ABSTRACT

A STUDY OF OFFSET $\pi-\pi$, C-H···O HYDROGEN BONDING INTERACTIONS AND PREPARATION OF A 2-BROMOGLUCOSIDE

by Mehul F. Patel

Experimental results have been obtained for the noncovalent weak interactions such as $\pi-\pi$ and C-H···O hydrogen bonding interactions. The 1,9-disubstituted triptycene model system has been employed in the determination of these attractive interactions. Variable temperature NMR experiments were performed in order to obtain the thermodynamic and kinetic parameters. Two opposite trends have been observed for the offset $\pi-\pi$ interactions. A charge-transfer effect is observed for models where the interactions are between strong donor and acceptors. Arene interactions for the systems with moderate electron donor and electron acceptor are controlled mainly by electrostatic interactions. The free energy of interactions for models with strong electron donors and acceptors do not follow a linear correlation in the Hammett plot. A preliminary study of C-H···O hydrogen bonding interactions has also been investigated successfully by modified triptycene system. The results are in good agreement with theoretical calculations. A 2-Bromoglucoside has also been successfully synthesized to study the one-pot synthesis of the tetrasaccharide unit of Durhamycin A.
A STUDY OF OFFSET $\pi$-$\pi$, C-H···O HYDROGEN BONDING INTERACTIONS AND
PREPARATION OF A 2-BROMOGLUCOSIDE

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Submitted to the
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Department of Chemistry and Biochemistry
by
Mehul F. Patel
Miami University
Oxford, Ohio
2005

Advisor
_______________________________
Dr. Benjamin W. Gung

Reader
_______________________________
Dr. Richard T. Taylor

Reader
_______________________________
Dr. James W. Hershberger

Reader
_______________________________
Dr. Thomas L. Riechel
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<td>7</td>
</tr>
<tr>
<td>7b</td>
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<td>7</td>
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<tr>
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</tr>
<tr>
<td>8c</td>
<td>X = CF₃</td>
<td>7</td>
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9b  \( X = \text{MeO} \)  7
9c  \( X = \text{Me} \)  7
9d  \( X = \text{H} \)  7
9e  \( X = \text{F} \)  7
9f  \( X = \text{CF}_3 \)  7

14

15

x
9g

[Chemical Structure]

18
R = 4-MeOPh

19
R = 4-MeOPh

20
R = 4-MeOPh

xii
21 \[R = 4-\text{MeOPh}\]

22 \[R = 4-\text{MeOPh}\]

23a \[R = 4-\text{MeOPh}, X = \text{CF}_3\]

23b \[R = 4-\text{MeOPh}, X = \text{CO}_2\text{CH}_3\]

23c \[R = 4-\text{MeOPh}, X = \text{CN}\]

24a \[R = 4-\text{MeOPh}, X = \text{CF}_3\]

24b \[R = 4-\text{MeOPh}, X = \text{CO}_2\text{CH}_3\]
The properties of organic compounds can be explained by various kinds of chemical interactions—attractive or repulsive, strong or weak. Strong covalent bonds bind the atoms together in a molecule, whereas weak noncovalent interactions play an important role in deciding the shape or conformation of the molecule.

A thorough knowledge of noncovalent interactions is crucial to the understanding of biological chemistry. One of the less well understood but significant weak interactions in nature is the aromatic interaction. These interactions are important in both biological and chemical recognitions. Weak interactions such as \( \pi-\pi \) interaction, hydrogen bonding, and cation-\( \pi \) interaction also play an important role in regulating biochemical processes.\(^1\) A profound understanding of these chemical processes is achieved by intricate combinations of weak intermolecular interactions of various sorts.

Weak interactions, although small in magnitude, being numerous, are believed to provide stability to duplex DNA\(^2\). They have been proposed to contribute to the unique properties of thermophilic proteins.\(^3\) Their understanding is essential for rational drug design and lead optimization in medicinal chemistry. Widespread interest has developed in this area. The

![Figure 1.1](image.png)

**Figure 1.1** Binding mode of the anti-Alzheimer drug E2020 within the active site of acetylcholinesterase\(^4\)
complex of the enzyme acetylcholinesterase (AchE) with the drug E2020 (Aricept), which was
developed to treat symptoms of Alzheimer’s disease, is a good example of the diversity of these
interactions, Figure 1.1.4 Interactions involved in this example are $\pi-\pi$ stacking, O-H/$\pi$ and
cation-\(\pi\) interactions that stabilize the association.

