF, etc.) was improved by converting them to diethyl esters, as in 6a and 6b, respectively, via transesterification reaction in dry EtOH and HCl gas with high yields (> 90%, Scheme 5). The methoxycarbonyl groups in 5g and 5k were also reduced to alcohol groups, as in 7a and 7b, respectively, by using NaBH₄ in EtOH:THF mixture (1:3) in high yields (80-83%, Scheme 2.5). The alcohol-containing 7a and 7b were the least soluble compounds among 5-8 due to possible H-bonding of the OH groups.
Moreover, the diols in 7b were converted to CH₂Cl groups, as in 8, by refluxing with SOCl₂ in CH₂Cl₂ with 86% yield (Scheme 2.5).

Scheme 2.5. Further 4,4''-functionalization of 4'-{(4-R)-2,2';6',2''-terpyridines: i) EtOH, HCl (gas), 8 h; ii) NaBH₄, EtOH/THF, 10 h; iii) SOCl₂, CH₂Cl₂, 24 h.

The ¹H NMR spectra of the symmetric di-substituted 4'-{(4-R)-phenyl}terpyridines (5a, 5b, 5c, 5k, 5l, 5m, 6a, 6b, and 8) revealed downfield shifts for the 5,5''-pyrH, 3,3''-pyrH, and 6,6''-pyrH resonances for dimethyl ester 5a (7.93, 8.73, and 8.87 ppm), 5k (7.93, 8.74, and 8.89 ppm), and 5m (7.93, 8.74, and 8.88 ppm), diethyl ester 6a and 6b (7.93, 8.74, and 8.86 ppm), dicyano 5b (7.63, 8.89, and 8.92 ppm), and di(chloromethyl) 8 (7.43, 8.66, and 8.75 ppm) as well as upfield shifts for the same signals assigned to the dimethyl terpyridine 5c (7.19, 8.47, and 8.58 ppm) and 5l (7.18, 8.47, and 8.58 ppm) compared to known terpyridines, such as 5d₃₃⁹ (7.35, 8.66, and 8.72 ppm) and 4'-phenylterpyridine₃₄¹ (7.33, 8.68, and 8.74 ppm). Dimethylterpyridines 5c and 5l showed a similar ¹H NMR pattern as that of 4'-{(4-chlorophenyl)-4,4''-dimethylterpyridine, but in order to confirm the proper assignments 2D correlation (COSY) NMR experiments were
conducted. HRMS spectra also supported the structural assignments of the dimethyl ester 5a; m/z = 526.0375 [M + Na]⁺, dicyano 5b; m/z = 438.0364 [M + H]⁺, 460.0194 [M + Na]⁺, dimethyl 5c; m/z = 438.0582 [M + Na]⁺, dimethyl ester 5k; m/z = 456.1566 [M + H]⁺, dimethyl 5l; m/z = 390.1585 [M + Na]⁺, dimethyl ester 5m; m/z = 552.0411 [M + H]⁺, diethyl ester 6a; m/z = 532.0867 [M + H]⁺, diethyl ester 6b; m/z = 580.0731 [M + H]⁺, diol 7b; m/z = 400.1670 [M + H]⁺ and di(chloromethyl) 8; m/z = 436.0981 [M + H]⁺.

The ¹H NMR spectra of the unsymmetrical mono-substituted 4'-(4-bromophenyl) terpyridines (5g, 5i, 5j) show unique proton resonances for each pyridine ring due to the diminished symmetry. The 5-pyrH resonance (¹H NMR) of ester 5g, cyano 5i, and methyl 5j appears as a doublet, whereas the 5''-pyrH resonance appeared as a doublet of doublets due to a coupling (J₅',₆' = 7.5 Hz, J₅',₄' = 4.8 Hz) with the adjacent protons. Additionally, the 5-pyrH resonance shifted downfield for ester 5g (7.9 → 7.35 ppm) and cyano 5i (7.56 → 7.4 ppm) but upfield for the methyl construct 5j (7.21 → 7.38 ppm). The 3-pyrH resonance follows the same pattern; it shifts downfield for ester 5g (9.14 → 8.72 ppm) and cyano 5i (8.9 → 8.63 ppm) and upfield for methyl 5j (8.49 → 8.66 ppm) when compared to the 3''-pyrH resonance as well as changing from a singlet (3-pyrH) to doublet (3''-pyrH). Rationale for these shifts is rooted in the deshielding effect of the electron-withdrawing groups for ester 5g and cyano 5i and the shielding effect caused by the electron-donating methyl group in terpyridine 5j. These assignments have been confirmed by 2D correlation (COSY) NMR experiments. Furthermore, ¹H and 2D correlation (COSY) NMR (Figure 2.2) spectra of the mono-substituted 4'- (4-bromophenyl)terpyridines (5g, 5i, and 5j) revealed splitting of the singlet (3',5'-pyrH) in the symmetric terpyridines (5a, 5b, and 5c) resulting in two doublets with small meta
coupling constants \( J_{3',5'} = 1.5 \text{ Hz} \). The ester \textbf{5g} and methyl \textbf{5j} showed similar \(^1\text{H} \) NMR patterns as that of \( 4'-(p\text{-toluyl})\text{-}4\text{-}(\text{methoxycarbonyl})\text{terpyridine} \) and \( 4'-(4\text{-chlorophenyl})\text{-}4\text{-methylterpyridine} \) respectively. HRMS spectra also supported the structural assignments of ester \textbf{5g}, cyano \textbf{5i}, and methyl terpyridine \textbf{5j} with a peak at \( m/z = 468.0331 \text{ [M} + \text{Na}]^+ \), \( m/z = 435.0235 \text{ [M} + \text{Na}]^+ \), and \( m/z = 424.0424 \text{ [M} + \text{Na}]^+ \), respectively.

Figure 2.2. The 2D correlation (COSY) NMR of cyano \textbf{5i}.

The \(^1\text{H} \) NMR spectra of the unsymmetric \textit{di}-substituted \( 4'-(4\text{-bromophenyl})\text{-}\text{terpyridines} \textbf{(5e, 5f, 5h)} \) showed unique proton resonances for each pyridine ring similar to the above \textit{mono}-substituted counterparts. The 5-pyrH resonance shifts downfield in the cases of the ester-cyano \textbf{5e} (7.95 \( \rightarrow \) 7.61 ppm), ester-methyl \textbf{5f} (7.9 \( \rightarrow \) 7.2 ppm), and cyano-methyl \textbf{5h} (7.58 \( \rightarrow \) 7.25 ppm) when compared to 5''-pyrH and 3-pyrH resonances that show the same pattern; it shifts downfield for the ester-cyano \textbf{5e} (9.08 \( \rightarrow \) 8.9 ppm), ester-methyl \textbf{5f} (9.16 \( \rightarrow \) 8.5 ppm), and cyano-methyl \textbf{5h} (8.93 \( \rightarrow \) 8.47 ppm) when
compared to 3'-pyrH resonance. Furthermore, $^1$H and 2D correlation (COSY) NMR spectra of these unsymmetric compounds 5e, 5f, and 5h revealed splitting of the 3',5'-pyrH peaks in symmetric terpyridines (5a, 5b, and 5c) resulting in two doublets with small meta coupling constants ($J_{3',5'} = 1.5 – 2.1$ Hz). HRMS spectra also support the structural assignments of the terpyridines: 5e, $m/z = 493.0274 \ [M + Na]^+$; 5f, $m/z = 482.0471 \ [M + Na]^+$; and 5h, $m/z = 449.0384 \ [M + Na]^+$.

X-ray crystal structures of ester 4a and 4f and cyano azachalcone 4b (Figure 2.3-5) confirmed the proposed structures. The data showed that ester 4a, and 4f, and cyano azachalcones 4f crystallized in a monoclinic cell with $P2_1/n$ space group, and a triclinic cell with $P1$ space group, respectively (Table 2.1). The X-ray data of ester 4a, and 4f and cyano azachalcone 4b revealed a trans double bond configuration with bond lengths (Å) of $C(7)-C(8) = 1.312(5)$, 1.309(14), and 1.342(4), respectively, which is similar to that of the 2'-azachalcone$^{342}$ and chalcones$^{342,343}$ [1.321(2) – 1.329(4) Å]. Furthermore, C=O bond lengths (Å) of ester 4a, O(1)-C(9) = 1.224(4) Å, 4b, O(1)-C(9) = 1.219(3) Å, and azachalcone 4f, O(1)-C(9) = 1.233(12) Å, were in agreement with the literature.$^{342,343}$

![Figure 2.3. Single crystal X-ray structure of ester 4a.](image-url)
Table 2.1. Crystallographic and structure data.

<table>
<thead>
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<th>Compound</th>
<th>4a</th>
<th>4b</th>
<th>4f</th>
<th>5a</th>
<th>5c</th>
<th>5g</th>
<th>5j</th>
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<td>100(2)</td>
<td>100(2)</td>
<td>100(2)</td>
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<td>Monoclinic</td>
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<td>P2(1)/n</td>
<td>Cc</td>
<td>P2(1)/c</td>
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<td>P2(1)/c</td>
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Figure 2.4. Single crystal X-ray structure of cyano 4b.

Figure 2.5. Single crystal X-ray structure of ester 4f.

X-ray crystal data of the diester 5a, dimethyl 5c, ester 5g, and methyl 5j (Figure 2.6-9) confirm the proposed structures. The crystallographic and structural data were summarized in Table 2.1. The three pyridine rings showed a transoid arrangement about the interannular C–C bonds, which was also in agreement with the literature. This configuration minimizes electrostatic interactions between the nitrogen lone pairs and the van der Waals interactions between the meta protons. The interannular C–C bond lengths of 5a, 5c, 5g, and 5j [1.481(8) – 1.494(4) Å] are comparable with 2,2';6',2″-terpyridines [1.480(1) – 1.498(3) Å] found in the literature. Moreover, the three pyridine rings are not exactly coplanar and the torsion angles of two terminal rings with the central pyridine ring are 5.16 and 3.88° for diester 5a, 9.48 and 1.06° for methyl 5c,
2.65 and 3.05° for ester 5g, and 6.59 and 0.97° for methyl 5j which is comparable to 4'-phenylterpyridine \(^{341}\) (5.7°) and 4'-(4-anilino)terpyridine \(^{345}\) (2.7 and 7.4°). The 4'-bromo-phenyl ring connected to the terpyridine is distorted with torsion angles of 22.83° for diester 5a, 39° for dimethyl 5c, 27.48° for ester 5g, and 39.75° for methyl 5j, which is higher than that of 4'-phenylterpyridine \(^{341}\) (10.9°), yet comparable to 4'-(4-anilino)terpyridine \(^{345}\) (27.5°), and lower than that of 4'-(2,4,6-trimethylphenyl)-terpyridine \(^{347}\) (67.5°) and 4'-(2,5-dimethoxyphenyl)terpyridine \(^{348}\) (50.4°).

![Figure 2.6. Single crystal X-ray structure of diester 5a.](image)

![Figure 2.7. Single crystal X-ray structure of dimethyl 5c.](image)
Only the diester 5a crystal packing revealed π – π interactions (interlayer distances smaller than 3.5 Å). Molecules of diester 5a (approximately coplanar) are stacked by the overlap of the central pyridine rings in consecutive layers with mean interplanar distances of 3.4 Å in the solid state (Figure 2.10a), which is comparable to 4’-(dimethylamino)terpyridine (3.47 Å) and 4’-(4-anilino)terpyridine (3.5 Å). They
possess adjacent planes that are parallel to each other in a head-to-tail fashion (Figure 2.10b). Moreover, the central pyridine rings are slightly slipped with respect to each other to maximize $\pi - \pi$ interactions between the stacked pyridine rings.\textsuperscript{349}

![Figure 2.10.](image)

Figure 2.10. (a) Stacking of diester 5a in the crystal lattice with distances (Å) between central pyridine rings and (b) The orientation of diester 5a in adjacent planes in the lattice, viewing along $c$ axis. Hydrogen atoms are omitted for clarity.

2.3 Conclusion

Substituted 2'-azachalcones (4a, 4b, 4e, and 4f) were conveniently synthesized using microwave-assisted solid-state aldol condensation procedures. Symmetrical and unsymmetrical mono- and di-substituted 4'-(4-bromophenyl)terpyridines (5a-m) were constructed by utilizing the two-step Kröhnke\textsuperscript{44} methodology with pyridinium iodide salts of substituted 2-acetylpyridines (3a-d) and modified 4-bromo-2'-azachalcones (4a-f). The methyl ester 5a and 5m were transesterified to give ethyl ester 6a and 6b to improve their poor solubility. Moreover, those methyl ester groups in 5g and 5k were
reduced to alcohol groups, as in 7a and 7b, and the alcohol groups in 7b was transformed to CH2Cl groups, as in 8. X-ray crystal structures of ester 4a and 4f azachalcone 4b, diester 5a, dimethyl 5c, ester 5g, and methyl 5j, as well as solid-state crystal packing of diester terpyridine 5a were obtained.

2.4 Experimental Section

General Remarks: 1a, 1b, 1c, 2d, 4-bromobenzaldehyde, 4-anisaldehyde and all the other chemicals were purchased except for 2a, 2b, 2c, 2d, 2e, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h, 4i, 4j, 4k, and 4-lodobenzaldehyde, which were prepared according to literature. Activated basic and acidic Al2O3 (standard grade I, ~150 mesh, 58 Å) was purchased and dried in vacuo at 120 ºC prior to use. Tetrahydrofuran (THF) was refluxed over benzophenone/Na° under N2 prior to use. All other commercially available solvents were used without further purification. Column chromatography was conducted using activated basic Al2O3 (standard grade I, ~150 mesh, 58 Å) with the stipulated solvent mixture. Milestone microwave reactor was used for microwave-assisted reactions. Melting point data were obtained in capillary tubes with a melting point apparatus and are uncorrected. 1H (300 MHz), COSY and 13C (75 MHz) NMR spectra were obtained in CDCl3, except where noted. HRMS data were obtained using a mass spectrometer equipped with an orthogonal electrospray source (Z-spray) operated in positive ion mode. Sodium iodide was used for mass calibration for a calibration range of m/z 100 – 2000. Samples were prepared such that a few crystals/flakes/grains were dissolved in 10 µL CHCl3 then diluted in 90 µL MeOH. The sample solutions were infused into the electrospray source.
at a rate of 5-10 µL min⁻¹. Optimal ESI conditions were obtained as follows; capillary voltage was 3000 V, source temperature was 110 °C, a cone voltage was 55 V, and the ESI gas was nitrogen. HRMS data were acquired in continuum mode until acceptable averaged data were obtained. The data set to determine crystal structures was collected on a CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The reflections from three different orientations were used to determine the unit cell. Multi-scan SADABS was used to make corrections. SHELX TL computer program was used to solve structures, refine, and model. The structures were obtained by full-matrix least-squares refinement of \( F^2 \) and the selection of appropriate atoms from the generated difference map.

2-Acetyl-4-methoxycarbonylpyridine\(^{333} \) (2a). To a stirred solution of excess paraaldehyde (82 g, 620 mmol) and methyl isonicotinate (17.5 g, 127 mmol) in MeCN (260 mL) at 25 °C, FeSO\(_4\)·7H\(_2\)O (600 mg, 2.16 mmol), TFA (14.86 g, 130 mmol), and 70% t-BuOOH (32.42 g, 252 mmol) were added and the mixture was refluxed 4 h with vigorous stirring. The mixture was concentrated \textit{in vacuo} and the residue was suspended in water (100 mL), and then extracted with toluene (3×75 mL). The combined organic fractions were dried (MgSO\(_4\)) and the solvent was removed \textit{in vacuo}. The resulting brown oil was distilled under high vacuum. First run at 85 °C was discharged and second run was collected at 114 °C to give the product 2a, as white crystals upon cooling: 15 g (66%); mp 42-43 °C; \(^1\)H NMR \( \delta \) 2.70 (s, 3 H, pyrCOC\(_3\)H), 3.94 (s, 3 H, pyrCO\(_2\)C\(_3\)H), 7.97 (dd, 1 H, 5-pyrH, \( J_1 = 3.6 \) Hz, \( J_2 = 1.5 \) Hz), 8.49 (s, 1 H, 3-pyrH), 8.79 (d, 1 H, 6-pyrH, \( J = 4.8 \) Hz); \(^{13}\)C NMR \( \delta \) 26, 53, 121, 126.2, 138.7, 150, 154.6, 165.1, 199.3.
2-Acetyl-4-cyanopyridine\textsuperscript{334} (2b). To a stirring solution of 4-cyanopyridine (15.6 g, 150 mmol), AgNO\textsubscript{3} (2.04 g, 12 mmol), and pyruvic acid (40 g, 454 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (250 mL) and H\textsubscript{2}O (150 mL) at 0 °C, concentrated H\textsubscript{2}SO\textsubscript{4} (9 mL, 162 mmol), and (NH\textsubscript{4})\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (51.46 g, 225 mmol) in H\textsubscript{2}O (100 mL) were added successively drop wise. The mixture was warmed to 25 °C and then refluxed at 50 °C for 3 hours with vigorous stirring. Upon cooling, the layers were separated, and the aqueous layer was neutralized with aqueous Na\textsubscript{2}CO\textsubscript{3} (1.5 M, 120 mL), the neutralized aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3×100 mL). The combined organic fraction was dried (MgSO\textsubscript{4}) and the solvent was removed \textit{in vacuo}. The remaining residue was column chromatographed (SiO\textsubscript{2}) eluting with EtOAc/hexane mixture (1:4) to give the product 2b, as white solid: 14.2 g (65%); mp 101-102 °C; \textsuperscript{1}H NMR \(\delta\) 2.64 (s, 3 H, pyrCOCH\textsubscript{3}), 7.69 (dd, 1 H, 5-pyr\(\text{H}\), \(J\textsubscript{1}\) = 3.3 Hz, \(J\textsubscript{2}\) = 1.5 Hz), 8.15 (s, 1 H, 3-pyr\(\text{H}\)), 8.83 (d, 1 H, 6-pyr\(\text{H}\), \(J\) = 4.8 Hz); \textsuperscript{13}C NMR \(\delta\) 20.9, 25.5, 115.9, 121.6, 123.3, 128.2, 150.1, 154.2, 198.1. The product was contaminated with a small quantity (3%) of 2,6-diacetyl-4-cyanopyridine identified by additional \textsuperscript{1}H NMR signals at \(\delta\) 2.75 (s, 6 H, pyrCOCH\textsubscript{3}), 8.33 (s, 2 H, 3,5-pyr\(\text{H}\)).

2-Acetyl-4-methylpyridine (2c).\textsuperscript{334} To a stirring solution of 4-picoline (22 g, 236 mmol), AgNO\textsubscript{3} (2.637 g, 15.5 mmol), and pyruvic acid (54.25 g, 616 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (300 mL) and H\textsubscript{2}O (150 mL) at 0 °C, concentrated H\textsubscript{2}SO\textsubscript{4} (20 mL, 361 mmol), and (NH\textsubscript{4})\textsubscript{2}S\textsubscript{2}O\textsubscript{8} (70 g, 307 mmol) in H\textsubscript{2}O (150 mL) were added successively drop wise. The mixture was warmed to 25 °C and then refluxed at 50 °C for 3 hours with vigorous stirring. Upon cooling, the layers were separated, and the aqueous layer was washed with CH\textsubscript{2}Cl\textsubscript{2} (2×100 mL). The combined organic fraction was dried (MgSO\textsubscript{4}) and the solvent...
was removed *in vacuo*. The remaining brown oil was distilled under high vacuum. First run at 50 °C was discharged. Second run at 75 °C was collected to give the product 2c, as white crystals upon cooling: 12.2 g (38%); mp 31-32 °C; \(^1\)H NMR \(\delta\) 2.28 (s, 3 H, pyr\(CH_3\)), 2.57 (s, 3 H, pyrCO\(CH_3\)), 7.16 (d, 1 H, 5-pyr\(H\), \(J = 5.1\) Hz), 7.71 (s, 1 H, 3-pyr\(H\)), 8.39 (d, 1 H, 6-pyr\(H\), \(J = 4.8\) Hz); \(^{13}\)C NMR \(\delta\) 20.96, 25.79, 122.36, 127.88, 148.11, 148.75, 153.38, 200.18.

1-[2-(4-Methoxycarbonyl-2-pyridyl)-2-oxoethyl]pyridinium iodide (3a). To a stirred warmed solution of I\(_2\) (3 g, 11.8 mmol) in pyridine (55 mL) under N\(_2\), 2a (2.1 g, 11.7 mmol) was added and refluxed for 3 h. The reaction mixture was kept at 25 °C overnight. The precipitate was filtered and washed with CHCl\(_3\) (2×25 mL), and Et\(_2\)O (2×25 mL) and recrystallized from EtOH to give the product 3a, as a yellow powder: 2.7 g (60%); mp 207-208 °C; \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) 3.96 (s, 3 H, CO\(2CH_3\)), 6.53 (s, 2 H, CO\(CH_2\)), 8.24 (d, 1 H, 5-pyr\(H\), \(J = 3.6\) Hz), 8.29 (t, 2 H, 3',5'-pyr\(H\), \(J = 7.2\) Hz), 8.35 (s, 1 H, 3-pyr\(H\)), 8.75 (t, 1 H, 4'-pyr\(H\), \(J = 7.5\) Hz), 9.02 (d, 2 H, 2',6'-pyr\(H\), \(J = 6.0\) Hz), 9.11 (d, 1 H, 6-pyr\(H\), \(J = 5.1\) Hz); \(^{13}\)C NMR (DMSO-d\(_6\)) \(\delta\) 53.28, 66.67, 120.27, 124.96, 127.78, 138.66, 139.31, 146.33, 146.46, 147.31, 150.94, 164.32, 190.84.

1-[2-(4-Cyano-2-pyridyl)-2-oxoethyl]pyridinium iodide (3b). To a stirred warmed (60 °C) solution of I\(_2\) (4.68 g, 18.5 mmol) in pyridine (27 mL) under N\(_2\), 2b (2.7 g, 18.5 mmol) was added and stirred at 100 °C for 1 h. The crystals that formed upon cooling were filtered and washed with CHCl\(_3\) (2×25 mL) and Et\(_2\)O (2×25 mL) to give 3b, as green crystals: 5.5 g (85%); mp 226-227 °C; \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) 6.58 (s, 2 H, CO\(CH_2\)), 8.32 (m, 3 H, 5-pyr\(H\), 3',5'-pyr\(H\)), 8.45 (s, 1 H, 3-pyr\(H\)), 8.78 (t, 1 H, 4'-pyr\(H\), \(J = 6.0\) Hz).
= 7.8 Hz), 9.07 (d, 2 H, 2',6'-pyrH, J = 6.6 Hz), 9.12 (d, 1 H, 6-pyrH, J = 4.8 Hz); 13C NMR (DMSO-d6) δ 66.4, 116.9, 121.1, 123.7, 127.7, 130.4, 146.1, 146.4, 150.6, 151.2, 190; HRMS (calc.): m/z = 224.0824 (224.0836, [M – I]+).

1-(3-Oxo-3-[2-(4-methoxycarbonylpyridyl)propen-1-yl]-4-bromobenzene (4a). A neat, stirred mixture of 2a (550 mg, 3.07 mmol) and 4-bromobenzaldehyde (570 mg, 3.08 mmol) was heated to 60 ºC, then acidic Al₂O₃ (9.94 g) was added. The mixture was then irradiated in the microwave at 250 W for 15 min. After cooling, CHCl₃ (3×50 mL) was added and the mixture was filtered. The filtrate was concentrated in vacuo to give a solid, which was washed with MeOH (3×25 mL) to afford 4a, as light yellow solid: 580 mg (55%); mp 163-164 ºC; ¹H NMR δ 4.01 (s, 3 H, pyrCO₂CH₃), 7.57 (d, 2 H, 3,5-ArH, J = 8.7 Hz), 7.58 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.92 (d, 1 H, COCH=CH, J = 16.2 Hz), 8.05 (dd, 1 H, 5-pyrH, J₁ = 4.8 Hz, J₂ = 1.8 Hz), 8.25 (d, 1 H, COCH=CH, J = 15.9 Hz), 8.7 (s, 1 H, 3-pyrH), 8.88 (dd, 1 H, 6-pyrH, J₁ = 4.8 Hz, J₂ = 0.9 Hz); 13C NMR δ 53.1, 121.4, 122.4, 125.3, 126.2, 130.4, 132.4, 134.2, 139, 144, 150, 155.3, 165.3, 188.6; HRMS (calc.): m/z = 367.9898 (367.9899, [M + Na]+).

1-(3-Oxo-3-[2-(4-cyanopyridyl)propen-1-yl]-4-bromobenzene (4b). To a stirred solution of 4-bromobenzaldehyde (2.07 g, 11.2 mmol) and 2b (1.72 g, 11.8 mmol) in THF (2 mL) at 25 ºC, basic Al₂O₃ (15 g) was added quickly. The mixture was then irradiated in the microwave at 250 W for 15 min. After cooling, CHCl₃ (3×50 mL) was added and the mixture was filtered. The filtrate was concentrated in vacuo to give a solid, which was washed with MeOH (3×25 mL) to afford 4b, as light yellow solid: 1.92 g
171

1-(3-Oxo-3-[2-(4-methylpyridyl)]propen-1-yl)-4-bromobenzene (4c). To a stirring solution of 4-bromobenzaldehyde (1.02 g, 5.53 mmol) and 2c (760 mg, 5.57 mmol) in MeOH (25 mL) at 25 ºC, aqueous NaOH (1 M, 5 mL) was added. The mixture was stirred for 1 hour at 25 ºC and then filtered and washed with H2O (15 mL). The precipitate was dissolved in CH2Cl2 (150 mL) and extracted with H2O (2×100 mL). The combined organic fractions were dried (MgSO4) and concentrated in vacuo to give 4c, as light yellow solid: 1 g (60%); mp 123-125 ºC; 1H NMR δ 2.47 (s, 3 H, pyrCH3), 7.32 (d, 1 H, 5-pyrH, J = 4.8 Hz) 7.56 (d, 2 H, 3,5-ArH, J = 9 Hz), 7.59 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.88 (d, 1 H, COCH=CH, J = 16.2 Hz), 8.03 (s, 1 H, 3-pyrH), 8.27 (d, 1 H, COCH=CH, J = 16.2 Hz), 8.6 (d, 1 H, 6-pyrH, J = 4.8 Hz); 13C NMR δ 21.3, 121.9, 124, 125, 128.1, 130.3, 132.3, 134.3, 143.3, 148.6, 148.9, 154.1, 189.7; HRMS (calc.): m/z = 324.0000 (323.9992, [M + Na]+).

1-(3-Oxo-3-[2-(4-methoxycarbonylpyridyl)]propen-1-yl)-4-methoxybenzene (4e). A neat, stirred mixture of 2a (3.6 g, 20 mmol) and 4-methoxybenzaldehyde (2.72 g, 19.9 mmol) was heated to 60 ºC, then acidic Al2O3 (9.94 g) was added. The mixture was then irradiated in the microwave at 250 W for 15 min. After cooling, CHCl3 (3×50 mL) was
added and the mixture was filtered. The filtrate was concentrated *in vacuo* to give a solid, which was washed with MeOH (3×25 mL) to afford **4e**, as light yellow solid: 2.1 g (35%); mp 148-149 °C; ¹H NMR δ 3.84 (s, 3 H, ArOCH₃), 3.98 (s, 3 H, pyrCO₂CH₃), 6.93 (d, 2 H, 3,5-ArH, J = 8.7 Hz), 7.68 (d, 2 H, 2,6-ArH, J = 8.7 Hz), 7.95 (d, 1 H, COCH=CH, J = 15.9 Hz), 8.01 (dd, 1 H, 5-pyrH, J₁ = 5.1 Hz, J₂ = 1.8 Hz), 8.11 (d, 1 H, COCH=CH, J = 15.9 Hz), 8.67 (s, 1 H, 3-pyrH), 8.87 (dd, 1 H, 6-pyrH, J₁ = 4.8 Hz, J₂ = 0.6 Hz); ¹³C NMR δ 53.03, 55.55, 114.54, 118.30, 122.24, 125.86, 127.96, 130.89, 138.78, 145.41, 149.80, 155.60, 162.04, 165.31, 188.60; HRMS (calc.): m/z = 320.0899 (320.0891, [M + Na]⁺).

1-(3-Oxo-3-[2-(4-methoxycarbonylpyridyl)]propen-1-yl)-4-iodobenzene (**4f**). A neat, stirred mixture of **2a** (7.81 g, 43.6 mmol) and 4-iodobenzaldehyde (10.12 g, 43.6 mmol) was heated to 60 °C, then acidic Al₂O₃ (9.94 g) was added. The mixture was then irradiated in the microwave at 250 W for 15 min. After cooling, CHCl₃ (4×100 mL) was added and the mixture was filtered. The filtrate was concentrated *in vacuo* to give a solid, which was washed with MeOH (4×50 mL) to afford **4f**, as light yellow solid: 5.24 g (31%); mp 175-176 °C; ¹H NMR δ 3.99 (s, 3 H, pyrCO₂CH₃), 7.44 (d, 2 H, 3,5-ArH, J = 8.4 Hz), 7.73 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.88 (d, 1 H, COCH=CH, J = 15.9 Hz), 8.04 (dd, 1 H, 5-pyrH, J₁ = 4.8 Hz, J₂ = 1.8 Hz), 8.24 (d, 1 H, COCH=CH, J = 15.9 Hz), 8.67 (s, 1 H, 3-pyrH), 8.87 (dd, 1 H, 6-pyrH, J₁ = 4.8 Hz, J₂ = 0.9 Hz); ¹³C NMR δ 53.12, 97.37, 121.29, 122.38, 126.18, 130.42, 134.63, 138.31, 138.92, 144.13, 149.91, 155.14, 165.2, 188.54; HRMS (calc.): m/z = 415.9760 (415.9786, [M + Na]⁺).
General Procedures for Preparation of 4'- (4-R-phenyl)-2,2';6',2''-terpyridines.

Route A: To a stirred solution of pyridinium iodide salt of substituted 2-acetylpyridines 3 and the modified 2'-azachalcones 4 in MeOH or EtOH, excess NH$_4$OAc was added and the mixture was refluxed overnight. The precipitate, which formed upon cooling, was filtered and washed with MeOH. The precipitate collected from filtration was column chromatographed (basic Al$_2$O$_3$) eluting with CHCl$_3$ to give the product.

Route B: To a stirred solution of pyridinium iodide salt of substituted 2-acetylpyridines 3 and the modified 2'-azachalcones 4 in AcOH, excess NH$_4$OAc was added and the mixture refluxed overnight. Solution was concentrated in vacuo to give a paste, which was neutralized with Na$_2$CO$_3$ (1 M) and extracted with CHCl$_3$. Organic layers were combined, dried (MgSO$_4$), and then the solvent was removed in vacuo to give a residue that was column chromatographed (basic Al$_2$O$_3$) eluting with EtOAc/hexane mixture (1:1) to give the product.

Route C: To a stirred solution of 2-acetylpyridines 2 and the aldehydes in MeOH or EtOH, 1 M NaOH was added and the mixture was stirred at 25 °C overnight. Solution was concentrated in vacuo to give the diketone intermediate, which was dried in vacuo. This intermediate was refluxed with excess NH$_4$OAc in AcOH for 12 h to afford the terpyridines. Purification of these terpyridines was achieved as in Route B.

4'- (4-Bromophenyl)-4,4''-dimethoxycarbonyl-2,2';6',2''-terpyridine (5a). To a stirred solution of 3a (1.1 g, 3.2 mmol) and 4a (1.22 g, 3.2 mmol) in MeOH (30 mL), excess NH$_4$OAc (8 g, 104 mmol) via Route A, the product 5a, was isolated as a light yellow solid: 820 mg (51%); mp 280-281 °C; $^1$H NMR $\delta$ 4.06 (s, 6 H, tpyCO$_2$CH$_3$), 7.67
(d, 2 H, 3,5-ArH, J = 8.4 Hz), 7.76 (d, 2 H, 2,6-ArH, J = 8.7 Hz), 7.93 (dd, 2 H, 5,5''-tpyH, J1 = 4.8 Hz, J2 = 1.5 Hz), 8.73 (s, 2 H, 3,3''-tpyH), 8.87 (d, 2 H, 6,6''-tpyH, J = 4.8 Hz), 9.18 (s, 2 H, 3',5'-tpyH); 13C NMR δ 53, 119.5, 121.1, 123.3, 123.9, 129.1, 132.5, 137.4, 138.8, 149.5, 150.1, 155.9, 157.3, 166; HRMS (calc.): m/z = 526.0378 (526.0375, [M + Na]+).

4''-(4-Bromophenyl)-4,4''-dicyano-2,2';6',2''-terpyridine (5b). To a stirred solution of 3b (1.5 g, 4.8 mmol) and 4b (1.69 g, 4.8 mmol) in AcOH (30 mL), excess NH4OAc (10 g) via Route B, the product 5b was isolated as a white solid: 1 g (48%); mp 342-343 °C; 1H NMR δ 7.63 (dd, 2 H, 5,5''-pyrH, J1 = 5.1 Hz, J2 = 1.8 Hz), 7.7 (d, 2 H, 3,5-ArH, J = 8.7 Hz), 7.75 (d, 2 H, 2,6-ArH, J = 8.7 Hz), 8.8 (s, 2 H, 3',5'-pyrH), 8.89 (dd, 2 H, 3,3''-pyrH, J1 = 1.5 Hz, J2 = 0.9 Hz), 8.92 (dd, 2 H, 6,6''-pyrH, J1 = 5.1 Hz, J2 = 0.9 Hz); HRMS (calc.): m/z = 438.0364 (438.0354, [M + H] +) and 460.0194 (460.0174, [M + Na]+).

4''-(4-Bromophenyl)-4,4''-dimethyl-2,2';6',2''-terpyridine (5c). To a stirred solution of 2c (1 g, 7.4 mmol) and 4-bromobenzaldehyde (660 mg, 3.57 mmol) in EtOH (150 mL), 1 M NaOH (8 mL, 8 mmol), and then AcOH (60 mL), excess NH4OAc (18 g) via Route C, the product 5c was isolated as a white solid: 520 mg (35%); mp 257-258 °C; 1H NMR δ 2.53 (s, 6 H, pyrCH3), 7.19 (d, 2 H, 5,5''-pyrH, J = 4.8 Hz), 7.64 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.76 (d, 2 H, 3,5-ArH, J = 7.8 Hz), 8.47 (s, 2 H, 3,3''-pyrH), 8.58 (d, 2 H, 6,6''-pyrH, J = 5.1 Hz), 8.68 (s, 2 H, 3',5'-pyrH); 13C NMR δ 21.6, 119.9, 122.3, 123.6,
125.1, 129.1, 132.3, 137.7, 148.3, 149.1, 149.2, 156.1, 156.5; H HRMS (calc.): \( m/z = 438.0582 \) (438.0582, [M + Na]+).

4'-(4-Bromophenyl)-4-methoxycarbonyl-4''-cyano-2,2';6',2''-terpyridine (5e). To a stirred solution of 3b (469 mg, 1.33 mmol) and 4a (462 mg, 1.33 mmol) in MeOH (20 mL), excess NH₄OAc (3.47 g) via Route A, the product 5e was isolated as a white solid: 240 mg (38%); mp 253-254 °C; \(^1\)H NMR \( \delta 4.08 \) (s, 3 H, pyrCO\( _2CH_3 \)), 7.61 (dd, 1 H, 5'-pyr\( H \), \( J_1 = 3.3 \) Hz, \( J_2 = 1.5 \) Hz), 7.68 (d, 2 H, 3,5-Ar\( H \), \( J = 8.7 \) Hz), 7.75 (d, 2 H, 2,6-Ar\( H \), \( J = 8.7 \) Hz), 7.95 (dd, 1 H, 5'-pyr\( H \), \( J_1 = 3.3 \) Hz, \( J_2 = 1.8 \) Hz), 8.74 (d, 1 H, 5'-pyr\( H \), \( J = 1.8 \) Hz), 8.78 (d, 1 H, 3'-pyr\( H \), \( J = 1.8 \) Hz), 8.9 (m, 3 H, 6,6'',3''-pyr\( H \)), 9.08 (dd, 1 H, 3-pyr\( H \), \( J_1 = 0.9 \) Hz, \( J_2 = 0.6 \) Hz); \(^{13}\)C NMR \( \delta 53.1, 117, 119.4, 120, 120.7, 121.7, 123.36, 123.45, 124.1, 125.3, 128.9, 132.5, 137, 138.9, 149.6, 150.2, 154.5, 156, 156.8, 157.4, 170; HRMS (calc.): \( m/z = 493.0274 \) (493.0276, [M + Na]+).

4'-(4-Bromophenyl)-4-methoxycarbonyl-4''-methyl-2,2';6',2''-terpyridine (5f). To a stirred solution of 3a (383 mg, 1 mmol) and 4c (303 mg, 1 mmol) in MeOH (16 mL), excess NH₄OAc (3 g) via Route A, the product 5f was isolated as a white solid: 180 mg (39%); mp 203-204 °C; \(^1\)H NMR \( \delta 2.54 \) (s, 3 H, pyr\( CH_3 \)), 4.05 (s, 3 H, pyr\( CO_2CH_3 \)), 7.2 (d, 1 H, 5''-pyr\( H \), \( J = 4.8 \) Hz), 7.66 (d, 2 H, 3,5-Ar\( H \), \( J = 8.7 \) Hz), 7.76 (d, 2 H, 2,6-Ar\( H \), \( J = 8.7 \) Hz), 7.9 (dd, 1 H, 5'-pyr\( H \), \( J_1 = 5.1 \) Hz, \( J_2 = 1.5 \) Hz), 8.5 (s, 1 H, 3''-pyr\( H \)), 8.58 (d, 1 H, 6''-pyr\( H \), \( J = 4.8 \) Hz), 8.69 (d, 1 H, 5'-pyr\( H \), \( J = 2.1 \) Hz), 8.72 (d, 1 H, 3'-pyr\( H \), \( J = 1.5 \) Hz), 8.86 (d, 1 H, 6-pyr\( H \), \( J = 5.1 \) Hz), 9.16 (s, 1 H, 3-pyr\( H \)); \(^{13}\)C NMR \( \delta 21.5, 52.9, 118.7, 119.2, 120.8, 122.3, 122.9, 123.7, 125.1, 128.9, 132.2, 137.3, 138.5, 148.2, 148.9, 175
4′-(4-Bromophenyl)-4-methoxycarbonyl-2,2′;6′,2″-terpyridine (5g). To a stirred solution of 3d (496 mg, 1.52 mmol) and 4a (526 mg, 1.52 mmol) in MeOH (25 mL), excess NH₄OAc (4.41 g) via Route A, the product 5g was isolated as a white solid: 250 mg (37%); mp 173-174 °C; ¹H NMR δ 4.04 (s, 3 H, pyrCO₂CH₃), 7.35 (dd, 1 H, 5″-pyrH, J₁ = 7.5 Hz, J₂ = 4.8 Hz), 7.65 (d, 2 H, 3,5-ArH, J = 8.4 Hz), 7.76 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.9 (m, 2 H, 5,4″-pyrH), 8.72 (m, 4 H, 3′,5′,3″,6″-pyrH), 8.84 (d, 1 H, 6-pyrH, J = 5.1 Hz), 9.14 (s, 1 H, 3-pyrH); ¹³C NMR δ 52.9, 118.8, 119, 120.8, 121.7, 123, 123.8, 124.2, 129, 132.3, 137.1, 137.4, 138.6, 149.16, 149.27, 150, 155.4, 155.9, 156.4, 157.4, 166; HRMS (calc.): m/z = 468.0331 (468.0323, [M + Na]⁺).

4′-(4-Bromophenyl)-4-cyano-4″-methyl-2,2′;6′,2″-terpyridine (5h). To a stirred solution of 3b (433 mg, 1.43 mmol) and 4c (504 mg, 1.44 mmol) in EtOH (20 mL), excess NH₄OAc (3.1 g) via Route A, the product 5h was isolated as a white solid: 250 mg (41%); mp 265-266 °C; ¹H NMR δ 2.58 (s, 3 H, pyrCH₃), 7.25 (d, 1 H, 5″-pyrH, J = 4.8 Hz), 7.58 (dd, 1 H, 5-pyrH, J₁ = 5.1 Hz, J₂ = 2.4 Hz), 7.66 (d, 2 H, 3,5-ArH, J = 8.7 Hz), 7.76 (d, 2 H, 2,6-ArH, J = 9 Hz), 8.47 (d, 1 H, 3″-pyrH, J = 0.9 Hz), 8.61 (d, 1 H, 6″-pyrH, J = 5.1 Hz), 8.71 (d, 1 H, 5′-pyrH, J = 1.8 Hz), 8.8 (d, 1 H, 3′-pyrH, J = 1.5 Hz), 8.89 (dd, 1 H, 6-pyrH, J₁ = 5.1 Hz, J₂ = 1.2 Hz), 8.93 (dd, 1 H, 3-pyrH, J₁ = 0.9 Hz, J₂ = 0.6 Hz); ¹³C NMR δ 21.7, 117.1, 118.9, 120.1, 121.6, 122.4, 123.4, 124, 125.1, 125.5, 176
4'-(4-Bromophenyl)-4-cyano-2,2';6',2''-terpyridine (5i). To a stirred solution of 3d (748 mg, 2.6 mmol) and 4b (975 mg, 2.76 mmol) in AcOH (7 mL), excess NH₄OAc (5 g) via Route B, the product 5i was isolated as a white solid: 620 mg (58%); mp 242-243 °C; ¹H NMR δ 7.4 (dd, 1 H, 5''-pyrH, J₁ = 7.5 Hz, J₂ = 4.8 Hz), 7.56 (dd, 1 H, 5-pyrH, J₁ = 4.8 Hz, J₂ = 1.5 Hz), 7.66 (d, 2 H, 3,5-ArH, J = 8.4 Hz), 7.73 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.94 (td, 1 H, 4''-pyrH, J₁ = 7.8 Hz, J₂ = 1.8 Hz), 8.63 (d, 1 H, 3''-pyrH, J = 7.8 Hz), 8.68 (d, 1 H, 3'-pyrH, J = 1.5 Hz), 8.73 (d, 1 H, 6''-pyrH, J = 4.8 Hz), 8.76 (d, 1 H, 5'-'pyrH, J = 1.5 Hz), 8.88 (d, 1 H, 6-pyrH, J = 4.8 Hz), 8.9 (s, 1 H, 3-pyrH); ¹³C NMR δ 117.1, 118.9, 119.8, 121.6, 122.3, 123.6, 124, 124.4, 125, 129, 132.5, 137.2, 137.3, 149.4, 149.6, 150.2, 154.2, 155.7, 156.7, 157.6; HRMS (calc.): m/z = 435.0235 (435.0221, [M + Na]+).

4'- (4-Bromophenyl)-4-methyl-2,2';6',2''-terpyridine (5j). To a stirred solution of 3c (480 mg, 1.59 mmol) and 4d (520 mg, 1.59 mmol) in AcOH (20 mL), excess NH₄OAc (2.86 g) via Route B, the product 5j was isolated as a white solid: 460 mg (72%); mp 203-204 °C; ¹H NMR δ 2.52 (s, 3 H, pyrCH₃), 7.21 (d, 1 H, 5-pyrH, J = 5.1 Hz), 7.38 (dd, 1 H, 5''-pyrH, J₁ = 7.5 Hz, J₂ = 4.8 Hz), 7.65 (d, 2 H, 3,5-ArH, J = 8.7 Hz), 7.77 (d, 2 H, 2,6-ArH, J = 8.7 Hz), 7.93 (td, 1 H, 4''-pyrH, J₁ = 7.5 Hz, J₂ = 2.4 Hz), 8.49 (s, 1 H, 3-pyrH), 8.6 (d, 1 H, 6-pyrH, J = 4.8 Hz), 8.66 (m, 3 H, 3',5',3''-pyrH), 8.74 (d, 1 H, 6''-pyrH, J = 4.8 Hz); ¹³C NMR δ 21.6, 118.7, 118.9, 121.6, 122.3, 123.6, 124.1, 125.1, 177
4'- (4-Methoxyphenyl)-4,4''-dimethoxycarbonyl-2,2';6',2''-terpyridine (5k). To a stirred solution of salt 3a (2.1 g, 5.47 mmol) and 2'-azachalcone 4e (1.6 g, 5.38 mmol) in MeOH (30 mL), excess NH₄OAc (8 g, 104 mmol) via Route A, the product 5k was isolated as a light yellow solid: 850 mg (35%); mp 253-254 °C; ¹H NMR δ 3.90 (s, 3 H, ArOC₃H₃), 4.06 (s, 6 H, tpyCO₂CH₃), 7.06 (d, 2 H, 3,5-ArH, J = 8.7 Hz), 7.89 (d, 2 H, 2,6-ArH, J = 9.0 Hz), 7.93 (dd, 2 H, 5,5''-tpyH, J₁ = 5.1 Hz, J₂ = 1.8 Hz), 8.74 (s, 2 H, 3,3''-tpyH), 8.89 (d, 2 H, 6,6''-tpyH, J = 5.1 Hz), 9.18 (s, 2 H, 3',5'-tpyH); HRMS (calc.): m/z = 456.1566 (456.1559, [M + H]+).

4'- (4-Methoxyphenyl)-4,4''-dimethyl-2,2';6',2''-terpyridine (5l). To a stirred solution of 2c (4.3 g, 31.4 mmol) and 4-methoxybenzaldehyde (2.1 mg, 15.4 mmol) in EtOH (400 mL), 1 M NaOH (31 mL, 31 mmol), and then AcOH (120 mL), excess NH₄OAc (40 g) via Route C, the product 5l was isolated as a white solid: 2.14 g (38%); mp 234-235 °C; ¹H NMR δ 2.51 (s, 6 H, pyrCH₃), 3.87 (s, 3 H, Ar-OCH₃), 7.01 (dd, 2 H, 2,6-ArH, J₁ = 6.9 Hz, J₂ = 2.1 Hz), 7.18 (d, 2 H, 5,5''-pyrH, J = 4.2 Hz), 7.89 (dd, 2 H, 3,5-ArH, J₁ = 6.9 Hz, J₂ = 2.1 Hz), 8.47 (s, 2 H, 3,3''-pyrH), 8.58 (d, 2 H, 6,6''-pyrH, J = 5.1 Hz), 8.69 (s, 2 H, 3',5'-pyrH); ¹³C NMR δ 21.6, 55.5, 114.5, 118.7, 122.4, 125, 128.7, 130.9, 148.4, 149, 149.9, 156.1, 156.3, 160.7; HRMS (calc.): m/z = 390.1585 (390.1582, [M + Na]+).
4'-((4-Iodophenyl)-4,4''-di(methoxycarbonyl)-2,2';6',2''-terpyridine (5m). To a stirred solution of iodopyridinium salt of substituted 2-acetylpyridine 3a (4.48 g, 11.7 mmol) and the modified 2'-azachalcone 4f (4.58 g, 11.6 mmol) in MeOH (30 mL), excess NH₄OAc (8 g, 104 mmol) via Route A, the product 5m was isolated as a light yellow solid: 2.57 g (40%); mp 281-282 ºC; ¹H NMR δ 4.06 (s, 6 H, tpyCO₂CH₃), 7.66 (d, 2 H, 3,5-ArH, J = 8.7 Hz), 7.86 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.93 (dd, 2 H, 5,5''-tpyH, J₁ = 4.8 Hz, J₂ = 1.8 Hz), 8.74 (s, 2 H, 3,3''-tpyH), 8.88 (d, 2 H, 6,6''-tpyH, J = 5.1 Hz), 9.18 (s, 2 H, 3',5'-tpyH); HRMS (calc.): m/z = 552.0411 (552.0420, [M + H]⁺).

4'-((4-Bromophenyl)-4,4''-di(ethoxycarbonyl)-2,2';6',2''-terpyridine (6a). To a stirred solution of dimethyl ester 5a (250 mg, 11.7 mmol) in EtOH (30 mL), HCl gas was bubbled and the mixture was refluxed overnight. After the solution was concentrated in vacuo, the residue was neutralized with Na₂CO₃ (1 M) and extracted with CHCl₃. Organic layers were combined, dried (MgSO₄), then the solvent was evaporated in vacuo to give a residue that was column chromatographed (basic Al₂O₃) eluting with CHCl₃ to give 6a, was isolated as light yellow solid: 248 mg (94%); mp 252-253 ºC; ¹H NMR δ 1.5 (t, 6 H, tpyCO₂CH₂CH₃, J = 7.2 Hz), 4.52 (q, 4 H, tpyCO₂CH₂CH₃, J = 7.2 Hz), 7.67 (d, 2 H, 3,5-ArH, J = 8.1 Hz), 7.86 (d, 2 H, 2,6-ArH, J = 8.1 Hz), 7.92 (dd, 2 H, 5,5''-tpyH, J₁ = 4.8 Hz, J₂ = 1.5 Hz), 8.73 (s, 2 H, 3,3''-tpyH), 8.88 (d, 2 H, 6,6''-tpyH, J = 4.8 Hz), 9.18 (s, 2 H, 3',5'-tpyH); HRMS (calc.): m/z = 532.0867 (532.0872, [M + H]⁺).

4'-((4-Iodophenyl)-4,4''-di(ethoxycarbonyl)-2,2';6',2''-terpyridine (6b). To a stirred solution of dimethyl ester 5m (2.48 g, 11.7 mmol) in EtOH (100 mL), HCl gas was
bubbled and the mixture was refluxed overnight. Solution was concentrated \textit{in vacuo} to give a residue, which was neutralized with Na$_2$CO$_3$ (1 M) and extracted with CHCl$_3$. Organic layers were combined, dried (MgSO$_4$) and then the solvent was evaporated \textit{in vacuo} to give a residue that was column chromatographed (basic Al$_2$O$_3$) eluting with CHCl$_3$ to give 6b, as light yellow solid: 2.4 g (92%); \textit{mp} 230-231 °C; \textit{^1}H NMR $\delta$ 1.5 (t, 6 H, tpyCO$_2$CH$_2$CH$_3$, $J$ = 7.2 Hz), 4.52 (q, 4 H, tpyCO$_2$CH$_2$CH$_3$, $J$ = 7.2 Hz), 7.66 (d, 2 H, 3,5-ArH, $J$ = 8.1 Hz), 7.85 (d, 2 H, 2,6-ArH, $J$ = 8.1 Hz), 7.93 (dd, 2 H, 5,5''-tpyH, $J_1$ = 4.8 Hz, $J_2$ = 1.5 Hz), 8.74 (s, 2 H, 3',5'-tpyH), 8.86 (d, 2 H, 6,6''-tpyH, $J$ = 4.8 Hz), 9.2 (s, 2 H, 3,3''-tpyH); $^{13}$C NMR $\delta$ 14.48, 62.08, 95.72, 119.32, 121.1, 123.31, 129.22, 137.92, 138.41, 139.22, 149.6, 150.05, 155.8, 157.18, 165.46; HRMS (calc.): $m/z$ = 580.0731 (580.0733, [M + H$^+$]).