Extensive work has focused on these interactions to determine their importance as
recognition elements. Model systems have also proved to be an informative method of
investigating the nature and significance of aromatic interactions as molecular recognition
elements in biological and non-biological systems. Although numerous computational studies
have been reported, very little is known about the experimental quantifications of C-H--O
hydrogen bonding and offset $\pi-\pi$ interactions. Our project focuses on the determination of these
weak interactions experimentally. We have employed the 1,9- disubstituted triptycene model
system\textsuperscript{5,6} in the determination of offset $\pi-\pi$ interactions, and C-H--O hydrogen bonding
interactions in organic solvents.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Sketches illustrating the \textit{syn} and \textit{anti} conformational isomers derived from 1,9-
diaryl-substituted triptycene derivative (the sketch is a modified version of the drawing by Oki).\textsuperscript{5}}
\end{figure}
Chapter 2 summarizes the study of $\pi-\pi$ interactions in the parallel-displaced orientation. The molecular model system derived from Oki’s triptycene system is shown in Figure 1.2. We have synthesized the model compound and performed variable temperature NMR experiments to obtain thermodynamic and kinetic parameters. The benzylic CH$_2$ protons changed from a singlet at higher temperature to two sets of signals, an AB quartet and a singlet, at lower temperature due to the slow rotations of the C(9)-benzyl carbon-carbon bond. Integration of the two sets of signals gives the ratio (equilibrium constants) of the syn/anti isomers. The free energies can be obtained using the equation: $\Delta G^o = -RT\ln K_{eq} = -RT\ln(1/2 \cdot \text{syn/anti})$.

Chapter 3 summarizes the preliminary study of the C-H⋯O hydrogen bond interaction. Modified triptycene system has been derived to reveal the weak C-H⋯O interactions. This system is such designed that C-H can form hydrogen bonding with O through six-member ring. The thermodynamic parameters for the C-H⋯O hydrogen bond has been determined based on the equilibrium constants between the syn and the anti isomers at different temperatures.

Chapter 4 discusses the ongoing study about the $\pi$-stacking interaction in asymmetric induction. We are trying to design an ideal model compound to study the role of this interaction in asymmetric induction.

Chapter 5 deals with the preparation of a 2-Bromoglucoside to study the one-pot synthesis of the tetrasaccharide unit of Durhamycin A, whereas Chapter 6 discusses the attempted preparation of a molecular DNA base receptor to expand our study in the area of weak noncovalent interactions.
Chapter 2.  Observation of Charge-Transfer Effect in Aromatic Interactions: a Quantitative Study of Offset $\pi$-$\pi$ Interactions

2.1 Introduction

Intermolecular interactions such as arene-arene interactions play an essential role in biological macromolecules such as DNA and proteins. Burley and Petsko have demonstrated in a study involving 34 proteins that on average 60% of aromatic side chains (Phe, Try, Tyr) are involved in $\pi$-$\pi$ interactions. Offset stacked orientation is commonly found in proteins, which is the geometry of base stacking in DNA. Stacking interactions play an essential role in mRNA-cap recognition by proteins. These interactions also play a key role in organic synthesis. $\pi$-$\pi$ stacking has been shown to be influential in stereoselective epoxidations with m-chloroperbenzoic acid.