4'-(4-Bromophenyl)-4-hydroxymethyl-2,2';6',2''-terpyridine (7a). To a stirred solution of 5g (291 mg, 650 µmol) in EtOH (10 mL) and THF (30 mL), excess NaBH$_4$ (64 mg, 1.69 mmol) was added and the mixture was refluxed overnight. Solution was concentrated \textit{in vacuo} and washed with H$_2$O to give the product 7a, as a light yellow solid: 218 mg (80%); \textit{mp} 233-234 °C; \textit{^1}H NMR (DMSO-$d_6$) $\delta$ 4.71 (s, 4 H, tpyCH$_2$OH), 5.59 (t, 2 H, tpyCH$_2$OH), 7.45 (d, 1 H, 5''-pyrH, $J$ = 4.5 Hz), 7.52 (t, 1 H, 5-pyrH, $J$ = 6.0 Hz), 7.76 (d, 2 H, 3,5-ArH, $J$ = 7.5 Hz), 7.76 (d, 2 H, 2,6-ArH, $J$ = 7.5 Hz), 8.06 (t, 1 H, 4''-pyrH, $J$ = 4.8 Hz), 8.72 (m, 5 H, 3',5',3,3'',6''-pyrH), 8.77 (d, 1 H, 6-pyrH, $J$ = 5.1 Hz); $^{13}$C NMR $\delta$ ; HRMS (calc.): $m/z$ = 440.0365 (440.0374, [M + Na$^+$]).
4’-(4-Methoxyphenyl)-4,4″-di(hydroxymethyl)-2,2';6',2″-terpyridine (**7b**). To a stirred solution of **5k** (523 mg, 1.15 mmol) in EtOH (15 mL) and THF (50 mL), excess NaBH₄ (200 mg, 5.3 mmol) was added and the mixture was refluxed overnight. Solution was concentrated *in vacuo* and washed with H₂O to give the product **7b**, as white a solid: 380 mg (83%); mp 267-268 °C; ¹H NMR (DMSO-**d₆**) δ 3.85 (s, 3 H, ArOC₃H₃), 4.72 (d, 4 H, tpyCH₂OH, J = 5.4 Hz), 5.59 (t, 2 H, tpyCH₂OH, J = 5.7 Hz) 7.15 (d, 2 H, 3,5-ArH, J = 9.0 Hz), 7.47 (d, 2 H, 5,5″-tpyH, J = 4.5 Hz), 7.90 (d, 2 H, 2,6-ArH, J = 8.7 Hz), 8.58 (s, 2 H, 3,3″-tpyH), 8.68 (s, 2 H, 3′,5′-tpyH), 8.69 (d, 2 H, 6,6″-tpyH, J = 4.8 Hz); ¹³C NMR (DMSO-**d₆**) δ 55.31, 61.81, 114.79, 117.50, 118.07, 121.78, 128.20, 129.61, 148.85, 149.11, 152.91, 154.94, 155.81, 160.43; HRMS (calc.): m/z = 400.1670 (400.1661, [M + H]⁺).

4’-(4-Methoxyphenyl)-4,4″-di(chloromethyl)-2,2';6',2″-terpyridine (**8**). To a stirred suspension of **7b** (320 mg, 0.8 mmol) in CH₂Cl₂ (15 mL), SOCl₂ (285 mg, 2.4 mmol) was added and the mixture was refluxed overnight. Solvent was evaporated *in vacuo* to give a residue that was column chromatographed (basic Al₂O₃) eluting with CHCl₃ to give the product **8**, as a yellow solid: 290 mg (83%); mp 208-209 °C; ¹H NMR δ 3.89 (s, 3 H, ArOCH₃), 4.74 (s, 4 H, pyrCH₂Cl), 7.04 (dd, 2 H, 2,6-ArH, J₁ = 6.9 Hz, J₂ = 1.8 Hz), 7.43 (dd, 2 H, 5,5″-pyrH, J₁ = 4.8 Hz, J₂ = 1.5 Hz), 7.88 (dd, 2 H, 3,5-ArH, J₁ = 6.9 Hz, J₂ = 2.1 Hz), 8.66 (s, 2 H, 3,3″-pyrH), 8.72 (s, 2 H, 3′,5′-pyrH), 8.75 (d, 2 H, 6,6″-pyrH, J = 5.1 Hz); ¹³C NMR δ 44.6, 55.6, 114.6, 119.2, 120.9, 123.3, 128.8, 130.5, 147.5, 149.6, 150.2, 155.3, 156.6, 160.9; HRMS (calc.): m/z = 436.0981 (436.0983, [M + H]⁺).
CHAPTER III

MISCELLANEOUS BY-PRODUCTS OF KRÖHNKE

4’-(4-R-PHENYL)-2,2’:6’,2”-TEPYRIDINE SYNTHESIS

3.1 Introduction

The growing interest in terpyridine transition metal complexes as a building block for supramolecular architectures has stimulated the synthesis and functionalization of novel terpyridine ligands.\textsuperscript{41} One particular class of these ligands that are widely used due to their facile functionalization is that of the 4’-arylterpyridines, which were prepared via Kröhnke\textsuperscript{44} method (Scheme 3.1). In Route A, benzaldehydes were reacted with one equivalent of 2-acetylpyridine to form the enone 1, which was treated with the iodopyridinium salt of 2-acetylpyridine, NH\textsubscript{4}OAc, and AcOH to afford the terpyridines as well as green or blue by-products, which have been identified as indolizinium salts.\textsuperscript{352,353} In Route B, two equivalents of 2-acetylpyridine were reacted with benzaldehydes to give the 1,5-diketone 2, which was treated with NH\textsubscript{4}OAc and AcOH to obtain desired terpyridines.\textsuperscript{46-48} The formation of the enone and diketone was achieved in a strong basic media (2 M NaOH) as well as allowing further condensation of the enone and diketone to give cyclohexanol or cyclohexanediol by-products in < 30% yield.\textsuperscript{354-356}
Scheme 3.1. Synthesis of 4'-aryl-terpyridines by a modified Kröhnke\textsuperscript{44} method.

In this chapter, the formation of by-miscellaneous by-products of Kröhnke\textsuperscript{44} terpyridine synthesis e.g. green dye 9 and cyclohexanol 16, is described. Single crystal X-ray structure of cyclobutane 18 as a result of [2+2]-photodimerization\textsuperscript{357} of azachalcone 17 is also discussed.

3.2 Results and Discussion

Kröck and Kröhnke\textsuperscript{352} reported the synthesis of blue azacyanines by heating an azachalcone with NH\textsubscript{4}OAc in AcOH in the presence of air. Since the Kröhnke\textsuperscript{44} terpyridine synthesis was conducted under similar conditions (Scheme 3.1, Route A), green or blue by-products were obtained along with terpyridines in < 20% yields; however, when the methoxycarbonyl azachalcone 3 was treated with 1-(2-pyridacyl)-pyridinium iodide and NH\textsubscript{4}OAc in AcOH in the presence of air for 2 hours at 110 °C it gave the green dye 9 in 85% yield instead of desired terpyridine 10,\textsuperscript{48} which was obtained in 37% yield by changing the solvent to MeOH (Scheme 3.2). Kröck and Kröhnke\textsuperscript{352} further proposed that the pyridine ring in azachalcone 3 added to its own double bond via
Michael addition to form the hydroxy-indolizine 4, which was protonated and then reacted with NH₄OAc to give the amino-indolizine 7. Further, the amine-containing indolizine 7 reacted with indolizinium salt 6 to give intermediate 8, which was oxidized to afford the dye 9 in the presence of air.

Scheme 3.2. Proposed mechanism for formation of the green dye 9: i) 1-(2-pyridacyl)-pyridinium iodide, AcOH, NH₄OAc, 110 °C, 2 h; ii) 1-(2-pyridacyl)pyridinium iodide, MeOH, NH₄OAc, 60 °C, 10 h.³⁵²

Proton resonances (¹H NMR) for the indolizine moiety of the di-methoxycarbonyl substituted green dye 9 displayed downfield shifts and a simpler pattern compared to similar dyes without functional groups.³⁵²,³⁵³ The UV-vis spectrum of the dye 9 revealed a greenish-blue absorption band at 660 nm, which has a lower energy compared to other
dyes (at ca. 630 nm). The HRMS spectrum of the green dye 9 further confirmed its structure by a single peak at \( m/z = 671.9960 \, [M – I (\text{MeCOO})]^+ \).

The 1,5-diketone 14 was formed by condensation of 4-iodobenzaldehyde with two equivalents of 2-acetylpyridine;\(^{351}\) however, the condensation does not stop at this stage. The diketone 14 further adds to azachalcone intermediate 13 to give a 1,3,5-triketone 15, which leads to the final condensation product - cyclohexanol 16 containing five non-equivalent aromatic moieties (Scheme 3.3). The structure of cyclohexanol 16 having a \( 1 \text{RS}, 2 \text{SR}, 3 \text{RS}, 4 \text{RS}, 5 \text{RS} \) configuration was established with its \(^1\text{H}\) and COSY NMR spectra agreed with proton assignments of similar structures.\(^{354-356}\) The HRMS spectrum of the cyclohexanol 16 further confirmed its structure by a single peak at \( m/z = 814.0039 \, [\text{M + Na}]^+ \). The yield of cyclohexanol by-products is strongly depended on functional groups on the arylaldehydes, the aldehyde : 2-acetylpyridine ratio, and reaction conditions.

![Scheme 3.3. Formation of condensation by-product 16: i) BH\(_3\)·THF, THF, 25 °C, 10 h; ii) PCC, DCM, 25 °C, 2 h; iii) NaOH (2 M), EtOH, 25 °C, 9 h.](image-url)
[2+2]-Photodimerization of *trans*-chalcones occurred either *via* head-to-tail or head-to-head arrangement with *syn* or *anti* addition giving different cyclobutane products depending on the solution, solid or molten state reaction (Scheme 3.4). Schmidt’s rule proposed that the distance between C=C groups has to be shorter than 4.2 Å in order for the possible photodimerization reaction to occur. Single crystal growth of azachalcone 17 in MeOH/CHCl₃ gave single crystals of cyclobutane 18, as a result of *syn*-head-to-tail addition of two azachalcones 17 under sunlight standing on a laboratory bench for a day. The cyclobutane structure was confirmed with C(8)-C(7) and C(8)-C(7A) distances being 1.582 and 1.541 Å, respectively, which are longer than usual C=C double bond distances (1.34 Å) in azachalcones (Figure 3.1).

![Scheme 3.4. Photodimerization of *trans*-chalcones afforded cyclobutane products.](image)

![Figure 3.1. The synthesis of cyclobutane 18 by [2+2]-photodimerization of azachalcone 17 and single crystal X-ray structure of cyclobutane 18.](image)

Figure 3.1. The synthesis of cyclobutane 18 by [2+2]-photodimerization of azachalcone 17 and single crystal X-ray structure of cyclobutane 18.

The yellow coloration of the solid azachalcone 17 surprisingly turned to white upon sitting on a bench under sunlight for two days. The white solid was washed with
MeOH and identified as cyclobutane 18 by its $^1$H, $^{13}$C, COSY NMR and HRMS spectra (a single peak at $m/z = 625.0106$ [M + Na]$^+$). Such [2+2]-photodimerization reactions usually occur under an irradiation source$^{357,358}$ and gave poor yields (< 30%); interestingly, other azachalcones are reported to be stable under prolonged sunlight.$^{48}$ The electron-donating methyl group on azachalcone 17 possibly contributed to facile formation of cyclobutane 18 by increasing the electron density of the C=C bond.

3.3 Conclusion

The Kröhnke$^{44}$ terpyridine synthesis gave a variety of by-products, such as green dye 9, cyclohexanol 16 or cyclobutane 18. Green dye 9 was formed from azachalcone 3 in the presence of acid and air; the cyclohexanol 16 was formed by further condensation of the azachalcone 13 and 1,3-diketone 14. Lastly, the solution and solid state [2+2]-photodimerization of azachalcone 17 afforded the cyclobutane 18, as a result of syn-head-to-tail addition. These studies hopefully will help to optimize the yield of the terpyridine synthesis.

3.4 Experimental Section

1-[3-(4-Bromophenyl)-7-methoxycarbonyl-indoliziny-1-imino]-3-(4-bromophenyl)-7-methoxycarbonyl-1H-indolizinium iodide or acetate (9): To a stirred solution of 3 (1.6 g, 4.64 mmol) and 1-(2-pyridacyl)pyridinium iodide (1.55 g, 4.77 mmol) in AcOH (40 mL), excess NH$_4$OAc (10 g, 154 mmol) was added, and then refluxed 3 hours.
The precipitate, which was formed upon cooling, was filtered and washed with H₂O and MeOH to give 9, as a green solid: 2.84 g (85%); mp 271-273 °C; ¹H NMR (DMSO-dma) δ 4.04 (s, 6 H, CO₂CH₃), 7.80 (m, 6 H, 2,6-ArH, 6,6'-indolizinH), 7.88 (d, 4 H, 2,6-ArH, J = 8.4 Hz), 8.1 (s, 2 H, 2,2'-i), 8.89 (m, 4 H, 5,5'-indolizinH, 8,8'-indolizinH); HRMS (calc.): m/z = 671.9960 (671.9954, [M – I (MeCOO)]⁺).

4-Iodobenzyl alcohol³⁵¹ (11): To a stirring solution of 4-iodobenzoic acid (50 g, 202 mmol) in THF (900 mL) at 0 °C, BH₃·THF (340 mL, 340 mmol) was added slowly through dropping funnel, then the mixture was warmed to 25 °C for 10 h. Excess hydride was carefully destroyed with water then the solution was concentrated in vacuo to give a paste, which was neutralized with Na₂CO₃ (1 M) and extracted with CHCl₃. Organic layers were combined, dried (MgSO₄) and then the solvent was evaporated in vacuo to give 11, as a white solid: 35.6 g (76%); mp 71-73 °C; lit.³⁵¹ mp 72-75 °C; ¹H NMR (CDCl₃) δ 3.55 (t, 1 H, CH₂OH, J = 6.9 Hz), 4.53 (s, 2 H, CH₂OH), 7.05 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.62 (d, 2 H, 3,5-ArH, J = 8.4 Hz); ¹³C NMR (CDCl₃) δ 64.22, 92.88, 128.85, 137.52, 140.7.

4-Iodobenzaldehyde³⁵¹ (12): To a stirring solution of PCC (50 g, 232 mmol) and Celite (40 g) in DCM (1 L), 11 (35 g, 150 mmol) was dissolved in CH₂Cl₂ (100 mL) and added slowly through dropping funnel. Ether (200 mL) was added to the mixture then after 1 h of vigorous stirring at 25 °C, the mixture was stirred for 1 additional h. Resulting dark brown solution was filtered through Celite then the filtrate was concentrated in vacuo followed by flash column chromatographed (SiO₂) eluting with
CH₂Cl₂ to give 12, as a white solid: 27.4 g (79%); mp 78-80 °C; lit.³⁵¹ mp 78-82 °C; ¹H NMR (CDCl₃) δ 7.60 (dt, 2 H, 2,6-Ar H, J₁ = 8.7 Hz, J₂ = 0.9 Hz), 7.90 (dt, 2 H, 3,5-Ar H, J₁ = 8.7 Hz, J₂ = 0.9 Hz), 9.96 (s, 1 H, CHO); ¹³C NMR (CDCl₃) δ 102.97, 130.98, 135.79, 139.61, 191.53.

2,4-Bis(pyridine-2-carbonyl)-1-(2-pyridyl)-3,5-bis(4-iodophenyl)cyclohexan-1-ol (16): To a stirring solution of 12 (8.4 g, 36.2 mmol) and 2-acetylpyridine (9.4 g, 77.6 mmol) in EtOH (250 mL) at 25 °C, aqueous NaOH (2 M, 35 mL) was added. The mixture was stirred for 9 h at 25 °C, then filtered and washed with EtOH (300 mL) and H₂O (100 mL) to give 16, as a white solid: 6.59 g (23%); mp 214-216 °C; ¹H NMR (CDCl₃) δ 1.98 (dd, 1 H, 6ax-cyclohex H, J₁ = 12.9 Hz, J₂ = 3.3 Hz), 3.49 (t, 1 H, 6eq-cyclohex H, J = 13.2 Hz), 4.11 (dt, 1 H, 5-cyclohex H, J₁ = 12.9 Hz, J₂ = 3.3 Hz), 4.45 (dd, 1 H, 3-cyclohex H, J₁ = 12.6 Hz, J₂ = 2.1 Hz), 5.52 (t, 1 H, 4-cyclohex H, J = 4.8 Hz), 5.73 (s, 1 H, cyclohex-OH), 6.21 (d, 1 H, 2-cyclohex H, J = 12.6 Hz), 6.86 (td, 1 H, 5-pyr₂ H, J₁ = 4.8 Hz, J₂ = 0.9 Hz), 7.02 (d, 2 H, 2,6-Ar₃ H, J = 8.4 Hz), 7.07 (d, 2 H, 2,6-Ar₃ H, J = 8.4 Hz), 7.11 (d, 2 H, 3,5-Ar₃ H, J = 8.4 Hz), 7.16 (m, 2 H, 5-pyr₁ H, 5-pyr₄ H), 7.33 (d, 2 H, 3,5-Ar₃ H, J = 8.4 Hz), 7.51 (td, 2 H, 4-pyr₁ H, 4-pyr₂ H, J₁ = 7.8 Hz, J₂ = 1.5 Hz), 7.41 (m, 2 H, 4-pyr₄ H, 3-pyr₂ H), 7.61 (d, 1 H, 3-pyr₄ H, J = 7.8 Hz), 7.84 (d, 1 H, 3-pyr₁ H, J = 8.1 Hz), 8.15 (d, 1 H, 6-pyr₄ H, J = 4.8 Hz), 8.19 (d, 1 H, 6-pyr₂ H, J = 4.8 Hz), 8.46 (d, 1 H, 6-pyr₁ H, J = 4.8 Hz); ¹³C NMR (CDCl₃) δ 38.07, 40.97, 45.12, 48.01, 48.58, 75.74, 91.75, 91.94, 121.24, 121.39, 121.9, 122.16, 126.28, 130.11, 130.79, 136.28, 136.42, 136.92, 137.05, 140.69, 141.98, 147.15, 148.25, 148.34, 154.01, 154.23, 162.38, 203.24, 205.24; HRMS (calc.): m/z = 814.0039 (814.0040, [M + Na]⁺).
1,3-Bis(4-methylpyridine-2-carbonyl)-2,4-bis(4-bromophenyl)cyclobutane (18):

A yellow solid 17 (1.2 g, 3.97 mmol) was exposed to the sunlight on a laboratory bench for 2 days and washed with MeOH to give 18, as a white solid: 980 g (82%); mp 221-223°C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.29 (s, 6 H, pyrCH\(_3\)), 4.88 (dd, 2 H, 2,4-cyclobutH, \(J_1 = 11.4\) Hz, \(J_2 = 7.5\) Hz), 5.39 (dd, 2 H, 1,3-cyclobutH, \(J_1 = 11.4\) Hz, \(J_2 = 7.5\) Hz), 7.06 (d, 4 H, 2,6-ArH, \(J = 8.4\) Hz), 7.14 (m, 6 H, 5-pyrH, 3,5-ArH), 7.38 (s, 2 H, 3-pyrH), 8.45 (d, 2 H, 6-pyrH, \(J = 5.1\)) \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 21.11, 41.38, 49.13, 120.52, 122.92, 127.92, 130.07, 131.05, 138.83, 148.23, 148.69, 153.12, 200.47; HRMS (calc.): \(m/z = 625.0106\) (625.0102, [M + Na])

Crystal data for 18: Monoclinic, P2(1)/c, \(a = 5.9386(6)\) Å, \(b = 10.0292(10)\) Å, \(c = 20.687(2)\) Å, \(\alpha = 90^\circ\), \(\beta = 93.477(2)^\circ\), \(\gamma = 90^\circ\), \(V = 1229.8(2)\) Å\(^3\), \(Z = 4\), \(\rho = 1.632\) Mg/m\(^3\), \(\mu = 3.328\) mm\(^{-1}\), \(F(000) = 608\), Final \(R\) indices (for 2928 parameters) \([I > 2\sigma(I)]\) were \(R1 = 0.0284\), and \(R1 = 0.0394\), \(wR2 = 0.0627\) for all 10355 data.
CHAPTER IV

DESIGN, CHARACTERIZATION AND X-RAY STRUCTURE OF AN INTERLOCKED DINUCLEAR CHAIR-LIKE METALLOMACROCYCLE‡

4.1 Introduction

Highly ordered, regularly repeating molecular architectures, constructed via self-assembly techniques, have gained importance over the last three decades due to their potential utilitarian applications. A key construction strategy has relied on the synthesis of specific building blocks capable of forming “higher-ordered” stable structures that have useful properties that can be used in molecular and supramolecular devices. In that sense, the creation of molecular devices that can perform mechanical work, such as brakes, gears, bearings, turnstiles, ratchets and switches has been an exciting new area of research. Specifically, terpyridine ligands were widely used as building blocks since they facilitate directed, metal-mediated self-assembly, and their transition metal complexes possess distinct photochemical and electronic properties. However, these complexes were mostly utilized as photovoltaic devices, molecular switches, and luminescent materials.

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Recently, \textit{bis}(terpyridine)-based ligands\textsuperscript{41} have been used for the construction of molecular architectures possessing trigonal-,\textsuperscript{372,373} square-,\textsuperscript{373} pentagonal-,\textsuperscript{320} and hexagonal-shaped\textsuperscript{47,374-376} motifs by metal-directed self-assembly. A series of dinuclear ruthenium(II) metallomacrocycles\textsuperscript{377,378} and a dinuclear octacationic box have also been reported by Constable \textit{et al.},\textsuperscript{379} while Stoddart \textit{et al.}\textsuperscript{380} have reported a covalently linked “blue-box.” These assemblies were not, however, intended to perform mechanical work.

In the early 1980s, Mislow and Iwamura\textsuperscript{362} studied internally crowded ditriptycyl systems ($\text{Tp}_2\text{X}$; $\text{Tp} = 9$-triptycyl, $\text{X} = \text{CH}_2, \text{O}$, \textit{etc.}) and their phase isomers which resembled three-toothed beveled gears. Later, structures that appeared like four-toothed beveled gears, such as tetraphenylcyclobutadiene containing metallocene\textsuperscript{363} and anti-\(\text{W(CO)}_5\)-complexed 9-methyl-9-phosphabicyclo[6.1.0]nonatriene\textsuperscript{364} were reported (Figure 4.1). In this chapter, a strategy for the self-assembly of a chair-like metallomacromolecule 5 resembling a four-toothed spur gear is discussed along with its single crystal X-ray structure and low temperature $^1$H NMR studies.

![Figure 4.1](image)

Figure 4.1. Interlocked systems that resemble three- and four-toothed bevel gears and a schematic representation of a spur gear.\textsuperscript{362-364}
4.2 Results and Discussion

4′-(3-Bromophenyl)terpyridine (3; Scheme 4.1) was prepared by the treatment of 1-(2-pyridacyl)pyridinium iodide\textsuperscript{335} with 3-bromo-2′-azachalcone\textsuperscript{381} (2) via Michael-type addition, followed by ring-closure of the intermediary diketone using NH\textsubscript{4}OAc in MeOH (Scheme 4.1). Proton resonances (\textsuperscript{1}H NMR) of three pyridine rings agreed with the literature,\textsuperscript{339} and as expected, the 3-bromophenyl ring exhibited a definitive proton pattern due to lack of symmetry. HRMS spectra further confirmed the structure of terpyridine 3 with a single peak at \( m/z = 410.0265 \) [M + Na]\textsuperscript{+}.

Synthesis of the desired ligand 4 was achieved via the Pd\textsuperscript{[0]}-mediated cross-coupling\textsuperscript{382} of intermediate 3 and 5-methyl-1,3-phenylenebisboronic acid\textsuperscript{383} (1). Proton resonances (\textsuperscript{1}H NMR) for the phenyl spacer between the terpyridine and central phenyl ring of ligand 4 showed downfield shifts for the 5-ArH (\( \delta = 7.61, \Delta\delta = 0.23 \)), 4-ArH (\( \delta = 7.75, \Delta\delta = 0.16 \)), 6-ArH (\( \delta = 7.88, \Delta\delta = 0.05 \)), and 2-ArH (\( \delta = 8.15, \Delta\delta = 0.09 \)) compared to terpyridine 3 due to Br-substitution. Moreover, new resonances from the central phenyl ring appeared in \textsuperscript{1}H NMR (\( \delta = 7.55, 2,4\)-ArH; 7.75, 6-ArH). 2D Correlation NMR experiments (COSY) were also conducted to ensure the proper assignments. The HRMS spectra of 4 further confirms its structure by a single peak at \( m/z = 707.2930 \) [M + H]\textsuperscript{+}.

Treatment of ligand 4 with an equimolar amount of FeCl\textsubscript{2}.4H\textsubscript{2}O in MeOH gave rise to a concentrated purple solution that was concentrated \textit{in vacuo} to afford a residue that was chromatographed (SiO\textsubscript{2}) eluting with MeCN : sat. KNO\textsubscript{3} (aq) : H\textsubscript{2}O (7:1:1) followed by counterion exchanged by the addition of excess NH\textsubscript{4}PF\textsubscript{6} (1 M) to give the purple microcrystalline 5[PF\textsubscript{6}]\textsubscript{4} (Scheme 4.2) in 89 % yield.
Scheme 4.1. Preperation of bis-terpyridine 4: i) t-BuLi, B(i-OPr)₃, THF, –90 ºC, 15 h; ii) NaOH (1 M), MeOH, 25 ºC, 3 h; iii) MeOH, 1-(2-pyridacyl)pyridinium iodide, NH₄OAc, 70 ºC, 7 h; iv) 1, DME, Pd(PPh₃)₄, K₂CO₃ (2 M), 85 ºC, 12 h, N₂.

Scheme 4.2. Preperation of crystalline 5[(H₂TCB)₂]: i) FeCl₂·4H₂O, MeOH, 70 ºC, 8 h, NH₄PF₆ (1 M); ii) H₄TCB, NaOH (1 M), MeCN, 5 days.

The ¹H NMR spectrum of the 5[PF₆]₄ revealed a singlet at δ = 2.67 for the methyl moiety, which suggests the presence of a single homogeneous environment for the methyl groups; this is in contrast to that expected for linear oligomeric structures. Furthermore, the spectra (¹H NMR; Figure 4.2A) of this complex showed notable upfield shifts for the doublet assigned to 6,6''-pyrH (δ = 7.03, ∆δ = –1.69), a triplet assigned to the 4,4''-pyrH (δ = 7.22, ∆δ = –0.66), and downfield shifts for the singlets of 2-ArH (δ = 9.01, ∆δ = 0.86),
and 6-BenH (δ = 8.49, ∆δ = 0.74), also the order of the peaks mentioned above changed when compared to the uncomplexed bis(terpyridine) 4 proton resonances (Figure 4.2B); 2D correlation (COSY) NMR was also conducted to ensure the proper assignments. These significant proton chemical shifts of the dimer complex could be explained by shielding affect inside the macrocyclic cavity.377

Figure 4.2. The 1H NMR spectrum (300 MHz) of the aromatic region of (A) 5[(PF6)4] in CD3CN, (B) 4 in CDCl3. * indicates the CDCl3.

The dinuclear structure was further established by ESI-MS by the unique signals corresponding to (5[(PF6)3])⁺ (m/z = 1960.5), (5[(PF6)2])²⁺ (m/z = 907.1), (5[(F)2])²⁺ (m/z = 781.1), (5[F])³⁺ (m/z = 514.4), and (5)⁴⁺ (m/z = 381.1). The F⁻ counterions are derived by (PF6⁻ → PF5 + F⁻) in ESI-MS.376,384 Moreover, the HRMS spectrum of (5[(PF6)2])²⁺ (m/z = 907.6907) perfectly matched the calculated mass and isotopic patterns.

To support the structure of the dinuclear complex, the UV-vis absorption spectrum was recorded in MeCN. The absorption spectra of 5[(PF6)4] revealed the lowest energy ligand-centered π-π* transition of the terpyridine moiety at ~322 (shoulder) nm.
Furthermore, the metal-ligand charge-transfer (MLCT) transitions that came from the promotion of an electron from the metal Fe(II)-centered d-orbitals to unfilled π* orbitals appeared at 568 nm.

Although attempts to grow single crystals of 5[(PF6)4] or 5[(NO3)4] failed due to insufficient crystal sizes and poor diffraction patterns, a high quality single crystal of 5 was based on the novel utilization of a multi-ionic organic counter ion, as opposed multiple single inorganic counter ions. Crystallization was achieved by layering a purple solution of 5[(PF6)4] in MeCN over a basic solution of sodium 1,2,4,5-benzenetetracarboxylate (H4TCB). After 5 days in a sealed environment, the dark purple quadrilateral-like crystals were collected in 85% yield (Scheme 4.2). X-ray analysis (100 K) confirmed the macrocyclic dimerization of metal-mediated, self-assembly (Figure 4.3A). Two H2TCB2- were unexpectedly coordinated with each dimer 5 in a 1:2 ratio of (5[4+]: H2TCB2-) instead of an 1:1 ratio of (5[4+]:TCB4-) arising from the complete deprotonation of the H4TCB, as originally assumed.

The toluene moieties in the π-electron conjugated dimer 5 were twisted with an average angle of 55° to the dinuclear plane, which induced a chair conformation. Viewing through the a axis of the crystal packing lattice (Figure 4.3B), the channels formed from macrocyclic dimers were filled with encapsulated water molecules and MeCN; H2TCB2- were inlaid between the dinuclear planes. Moreover, the planes themselves were partially overlapped through π-π interactions. The Fe-Fe distance in asymmetric unit was observed to be 8.814 Å; the angles of N-Fe-N' in each terpyridine (N from side pyridines and N' from center pyridines) were found to be nearly identical having an average angle of 80.70°. Figure 1.4A shows an aligned molecular packing along the b axis. The distance between
the dimer planes was calculated to be 15.285 Å. H-bonding, dominated by TCB and water molecule coordination, plays a crucial role in the crystallization process (Figure 4.4B), while the MeCN and part of water molecules did not participate the $H$-bonding associations.

Figure 4.3. The illustration of crystal structure of complex 5; (A) the asymmetric unit, containing a complex dimer, two encapsulated MeCN molecules (line bar), three water molecules and two partially deprotonated TCBs; (B) molecular packing of crystal 5 (along $a$ axis); water and MeCN molecules were omitted for clarity.

Figure 4.4. (A) An ordered packing motif of 5 along with $b$ axis; (B) $H$-bonding representative (green and red lines) between carboxylic acid and water molecules (along $c$ axis).
The dimer complex 5 was expected to show correlated rotation of the moieties as in a molecular gear due to the proximity of tpy-Fe-tpy moieties (2.93 – 3.74 Å) observed in the single crystal (Figure 4.3A).\textsuperscript{362-364} The low temperature \textsuperscript{1}H NMR experiment of 5 in CD\textsubscript{3}CD\textsubscript{2}OD:CD\textsubscript{3}CN (2:1) at – 65 °C (Figure 4.5) was conducted to freeze the molecular rotation of the molecular spur gear 5. As a result, it showed broadening and downfield shifts of the peaks specifically for 4, 5, 6-pyr\textsubscript{H} caused by slowing down the concerted rotation of the interlocked tpy-Fe-tpy moieties. The expected different set of peaks for 4, 5, 6-pyr\textsubscript{H} was not observed after broadening of these peaks because of possible gear slippage or the temperature that was not low enough to freeze the rotation completely.

Figure 4.5. The variable low temperature \textsuperscript{1}H NMR (400 MHz) of 5[(PF\textsubscript{6})\textsubscript{4}] in CD\textsubscript{3}CD\textsubscript{2}OD:CD\textsubscript{3}CN (2:1).

Cyclic voltammetry of 5[(PF\textsubscript{6})\textsubscript{4}], along with Fe(II) \textit{bis}(4'-tolyl)-2,2';6',2''-terpyridine [(Fe(ttpy)\textsubscript{2})], was conducted at 25 °C in argon saturated solutions with sample
concentrations of 1.0 mM in 0.1 M Bu₄NPF₆ in dry MeCN. The dinuclear complex exhibited a reversible one-electron Fe⁢³⁺/²⁺ couple at 1.20 V vs. Fc/Fc⁺, which was found to oxidize at a slightly higher potential than [Fe(tpy)₂] (Fe³⁺/²⁺ E½ = 1.07 V vs. Fc/Fc⁺). The complex 5[(PF₆)₄] exhibited a broad, irreversible wave in the negative region at –1.30 V (vs. Fc/Fc⁺) corresponding to the reduction of the terpyridine ligand with a sharp peak in the anodic region indicative of deposition of the sample on the electrode surface.

4.3 Conclusion

A dinuclear tetracationic Fe(II) complex 5 was prepared via metal-directed self-assembly. This chair-like molecular architecture was primarily characterized by X-ray crystallography, mass spectroscopy (ESI-MS), as well as ¹H NMR, UV-vis, and CV experiments, which were also conducted for further confirmation. Crystal packing of 5 revealed that it formed channels that encapsulated water and MeCN. The low temperature ¹H NMR studies suggested that tpy-Fe-tpy moieties in the dimer were interlocked and resembled a spur gear relationship.

4.4 Experimental Section

5-Methyl-1,3-phenylenebisboronic acid³⁸³ (1): To a stirred solution of 3,5-dibromotoluene (1.33 g, 5.34 mmol) in dry THF (60 mL) under N₂ at –90 ºC, excess t-BuLi (1.7 M, 20 mL, 34 mmol) was added drop wise. The solution stirred at –90 ºC for 1
hour, warmed to −50 ºC, stirred for 1 additional hour, and cooled down to −90 ºC, then excess B(i-OPr)_3 (10 mL, 43 mmol) was added quickly. The reaction mixture was warmed to 25 ºC and stirred overnight. The solution was concentrated in vacuo and dried under high vacuum. The solid was dissolved in H_2O (30 mL) and kept at 5 ºC for 4 hours and the precipitated borate salts were filtered. The filtrate was concentrated in vacuo and kept at 5 ºC overnight to afford 1, as a white crystalline precipitate: 593 mg (62%); ^1_H NMR (DMSO-d_6) δ 2.5 (s, 3 H, Ben-CH_3), 3.8 [b, 4 H, B(OH)_2], 7.61 (s, 2 H, 2,4-BenH), 7.99 (s, 1 H, 5-BenH); ^13_C NMR (DMSO-d_6) δ 21.2, 99.6, 134.7, 136.5, 137.6.

1-(3-Oxo-3-[2-(pyridinyl)]propen-1-yl)-3-bromobenzene^381 (2): To a stirring solution of 3-bromobenzaldehyde (3.77 g, 20.3 mmol) and 2-acetylpyridine (2.6 g, 21.4 mmol) in MeOH (45 mL) at 25 ºC, aqueous NaOH (1 M, 15 mL) was added. The mixture was stirred 3 hours at 25 ºC and then filtered and washed with H_2O (15 mL). The precipitate was dissolved in CH_2Cl_2 (150 mL) and extracted with H_2O (2×100 mL). The combined organic fraction was dried (MgSO_4) and concentrated in vacuo to give 2, as a light yellow solid: 2.83 g (48%); ^1_H NMR (CDCl_3) δ 7.28 (d, 1 H, 5-pyrH, J = 4.2 Hz) 7.52 (m, 2 H, 4,5-ArH), 7.61 (d, 1 H, 6-ArH, J = 7.5 Hz), 7.86 (m, 2H, 4-pyrH, 2-ArH), 7.88 (d, 1 H, COCH=CH, J = 16.2 Hz), 8.18 (d, 1 H, 3-pyrH, J = 7.8 Hz), 8.27 (d, 1 H, COCH=CH, J = 16.2 Hz), 8.75 (d, 1 H, 6-pyrH, J = 4.2 Hz); ^13_C NMR (CDCl_3) δ 122.3, 123.1, 123.2, 127.2, 127.7, 130.5, 131.3, 133.4, 137.2, 137.4, 143, 149.1, 154.1, 189.3.

4’-(3-Bromophenyl)-2,2’;6’,2″-terpyridine (3): To a stirred solution of 2 (1.14 g, 3.96 mmol) and 1-(2-pyridacyl)pyridinium iodide (1.3 g, 3.99 mmol) in MeOH (30 mL),
excess NH₄OAc (8 g, 104 mmol) was added and the mixture was refluxed 7 hours. The precipitate, which was formed upon cooling, was filtered and washed with MeOH. The precipitate collected from filtration was column chromatographed (basic Al₂O₃) eluting with CHCl₃ to give 3, as a light yellow solid: 1.1 g (71%); mp 173-174 ºC; \(^1\)H NMR (CDCl₃)  δ 7.38 (m, 3 H, 5,5''-pyrH, 5-ArH), 7.59 (ddd, 1 H, 4-ArH, \(J_1 = 7.8\) Hz, \(J_2 = 1.8\) Hz, \(J_3 = 1.2\) Hz), 7.83 (ddd, 1 H, 6-ArH, \(J_1 = 7.5\) Hz, \(J_2 = 1.8\) Hz, \(J_3 = 0.9\) Hz), 7.88 (td, 2 H, 4,4''-pyrH, \(J_1 = 7.5\) Hz, \(J_2 = 1.8\) Hz), 8.06 (t, 1 H, 2-ArH, \(J = 1.8\) Hz), 8.7 (dt, 2 H, 3,3''-pyrH, \(J_1 = 8.1\) Hz, \(J_2 = 1.2\) Hz), 8.72 (s, 2 H, 3',5'-pyrH), 8.76 (ddd, 2 H, 6,6''-pyrH, \(J_1 = 4.8\) Hz, \(J_2 = 1.8\) Hz, \(J_3 = 0.9\) Hz); \(^1\)3C NMR (CDCl₃)  δ 118.86, 121.49, 123.28, 124.04, 126.12, 130.38, 130.57, 132.07, 136.97, 140.78, 148.83, 149.26, 156.1, 156.19; HRMS (calc.): \(m/z = 410.0265\) (410.0269, [M + Na]+).

3,5-Bis(2,2':6',2''-terpyridin-4'-phen-3-yl)toluene (4): To a stirring solution of 3 (323 mg, 830 µmol) and 1 (75 mg, 420 µmol) in DME (30 mL), aqueous K₂CO₃ (270 mg, 1.95 mmol) was added. The mixture was degassed and back-filled with argon (3X) then tetrakis(triphenylphosphine)palladium(0) (27.1 mg, 24 µmol, 3 % per coupling site) was added to the flask and the mixture was degassed and back-filled with argon (2X), then stirred at 60 ºC for 12 hours. The mixture was filtered and washed with DME (20 mL). The precipitate that formed upon cooling was filtered and washed with DME (20 mL) and MeOH (20 mL). The resultant precipitate was column chromatographed (basic Al₂O₃) eluting with CHCl₃ to give 4, as a white solid: 216 mg (73%); mp 260-261 ºC; \(^1\)H NMR (300 MHz, CDCl₃)  δ 2.57 (s, 3 H, CH₃), 7.35 (ddd, 4 H, 5,5''-pyrH, \(J_1 = 7.5\) Hz, \(J_2 = 6.0\) Hz, \(J_3 = 1.2\) Hz), 7.55 (t, 2 H, 2,4-BenH, \(J = 0.9\) Hz), 7.61 (t, 2 H, 5-ArH, \(J = 7.8\) Hz, \(J_2 = 1.8\) Hz), 8.05 (t, 1 H, 2-ArH, \(J = 1.8\) Hz), 8.7 (dt, 2 H, 3,3''-pyrH, \(J_1 = 8.1\) Hz, \(J_2 = 1.2\) Hz), 8.72 (s, 2 H, 3',5'-pyrH), 8.76 (ddd, 2 H, 6,6''-pyrH, \(J_1 = 4.8\) Hz, \(J_2 = 1.8\) Hz, \(J_3 = 0.9\) Hz); \(^1\)3C NMR (CDCl₃)  δ 118.86, 121.49, 123.28, 124.04, 126.12, 130.38, 130.57, 132.07, 136.97, 140.78, 148.83, 149.26, 156.1, 156.19; HRMS (calc.): \(m/z = 410.0265\) (410.0269, [M + Na]+).
Hz), 7.75 (m, 3 H, 4-ArH, 6-BenH), 7.88 (m, 6 H, 6-ArH, 4,4"-pyrH), 8.15 (t, 2 H, 2-ArH, J = 1.8 Hz), 8.7 (dt, 4 H, 3,3"-pyrH, J1 = 8.1 Hz, J2 = 1.2 Hz), 8.72 (ddd, 4 H, 6,6"-pyrH, J1 = 4.8 Hz, J2 = 1.8 Hz, J3 = 0.9 Hz), 8.81 (s, 4 H, 3',5'-pyrH); ESI-MS (calc.):
HRMS (calc.): m/z = 707.2930 (707.2923, [M + H]+).

[FeII(3,5-bis(2,2':6',2"-terpyridin-4'-phen-3-yl)toluene)2][(PF6)4] (5[(PF6)4]): To a stirring solution of 4 (46.6 mg, 66 µmol) in MeOH (40 mL), FeCl2·4H2O (13.2 mg, 66 µmol) was added then the mixture was refluxed for 8 hours. Solution was concentrated in vacuo to give a deep purple precipitate that was column chromatographed (SiO2) eluting with MeCN : sat. KNO3 (aq) : H2O (7:1:1) then counterion exchanged to PF6− by treating with an excess NH4PF6 (1 M) to give 5[(PF6)4], as purple microcrystals: 61.8 mg (89 %);

1H NMR (CD3CN) δ 2.67 (s, 6 H, CH3), 6.62 (ddd, 8 H, 5,5"-pyrH, J1 = 7.5 Hz, J2 = 5.7 Hz, J3 = 1.2 Hz), 7.03 (d, 8 H, 6,6"-pyrH, J = 4.8 Hz), 7.22 (td, 8 H, 4,4"-pyrH, J1 = 7.8 Hz, J2 = 1.5 Hz), 7.89 (s, 4 H, 2,4-BenH), 7.96 (t, 4 H, 5-ArH, J = 7.8 Hz), 8.15 (d, 4 H, 4-ArH, J = 8.1 Hz), 8.43 (d, 6 H, 6-ArH, J = 7.8 Hz), 8.49 (s, 2 H, 6-BenH), 8.51 (d, 8 H, 3,3"-pyrH, J = 7.8 Hz), 9.01 (s, 4 H, 2-ArH), 9.35 (s, 8 H, 3',5'-pyrH); ESI-MS (calc.):
m/z = 907.6907 (907.6848 [M – 2PF6]2+).

Crystal preparation of 5[(H2TCB)2]: A solution of 5[(PF6)4] (16 mg, 7.6 µmol) in MeCN was carefully laid over a basic solution of 1,2,4,5-benzenetetracarboxylic acid (H4TCB, 1.2 mg, 7.7 µmol) at 25 ºC, the dark purple crystals of 5[(H2TCB)2] were
collected after 5 days: 13.1 mg (85%). Crystal data for 5[(H2TCB)2]: Triclinic, P-1, $a = 13.6606(17) \text{ Å}, b = 14.6604(18) \text{ Å}, c = 15.2850(19) \text{ Å}, \alpha = 96.396 (2)^\circ, \beta = 98.395 (2)^\circ, \gamma = 98.598 (2)^\circ, V = 2966.4 (6) \text{ Å}^3, Z = 1, \rho = 1.282 \text{ Mg/m}^3, \mu = 0.321 \text{ mm}^{-1}, F(000) = 1184$, Final $R$ indices (for 754 parameters) [$I > 2\sigma(I)$] were $R1 = 0.0549$, and $R1 = 0.0706$, $wR2 = 0.1433$ for all 12817 data.
CHAPTER V
ONE POT SELF-ASSEMBLY OF DI- AND TRINUCLEAR
METALLOMACROCYCLES AND THEIR MALDI-TOF ANALYSIS

5.1 Introduction

Diverse transition metal chelating ligands containing two terpyridine moieties have been frequently used as a molecular building block to form metallomacrocycles and/or metallopolymers. Various linkers have been used to connect two terpyridines via their 4'-positions, e.g.; flexible linkers that favor metallo-polymerization over macrocycle formation and rigid linkers that afforded either the self-assembly of macrocycles or linear rigid polymeric structures depending on the angle between terpyridines and metals used for complexation. Juxtaposed bis(terpyridine) ligands possessing 120° – 0° bond angles with rigid linkers self-assemble to give hexa- [6+6], penta- [5+5], tetra- [4+4], tri- [3+3], and dinuclear [2+2] metallomacrocycles with Fe(II) in 70-90% yields or Ru(II) in 10-50% yields; further, linear bis(terpyridine) ligands with a rigid linker can give polymeric structures (Figure 5.1). High yield cyclic assemblies of Fe(II) were rationalized by a possible metal exchange in a process that favored the entropy-driven formation of macrocycles; however, Ru(II) containing macrocycles were obtained with lower yields due to Ru(II) bis(terpyridine) complex that favored
kinetically stable and statistical distribution of linear and cyclic products. The bis(terpyridine) ligands possess flexible linkers for the most part formed linear metallopolymers with transition metals; however, in some cases, they afforded mono-[1+1], di-[2+2], tri-[3+3], and tetranuclear [4+4] macrocycles with 10-50% yields depending on the length of the linker and the metal used.

Figure 5.1. The self-assembly of metallomacrocycles containing bis(terpyridine) ligand with rigid linkers and formation of polymeric structures.

In this section, the synthesis of a new bis(terpyridine) ligand and its dinuclear complex with Fe(II) and di- and trinuclear metallomacrocycle formation with Ru(II) is
described. Various angles between juxtaposed terpyridine moieties in the ligand 7 due to its rotational isomers, which opened new possibilities to self-assemble different size and shape macrocycles in an one-pot reaction. Structures of these macrocycles were established by their ESI-MS, MALDI-TOF and $^1$H NMR spectroscopy.

5.2 Results and Discussion

4’-(3-Iodophenyl)terpyridine (4; Scheme 5.1) was prepared by a treatment of 2 equivalent 2-acetylpyridine with 3-iodobenzaldehyde$^{407}$ (4) by means of the diketone intermediate 5. The ring-closure of the intermediate 5 was achieved by its reaction with NH$_4$OAc in AcOH to afford the desired terpyridine 6. Proton resonances ($^1$H NMR) of three pyridine rings of 6 agreed with the literature,$^{390}$ and as expected, the 3-iodophenyl moiety exhibited a distinct proton pattern due to lack of symmetry. HRMS spectra further confirmed the structure of terpyridine 6 with a single peak at $m/z$ = 458.0122 [M + Na]$^+$. Preparation of the desired ligand 7 was achieved via Pd[0]-mediated cross-coupling$^{382}$ of terpyridine 6 and 1,3-diethynyltoluene$^{408}$ (2). Proton resonances ($^1$H NMR) for the phenyl spacer between the terpyridine and central phenyl ring of ligand 7 showed downfield shifts for the 5-ArH ($\delta = 7.51, \Delta\delta = 0.27$), 6-ArH ($\delta = 7.62, \Delta\delta = 0.05$) and upfield shifts for 4-ArH ($\delta = 7.62, \Delta\delta = 0.15$) and 2-ArH ($\delta = 8.15, \Delta\delta = 0.08$) compared to terpyridine 6 due to iodo moiety. Furthermore, new resonances ($\delta = 7.40, \text{2,4-ArH}; 7.62, \text{6-ArH}$) from the central phenyl ring appeared in $^1$H NMR. The 2D correlation NMR experiments (COSY) were also conducted to ensure the proper assignments. The HRMS spectra of 7 confirms its structure by a single peak at $m/z$ = 755.2903 [M + H]$^+$. 
Scheme 5.1. Preparation of bis(terpyridine) 7: i) Me$_3$Si-CH=CH, Pd(PPh$_3$)$_2$Cl$_2$, PPh$_3$, CuI, NEt$_3$, 80 °C, 3 days, Argon; ii) KF, MeOH/THF, 25 °C, 10 h; iii) BH$_3$·THF, THF, 25 °C, 10 h; iv) PCC, DCM, 25 °C, 2 h; v) NaOH (1 M), MeOH, 25 °C, 9 h; vi) AcOH, NH$_4$OAc, 110 °C, 11 h; vii) 2, Pd(PPh$_3$)$_4$, CuI, THF/DIPA, 80 °C, 12 h, Argon.

Treatment of ligand 7 with an equimolar amount of FeCl$_2$·4H$_2$O in MeOH gave a purple solution that was concentrated in vacuo to afford a residue that was chromatographed (SiO$_2$) eluting with MeCN : sat. KNO$_3$ (aq) : H$_2$O (7:1:1) followed by counterion exchange by the addition of excess NH$_4$PF$_6$ (1 M) to give the purple microcrystalline 8[(PF$_6$)$_4$] (Scheme 5.2) in 90 % yield. The high yield formation of 8[(PF$_6$)$_4$] can be explained by a possible metal exchange in the process that favored the entropically more stable dinuclear macrocycle compared to other cyclic and linear oligomeric products.
Scheme 5.2. One pot self-assembly of the dinuclear $8^{[[PF_6]_4]}$ and $9^{[[PF_6]_4]}$ and the trinuclear $10^{[[PF_6]_6]}$: i) FeCl$_2$·4H$_2$O, MeOH, 70 °C, 8 h, NH$_4$PF$_6$ (1 M); ii) RuCl$_3$, N-Ethylmorpholine, MeOH, 70 °C, 12 h, NH$_4$PF$_6$ (1 M).

The dinuclear structure of $8^{[[PF_6]_4]}$ was established by ESI-MS by the unique signals corresponding to $8^{[[PF_6]_3]^+}$ ($m/z = 2056.6$), $8^{[[PF_6]_2]^{2+}}$ ($m/z = 955.7$), $8^{[(F)_2]^{3+}}$ ($m/z = 829.2$), $8^{[PF_6]^{3+}}$ ($m/z = 588.8$), $8^{[F]^{3+}}$ ($m/z = 546.5$), and $8^{[F]^{4+}}$ ($m/z = 405.1$) as well as its $^1$H NMR spectrum. The F$^-$ counterions are derived by (PF$_6^-$ → PF$_5^-$ → PF$_4^-$ → PF$_3^-$ → PF$_2^-$ → PF$^-$).
The $^1$H NMR spectrum of the dinuclear 8[(PF$_6$)$_4$] displayed significant differences in the aromatic region compared to 5[(PF$_6$)$_4$] in chapter 4 (Figure 5.2). It is important note that these extraordinary shifts of the peaks for the two very similar structures are due to the close proximity of terpyridine moieties in 5[(PF$_6$)$_4$] from chapter 4 and their gear-like correlated rotation, which does not exist in 9[(PF$_6$)$_4$].