Hunter and Sanders proposed a model of a $\pi$-system for aromatic interactions, Figure 2.1. In this model an aromatic ring described as a positively charged $\sigma$-framework, which is sandwiched between two negatively charged $\pi$-systems. However, this model system has been challenged. It should be noted that the benzene has an uneven distribution of charge, with greater electron-density on the face of the ring and reduced electron-density on the edge, which gives rise to the quadrupole moment even though it has no net dipole. The edge-to-face geometry (a) is found in benzene in the solid state, which can be considered a CH-$\pi$ interaction. It is commonly observed between aromatic residues in proteins. The offset stacked orientation (b) is also commonly found in proteins and as stated before is the geometry of base stacking in DNA. This orientation appears to be more common when the electron density on the face of one or both rings is reduced. Face-to-face stacked orientation (c) is the third possible geometry. This is commonly observed with donor-acceptor pairs and compounds that have opposite quadrupole moments, such that the interaction between the faces of the rings is attractive. The benzene-perfluorobenzene interaction is an excellent example of this type of aromatic interaction. It has been calculated to provide $-15.5$ kJ mol$^{-1}$ in stability.
Most reported recent studies have demonstrated the importance of dispersion and electrostatic contributions, but not charge-transfer to aromatic interactions. Chemists have known for a long time that the mixing of aniline and dinitrobenzene produced the UV-visible spectrum that showed bands belonging to the two original compounds and also an additional broad band in the long-wave length region—a charge-transfer (CT) band. When a molecule (or group) that is good electron donor comes into contact with a molecule (or group) that is a good electron acceptor, the donor may transfer some of its charge to the acceptor. This forms a charge-transfer complex, which, in effect, is a molecular dipole-dipole interaction. Many complexes of electron donor and electron acceptors have been found to have such absorption bands. Nevertheless, many other arene-arene complexes do not show such bands. Moreover, the results from the study in our lab support that electrostatic forces, and not charge-transfer interactions, contribute to control the arene-arene interactions. So the question is obvious: under what circumstances do CT interactions control the arene-arene interactions? To find out the answer, we have initiated this project.
Figure 2.2 Complexes formed by aniline and dinitrobenzene are colorful and show a broad charge transfer band in 350-600 nm range.\textsuperscript{16}

Literature references have shown many chemical model systems, which are designed to investigate the edge-to-face geometry of interacting aromatic rings.\textsuperscript{21-25} Despite of this fact, few chemical model systems have been designed to evaluate the role of substitution and the underlying forces in the attraction of aromatic rings in the parallel-displaced configuration.\textsuperscript{26} We have employed the 1,9-disubstituted triptycene model system\textsuperscript{5,6} Figure 1.2, in the determination of offset arene-arene stacking interactions.\textsuperscript{27} Latest report in our lab has shown that the syn conformation in the triptycene system allows an offset stacking interaction between the two-arene groups while the anti conformation does not. The conformational equilibrium between the symmetrical anti form and chiral syn forms were measured by performing the variable temperature NMR experiments. The benzyl CH\textsubscript{2} protons changed from a singlet at higher temperature to two sets of signals, an AB quartet and a singlet, at lower temperature due to the slow rotation of the C(9)-benzyl carbon-carbon bond. Integration of the two sets of signals gives the ratio (equilibrium constants) of the syn/anti isomers. A greater than 2:1 syn/anti ratio indicates an attractive interaction while a smaller ratio is indicative of a repulsive interaction. The free energies were obtained using the equation: \[ \Delta G^o = -RT\ln K_{eq} = -RT\ln(1/2 \cdot \text{syn/anti}). \]
2.2 Results and Discussion

To study the charge-transfer (CT) interactions which contribute to the arene-arene interactions, we have synthesized model compounds 7-12 bearing a wide range of electron-acceptors and donors, including the strong acceptors 7a-f and 8a-c with C(1) pentafluorobenzoate and dinitrobenzoate from the starting material 9-Bromoanthracene 2

Scheme 2.1

\[ 2 \rightarrow 3 \rightarrow 4 \rightarrow 7-12 \]

\[ 7a-f : X = \text{NMe}_2, \text{MeO}, \text{CH}_3, \text{H}, \text{F}, \text{CF}_3 \]

\[ \text{Ar} = \text{F} \]

\[ 7 \rightarrow 8 \rightarrow 9 \rightarrow 10 \rightarrow 11 \rightarrow 12 \]
(Scheme 2.1). Variable temperature NMR studies have been performed for each compound in CDCl₃ and C₆D₅Br. Xiaowen Xue has made the compounds 10-12 and has collaborated with me to work on this project. The interaction measured here is parallel displaced because the edge-to-face orientation is prohibited due to the triptycene skeleton. Substitution effect was investigated through the changes of substituents X and Ar. The syn/anti isomeric ratios at -15°C are described in Table 2.1.