![Figure 5.2. The $^1$H NMR spectrum (300 MHz) of the aromatic region of (A) 9[(PF$_6$)$_4$] and (B) 5[(PF$_6$)$_4$] from chapter 4 in CD$_3$CN.](image)

Construction of Ru(II)-containing di- and trinuclear macrocycles, 9[(PF$_6$)$_4$] and 10[(PF$_6$)$_6$], respectively, was achieved by treating the ligand 7 with an equimolar amount of RuCl$_3$ in EtOH and 4-ethylmorpholine (5 drops) resulting a dark red solution. The separation of macrocycles was accomplished by loading a concentrated reaction mixture on a preparative TLC plate (SiO$_2$) eluting with a solvent mixture of MeCN : sat. KNO$_3$ (aq) : H$_2$O (20:1:1). The well-separated top two bands were removed and washed with the eluting solvent, followed by counterion exchange by the addition of excess NH$_4$PF$_6$ (1 M) to afford the desired dinuclear 9[(PF$_6$)$_4$] and trinuclear 10[(PF$_6$)$_4$] in 32% and 28%
yield, respectively (Scheme 5.2). The rest of the bands on the plate were unidentified because adequate characterization was not obtained; however, they were assumed to be other larger oligomeric structures.

A structural confirmation of di- and trinuclear macrocycles is found on the basis of MALDI-TOF-MS data in addition to the $^1$H NMR spectra. The $^1$H NMR spectra of macrocycles 9 and 10 revealed a singlet at $\delta$ 2.49 ppm for the methyl moiety suggesting the presence of a single homogeneous environment for the methyl groups, which supported the macrocyclic architecture vs. linear oligomeric products. The dinuclear 9 displayed significant downfield shifts for the 4,4''-tpy$H$ ($\Delta \delta = 0.06$) and 5,5''-tpy$H$ ($\Delta \delta = 0.07$), and upfield shifts for the 2-Ar$H$ ($\Delta \delta = 0.06$) compared to the trinuclear 10. These shifts could be explained by a shielding effect inside the macrocyclic cavity of 9 with a closer proximity of the terpyridine moieties compared to 10.

The MALDI-TOF experiments for 9 and 10 were performed by using 2,5-dihydroxybenzoic acid (DHB), as a matrix, which is typically used for peptides, oligosaccharides, and synthetic polymers. The MALDI-TOF spectrum of the first band from the preparative TLC confirmed the dinuclear structure ($9[(PF_6)_4]$, Figure 5.3) and remarkably showed all the ionic species from the parent molecule such as; ($9[(PF_6)_3]^{+}$ ($m/z = 2147.8$), ($9[(PF_6)_2]^{2+}$ ($m/z = 2002.8$), ($9[(PF_6)]^{3+}$ ($m/z = 1857.7$), and ($9)^{4+}$ ($m/z = 1710.6$). The isotope patterns of these peaks perfectly matched the theoretical values; e.g. the peak for [M – 3PF$_6$]$^{3+}$ is depicted in Figure 5.4. The peak at 1610.7 was assigned to [M – 4PF$_6$ – Ru]$^{2+}$, which has not been reported before, because Ru(II) does not de-complex with terpyridine ligands, for the most part.
Figure 5.3. MALDI-TOF-MS analysis of \(9[(PF_6)_4]\).

Figure 5.4. (A) Theoretical and (B) experimental isotope patterns of the \([M - 3PF_6]^{3+}\) peak of \(9[(PF_6)_4]\) in the MALDI-TOF-MS.
The UV-vis absorption spectra of \(8[(PF_6)_4]\), \(9[(PF_6)_4]\), and \(10[(PF_6)_6]\) displayed the lowest energy ligand-centered \(\pi-\pi^*\) transition of the terpyridine moiety at \(~310\) (shoulder) nm. The high energy metal-ligand charge-transfer (MLCT) transitions came from the promotion of an electron from the metal-centered d-orbitals to unfilled \(\pi^*\) orbitals appearing at 565, 486, and 489 nm for \(8[(PF_6)_4]\), \(9[(PF_6)_4]\), and \(10[(PF_6)_6]\), respectively.

The MALDI-TOF spectrum of the second band from the preparative TLC established the trinuclear structure (\(10[(PF_6)_6]\), Figure 5.5) in which the unique signals corresponded to \((10[(PF_6)_3(F)])[2^+] (m/z = 3022.4), (10[(PF_6)_2(F)])[3^+] (m/z = 2879.8), (10[(PF_6)(F)])[4^+] (m/z = 2733.3), and (10[F])[5^+] (m/z = 2588.6). The F\(^-\) counterions are derived by \((PF_6^- \rightarrow PF_5 + F^-)\) in the MALDI-TOF-MS.\(^{376,384}\) It is important to note that the spectra of trinuclear 10 does not contain any signal of the dinuclear 9, and vice versa.

![MALDI-TOF-MS analysis of 10[(PF_6)_6] (Figure 5.5)](image)

The table displays the theoretical and experimental exact mass of the selected peaks.

<table>
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<th>Ion</th>
<th>Measured</th>
<th>Calculated</th>
</tr>
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<tr>
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<td>2587.565</td>
</tr>
<tr>
<td>([M - 4PF_6 - PF_5]^4+)</td>
<td>2733.297</td>
<td>2732.529</td>
</tr>
<tr>
<td>([M - 3PF_6 - PF_5]^3+)</td>
<td>2879.810</td>
<td>2877.493</td>
</tr>
<tr>
<td>([M - 2PF_6 - PF_5]^2+)</td>
<td>3022.457</td>
<td>3022.034</td>
</tr>
</tbody>
</table>

Figure 5.5. MALDI-TOF-MS analysis of \(10[(PF_6)_6]\): inset table displays the theoretical and experimental exact mass of the selected peaks.
The molecular modeling of the di- and trinuclear macrocycles was depicted in Figure 5.6. The dinuclear 9 had an edge-to-edge distance of 2.9 nm and the trinuclear 10 displayed an uniform shape with a radius of 3.3 nm. The dinuclear 9 did not show any correlated rotation as in dinuclear 5[(PF$_6$)$_4$] in chapter 4 because terpyridine moieties in dinuclear 9 are not close enough to trigger such motion.

Figure 5.6. Molecular modeling of dinuclear 9 and trinuclear 10.

5.3 Conclusion

The Fe(II)-containing dinuclear macrocycle 8 was assembled from a bis(terpyridine) ligand 7 in a high yield and characterized by ESI-MS, $^1$H and COSY NMR, and UV-vis spectroscopy. However, treatment of the ligand 7 with RuCl$_3$ gave mixture of different macrocyclic and polymeric products in which only di- (9) and trinuclear (10) macrocycles could be separated and characterized by MALDI-TOF, $^1$H and COSY NMR, and UV-vis spectroscopy. The Fe(II)-containing 8, as entropically the
most stable product, formed in a high yield as a result of possible metal exchange in the process. On the other hand, the kinetically more stable products, Ru(II) macrocycles 9 and 10, were constructed due to rotational isomers of the ligand 7.

5.4 Experimental Section

Uniplate™ preparative TLC plates (20 × 20 cm, 200 microns; Analtech) were used for the separation of metallomacrocycles 9 and 10. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS was performed on a Bruker Reflex III (Bruker; Breman, Germany) mass spectrometer operated in linear, positive ion mode with a N2 laser. Laser power was used at the threshold level required to generate signal; accelerating voltage was set to 28 kV. The instrument was calibrated with peptide standards bracketing the molecular weights of the samples (typically mixtures of Bradykinin fragment 1-5 and Adrenocorticotropic hormone fragment 18-39). Samples were prepared in 0.1% TFA at an approximate concentration of 50 pmol/ul. 2,5-Dihydroxybenzoic acid was used as the matrix and prepared as a saturated solution in 50% MeCN / 0.1% TFA (in water). Allotments of 1 µL of matrix and 1 µL of sample were thoroughly mixed together; 0.5 µL of this mixture was spotted on the target plate and allowed to dry.

1,3-Bis[(trimethylsilyl)ethynyl]toluene⁴⁰⁸ (1): To a stirring solution of 3,5-dibromotoluene (3.22 g, 12.9 mmol) and trimethylsilylacetylene (3 g, 30.54 mmol) in NEt₃ (60 mL), Pd(PPh₃)₂Cl₂ (920 mg, 1.31 mmol), PPh₃ (680 mg, 2.6), and Cul (490 mg,
2.58 mmol) were added. The mixture was degassed and back-filled with argon (3X), then stirred for 3 days at 80 °C. The mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue that was column chromatographed (SiO₂) eluting with hexane to give 1, as a viscous oil: 2.54 g (69%); ¹H NMR (CDCl₃) δ 0.26 [s, 18 H, C≡C–Si(CH₃)₃], 2.29 (s, 3 H, CH₃), 7.23 (s, 2 H, 2,6-ArH), 7.42 (s, 1 H, 4-ArH); ¹³C NMR (CDCl₃) δ 0.14, 21.13, 94.63, 104.54, 123.38, 132.77, 132.82, 138.21.

1,3-Diethynyltoluene ⁴⁰⁸ (2): To a stirring solution of 1 (2.54 g, 8.9 mmol) in THF (50 mL) and MeOH (50 mL), KF (1.14 g, 19.6 mmol) was added, then the mixture was stirred for 10 h at 25 °C. Solution was concentrated *in vacuo* to give a oily residue that was column chromatographed (SiO₂) eluting with hexane to give 2, as a colorless oil: 1.2 g (96%); ¹H NMR (CDCl₃) δ 2.32 (s, 3 H, CH₃), 3.07 (s, 2 H, C≡C–H), 7.3 (s, 2 H, 2,6-ArH), 7.45 (s, 1 H, 4-ArH); ¹³C NMR (CDCl₃) δ 21.12, 77.72, 88.99, 122.47, 132.97, 133.3, 138.49.

3-Iodobenzyl alcohol ⁴⁰⁹ (3): To a stirring solution of 3-iodobenzoic acid (11 g, 44.35 mmol) in THF (300 mL) at 0 °C, BH₃·THF (66 mL, 66 mmol) was added slowly through dropping funnel then the mixture was warmed to 25 °C and stirred for 10 h. Excess hydride was carefully destroyed with water then the solution was concentrated *in vacuo* to give a paste, which was neutralized with Na₂CO₃ (1 M) and extracted with CHCl₃. Organic layers were combined, dried (MgSO₄) and then the solvent was evaporated *in vacuo* to give 3, as a colorless oil: 10 g (96%); ¹H NMR (CDCl₃) δ 3.39 (broad, 1 H, CH₂OH), 4.5 (s, 2 H, CH₂OH), 7.03 (t, 1 H, 5-ArH, J = 7.5 Hz), 7.21 (d, 1
H, 6-ArH, J = 7.8 Hz), 7.55 (d, 1 H, 4-ArH, J = 7.8 Hz), 8.02 (s, 1 H, 2-ArH); $^{13}$C NMR (CDCl$_3$) $\delta$ 63.97, 94.58, 126.04, 130.28, 135.77, 136.48, 143.26.

3-Iodobenzaldehyde$^{407}$ (4): To a stirring solution of PCC (12 g, 55.7 mmol) and Celite (9 g) in DCM (300 mL), 3 (10 g, 42.7 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL) and added slowly through dropping funnel. Ether (100 mL) was added to the mixture after 1 h vigorous stirring at 25 ºC and the mixture was stirred for 1 additional hour. The resulting dark brown solution was filtered through Celite, then the filtrate was concentrated in vacuo, then flash column chromatographed (SiO$_2$) eluting with CH$_2$Cl$_2$ to give 4, as a white solid: 8.6 g (86%); mp 57-59 ºC; $^1$H NMR (CDCl$_3$) $\delta$ 7.15 (t, 1 H, 5-ArH, J = 8.1 Hz), 7.68 (dt, 1 H, 6-ArH, $J_1 = 7.5$ Hz, $J_2 = 1.2$ Hz), 7.77 (ddd, 1 H, 4-ArH, $J_1 = 8.1$ Hz, $J_2 = 1.5$ Hz, $J_3 = 1.2$ Hz), 8.02 (t, 1 H, 2-ArH, J = 2.1Hz), 9.79 (s, 1 H, CHO); $^{13}$C NMR (CDCl$_3$) $\delta$ 94.71, 128.72, 130.54, 137.66, 137.92, 142.77, 190.32.

4'-(3-Iodophenyl)-2,2';6',2''-terpyridine (6): To a stirring solution of 4 (2.54g, 10.9 mmol) and 2-acetylpyridine (2.98 g, 24.6 mmol) in EtOH (250 mL) at 25 ºC, aqueous NaOH (1 M, 22 mL) was added. The mixture was stirred for 9 h at 25 ºC then concentrated in vacuo to yield a dark brown diketone intermediate. To a stirring solution of this intermediate in AcOH (80 mL), NH$_4$OAc (13 g, excess) was added and the mixture was refluxed for 11 h. Solution was concentrated in vacuo to give a paste, which was neutralized with Na$_2$CO$_3$ (1 M) and extracted with CHCl$_3$. Organic layers were combined, dried (MgSO$_4$) and then the solvent was evaporated in vacuo to give a residue that was column chromatographed (basic Al$_2$O$_3$) eluting with EtOAc/Hexane mixture.
(1:1) to give 6, as a white solid: 1.6 g (34%); mp 156-158 °C; $^1$H NMR (CDCl$_3$) $\delta$ 7.24 (t, 1 H, 5-ArH, $J = 8.1$ Hz), 7.35 (ddd, 2 H, 5,5''-tpyH, $J_1 = 7.5$ Hz, $J_2 = 4.8$ Hz, $J_3 = 1.2$ Hz), 7.77 (ddd, 1 H, 4-ArH, $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz, $J_3 = 0.9$ Hz), 7.83 (ddd, 1 H, 6-ArH, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz, $J_3 = 0.9$ Hz), 7.88 (td, 2 H, 4,4''-tpyH, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz), 8.23 (t, 1 H, 2-ArH, $J = 1.8$ Hz), 8.65 (dt, 2 H, 3,3''-tpyH, $J_1 = 8.1$ Hz, $J_2 = 1.2$ Hz), 8.68 (s, 2 H, 3',5'-tpyH), 8.73 (ddd, 2 H, 6,6''-tpyH, $J_1 = 4.8$ Hz, $J_2 = 1.8$ Hz, $J_3 = 0.9$ Hz); $^{13}$C NMR (CDCl$_3$) $\delta$ 95.04, 118.95, 121.58, 124.15, 126.87, 130.75, 136.27, 137.1, 138.11, 140.92, 148.83, 149.97, 156.2, 156.25; HRMS (calc.): m/z = 458.0122 (458.0130, [M + Na]$^+$).

1,3-Bis(2,2';6',2"-terpyridin-4'-phen-3-ylethynyl)toluene (7): To a stirring solution of 6 (984 mg, 2.26 mmol) in DME (70 mL) and diisopropylamine (25 mL), 1,3-bis(diethynyl)toluene (136.5 mg, 974 µmol) was added. The mixture was degassed and back-filled with argon (3X) then tetrakis(triphenylphosphine)palladium(0) (91.4 mg, 80 µmol, 4 % per coupling site) and CuI (9.2 mg, 50 µmol) was added to the flask and the mixture was degassed and back-filled with argon (2X), then stirred for 12 h at 80 °C. The mixture was filtered and washed with DME (20 mL). The precipitate was dissolved in CHCl$_3$ and was column chromatographed (basic Al$_2$O$_3$) eluting with CHCl$_3$ to give 7, as a light yellow solid: 550 mg (75 %); mp 247-249 °C; $^1$H NMR (CDCl$_3$) $\delta$ 2.41 (s, 3 H, CH$_3$), 7.35 (ddd, 4 H, 5,5'-tpyH, $J_1 = 7.5$ Hz, $J_2 = 4.8$ Hz, $J_3 = 1.2$ Hz), 7.4 (t, 2 H, 2,4-BenH, $J = 0.9$ Hz), 7.51 (t, 2 H, 5-ArH, $J = 7.8$ Hz), 7.62 (m, 3 H, 4-ArH, 6-BenH), 7.88 (m, 6 H, 6-ArH, 4,4'-tpyH), 8.11 (t, 2 H, 2-ArH, $J = 1.5$ Hz), 8.66 (dt, 4 H, 3,3'-tpyH, $J_1 = 8.1$ Hz, $J_2 = 1.2$ Hz), 8.73 (ddd, 4 H, 6,6'-tpyH, $J_1 = 4.8$ Hz, $J_2 = 1.8$ Hz, $J_2 = 0.9$ Hz), 8.76 (s, 4 H, 3',5'-pyrH); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.31, 89.52, 89.62, 114.96, 119.05,
121.58, 123.52, 124.1, 124.17, 127.51, 129.23, 130.75, 132.25, 132.51, 137.07, 138.58, 139, 149.36, 149.66, 156.24, 156.33; HRMS (calc.): \( m/z = 755.2903 \) (755.2923, [M + H]^+).

\[
[\text{Fe}_{2}^{II}(1,3\text{-bis}(2,2';6',2''\text{-terpyridin-4'-phen-3-ylethynyl})\text{toluene})_{2}][(\text{PF}_{6})_{4}]
\]

(8[(PF_6)_4]): To a stirring solution of 7 (51.3 mg, 68 \( \mu \)mol) in MeOH (40 mL), FeCl_2.4H_2O (13.5 mg, 68 \( \mu \)mol) was added, then the mixture was refluxed overnight. Solution was concentrated in vacuo to give a deep purple precipitate that was column chromatographed (SiO_2) eluting with MeCN : sat. KNO_3 (aq) : H_2O (7:1:1) then counterion exchanged by treating with excess NH_4PF_6 (1 M) to give 8[(PF_6)_4], as purple microcrystals: 67.3 mg (90 %); \(^1\)H NMR (CD_3CN) \( \delta \) 2.51 (s, 6 H, \( CH_3 \)), 6.96 (ddd, 8 H, \( J_1 = 7.5 \) Hz, \( J_2 = 5.7 \) Hz, \( J_3 = 1.2 \) Hz), 7.14 (d, 8 H, 6,6''-tpyH, \( J = 4.8 \) Hz), 7.55 (s, 4 H, 2,4-BenH), 7.79 (td, 8 H, 4,4''-tpyH, \( J_1 = 7.8 \) Hz, \( J_2 = 1.5 \) Hz), 7.88 (m, 10 H, 4-ArH, 5-ArH, 6-BenH), 8.36 (dt, 4 H, 6-ArH, \( J_1 = 6.9 \) Hz, \( J_2 = 2.1 \) Hz), 8.63 (m, 12 H, 3,3''-tpyH, 2-ArH), 9.26 (s, 8 H, 3',5'-tpyH); ESI-MS (calc.): \( m/z = 2056.6 \) (2055.3, [M – PF_6]), 955.7 (955.7, [M – 2PF_6]^2+), 829.2 (829.2 [M – 2PF_6 – 2PF_3]^2+), 588.8 (588.5 [M – 3PF_6]^3+), 546.5 (546.5 [M – 3PF_6 – PF_3]^3+), 405.1 (405.1, [M – 4PF_6]^4+).

Procedure for one-pot self-assembly of \([\text{Ru}_2^{II}(1,3\text{-bis}(2,2';6',2''\text{-terpyridin-4'-phen-3-ylethynyl})\text{toluene})_{2}][(\text{PF}_{6})_{4}]\) (9[(PF_6)_4]) and \([\text{Ru}_3^{II}(1,3\text{-bis}(2,2';6',2''\text{-terpyridin-4'-phen-3-ylethynyl})\text{toluene})_{3}][(\text{PF}_{6})_{6}]\) (10[(PF_6)_6]): To a stirring solution of 7 (73.6 mg, 97 \( \mu \)mol) in EtOH (30 mL), RuCl_3 (20.2 mg, 97 \( \mu \)mol) and 4-ethylmorpholine (7 drops) were added then the mixture was refluxed for overnight. Solution was concentrated in vacuo to give a red solution that was loaded on a preparative TLC plate (SiO_2) eluting with MeCN : sat.
KNO₃ (aq) : H₂O (20:1:1), the top two bands were removed from the plate and washed with an eluting solvent, followed by counterion exchange by the addition of excess NH₄PF₆ (1 M) to afford the dinuclear 9[(PF₆)₄] and trinuclear 10[(PF₆)₆] macrocycles.

The dinuclear 9[(PF₆)₄]: 35.6 mg (32 %); ¹H NMR (CD₃CN) δ 2.49 (s, 6 H, CH₃), 7.17 (ddd, 8 H, 5,5‴-tpyH, J₁ = 7.5 Hz, J₂ = 5.4 Hz, J₃ = 1.2 Hz), 7.53 (s, 4 H, 2,4-BenH), 7.54 (d, 8 H, 6,6‴-tpyH, J = 6.0 Hz), 7.83 (m, 10 H, 4-ArH, 5-ArH, 6-BenH), 7.92 (td, 8 H, 4,4‴-tpyH, J₁ = 7.8 Hz, J₂ = 1.2 Hz), 8.33 (dt, 4 H, 6-ArH), J₁ = 7.2 Hz, J₂ = 1.5 Hz), 8.60 (s, 4 H, 2-ArH), 8.91 (d, 8 H, 3,3‴-tpyH, J = 8.1 Hz), 9.32 (s, 8 H, 3′,5′-tpyH); MALDI-TOF (calc.): m/z = 2147.814 (2147.270, [M – PF₆]+), 2002.777 (2002.306, [M – 2PF₆]²⁺), 1857.697 (1857.342, [M – 3PF₆]³⁺), 1710.621 (1712.378, [M – 4PF₆]⁴⁺), 1610.726 (1610.473, [M – 4PF₆ – Ru]²⁺).

The trinuclear 10[(PF₆)₆]: 31.1 mg (28 %); ¹H NMR (CD₃CN) δ 2.49 (s, 9 H, CH₃), 7.24 (ddd, 12 H, 5,5‴-tpyH, J₁ = 7.5 Hz, J₂ = 5.4 Hz, J₃ = 1.2 Hz), 7.52 (s, 6 H, 2,4-BenH), 7.56 (d, 12 H, 6,6‴-tpyH, J = 5.4 Hz), 7.71 (s, 3 H, 6-BenH), 7.83 (m, 12 H, 4-ArH, 5-ArH), 7.98 (td, 12 H, 4,4‴-tpyH, J₁ = 7.8 Hz, J₂ = 1.2 Hz), 8.35 (dt, 6 H, 6-ArH), J₁ = 7.2 Hz, J₂ = 1.8 Hz), 8.54 (s, 6 H, 2-ArH), 8.89 (d, 12 H, 3,3‴-tpyH, J = 7.5 Hz), 9.31 (s, 12 H, 3′,5′-tpyH); MALDI-TOF (calc.): m/z = 3292.076 (3293.387, [M – PF₆]⁺), 3022.457 (3022.034, [M – 2PF₆ – PF₅]²⁺), 2879.810 (2877.493, [M – 3PF₆ – PF₅]³⁺), 2733.297 (2732.529, [M – 4PF₆ – PF₅]⁴⁺), 2588.659 (2587.565, [M – 5PF₆ – PF₅]⁵⁺), 2464.800 (2466.662, [M – 6PF₆ – Ru]⁴⁺).
6.1 Introduction

There is considerable research that has been conducted on octahedral terpyridine transition metal complexes, especially regarding the fine-tuning of their electrochemical, photophysical, and optical properties or utilization of these complexes as precursors to build supramolecular architectures.41 However, functionalized terpyridine complexes have been investigated to a lesser degree relative to their unsubstituted terpyridines counterparts due to their limited accessibility and the general poor yields of metal complexation, even though they have been shown to possess interesting novel luminescent properties.195,302-305 They have also been utilized as chemosensors,23,306 fluorescent immunoassay agents,307-310 as well as catalysis311-314 and dye-sensitized solar cells.315-320

Terpyridine carboxylic acids or carboxylates have been the favored functional groups since they play a crucial role in surface anchoring and can be potential internal counterions. For example, a black dye containing three carboxylates was attached to nanocrystalline TiO2 surface to be utilized as a solar cell, yielding an overall conversion
efficiency of 10.4% (Figure 6.1). Carboxylate groups have also been introduced on the 4-position of terpyridine Ru(II) complex ([Ru(4'-phenyl-4-carboxylate-2,2':6',2''-terpyridine)$_2$]), which promoted a photoinduced electron transfer via ionic interactions with methyl viologen.

![Figure 6.1. Structures of carboxylate functionalized Ru(II)-terpyridine complexes.](image)

The construction of “benzenoid-based” metallomacrocycles was achieved via either an one-pot self-assembly or a step-wise sequence from 120° juxtaposed bis(terpyridine) ligands and various transition metals [Fe(II), Ru(II), Zn(II), Figure 6.2]. These supramolecular architectures displayed luminescence properties when they possess Zn(II), they can be electrostatically attached to multi-wall carbon nanotubes and have been utilized as a molecular nanotemplate.

In this section, an alternative coupling route to construct the functionalized dinuclear containing two free terpyridines is described. This dinuclear complex was used as a precursor to assemble a hexanuclear metallomacrocycle containing mixed metals (Ru$_4$Fe$_2$) and three different terpyridyl moieties with eight methyl and eight ethoxycarbonyl groups. Furthermore, the synthesis and characterization of functionalized mononuclear Fe(II) and Ru(II) complexes, as well as a preparation of
tetra(ethoxycarbonyl) bis(terpyridine) 15 and tetramethyl bis(terpyridine) 8 and 9 via Pd[0]-coupling and Kröhnke method, respectively, are also discussed. The facile and high yield complexation procedures of dimethyl terpyridines with di(ethoxycarbonyl) 32 were used as a basic strategy to prepare dinuclear 40 and 44, which are the precursors for the dinuclear trimer 46. The single crystal X-ray structures of bis(terpyridine) 9 and homoleptic complex 36 are also presented.

Scheme 6.1. The construction of hexanuclear metallomacrocycles via either self-assembly or step-wise manner.\(^{376,386,387,411-415}\)
6.2 Results and Discussion

Synthesis of tetramethyl substituted bis(terpyridines) 8 and 9 was achieved via a two-step Kröhnke\textsuperscript{44} procedure (Scheme 6.2). Treatment of dialdehydes 2 and 5 with four equivalents of 2-acetyl-4-methylpyridine gave bis(diketone) intermediates 6 and 7, respectively, then the ring closure of these intermediates in the presence of NH\textsubscript{4}OAc and AcOH afforded the desired bis(terpyridines) 8 and 9 in albeit poor yields. Proton resonances (\textsuperscript{1}H NMR) for the terpyridyl moieties of ligands 8 and 9 showed upfield shifts for 5,5''-, 6,6''-, and 3,3''-tpyHs (\(\Delta\delta = 0.16-0.23\)) compared to 1,3-bis(2,2':6',2''-terpyridin-4'-yl)-5-R-benzene\textsuperscript{387} (R = Br, Me) due to shielding effect of four electron-donating methyl moieties. The HRMS spectra of 8 further confirmed its structure by a single peak at \(m/z = 675.1850\) [M + H]+.

Scheme 6.2. Synthesis of bis(terpyridines) 8 and 9 via Kröhnke\textsuperscript{44} method: i) BH\textsubscript{3}·THF, THF, 25 °C, 10 h; ii) PCC, DCM, 25 °C, 2 h; iii) HTMA, CHCl\textsubscript{3}, 70 °C, 1 h, N\textsubscript{2}; iv) AcOH/H\textsubscript{2}O (1:9), 98 °C, 1 h, N\textsubscript{2}; v) NaOH (4 M), MeOH, 25 °C, 9 h; vi) AcOH, NH\textsubscript{4}OAc, 110 °C, 11 h.
The single crystal X-ray structure of ligand 9 supported the proposed structure (Figure 6.2). The three pyridine rings showed a transoid arrangement about the interannular C–C bonds, which was in agreement with the literature.\textsuperscript{341,344-346} This configuration minimizes electrostatic interactions between the nitrogen lone pairs and the van der Waals interactions between the meta protons.\textsuperscript{341} The interannular C–C bond lengths of bis(terpyridine) 9 [1.487(8) – 1.496(4) Å] are comparable with terpyridines [1.480(1) – 1.498(3) Å] found in the literature.\textsuperscript{341,344,345} The three pyridine rings are not exactly coplanar and the torsion angles of two terminal rings with the central pyridine ring are 13.08, 19.72 and 8.34, 12.08° for each terpyridine moiety of 9, which are higher than 4’-(4-bromophenyl)-4,4”-dimethylterpyridine\textsuperscript{418} (9.48 and 1.06°). The central benzene ring connected to the terpyridines is also distorted with torsion angles of 57.53 and 36.61°, which are comparable to that of 4’-(4-bromophenyl)-4,4”-dimethylterpyridine\textsuperscript{418} (39°) and 4’-(2,5-dimethoxyphenyl)terpyridine\textsuperscript{348} (50.4°).

![Figure 6.2. Single crystal X-ray structure of bis(terpyridine) 9.](image)

Preparation of the other bis(terpyridines) ligands 14 and 15 was achieved via Pd[0]-mediated cross-coupling\textsuperscript{382} of terpyridines 12 and 13 with 1,3-diethynyltoluene\textsuperscript{408}.
Proton resonances (\(^1\)H NMR) for the terpyridyl moiety of the ligand 15 showed downfield shifts for the 5,5\(^{-}\)-tpy\(\text{H} \) (\(\delta = 7.94, \Delta \delta = 0.58\)) and 3,3\(^{-}\)-tpy\(\text{H} \) (\(\delta = 9.22, \Delta \delta = 0.52\)) compared to bis(terpyridine) 14 due to deshielding effect of four electron-withdrawing ethoxycarbonyl moieties. The HRMS spectra of 14 and 15 further confirms their structure by a single peak at \(m/z = 755.2910 \) and 1043.3726 \([M + H]^+\), respectively. Terpyridines 17 and 20 containing a free acetylene functionality were prepared by deprotecting trimethylsilyl groups on terpyridines 19 and 16, which were each

![Scheme 6.3. Synthesis of bis(terpyridines) 14 and 15 and terpyridines 16, 17, 19 and 20 via coupling strategy: i) \(n\)-BuLi, Me\(_3\)SiCl, THF, –78 \(^\circ\)C, 6 h, N\(_2\); ii) 12 or 13, Pd(PPh\(_3\))\(_4\), CuI, THF/NEt\(_3\), 80 \(^\circ\)C, 11 h, Argon; iii) KF, THF/EtOH, 25 \(^\circ\)C, 10 h; iv) Me\(_3\)Si≡CH, Pd(PPh\(_3\))\(_4\), CuI, THF/NEt\(_3\), 80 \(^\circ\)C, 11 h, Argon; v) \((n\text{-Bu})_4\)NF·3H\(_2\)O, THF, 25 \(^\circ\)C, 6 h.](image-url)
synthesized via Pd[0]-mediated coupling of the aryl iodide 13 with 11 and 18 with Me₃Si-C≡CH, respectively. Structures of terpyridines 16-20 were confirmed by ¹H, ¹³C, COSY NMR and HRMS spectroscopy (experimental section).

Treatment of functionalized terpyridines 21-24 with 0.5 equivalence of FeCl₂·4H₂O in MeOH gave a purple solution that was concentrated in vacuo and dried to afford complexes 25-28 (Scheme 6.4) in > 90 % yield. The ¹H NMR spectra of these complexes displayed a characteristic upfield shift of 6,6''-tpyH (Δδ = 1.25 – 1.59) compared to the ligands because the 6,6''-protons are located above the ring plane of the aromatic ring of the adjacent ligand. The complexes 26-28 containing unsymmetrical ligands showed unique proton resonances for each pyridine ring as a result of diminished symmetry. The di-substituted complexes 26-28 are structurally chiral because these octahedral complexes are not superimposable on their mirror images; however, attempts to separate the structural isomers were unsuccessful. The structures of 25-28 were established via HRMS and ESI-MS by the unique signal at m/z = 444.0342, 430.0191, 441.0, and 473.0 corresponding to [M – 2Cl]²⁺, respectively, and their ¹H NMR spectra.

Scheme 6.4. Synthesis of mononuclear Fe(II)-complexes 25-28: i) FeCl₂·4H₂O, MeOH, 60 °C, 8-20 h, then NH₄PF₆.
The UV-vis spectra of these complexes revealed a characteristic MLCT band at 570-577 nm in MeOH at 25 ºC (Figure 6.3). This absorption lies in the visible region and is responsible for the intense purple color of the complexes. The complexes 27 and 28 containing electron-withdrawing cyano and methoxycarbonyl groups displayed a slightly blue shifted MLCT (7 nm) compared to complexes 25 and 26 with electron-donating methyl groups.

![UV-vis spectra of Fe(II)-terpyridine complexes 25-28 in MeOH at 25 ºC.](image)

Figure 6.3. UV-vis spectra of Fe(II)-terpyridine complexes 25-28 in MeOH at 25 ºC.

Homoleptic Ru(II)-terpyridine complexes 33 and 34 were obtained by refluxing dimethyl 21 and di(methoxycarbonyl) 30 with 0.5 equivalents of RuCl₃·3H₂O in MeOH under reducing conditions (N-ethylmorpholine) for 10 and 20 hours, respectively (Scheme 6.5). The poor reaction yield of 34 (40%) compared to 33 (98%) was rationalized by insolubility of the ligand 30 and electron-withdrawing di(methoxycarbonyl) moieties, which are electron withdrawing relative to the lone pair electrons of pyridine making them less available for metal complexation. To improve the yield, the di(methoxycarbonyl) groups were converted to di(ethoxycarbonyl)s, as in 29.
Scheme 6.5. Synthesis of mononuclear Ru(II)-complexes 35-41: i) 29 or 13, RuCl₃·3H₂O (> 1 eq.), EtOH/THF, 70 °C, 15 h; ii) 13, or 21, N-ethylmorpholine, EtOH, 70 °C, 10-24 h, then NH₄PF₆; iii) 21 or 30, RuCl₃·3H₂O (0.5 eq.), N-ethylmorpholine, MeOH, 70 °C, 10-20 h; iv) NaOH (1 M), DMF, 60 °C, 12 h, TFA.

and 13, and the metalated adducts 31 and 32 were prepared by treating these terpyridines with RuCl₃·3H₂O (> 1 eq.) in > 80%. The adduct 32 was treated with one equivalents of the ligand 13 under reducing conditions (N-ethylmorpholine) to give homoleptic complex 38 in 55% yield. The yield was finally optimized when the adduct 31 was treated with dimethyl 21 affording the heteroleptic complex 36 in quantitative yield. The complexes 33, 34, 36, and 38 exhibited a characteristic upfield shift (¹H NMR) of the 6,6''-tpyH (Δδ = 1.22 – 1.30) compared to the free ligands; moreover, heteroleptic 36 displayed two different set of terpyridine peaks. Mass spectral data (HRMS) of 33-39 were also in
accord with the assigned structures and isotope patterns of the peaks perfectly matched the theoretical values (experimental section). The methoxy- and ethoxycarbonyl groups in 34, 36, and 38 were hydrolyzed with aqueous NaOH (1 M, excess) in DMF at 60 °C for 12 hours affording sodium carboxylate salts, which were protonated in the presence of TFA to give the desired carboxylic acid terpyridine complexes 35, 37, and 39, respectively, in > 90% yields. The 1H NMR spectra of these acids were identical to their starting ester complexes except absent the methoxy- or ethoxycarbonyl peaks.

Single crystals of homoleptic complex 38[(PF6)2] were grown in MeCN and the X-ray analysis (100 K) confirmed the proposed pseudo-octahedral structure (Figure 6.4A). The crystal system is orthorhombic with space group P2(1)2(1)2(1) and each complex has two PF6− ions and one MeCN in the lattice. The angle of N(1)-Ru(1)-N(2) is 178° and the mean angle between the two terpyridines is 92.8°, thus the two terpyridines are tilted 2-2.8° from perfect orthogonality. The torsion angles of two terminal pyridine rings with central pyridine ring are between 1.14-3.60°, which are almost perfectly coplanar. The edge-to-edge distances of the complex 38 are 20 and 22 Å (Figure 6.4B). The shortest distance between Ru(II) metals is 10.1 Å in the lattice and Ru(II) metal centers are 4.88 and 7.18 Å away from MeCN and PF6−, respectively.

The molecular packing of crystals of 38 did not show any π-π interactions between aromatic rings (Figure 6.4C); however, it revealed short distances between I⋯O=C (3.15-3.2 Å) when looking along b axis (Figure 6.5). These short iodo-carbonyl interactions dominated the lattice and played a crucial role in the crystallization process, while MeCN molecules did not show any bonding.
Figure 6.4. (A) Single crystal X-ray structure of 38[(PF₆)₂] and (B) its space filling model and (C) molecular packing (along c axis); MeCN and PF₆⁻ are omitted for clarity.

Figure 6.5. Molecular packing of crystals of 38 (along b axis); MeCN and PF₆⁻ molecules are omitted for clarity.
The UV-vis spectra of tetramethyl Ru(II)-complex 33 displayed the characteristic MLCT peak at 493 nm; whereas the MLCT of carbonyl Ru(II)-complexes 35-39 appeared at 503 nm in MeCN at 25 ºC (Figure 6.6). These absorptions lie in the visible region and are responsible for the complexe’s intense red coloration. The hypsochromic shift (10 nm) of MLCT of complex 33 compared to 35-39 is due to its electron-donating four methyl moieties. Further, MLCT band (503 nm) of complexes 36 and 37 showed a shoulder at ca. 490 nm because of the two methyl moieties.

Figure 6.6. UV-vis spectra of Fe(II)-terpyridine complexes 33-39 in MeCN at 25 ºC.

The construction of dinuclear Ru(II)-complexes 40 and 44 containing di-iodo functionality was achieved by treating bis(terpyridines) 14 and 8 with two equivalents of the metalated adduct 32, respectively, under reducing conditions (N-ethylmorpholine, Scheme 6.6 and 6.7). The reaction mixture of 14 and 32 was chromatographed (SiO₂) eluting with MeCN : sat. KNO₃ (aq) : H₂O (20:1:1) then counterion exchanged by treating with an excess NH₄PF₆ (1 M) to afford the desired dinuclear 40[(PF₆)₂] in 57% yield. On the other hand, dimetallic 44[(Cl)₂] was obtained in quantitative yield by just
removing the solvent and drying the residue in vacuo. The $^1$H NMR spectra of 40[(PF$_6$)$_2$] in CD$_3$CN and 44[(Cl)$_2$] in CD$_3$OD displayed two set of proton peaks for each terpyridine moiety with 1:1 proton integration ratio supporting the dinuclear structures and they also showed the characteristic upfield and downfield shifts for 6,6''-tpyH ($\Delta \delta = 1.20 - 1.35$) and 3',5'-tpyH ($\Delta \delta = 0.33 - 0.54$), respectively. Moreover, the complex 44 revealed notable downfield shifts for 4,6-BenH ($\Delta \delta = 0.62$) and 2-BenH ($\Delta \delta = 0.77$). The structure of 40[(PF$_6$)$_2$] was further confirmed with HRMS by the unique signal at m/z 529.0571 corresponding to [M – 2PF$_6$]$^{2+}$, and isotope patterns of the peak perfectly matched the theoretical values. Later, the dinuclear 40 and 44 were hydrolyzed by treatment with aqueous NaOH (1 M, excess) in DMF at 60 °C for 12 hours affording sodium carboxylate salts, which were protonated in the presence of TFA to give carboxylic acid functionalized complexes 41 and 45 in > 90% yield. The $^1$H NMR spectra of these acids were identical to their starting ester complexes except they did not contain proton peaks for CO$_2$CH$_2$CH$_3$. The UV-vis spectra of dinuclear complexes 40, 41, 44, and 45 displayed the characteristic MLCT peak at ca. 501-507 nm in MeCN at 25 °C.

The initial attempt to prepare the dinuclear complex 42 containing two free terpyridyl moieties via Pd[0]-coupling strategy was unsuccessful (Scheme 6.6). The terpyridine 17 containing a free acetylene group was intended to couple with bis-iodo functionality of dinuclear 40 in presence of Pd(PPh$_3$)$_4$/CuI in THF/MeCN/NEt$_3$ under argon; however, the free acetylene of 17 coupled via CuI catalysis with another acetylene of 17 to give the bis(terpyridine) 43 in 64% yield and unreacted starting material 40. The $^1$H NMR spectrum of bis(terpyridine) 43 displayed similar proton resonances with starting ligand 17, except lacking acetylenic proton. The structure of 43 was further
confirmed via HRMS by the unique signal at \( m/z = 1181.4253 \) corresponding to \([\text{M} + \text{H}]^+\).

The construction of dinuclear 46, which was functionalized with two terpyridyl moieties, was achieved by treating the dinuclear 44 with two equivalents of ligand 20 in presence of \( \text{Pd(PPh}_3)_4 \) in DMF/NEt\(_3\). Copper catalysis (CuI) was intentionally omitted to circumvent the acetylene-acetylene coupling of the ligand 20. The separation of dinuclear 46 from other by-products was accomplished by loading the concentrated reaction mixture on a preparative TLC plate (SiO\(_2\)) eluting with a solvent mixture of MeCN : sat. KNO\(_3\) (aq) : H\(_2\)O (7:1:1). The darkest band (3\(^{rd}\) band from the top) was removed from the plate and washed with the eluting solvent, followed by counterion exchange by the addition of excess NH\(_4\)PF\(_6\) (1 M) to afford the desired dinuclear 46[(PF\(_6\)_4] in 35% yield (Scheme 6.7). The \(^1\)H NMR of the \textit{bis}(Ru\(^{II}\)) trimer 46 displayed three sets of terpyridine proton resonances, two for complexed terpyridines and one for free terpyridine, with 1:1:1 5,5\(^-\)-terpyridine proton integration ratio confirming the two iodo-acetylene couplings (Figure 6.6B). The 2D correlation NMR experiments (COSY) were conducted to ensure the proper assignments. The first band from the preparative TLC plate was also collected and found to be a mono-coupling product in 24% yield rationalizing the poor yield of the trimer 46. The UV-vis spectra of trimer 46 displayed the characteristic MLCT peak at 508 nm in MeCN at 25 °C, which is similar to dinuclear 44 (507 nm).
Scheme 6.6. Synthesis of Ru(II) dinuclear 40 and 41 and bis(terpyridine) 43: i) N-ethylmorpholine, EtOH, 70 °C, 24 h, then NH₄PF₆; ii) NaOH (1 M), DMF, 60 °C, 12 h, TFA; iii) 17, Pd(PPh₃)₄, Cul, THF/MeCN/NEt₃, 70 °C, 12 h, Argon.

The self-assembly of hexanuclear macrocycle 47[(PF₆)₁₂] was achieved by treating the trimer 46[(PF₆)₄] with an equimolar amount of FeCl₂·4H₂O in EtOH and acetone (Scheme 6.7). The macrocycle 47 was obtained in 24% yield after purifying with
Scheme 6.7. Synthesis of Ru(II) dinuclear 44-46 and hexanuclear Ru(II)-Fe(II) 47: i) N-ethylnorpholine, EtOH, 70 °C, 9 h; ii) NaOH (1 M), DMF, 60 °C, 12 h, TFA; iii) 20, Pd(PPh3)4, DMF/NEt3, 70 °C, 48 h, Argon, then NH4PF6; iv) FeCl2·4H2O, EtOH/acetone, 60 °C, 20 h, then NH4PF6.
a preparative TLC plate (SiO2) eluting with a solvent mixture of MeCN : sat. KNO3 (aq) : H2O (7:1:1). This heteronuclear macrocycle contains four Ru(II) and two Fe(II) metals with eight methyl and eight ethoxycarbonyl groups. The 1H NMR of the macrocycle 47 displayed three sets of terpyridine proton resonances with 1:1:1 5,5''-terpyridine proton integration ratio and did not contain any free terpyridine proton peaks. Further, 6,6''-tpy3H and 3',5'-tpy3H protons of 47 displayed the characteristic upfield (Δδ = 0.65) and downfield shifts (Δδ = 0.39), respectively, compared to the dinuclear 46 (Figure 6.6A). The UV-vis spectrum of the macrocycle 47 was further confirmed the proposed structure by revealing two different MLCT for Ru(II) and Fe(II) at 511 and 569 nm, respectively, in MeCN at 25 °C.

Figure 6.7. Aromatic region of 1H NMR (300 MHz) of (A) 47[(PF6)12] and (B) 46[(PF6)4] in CD3CN at 25 °C.
6.3 Conclusion

The 4,4''-dimethyl functionalized bis(terpyridine)s 8 and 9 were synthesized via Kröhnke method and single crystal X-ray structure of 9 was obtained. A novel 4,4''-di(ethoxycarbonyl) functionalized bis(terpyridines) 15 was prepared via Pd[0]-mediated cross-coupling method. The synthesis of heteroleptic Ru(II) complex 36 was accomplished in a quantitative yield; whereas, homoleptic complexes 34 and 38 were obtained in only moderate yields. The single crystals X-ray structure of the homoleptic complex 38 revealed short iodo-carbonyl interactions. The high yield complexation reactions of the carbonyl functionalized metalated adduct 32 with methyl substituted mono- and bis-terpyridines were adapted as a main strategy to construct a bis-iodo functionalized dinuclear 44, which was coupled with terpyridine 20 containing a free acetylene group to form the dinuclear trimer 46. The heteronuclear (Ru₄Fe₂) metallomacrocycle 47 was finally assembled by treatment of the trimer 46 with an equimolar amount of FeCl₂·4H₂O. The carboxylic acid functionalized Ru(II) complexes were prepared to investigate their solar cell applications and supramolecular aggregation behavior through H-bonding.

6.4 Experimental Section

3,5-Bis(hydroxymethyl)-1-bromobenzene\(^{419}\) (1): To a stirring solution of 5-bromoisophthalic acid (10 g, 41 mmol) in THF (200 mL) at 0 °C, BH₃·THF (410 mL, 410 mmol) was slowly added, then the mixture was warmed to 25 °C and stirred for 10 h.
Excess hydride was carefully destroyed with water, then the solution was concentrated in vacuo to give a paste, which was neutralized with Na$_2$CO$_3$ (1 M) and extracted with CHCl$_3$. The combined organic extract was dried (MgSO$_4$) and then evaporated in vacuo to give 1, as a white solid: 6.82 g (77%); mp 90-91 °C; lit.\textsuperscript{419} mp 90-91 °C; $^1$H NMR (CDCl$_3$) $\delta$ 3.36 (s, 2 H, BenCH$_2$OH), 4.47 (s, 4 H, BenCH$_2$OH), 7.24 (s, 1 H, 2-BenzH), 7.35 (s, 2 H, 4,6-BenzH); $^{13}$C NMR (CDCl$_3$) $\delta$ 62.15, 121.29, 123.17, 127.16, 145.21.

5-Bromoisophthalaldehyde\textsuperscript{419} (2): To a stirring solution of PCC (18.7 g, 86.8 mmol) and Celite (15 g) in CH$_2$Cl$_2$ (430 mL), diol 1 (7.3 g, 33.6 mmol) was dissolved in CH$_2$Cl$_2$ (50 mL) and slowly added. Ether (100 mL) was added to the mixture, after 1 h vigorous stirring at 25 °C, then 1 additional h. Resulting dark brown solution was filtered through Celite, then filtrate was concentrated in vacuo, flash column chromatographed (SiO$_2$) eluting with CH$_2$Cl$_2$ to give 2, as a white solid: 4.6 g (64%); mp 122-124 °C; lit.\textsuperscript{419} mp 125 °C; $^1$H NMR (CDCl$_3$) $\delta$ 8.26 (s, 2 H, 4,6-BenzH), 8.31 (s, 1 H, 2-BenzH), 10.06 (s, 2 H, BenCHO); $^{13}$C NMR (CDCl$_3$) $\delta$ 129.6, 129.46, 137.41, 138.64, 189.71.

5-Methylisophthalaldehyde\textsuperscript{420} (5): To a stirring solution of HTMA (12.6 g, 89.9 mmol) in CHCl$_3$ (150 mL), 4 (11.2 g, 40.3 mmol) was added. The mixture was refluxed for 1 h under N$_2$, then cooled to 0 °C and maintained for 3 h to give HTMA salt 4, as an intermediate, which was filtered and dried in vacuo. The salt intermediate 4 was refluxed in AcOH/H$_2$O (1:9, 200 mL) for 1 h under N$_2$, then cooled to 0 °C to give 5, as a white microcrystalline solid: 3.34 g (56%); mp 96-97 °C; lit.\textsuperscript{420} mp 95-98 °C; $^1$H NMR (CDCl$_3$)
δ 2.55 (s, 3 H, BenCH₃), 7.98 (s, 2 H, 4,6-BenH), 8.22 (s, 1 H, 2-BenH), 10.11 (s, 2 H, BenCHO); ^1^C NMR (CDCl₃) δ 21.56, 129.19, 135.63, 137.48, 140.64, 191.61.

3,5-Bis(4,4''-dimethyl-2,2':6',2''-terpyridin-4'-yl)-1-bromobenzene (8): To a stirred solution of 3 (2.02 g, 9.48 mmol) and 2-acetyl-4-methylpyridine (5.31 g, 39.3 mmol) in EtOH (300 mL) at 25 ºC, an aqueous NaOH (4 M, 10 mL) was added. The mixture was stirred for 9 h at 25 ºC, then concentrated in vacuo to yield a dark brown diketone intermediate 6. To a stirred solution of intermediate 6 in AcOH (50 mL), NH₄OAc (30 g, excess) was added and the mixture was refluxed for 11 h. Solution was concentrated in vacuo to give a paste, which was neutralized with Na₂CO₃ (1 M) and extracted with CHCl₃. The combined extract was dried (MgSO₄) and then the solvent was evaporated in vacuo to give a residue that was column chromatographed (basic Al₂O₃) eluting with EtOAc/hexane mixture (1:1) to give 8, as a light yellow solid: 820 mg (13%); mp 317-319 ºC; ^1^H NMR (CDCl₃) δ 2.54 (s, 12 H, tpyCH₃), 7.20 (d, 4 H, 5',5''-tpyH, J = 4.8 Hz), 8.1 (d, 2 H, 2,6-BenH, J = 1.2 Hz), 8.24 (s, 1 H, 4-BenH), 8.5 (s, 4 H, 3',3''-tpyH), 8.61 (d, 4 H, 6',6''-tpyH, J = 4.8 Hz), 8.74 (s, 4 H, 3',5'-tpyH), ^1^C NMR (CDCl₃) 21.53, 119.31, 122.31, 123.81, 124.82, 125.12, 130.84, 141.55, 148.23, 148.66, 149.12, 155.86, 156.48; HRMS (calc.): m/z = 675.1850 (675.1866, [M + H]^+).