Table 2.1 Substituent Effect on the Ratios of syn/anti Isomers and the Free Energies in kcal/mol (in parenthesis) for Arene-Arene Interactions. The errors are estimated at ± 0.05 kcal/mol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>X</th>
<th>Ar</th>
<th>syn/anti Ratio (-ΔG°_{anti→syn}) (-15°C)</th>
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<tr>
<td>1</td>
<td>7a</td>
<td>NMe₂ C₆F₅</td>
<td></td>
<td>21.7 (1.22) in CDCl₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.5 (1.14) in BrC₆D₅</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>MeO C₆F₅</td>
<td></td>
<td>16.8 (1.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.9 (0.99)</td>
</tr>
<tr>
<td>3</td>
<td>7c</td>
<td>Me C₆F₅</td>
<td></td>
<td>14.4 (1.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.8 (0.91)</td>
</tr>
<tr>
<td>4</td>
<td>7d</td>
<td>H C₆F₅</td>
<td></td>
<td>13.7 (0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.8 (0.86)</td>
</tr>
<tr>
<td>5</td>
<td>7e</td>
<td>F C₆F₅</td>
<td></td>
<td>13.5 (0.98)</td>
</tr>
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<td></td>
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<td></td>
<td>10.5 (0.85)</td>
</tr>
<tr>
<td>6</td>
<td>7f</td>
<td>CF₃ C₆F₅</td>
<td></td>
<td>13.5 (0.98) a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.3 (0.84)</td>
</tr>
<tr>
<td>7</td>
<td>8a</td>
<td>NMe₂ C₆H₃(NO₂)₂</td>
<td>&gt;50 (&gt; 1.65)</td>
<td>&gt;50 (&gt; 1.65)</td>
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<tr>
<td>8</td>
<td>8b</td>
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<td>&gt;50 (&gt; 1.65)</td>
<td>&gt;50 (&gt; 1.65)</td>
</tr>
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<td>9</td>
<td>8c</td>
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<td>&gt;50 (&gt; 1.65)</td>
<td>&gt;50 (&gt; 1.65)</td>
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<td>10</td>
<td>9a</td>
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<tr>
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<td>11b</td>
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<tr>
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<td>11d</td>
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<td>C₆H₅I</td>
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<tr>
<td>24</td>
<td>12a</td>
<td>Me</td>
<td>(c-pentyl)</td>
<td>2.2 (0.05)</td>
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<tr>
<td>25</td>
<td>12b</td>
<td>H</td>
<td>(c-pentyl)</td>
<td>2.5 (0.11)</td>
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<tr>
<td>26</td>
<td>12c</td>
<td>F</td>
<td>(c-pentyl)</td>
<td>2.8 (0.17)</td>
</tr>
<tr>
<td>27</td>
<td>12d</td>
<td>CF₃</td>
<td>(c-pentyl)</td>
<td>2.9 (0.19)</td>
</tr>
</tbody>
</table>

The *syn/anti* ratio was 13.3 in CD₂Cl₂ and 10.5 in toluene-d₈.

**Figure 2.3.** Illustration for the appearance of the benzyl CH₂ protons in ¹H NMR spectra for triptycene derivatives. Experimental (left column) and simulated (right column) ¹H NMR spectrum for the benzyl CH₂ protons of compound 7f at different temperatures.
The rotational rate constants $K_{ab}$ (see Figure 1.1) about the C-C bond at C(9) have been determined by line shape analysis at each temperature using the WinDNMR program. Sample rate constants at various temperatures measured for compound $7f$ are listed in Table 2.2. The rotational barrier $\Delta H^\neq$ and $\Delta S^\neq$ around this C-C bond has been calculated using the Eyring equation based on the rotational rate constants.

The Eyring equation:

$$\Delta H^\neq - T\Delta S^\neq = -RT\ln K^\neq = -RT\ln[(h/k_B)(k/T)]$$

$$\ln(k/T) = -(\Delta H^\neq/RT) + (\Delta S^\neq/R) - \ln(h/k_B)$$

$\Delta H^\neq$ and $\Delta S^\neq$ can be extracted by plotting $\ln(k/T)$ vs. $(1/T)$.