1,3-Bis(4,4''-dimethyl-2,2':6',2''-terpyridin-4'-yl)-5-methylbenzene (9): To a stirred solution of 5 (208 mg, 1.41 mmol) and 2-acetyl-4-methylpyridine (800 mg, 5.91 mmol) in EtOH (50 mL) at 25 ºC, aqueous NaOH (1 M, 6 mL) was added. The mixture was stirred for 9 h at 25 ºC then concentrated in vacuo to yield a dark brown diketone
intermediate 7. To a stirring solution of the intermediate 7 in AcOH (10 mL), NH₄OAc (10 g, excess) was added and the mixture was refluxed for 11 h. The solution was concentrated in vacuo to give a paste, which was neutralized with Na₂CO₃ (1 M) and extracted with CHCl₃. The combined extract was dried (MgSO₄) and concentrated in vacuo to give a residue that was column chromatographed (basic Al₂O₃) eluting with EtOAc/hexane mixture (1:1) to give 9, as a white solid: 50 mg (6%); mp 258-260 °C; ¹H NMR (CDCl₃) δ 2.54 (s, 12 H, tpyCH₃), 2.56 (s, 3 H, BenCH₃), 7.20 (d, 4 H, 5',5''-tpyH, J = 4.5 Hz), 7.8 (s, 2 H, 4,6-BenH), 8.15 (s, 1 H, 2-BenH), 8.52 (s, 4 H, 3',3''-tpyH), 8.61 (d, 4 H, 6',6''-tpyH, J = 4.8 Hz), 8.78 (s, 4 H, 3',5'-tpyH); ¹³C NMR (CDCl₃) δ 21.58, 29.89, 119.6, 122.41, 123.69, 125.03, 129.03, 139.51, 139.62, 148.32, 149.12, 150.44, 156.2, 156.28; HRMS (calc.): m/z = 633.2743 (633.2752, [M + Na]⁺). Crystal data for 9: Orthorhombic, Pbca, a = 11.800(3) Å, b = 13.208(3) Å, c = 41.505(9) Å, α = 90°, β = 93.477(2)°, γ = 90°, V = 6469(2) Å³, Z = 8, ρ = 1.254 Mg/m³, μ = 0.075 mm⁻¹, F(000) = 2576, Final R indices (for 4792 parameters) [I > 2σ(I)] were R1 = 0.0725, and R1 = 0.0990, wR2 = 0.1614 for all 38777 data.

1-(Trimethylsilyl)ethynyl-3-ethynyltoluene (11): To a stirring solution of 10 (600 mg, 4.28 mmol) in dry THF (30 mL) under N₂ at –78 °C, n-BuLi (2.5 M, 1.8 mL, 4.5 mmol) was added drop wise. The solution was stirred at –78 °C for 2 h, and then trimethylsilylchloride (697 mg, 6.42 mmol) was added quickly. The reaction mixture was warmed to 25 °C and stirred overnight. The solution was concentrated in vacuo to give an oily residue that was column chromatographed (SiO₂) eluting with hexane to give 11, as a colorless oil: 409 mg (45%); ¹H NMR δ 0.27 (s, 9 H, (CH₃)₃-Si), 2.30 (s, 3 H, BenCH₃), 2.40
3.05 (s, 1 H, C≡C-H), 7.25 (s, 1 H, 4-BenH), 7.27 (s, 1 H, 2-BenH), 7.43 (s, 1 H, 6-BenH); ¹³C NMR δ 0.11, 21.11, 77.57, 83.09, 94.79, 104.39, 122.39, 123.48, 132.84, 132.95, 133.1, 138.31.

4'-((4-Iodophenyl)-2,2':6',2''-terpyridine⁴²¹ (12): To a stirring solution of 4-iodobenzaldehyde (5.88 g, 25.3 mmol) and 2-acetylpyridine (6.44 g, 53.5 mmol) in EtOH (430 mL) at 25 ºC, aqueous NaOH (5 M, 10 mL) was added. The mixture was stirred for 9 h at 25 ºC, concentrated in vacuo to yield a dark brown diketone intermediate. To a stirring solution of this intermediate in AcOH (150 mL), NH₄OAc (60 g, excess) was added and the mixture was refluxed for 11 h. Solution was concentrated in vacuo to give a paste, which was neutralized with Na₂CO₃ (1 M) and extracted with CHCl₃. The combined extract was dried (MgSO₄), and then concentrated in vacuo to give a residue, which was recrystallized in EtOH to give 12, as a light brown solid: 3.63 g (33%); mp 179-181 ºC; ¹H NMR δ 7.33 (dd, 2 H, 5,5''-tpyH, J₁ = 4.8 Hz, J₂ = 1.2 Hz), 7.62 (d, 2 H, 3,5-ArH, J = 8.4 Hz), 7.80 (d, 2 H, 2,6-ArH, J = 8.4 Hz), 7.85 (td, 2 H, 4,4''-tpyH, J₁ = 7.8 Hz, J₂ = 2.1 Hz), 8.62 (d, 2 H, 3,3''-tpyH, J = 8.1 Hz), 8.70 (s, 2 H, 3',5'-tpyH), 8.71 (d, 2 H, 6,6''-tpyH, J = 4.8 Hz); ¹³C NMR δ 95.45, 118.57, 121.5, 124.06, 129.16, 137.01, 138.09, 138.2, 149.16, 149.28, 156.15, 156.2.

1,3-Bis(2,2';6',2''-terpyridine-4'-phen-4'-ylethynyl)toluene (14): To a stirred solution of 12 (1.77 g, 4.06 mmol) in THF (50 mL) and NEt₃ (50 mL), 10 (250 mg, 1.78 mmol) was added. The mixture was degassed and back-filled with argon (3X) then Pd(PPh₃)₄ (207 mg, 180 µmol, 5% per coupling site) and CuI (27 mg, 150 µmol) was
added, then stirred for 12 h at 70 °C. The mixture was filtered and washed with THF (20 mL). The filtrate was concentrated *in vacuo* to give a residue that was column chromatographed (basic Al₂O₃) eluting with CHCl₃ to give 14, as a light yellow solid: 1.14 g (85%); mp 178-179 °C; ¹H NMR δ 2.4 (s, 3 H, BenCH₃), 7.36 (dd, 4 H, 5,5''-tpyH, J₁ = 4.8 Hz, J₂ = 1.2 Hz), 7.39 (s, 2 H, 2,4-BenH), 7.62 (s, 1 H, 6-BenH), 7.70 (d, 4 H, 3,5-ArH, J = 8.4 Hz), 7.89 (td, 4 H, 4,4''-tpyH, J₁ = 7.5 Hz, J₂ = 1.8 Hz), 7.92 (d, 4 H, 2,6-ArH, J = 8.4 Hz), 8.7 (dt, 4 H, 3,3''-tpyH, J₁ = 7.8 Hz, J₂ = 0.9 Hz), 8.74 (dd, 4 H, 6,6''-tpyH, J₁ = 4.8 Hz, J₂ = 0.9 Hz), 8.77 (s, 4 H, 3',5'-tpyH); ¹³C NMR δ 21.3, 89.62, 90.43, 118.86, 121.58, 123.55, 124.1, 127.5, 132.14, 132.42, 132.5, 137.1, 138.47, 138.6, 149.36, 149.55, 156.26, 156.35; HRMS (calc.): m/z = 755.2910 (755.2923, [M + H]+).

1,3-Bis[4,4'-di(ethoxycarbonyl)-2,2';6',2''-terpyridin-4'-phen-4'-ylethynyl]toluene (15): To a stirring solution of diester 13 (643.3 mg, 1.11 mmol) in THF (70 mL) and diisopropylamine (25 mL), 10 (66.6 mg, 475 µmol) was added. The mixture was degassed and back-filled with argon (3X), then Pd(PPh₃)₄ (44 mg, 38 µmol, 4% per coupling site) and CuI (5.2 mg, 27 µmol) was added to the flask, then stirred for 12 h at 70 °C. The mixture was filtered and washed with THF (20 mL). The filtrate was concentrated *in vacuo* to give a residue that was column chromatographed (basic Al₂O₃) eluting with CHCl₃ to give 15, as a light yellow solid: 431 mg (87%); mp 314-315 °C; ¹H NMR δ 1.51 (t, 12 H, tpyCO₂CH₂CH₃, J = 7.2 Hz), 2.4 (s, 3 H, BenCH₃), 4.5 (q, 8 H, tpyCO₂CH₂CH₃, J = 7.2 Hz), 7.39 (s, 2 H, 2,4-BenH), 7.62 (s, 1 H, 6-BenH), 7.71 (d, 4 H, 3,5-ArH, J = 8.7 Hz), 7.94 (m, 8 H, 2,6-ArH, 5,5''-tpyH), 8.8 (s, 4 H, 3',5'-tpyH), 8.88 (dd, 4 H, 6,6''-tpyH, J₁ = 5.1 Hz, J₂ = 0.9 Hz), 9.22 (s, 4 H, 3,3''-tpyH); ¹³C NMR δ 14.46,
1-[4,4''-Di(ethoxycarbonyl)-2,2';6',2''-terpyridine-4'-phen-4-ylethynyl]-3-[(trimethylsilyl)ethynyl]toluene (16): To a stirring solution of diester 13 (234 mg, 400 µmol) in THF (60 mL) and NEt₃ (60 mL), 11 (85 mg, 400 µmol) was added. The mixture was degassed and back-filled with argon (3X) then Pd(PPh₃)₄ (34 mg, 29.4 µmol, 7% per coupling site) and CuI (8 mg, 42 µmol) was added to the flask then stirred for 12 h at 70 ºC. The mixture was filtered and washed with THF (20 mL). The filtrate was concentrated in vacuo to give a residue that was column chromatographed (basic Al₂O₃) eluting with CHCl₃ to give 16, as a light yellow solid: 220 mg (83%); mp 247-248 ºC; ¹H NMR δ 0.26 [s, 9 H, (CH₃)₃-Si], 1.48 (t, 6 H, tpyCO₂CH₂CH₃, J = 7.2 Hz), 2.32 (s, 3 H, BenCH₃), 4.47 (q, 4 H, tpyCO₂CH₂CH₃, J = 7.2 Hz), 7.26 (s, 1 H, 4-BenH), 7.31 (s, 1 H, 2-BenH), 7.59 (s, 1 H, 6-BenH), 7.62 (d, 2 H, 3,5-ArH, J = 8.1 Hz), 7.85 (m, 4 H, 2,6-ArH, 5,5''-tpyH), 8.68 (s, 2 H, 3',5'-tpyH), 8.8 (d, 2 H, 6,6''-tpyH, J₁ = 4.8 Hz), 9.13 (s, 2 H, 3,3''-tpyH); ¹³C NMR δ 0.12, 14.41, 21.17, 61.97, 89.4, 90.48, 94.75, 104.51, 119.16, 120.88, 123.11, 123.28, 123.49, 124.2, 127.29, 132.35, 132.41, 132.46, 132.74, 137.89, 138.37, 138.97, 149.38, 149.94, 155.53, 157.11, 165.37; HRMS (calc.): m/z = 664.2638 (664.2631, [M + H]⁺).

1-[4,4''-Di(ethoxycarbonyl)-2,2';6',2''-terpyridine-4'-phen-4-ylethynyl]-3-ethynyl-toluene (17): To a stirring solution of 16 (170 mg, 256 µmol) in THF (20 mL) and EtOH
(20 mL), KF (24 mg, 413 µmol) was added then the mixture was stirred for 10 h at 25 °C. Solution was concentrated in vacuo to give a residue that was column chromatographed (Al₂O₃) eluting with CHCl₃ to give 17, as a white solid: 139 mg (92%); mp 237-238 °C; ¹H NMR δ 1.5 (t, 6 H, tpyCO₂CH₂CH₃, J = 7.2 Hz), 2.32 (s, 3 H, BenCH₃), 3.1 (s, 1 H, C≡C-H), 4.48 (q, 4 H, tpyCO₂CH₂CH₃, J = 7.2 Hz), 7.28 (s, 1 H, 4-BenH), 7.35 (s, 1 H, 2-BenH), 7.5 (s, 1 H, 6-BenH), 7.64 (d, 2 H, 3,5-ArH, J = 8.1 Hz), 7.88 (m, 4 H, 2,6-ArH, 5,5''-tpyH), 8.72 (s, 2 H, 3',5'-tpyH), 8.83 (d, 2 H, 6,6''-tpyH, J₁ = 4.8 Hz), 9.16 (s, 2 H, 3,3''-tpyH); ¹³C NMR δ 14.43, 21.19, 61.99, 77.68, 83.12, 89.53, 90.33, 119.24, 120.92, 122.51, 123.15, 123.41, 124.15, 127.34, 132.4, 132.5, 132.82, 132.94, 138.02, 138.52, 139.02, 149.46, 149.97, 155.6, 157.15, 165.41; HRMS (calc.): m/z = 592.2233 (592.2236, [M + H]+).

4'-[3-(Trimethylsilyl)ethynylphenyl]-2,2';6',2''-terpyridine (19): To a stirring solution of 18 (1.53 g, 3.48 mmol) in THF (120 mL) and NEt₃ (90 mL), trimethylsilylacetylene (662 mg, 6.74 mmol) was added. The mixture was degassed and back-filled with argon (3X) then Pd(PPh₃)₄ (238 mg, 206 µmol, 6% per coupling site) and CuI (37.7 mg, 197 µmol) was added to the flask and the mixture was degassed and back-filled with argon (2X) then stirred for 12 h at 70 °C. The mixture was filtered and washed with THF (20 mL). The filtrate was concentrated in vacuo to give a residue that was column chromatographed (basic Al₂O₃) eluting with CHCl₃ to give 19, as a white solid: 1.2 g (85%); mp 141-143 °C; ¹H NMR (CDCl₃) δ 0.3 [s, 9 H, (CH₃)₃-Si], 7.37 (dd, 2 H, 5,5''-tpyH, J₁ = 5.7 Hz, J₂ = 1.5 Hz), 7.46 (t, 1 H, 5-ArH, J = 7.8 Hz), 7.55 (d, 1 H, 4-ArH, J = 7.5 Hz), 7.85 (d, 1 H, 6-ArH, J = 7.5 Hz), 7.90 (td, 2 H, 4,4''-tpyH, J₁ = 7.8 Hz).
Hz, $J_2 = 1.5$ Hz), 8.03 (s, 1 H, 2-Ar$H$), 8.67 (d, 2 H, 3,3''-tpy$H$, $J = 4.8$ Hz); $^{13}$C NMR (CDCl$_3$) $\delta$ 0.19, 95.15, 104.82, 119.18, 121.72, 124.18, 127.7, 129.1, 131.01, 132.63, 137.35, 138.76, 149.15, 149.79, 155.99, 156.11; HRMS (calc.): $m/z = 428.1563$ (428.1559, [M + Na]$^+$).

$4'-(3$-Ethynylphenyl)$-2,2';6',2''$-terpyridine (20): To a stirring solution of 19 (420 mg, 1.04 mmol) in THF (30 mL), ($n$-Bu)$_4$NF·3H$_2$O (500 mg, 1.59 mmol) was added, then the mixture was stirred for 6 h at 25 ºC. Solution was concentrated in vacuo to give a residue that was column chromatographed (Al$_2$O$_3$) eluting with CHCl$_3$ to give 20, as a light yellow solid: 330 mg (95%); mp 173-175 ºC; $^1$H NMR (CDCl$_3$) $\delta$ 3.16 (s, 1 H, ArC≡C-H), 7.37 (dd, 2 H, 5,5''-tpy$H$, $J_1 = 5.7$ Hz, $J_2 = 1.5$ Hz), 7.47 (t, 1 H, 5-Ar$H$, $J = 7.8$ Hz), 7.57 (d, 1 H, 4-Ar$H$, $J = 7.8$ Hz), 7.88 (m, 3 H, 6-Ar$H$, 4,4''-tpy$H$), 8.05 (s, 1 H, 2-Ar$H$), 8.66 (d, 2 H, 3,3''-tpy$H$, $J = 7.8$ Hz), 8.72 (s, 2 H, 3',5'-tpy$H$), 8.74 (d, 2 H, 6,6''-tpy$H$, $J = 5.1$ Hz); $^{13}$C NMR (CDCl$_3$) $\delta$ 78.04, 83.45, 119.05, 121.61, 123.06, 124.15, 127.98, 129.18, 131.16, 132.73, 137.22, 138.88, 149.22, 149.49, 156.09; HRMS (calc.): $m/z = 356.1164$ (356.1163, [M + Na]$^+$).

25[(Cl)$_2$]: To a stirring solution of 21 (63.1 mg, 152 µmol) in MeOH (50 mL), FeCl$_2.4$H$_2$O (15.2 mg, 76 µmol) was added then the mixture was refluxed for 8 h. The solution was concentrated in vacuo and dried to give 25, as a purple solid: 69.6 mg (95%); $^1$H NMR (CD$_3$OD) $\delta$ 2.46 (s, 12 H, tpyCH$_3$), 7.03 (d, 4 H, 5,5''-tpy$H$, $J = 5.1$ Hz), 7.06 (d, 4 H, 6,6''-tpy$H$, $J = 5.4$ Hz), 7.97 (d, 4 H, 3,5-Ar$H$, $J = 8.1$ Hz), 8.35 (d, 4 H, 2,6-
ArH, J = 8.1 Hz), 8.76 (s, 4 H, 3,3'-tpyH), 9.43 (s, 4 H, 3',5'-tpyH); HRMS (calc.): m/z = 444.0342 (444.0347, [M – 2Cl]^{2+}).

26[(PF_6)_2]: To a stirring solution of 22 (79 mg, 196 µmol) in MeOH (50 mL), FeCl_2.4H_2O (19.6 mg, 98 µmol) was added, then refluxed for 8 h. The solution was concentrated in vacuo to give a deep purple precipitate that was column chromatographed (SiO_2) eluting with MeCN : sat. KNO_3 (aq) : H_2O (7:1:1) then counterion exchanged by treating with an excess NH_4PF_6 (1 M) then dried to give 26, as a purple solid: 89 mg (91%); ^1H NMR (CD_3CN) δ 2.42 (s, 6 H, tpyCH_3), 6.94 (d, 2 H, 6'-tpyH, J = 5.1 Hz), 6.98 (d, 2 H, 6-tpyH, J = 5.7 Hz), 7.07 (t, 2 H, 5'-tpyH, J = 6.9 Hz), 7.16 (d, 2 H, 5-tpyH, J = 5.4 Hz), 7.90 (t, 2 H, 4'-tpyH, J = 7.8 Hz), 8.00 (d, 4 H, 3,5-ArH, J = 8.7 Hz), 8.22 (d, 4 H, 2,6-ArH, J = 8.1 Hz), 8.52 (s, 2 H, 3-tpyH), 8.59 (d, 2 H, 3'-tpyH, J = 8.1 Hz), 9.13 (s, 2 H, 3'-tpyH), 9.15 (s, 2 H, 5'-tpyH); ^13C NMR (CD_3CN) δ 21.12, 122.43, 122.55, 125.46, 126.37, 126.52, 128.84, 129.89, 131.03, 134.14, 137.28, 140.12, 151.03, 153.06, 153.36, 154.14, 159.07, 159.77, 162.1, 162.18; HRMS (calc.): m/z = 430.0191 (430.0190, [M – 2PF_6]^{2+}).

27[(Cl)_2]: To a stirring solution of 23 (164.3 mg, 397 µmol) in MeOH (60 mL), FeCl_2.4H_2O (39.5 mg, 198 µmol) was added then refluxed for 20 h. The solution was concentrated in vacuo and dried to give 27, as a purple solid: 178 mg (94%); ^1H NMR (CD_3OD) δ 7.22 (t, 2 H, 5'-tpyH, J = 6.0 Hz), 7.3 (d, 2 H, 6'-tpyH, J = 5.4 Hz), 7.48 (d, 2 H, 5-tpyH, J = 5.1 Hz), 7.53 (d, 2 H, 6-tpyH, J = 5.7 Hz), 7.98 (d, 4 H, 3,5-ArH, J = 8.1 Hz), 8.03 (t, 2 H, 4'-tpyH, J = 7.8 Hz), 8.33 (d, 4 H, 2,6-ArH, J = 8.4 Hz), 8.86 (d, 2 H,
3"-tpyH, J = 7.8 Hz), 9.25 (s, 2 H, 3-tpyH), 9.51 (s, 2 H, 5'-tpyH), 9.58 (s, 2 H, 3'-tpyH);
MALDI-TOF (calc.): m/z = 882.342 (881.998, [M – 2Cl]^{2+}).

28[(Cl)₂]: To a stirring solution of 24 (100.1 mg, 224 µmol) in MeOH (50 mL), FeCl₂·4H₂O (22.2 mg, 112 µmol) was added then refluxed for 8 h. The solution was concentrated in vacuo and dried to give 28, as a purple solid: 108 mg (95%); ¹H NMR (CD₃OD) δ 3.94 (s, 6 H, tpyCO₂C₃), 7.21 (t, 2 H, 5"-tpyH, J = 6.0 Hz), 7.31 (d, 2 H, 6"-tpyH, J = 5.1 Hz), 7.52 (d, 2 H, 5-tpyH, J = 5.7 Hz), 7.62 (d, 2 H, 6-tpyH, J = 5.4 Hz), 7.99 (d, 4 H, 3,5-ArH, J = 8.1 Hz), 8.01 (t, 2 H, 4"-tpyH, J = 7.8 Hz), 8.37 (d, 4 H, 2,6-ArH, J = 8.4 Hz), 8.87 (d, 2 H, 3"-tpyH, J = 7.8 Hz), 9.29 (s, 2 H, 3-tpyH), 9.5 (s, 2 H, 5'-tpyH), 9.62 (s, 2 H, 3'-tpyH); MALDI-TOF (calc.): m/z = 948.276 (948.018, [M – 2Cl]^{2+}), 860.117 (860.038, [M – 2Cl – 2CO₂]^{2+}),

31: To a stirred solution of 29 (56 mg, 105 µmol) in EtOH (10 mL) and THF (30 mL), RuCl₃·3H₂O (35.9 mg, 137 µmol) was added then refluxed for 15 h. After cooling, the mixture was filtered and washed with EtOH (3 × 50 mL) and THF (3 × 50 mL) to give 31, as a dark red solid: 62 mg (80%).

32: To a stirred solution of 13 (331 mg, 571 µmol) in EtOH (25 mL) and THF (75 mL), RuCl₃·3H₂O (155 mg, 594 µmol) was added then refluxed for 15 h. After cooling, the mixture was filtered and washed with EtOH (3 × 50 mL) and THF (3 × 50 mL) to give 32, as a dark red solid: 380 mg (85%).
33[(Cl)2]: To a stirred solution of 21 (103 mg, 247 µmol) in MeOH (50 mL), RuCl3·3H2O (32.6 mg, 124 µmol) and N-ethylmorpholine (6 drops) was added then refluxed for 10 h. The solution was concentrated in vacuo and dried to give 33, as a dark red solid: 124 mg (98%); 1H NMR (CD3OD) δ 2.54 (s, 12 H, tpyCH3), 7.15 (d, 4 H, 5,5''-tpyH, J = 5.4 Hz), 7.35 (d, 4 H, 6,6''-tpyH, J = 5.7 Hz), 7.93 (d, 4 H, 3,5-ArH, J = 8.4 Hz), 8.28 (d, 4 H, 2,6-ArH, J = 8.7 Hz), 8.83 (s, 4 H, 3,3''-tpyH), 9.28 (s, 4 H, 3',5'-tpyH); HRMS (calc.): m/z = 467.0196 (467.0198, [M – 2Cl]2+).

34[(PF6)2]: To a stirring solution of 30 (101.3 mg, 201 µmol) in MeOH (60 mL), RuCl3·3H2O (26.1 mg, 100 µmol) and N-ethylmorpholine (6 drops) was added then the mixture was refluxed for 20 h. The solution was concentrated in vacuo to give a red precipitate that was column chromatographed (SiO2) eluting with MeCN : sat. KNO3 (aq) : H2O (7:1:1) then counterion exchanged by treating with an excess NH4PF6 (1 M) and dried to give 34, as a dark red solid: 55 mg (40%); 1H NMR (CD3CN) δ 3.94 (s, 12 H, tpyCO2CH3), 7.6 (s, 8 H, 5,5''-tpyH, 6,6''-tpyH), 7.99 (d, 4 H, 3,5-ArH, J = 8.4 Hz), 8.19 (d, 4 H, 2,6-ArH, J = 8.7 Hz), 9.12 (s, 4 H, 3,3''-tpyH), 9.21 (s, 4 H, 3',5'-tpyH).

35[(CF3CO2)2]: To a stirring solution of 34[(PF6)2] (27.6 mg, 19.7 µmol) in DMF (15 mL), NaOH (1 M, 5 mL) was added then the mixture was stirred at 60 °C for 12 h. The solvent was removed and TFA in MeCN was added, then the solution was concentrated in vacuo to afford a residue that was washed with H2O (50 mL) to give 35, as a dark red solid: 24.4 mg (92%); 1H NMR (CD3CN + CF3CO2D) δ 7.61 (s, 8 H, 5,5''-tpyH, 6,6''-tpyH), 7.97 (d, 4 H, 3,5-ArH, J = 8.1 Hz), 8.19 (d, 4 H, 2,6-ArH, J = 8.74 Hz), 7.61 (s, 8 H, 5,5''-tpyH, 6,6''-tpyH), 7.97 (d, 4 H, 3,5-ArH, J = 8.1 Hz), 8.19 (d, 4 H, 2,6-ArH, J = 8.74 Hz),
9.14 (s, 4 H, 3,3''-tpyH), 9.22 (s, 4 H, 3',5'-tpyH); MALDI-TOF (calc.): \( m/z = 1054.200 \) (1053.936, \([M – 2CF_3CO_2]^{2+}\)), 1010.215 (1009.946, \([M – 2CF_3CO_2 – CO_2]^{2+}\)), 966.225 (965.956, \([M – 2CF_3CO_2 – 2CO_2]^{2+}\)), 922.198 (921.966, \([M – 2CF_3CO_2 – 3CO_2]^{2+}\)), 878.251 (877.977, \([M – 2CF_3CO_2 – 4CO_2]^{2+}\)).

36[(Cl)\(_2\)]: To a stirring solution of 31 (35 mg, 47.4 \(\mu\)mol) and 21 (19.7 mg, 47.3 \(\mu\)mol) in EtOH (20 mL), \(N\)-ethylmorpholine (6 drops) was added then the mixture was refluxed for 10 h. The solution was concentrated \(in\ vacuo\) and dried to give 36, as a dark red solid: 53 mg (99%); \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 1.38 (t, 6 H, tpy\(_1\)CO\(_2\)CH\(_2\)CH\(_3\), \(J = 6.9\) Hz), 2.52 (s, 6 H, tpy\(_2\)CH\(_3\)), 4.43 (q, 4 H, tpy\(_1\)CO\(_2\)CH\(_2\)CH\(_3\), \(J = 6.9\) Hz), 7.11 (d, 2 H, 5,5''-tpy\(_2\)H, \(J = 5.7\) Hz), 7.3 (d, 2 H, 6,6''-tpy\(_2\)H, \(J = 5.7\) Hz), 7.74 (dd, 2 H, 5,5''-tpy\(_1\)H, \(J_1 = 6.0\) Hz, \(J_2 = 1.8\) Hz), 7.77 (d, 2 H, 6,6''-tpy\(_1\)H, \(J = 5.7\) Hz), 7.93 (dd, 4 H, 3,5-Ar\(_1\)H, 3,5-Ar\(_2\)H, \(J_1 = 8.7\) Hz, \(J_2 = 0.9\) Hz), 8.28 (m, 4 H, 2,6-Ar\(_1\)H, 2,6-Ar\(_2\)H), 8.82 (s, 2 H, 3,3''-tpy\(_2\)H), 9.29 (s, 4 H, 3',5'-tpy\(_2\)H, 3,3''-tpy\(_1\)H), 9.43 (s, 2 H, 3',5'-tpy\(_1\)H); HRMS (calc.): \( m/z = 524.0260 \) (524.0261, \([M – 2Cl]^{2+}\)).

37[(CF\(_3\)CO\(_2\))\(_2\)]: To a stirring solution of 36[(Cl)\(_2\)] (42 mg, 37.6 \(\mu\)mol) in DMF (15 mL), NaOH (1 M, 5 mL) was added then the mixture was stirred at 60 °C for 12 h. The solvent was removed and TFA in MeCN was added then the solution was concentrated \(in\ vacuo\) to afford a residue that was washed with H\(_2\)O (50 mL) to give 37, as a dark red solid: 46.3 mg (96%); \(^1\)H NMR (CD\(_3\)CN + CF\(_3\)CO\(_2\)D) \(\delta\) 2.46 (s, 6 H, tpy\(_2\)CH\(_3\)), 7.02 (d, 2 H, 5,5''-tpy\(_2\)H, \(J = 5.7\) Hz), 7.18 (d, 2 H, 6,6''-tpy\(_2\)H, \(J = 5.7\) Hz), 7.61 (s, 4 H, 5,5''-tpy\(_1\)H, 6,6''-tpy\(_1\)H), 7.93 (m, 4 H, 3,5-Ar\(_1\)H, 3,5-Ar\(_2\)H), 8.15 (m, 4 H, 2,6-Ar\(_1\)H, 2,6-Ar\(_2\)H), 8.55

38[(PF6)2]: To a stirring solution of 32 (195 mg, 248 µmol) and 13 (144 mg, 249 µmol) in EtOH (20 mL), N-ethylmorpholine (6 drops) was added then the mixture was refluxed for 20 h. The solution was concentrated in vacuo to give a red precipitate that was column chromatographed (SiO2) eluting with MeCN : sat. KNO3 (aq) : H2O (7:1:1) then counterion exchanged by treating with an excess NH4PF6 (1 M) to and dried to give 38, as a dark red solid: 210 mg (55%); 1H NMR (CD3CN) δ 1.36 (t, 12 H, tpyCO2CH2CH3, J = 6.9 Hz), 4.41 (q, 8 H, tpyCO2CH2CH3, J = 6.9 Hz), 7.6 (s, 8 H, 5,5''-tpyH, 6,6''-tpyH), 8.06 (d, 4 H, 3,5-ArH, J = 8.7 Hz), 8.16 (d, 4 H, 2,6-ArH, J = 8.4 Hz), 9.1 (s, 4 H, 3,3''-tpyH), 9.2 (s, 4 H, 3',5'-tpyH); HRMS (calc.): m/z = 630.0170 (630.0177, [M – 2PF6]2+); Crystal data for 38: Orthorhombic, P2(1)2(1)2(1), a = 14.3505(12) Å, b = 14.4204(12) Å, c = 33.419(3) Å, α = 90°, β = 90°, γ = 90°, V = 6915.8(10) Å3, Z = 4, ρ = 1.528 Mg/m3, µ = 1.250 mm-1, F(000) = 3136, Final R indices (for 16295 parameters) [I > 2σ(I)] were R1 = 0.0467, and R1 = 0.0630, wR2 = 0.1175 for all 60158 data.

39[(CF3CO2)2]: To a stirred solution of 38[(PF6)2] (75 mg, 48.4 µmol) in DMF (15 mL), NaOH (1 M, 5 mL) was added then the mixture was stirred at 60 °C for 12 h. The solvent was removed and TFA in MeCN was added then the solution was
concentrated *in vacuo* to afford a residue that was washed with H\(_2\)O (50 mL) to give 39, as a dark red solid: 66.1 mg (95%); \(^1\)H NMR (CD\(_3\)CN + CF\(_3\)CO\(_2\)D) \(\delta\) 7.6 (s, 8 H, 5,5''-tpy\(H\), 6,6''-tpy\(H\)), 8.05 (d, 4 H, 3,5-Ar\(H\), \(J = 8.7\) Hz), 8.12 (d, 4 H, 2,6-Ar\(H\), \(J = 8.4\) Hz), 9.13 (s, 4 H, 3,3''-tpy\(H\)), 9.21 (s, 4 H, 3',5'-tpy\(H\)); MALDI-TOF (calc.): \(m/z = 1148.197\) (1147.910, [M – 2CF\(_3\)CO\(_2\)]\(^2+\)), 1104.278 (1103.920, [M – 2CF\(_3\)CO\(_2\) – CO\(_2\)]\(^2+\)), 1060.281 (1059.930, [M – 2CF\(_3\)CO\(_2\) – 2CO\(_2\)]\(^2+\)), 1016.272 (1015.941, [M – 2CF\(_3\)CO\(_2\) – 3CO\(_2\)]\(^2+\)), 972.240 (971.951, [M – 2CF\(_3\)CO\(_2\) – 4CO\(_2\)]\(^2+\)).

40[(PF\(_6\))\(_4\)]: To a stirred solution of 32 (97.9 mg, 62 \(\mu\)mol) and 14 (46.9 mg, 124 \(\mu\)mol) in EtOH (20 mL), N-ethylmorpholine (6 drops) was added then the mixture was refluxed for 24 h. The solution was concentrated *in vacuo* to give a red precipitate that was column chromatographed (SiO\(_2\)) eluting with MeCN : sat. KNO\(_3\) (aq) : H\(_2\)O (20:1:1) then counterion exchanged by treating with an excess NH\(_4\)PF\(_6\) (1 M) and dried to give 40, as dark red solid: 95 mg (57%); \(^1\)H NMR (CD\(_3\)CN) \(\delta\) 1.37 (t, 12 H, tpy\(_2\)CO\(_2\)CH\(_2\)CH\(_3\), \(J = 6.9\) Hz), 2.44 (s, 3 H, BenCH\(_3\)), 4.39 (q, 8 H, tpy\(_2\)CO\(_2\)CH\(_2\)CH\(_3\), \(J = 6.9\) Hz), 7.21 (t, 4 H, 5,5''-tpy\(_1\)\(H\), \(J = 6.3\) Hz), 7.41 (d, 5 H, 6,6''-tpy\(_1\)\(H\), \(J = 4.5\) Hz), 7.48 (s, 2 H, 2,6-Ben\(H\)), 7.64 (dd, 4 H, 5,5''-tpy\(_2\)\(H\), \(J\_1 = 5.7\) Hz, \(J\_2 = 1.5\) Hz), 7.67 (d, 4 H, 6,6''-tpy\(_2\)\(H\), \(J = 5.7\) Hz), 7.97 (m, 12 H, 4,4''-tpy\(_1\)\(H\), 3,5-Ar\(_1\)\(H\), 2,6-Ar\(_1\)\(H\), 6-Ben\(H\)), 8.14 (d, 4 H, 3,5-Ar\(_2\)\(H\), \(J = 8.4\) Hz), 8.28 (d, 4 H, 2,6-Ar\(_2\)\(H\), \(J = 8.4\) Hz), 8.70 (d, 4 H, 3,3''-tpy\(_1\)\(H\), \(J = 8.1\) Hz), 9.07 (s, 4 H, 3',5'-tpy\(_1\)\(H\)), 9.11 (s, 4 H, 3,3''-tpy\(_2\)\(H\)), 9.18 (s, 4 H, 3',5'-tpy\(_2\)\(H\)); HRMS (calc.): \(m/z = 529.0571\) (529.0561, [M – 4PF\(_6\)]\(^{4+}\)).
To a stirred solution of 40[(PF$_6$)$_4$] (27 mg, 10 µmol) in DMF (15 mL), NaOH (1 M, 5 mL) was added then the mixture was stirred at 60 °C for 12 h. The solvent was removed and TFA in MeCN was added then the solution was concentrated in vacuo to afford a residue that was washed with H$_2$O (50 mL) to give 41, as a dark red solid: 22 mg (95%); $^1$H NMR (CD$_3$CN + CF$_3$CO$_2$D) δ 2.46 (s, 3 H, BenC$_3$H), 7.20 (t, 4 H, 5,5''-tpy$_1$H, $J$ = 6.3 Hz), 7.40 (d, 5 H, 6,6''-tpy$_1$H, $J$ = 4.5 Hz), 7.53 (s, 2 H, 2,6-BenH), 7.62 (dd, 4 H, 5,5''-tpy$_2$H, $J_1$ = 5.7 Hz, $J_2$ = 1.5 Hz), 7.66 (d, 4 H, 6,6''-tpy$_2$H, $J$ = 5.7 Hz), 7.98 (m, 12 H, 4,4''-tpy$_1$H, 3,5-Ar$_1$H, 2,6-Ar$_1$H, 6-BenH), 8.12 (d, 4 H, 3,5-Ar$_2$H, $J$ = 8.4 Hz), 8.27 (d, 4 H, 2,6-Ar$_2$H, $J$ = 8.4 Hz), 8.71 (d, 4 H, 3''-tpy$_1$H, $J$ = 8.1 Hz), 9.07 (s, 4 H, 3',5'-tpy$_1$H), 9.14 (s, 4 H, 3''-tpy$_2$H), 9.20 (s, 4 H, 3',5'-tpy$_2$H); MALDI-TOF (calc.): m/z = 2003.400 (2003.102, [M – 4CF$_3$CO$_2$]$^{4+}$), 1961.422 (1961.113, [M – 4CF$_3$CO$_2$– CO$_2$]$^{4+}$), 1914.445 (1914.124, [M – 4CF$_3$CO$_2$– 2CO$_2$]$^{4+}$), 1872.485 (1872.130, [M – 4CF$_3$CO$_2$– 3CO$_2$]$^{4+}$), 1831.518 (1831.144, [M – 4CF$_3$CO$_2$– 4CO$_2$]$^{4+}$).

To a stirred solution of diester 40[(PF$_6$)$_4$] (104 mg, 40 µmol) in THF (30 mL), MeCN (30), and NEt$_3$ (50 mL), 17 (59 mg, 100 µmol) was added. The mixture was degassed and back-filled with argon (3X), then Pd(PPh$_3$)$_4$ (10.1 mg, 8.7 µmol, 10% per coupling site) and CuI (1.4 mg, 7.3 µmol) was added to the flask and, then stirred for 12 h at 70 °C. The mixture was concentrated in vacuo and washed with MeCN to give a residue that was column chromatographed (basic Al$_2$O$_3$) eluting with CHCl$_3$ to give 43, as a yellow solid: 36 mg (64%); mp 275-277 °C; $^1$H NMR δ 1.51 (t, 12 H, tpyCO$_2$CH$_2$CH$_3$, $J$ = 6.9 Hz), 2.38 (s, 6 H, BenCH$_3$), 4.51 (q, 8 H, tpyCO$_2$CH$_2$CH$_3$, $J$ = 6.9 Hz), 7.35 (s, 2 H, 4-BenH), 7.41 (s, 2 H, 2-BenH), 7.57 (s, 2 H, 6-BenH), 7.71 (d, 4
H, 3,5-ArH, J = 7.8 Hz), 7.94 (m, 8 H, 2,6-ArH, 5,5''-tpyH), 8.8 (s, 4 H, 3',5'-tpyH), 8.88 (d, 4 H, 6,6''-tpyH, J = 4.8 Hz), 9.23 (s, 4 H, 3,3''-tpyH); HRMS (calc.): m/z = 1181.4253 (1181.4238, [M + H]^+). The MeCN filtrate was concentrated in vacuo to afford a red microcrystalline solid, which is the starting material, dinuclear 40[(PF₆)₄] (95 mg).

44[(Cl)₄]: To a stirred solution of 32 (128 mg, 162.6 µmol) and 8 (54.9 mg, 81.3 µmol) in EtOH (80 mL), N-ethylmorpholine (6 drops) was added, then the mixture was refluxed for 9 h. The solution was concentrated in vacuo and dried to give 44, as a dark red solid: 174 mg (98%); ¹H NMR δ 1.4 (t, 12 H, tpy₂CO₂CH₂CH₃, J = 7.2 Hz), 2.58 (s, 12 H, tpy₁CH₃), 4.46 (q, 8 H, tpy₂CO₂CH₂CH₃, J = 7.2 Hz), 7.14 (d, 4 H, 5,5''-tpy₁H, J = 5.4 Hz), 7.33 (d, 4 H, 6,6''-tpy₁H, J = 5.7 Hz), 7.81 (d, 4 H, 5,5''-tpy₂H, J = 5.7 Hz), 7.88 (d, 4 H, 6,6''-tpy₂H, J = 5.7 Hz), 8.15 (s, 8 H, 3,5-ArH, 2,6-ArH), 8.82 (s, 2 H, 2,6-BenH), 9.19 (s, 4 H, 3,3''-tpy₁H), 9.31 (s, 4 H, 3',5'-tpy₂H), 9.46 (s, 5 H, 3,3''-tpy₂H, 4-BenH), 9.72 (s, 4 H, 3',5'-tpy₁H); MALDI-TOF (calc.): m/z = 2190.458 (2190.146, [M – 4Cl + DHB]⁴⁺), 2143.432 (2143.027, [M – Cl]⁺), 2036.611 (2036.119, [M – 4Cl]⁴⁺).

45[(CF₃CO₂)₄]: To a stirred solution of 44[(PF₆)₄] (34 mg, 15.6 µmol) in DMF (15 mL), NaOH (1 M, 5 mL) was added then the mixture was stirred at 60 °C for 12 h. The solvent was removed and TFA in MeCN was added then the solution was concentrated in vacuo to afford a residue that was washed with H₂O (50 mL) to give 45, as a dark red solid: 30 mg (98%); ¹H NMR (CD₃CN + CF₃CO₂D) 2.55 (s, 12 H, tpy₁CH₃), 7.17 (d, 4 H, 5,5''-tpy₁H, J = 5.4 Hz), 7.24 (d, 4 H, 6,6''-tpy₁H, J = 5.7 Hz), 7.66 (d, 4 H, 5,5''-tpy₂H, J = 5.7 Hz), 7.67 (d, 4 H, 6,6''-tpy₂H, J = 5.7 Hz), 8.06 (d, 4 H,
3,5-Ar\(H\), \(J = 8.7\) Hz\), 8.14 (d, 4 H, 2,6-Ar\(H\), \(J = 8.4\) Hz\), 8.68 (s, 4 H, 3,3''-tpy\(_1\)\(H\)), 72 (s, 2 H, 2,6-Ben\(H\)), 9.01 (s, 1 H, 4-Ben\(H\)), 9.14 (s, 4 H, 3',5'-tpy\(_2\)\(H\)), 9.20 (s, 4 H, 3,3''-tpy\(_2\)\(H\)), 9.25 (s, 4 H, 3',5'-tpy\(_1\)\(H\))\); MALDI-TOF (calc.): \(m/z = 1924.421\) (1923.994, \([M – 4CF_3CO_2]^{4+}\)\), 1880.342 (1880.004, \([M – 4CF_3CO_2 – CO_2]^{4+}\)\).

46\([(PF_6)_4]\): To a stirred solution of diester 45\([(PF_6)_4]\) (102 mg, 51 \(\mu\)mol) in DMF (30 mL), and NEt\(_3\) (30 mL), 20 (41 mg, 123 \(\mu\)mol) was added. The mixture was degassed and back-filled with argon (3X) then Pd(PPh\(_3\))\(_4\) (9.5 mg, 8.2 \(\mu\)mol, 8% per coupling site) was added to the flask then stirred for 2 days at 70 \(^\circ\)C. The mixture was concentrated \textit{in vacuo} to give a red solution that was loaded on a preparative TLC plate (SiO\(_2\)) eluting with MeCN : sat. KNO\(_3\) (aq) : H\(_2\)O (7:1:1), the third band (darkest) were removed from the plate and washed with an eluting solvent, followed by counterion exchange by the addition of excess NH\(_4\)PF\(_6\) (1 M) to give 46, as a dark red solid: 55 mg (35%); \(^1\)H NMR (CD\(_3\)CN) \(\delta\) 1.38 (t, 12 H, tpy\(_2\)CO\(_2\)CH\(_2\)CH\(_3\), \(J = 7.2\) Hz\), 2.52 (s, 12 H, tpy\(_1\)CH\(_3\)), 4.41 (q, 8 H, tpy\(_2\)CO\(_2\)CH\(_2\)CH\(_3\), \(J = 7.2\) Hz\), 7.08 (d, 4 H, 5,5''-tpy\(_1\)\(H\), \(J = 5.1\) Hz\), 7.27 (d, 4 H, 6,6''-tpy\(_1\)\(H\), \(J = 5.7\) Hz\), 7.47 (t, 4 H, 5,5''-tpy\(_3\)\(H\), \(J = 5.4\) Hz\), 7.70 (d, 4 H, 5,5''-tpy\(_2\)\(H\), \(J = 5.7\) Hz\), 7.74 (d, 4 H, 6,6''-tpy\(_2\)\(H\), \(J = 6.0\) Hz\), 7.9 (m, 6 H, 6,6''-tpy\(_3\)\(H\), 5-Ar\(_2\)\(H\)), 8.03 (m, 6 H, 3,5-Ar\(_1\)\(H\), 4-Ar\(_2\)\(H\)), 8.24 (m, 6 H, 4,4''-tpy\(_3\)\(H\), 6-Ar\(_2\)\(H\)), 8.41 (d, 4 H, 2,6-Ar\(_1\)\(H\), \(J = 8.1\) Hz\), 8.5 (s, 2 H, 2-Ar\(_2\)\(H\)), 8.71 (s, 2H, 2,6-Ben\(H\)), 8.76 (s, 4 H, 3',5'-tpy\(_3\)\(H\)), 8.79 (d, 4 H, 3,3''-tpy\(_3\)\(H\), \(J = 8.1\) Hz\), 9.09 (s, 5 H, 3,3''-tpy\(_1\)\(H\), 4-Ben\(H\)), 9.16 (s, 4 H, 3',5'-tpy\(_1\)\(H\)), 9.26 (s, 4 H, 3,3''-tpy\(_2\)\(H\)), 9.32 (s, 4 H, 3',5'-tpy\(_1\)\(H\))\); MALDI-TOF (calc.): \(m/z = 2736.004\) (2736.481, \([M – 2PF_6]^{2+}\)\), 2593.831 (2593.519, \([M – 3PF_6]^{3+}\)\).
47[(PF₆)₁₂]: To a stirring solution of 46[(PF₆)₄] (5.6 mg, 1.82 µmol) in EtOH (8 mL) and acetone (10 mL), FeCl₂•4H₂O (370 µg, 1.83 µmol) was added then the mixture was refluxed for 8 h. Solution was concentrated in vacuo to give a red solution that was loaded on a preparative TLC plate (SiO₂) eluting with MeCN : sat. KNO₃ (aq) : H₂O (7:1:1), the top band was removed from the plate and washed with an eluting solvent, followed by counterion exchange by the addition of excess NH₄PF₆ (1 M) to afford the hexanuclear 47[(PF₆)₁₂], as a pink solid: 2.4 mg (42%); ¹H NMR (CD₃CN) ¹H NMR (CD₃CN) δ 1.37 (t, 24 H, tpy₂CO₂CH₂CH₃, J = 7.2 Hz), 2.55 (s, 24 H, tpy₁CH₃), 4.43 (q, 16 H, tpy₂CO₂CH₂CH₃, J = 7.2 Hz), 7.06 (d, 8 H, 5,5"-tpy₁H, J = 6.0 Hz), 7.47 (t, 8 H, 5,5"-tpy₃H, J = 6.6 Hz), 7.26 (m, 16 H, 6,6"-tpy₁H, 6,6"-tpy₃H), 7.70 (d, 8H, 5,5"-tpy₂H, J = 5.7 Hz), 7.74 (d, 8 H, 6,6"-tpy₂H, J = 6.0 Hz), 7.98 (m, 16 H, 4,4"-tpy₃H, 4-Ar₂H, 5-Ar₂H), 8.06 (d, 8 H, 3,5-Ar₁H, J = 8.1 Hz), 8.43 (d, 12 H, 2,6-Ar₁H, 6-Ar₂H, J = 8.1 Hz), 8.65 (s, 4 H, 2,6-BenH), 8.74 (d, 12 H, 3,3"-tpy₂H, 2-Ar₂H, J = 8.1 Hz), 9.02 (s, 8 H, 3,3"-tpy₁H), 9.16 (s, 8 H, 3,3"-tpy₂H), 9.27 (s, 8 H, 3',5'-tpy₃H), 9.32 (s, 8 H, 3',5'-tpy₂H), 9.59 (s, 8 H, 3',5'-tpy₁H).
CHAPTER VII
SUMMARY

The first microwave-assisted, solid-state aldol condensation procedure for the preparation of \(-\text{CO}_2\text{Me}\) and \(-\text{CN}\) substituted 2'-azachalcones and the facile synthesis of new \textit{mono-} and \textit{di-}substituted 4'-(4-R-phenyl)terpyridines were prepared \textit{via} the two-step Kröhnke method, which also gave a variety of by-products, such as a green dye, a cyclohexanol or a cyclobutane. Different methyl-, methyl ester- and cyano-substitution patterns on the 4,4''-positions of 4'-R-phenylterpyridine were initially chosen since these functionalities afforded simple routes to a variety of useful substituted building blocks for higher-ordered supramacromolecular architectures. Single crystal X-ray studies of these terpyridines revealed that molecules of the diester terpyridine (approximately coplanar) are stacked by the overlap of the central pyridine rings in consecutive layers with mean interplanar distances of 3.4 Å (\(\pi-\pi\) interactions) in the solid state. The 4,4''-dimethyl functionalized \textit{bis}(terpyridines) were synthesized \textit{via} Kröhnke method; whereas, 4,4''-di(ethoxycarbonyl) functionalized \textit{bis}(terpyridines) was prepared \textit{via} Pd[0]-mediated cross-coupling method.

The self-assembly of 3,5-bis(2,2':6',2''-terpyridin-4'-phen-3-yl)-toluene with an equimolar amount of a Fe(II) salt afforded a high-yield of an interlocked dinuclear tetracationic “molecular gear” that was confirmed by single crystal X-ray data. Due to the
proximity of the tpy-Fe-tpy moieties (3.7 – 3.9 Å) observed in the crystal structure of the dimer linked through the rigid terphenyl spacer, the dimer complex was expected to show correlated rotation of the moieties as in a molecular gear. Low temperature $^1$H NMR experiments in CD$_2$CD$_2$OD:CD$_3$CN (2:1), at – 65 °C showed broadening and downfield shifts of the peaks specifically for the 4-, 5-, and 6-tpyHs caused by the deshielding effects of the adjacent tpy-Fe-tpy moieties.

Similarly, a dinuclear metallomacrocycle was formed in high yield (90%) when 1,3-bis(2,2';6',2''-terpyridin-4'-phen-3-ylethynyl)toluene was treated with an equimolar amount of a Fe(II) salt. However, treatment of this ligand with one equivalent of RuCl$_3$ under reducing conditions ($N$-ethylmorpholine) gave mixture of different macrocyclic and polymeric products in which only di- and trinuclear macrocycles could be separated and characterized by MALDI-TOF and $^1$H NMR spectroscopy. The Fe(II)-containing macrocycle, as entropically the most stable product, formed in a high yield as a result of possible metal exchange in the process. The kinetically more stable products, di- and trinuclear Ru(II) macrocycles were constructed due to rotational isomers of the ligand.

The synthesis of heteroleptic Ru(II) complexes was accomplished in a quantitative yield; whereas, homoleptic complexes were obtained in only moderate yields. The single crystals X-ray structure of a homoleptic complex with four ethoxycarbonyl and two iodo functionality revealed short iodo-carbonyl interactions. The construction of a heretonuclear (Ru$_4$Fe$_2$) hexameric metallomacrocycle with methyl- and carbonyl functionalized bis(terpyridyl) moieties was achieved by a self-assembly of a dinuclear trimer, which was prepared in high yield via Pd(0) coupling of bis-iodo functionalized dinuclear complex with a terpyridine possessing an acetylene group.
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260


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264


265