**Table 2.2** Sample rate constants at various temperatures measured for compound $7f$.

<table>
<thead>
<tr>
<th>T(K)$^a$</th>
<th>1000/T</th>
<th>k(sec$^{-1}$)$^b$</th>
<th>ln(k/T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>353</td>
<td>2.83</td>
<td>9301</td>
<td>3.27</td>
</tr>
<tr>
<td>323</td>
<td>3.10</td>
<td>3853</td>
<td>2.48</td>
</tr>
<tr>
<td>313</td>
<td>3.19</td>
<td>383</td>
<td>0.20</td>
</tr>
<tr>
<td>303</td>
<td>3.30</td>
<td>205</td>
<td>-0.39</td>
</tr>
<tr>
<td>293</td>
<td>3.41</td>
<td>98</td>
<td>-1.10</td>
</tr>
<tr>
<td>273</td>
<td>3.66</td>
<td>18.9</td>
<td>-2.67</td>
</tr>
<tr>
<td>263</td>
<td>3.80</td>
<td>8.1</td>
<td>-3.48</td>
</tr>
<tr>
<td>253</td>
<td>3.95</td>
<td>2.7</td>
<td>-4.54</td>
</tr>
</tbody>
</table>

$^a$ Temperature calibrated with $^{13}$C internal thermometer. $^b$ Rotational rate constants obtained by computer simulations using the WinDNMR program.
\[
\ln(k/T) = -7.1811(1000/T) + 23.673 \\
R^2 = 0.9676
\]

**Figure 2.4** \(\ln(k/T)\) vs. 1000/T for the equilibrium between *anti* and *syn* conformations for compound 7f.

\[
\Delta H^e = -R(slope) = -1.987 \times (-7.18) \times 1000 \text{ cal mol}^{-1} = 14.27 \pm 1.1 \text{ kcal mol}^{-1} \\
\Delta S^e = R(y\text{-int} - 23.76) = 1.987 \times (23.67 - 23.76) = -0.17 \pm 0.3 \text{ cal mol}^{-1} \text{ K}^{-1}
\]

Based on this study, the rotational barrier for compound 7f has \(\Delta H^e = 14.27 \pm 1.1 \text{ kcal mol}^{-1}\) and \(\Delta S^e = -0.17 \pm 0.3 \text{ cal mol}^{-1} \text{ K}^{-1}\). Standard error was calculated by linear regression analysis (see page 31).

Different results are obtained in this study based on quantitative investigations of a series of triptycene compounds (7-12) bearing a wide range of electron-acceptors and donors, including the strong acceptors 7a-f and 8a-c with C(1) pentafluorobenzoate and dinitrobenzoate. The strongest attractions (>50:1 *syn/anti* ratio) are found for compounds 8a-c in CDCl₃ as well as in C₆D₅Br as shown in Table 2.1 (entries 7-9). These series of compound shows explicitly *syn* conformation in CDCl₃ and in C₆D₅Br. Fortunately, we have found C₆D₅Br as a good solvent to study this kind of interaction. Due to the competitive \(\pi-\pi\) interactions with solvent, the *syn/anti* ratios are smaller in C₆D₅Br than in the solvent CDCl₃. When the substituent on the C(9) arene is an N,N-dimethylamino group, strongest attractions are exhibited by compound 7a and 8a, while the smallest attraction was observed when the corresponding substituent is CF₃ (10.3 *syn/anti* ratio) in this series. From the observed experimental *syn/anti* ratio described in Table 2.1, the
population of the *syn* isomer is dependent on the X-substituent in the following order: \( \text{CF}_3 < \text{F} < \text{H} < \text{Me} < \text{MeO} < \text{NMe}_2 \).

We have examined the electronic effects of aromatic interactions with a study of electronic absorption spectra in order to gain a better understanding of the structure of the model system. The solution of compound 7a has a yellow color in dichloromethane. Compound 7a shows a charge-transfer (CT) band at 321 nm in dichloromethane, while it is absent in the solutions of the precursors hydroquinone (6a) and pentafluorobenzoyl chloride (13). Previously, it has been reported that the intermolecular complex between hexafluorobenzene and N,N-dimethylamino benzene exhibit a charge-transfer band at 316 nm.\(^{30}\)

![Figure 2.5](image.png)

**Figure 2.5** Absorption spectra of compound 7a (—), 6a (—), and 13 (—) in CH\(_2\)Cl\(_2\). The position of absorption band at 321 nm remains unchanged for compound 7a at various concentrations from 0.06mM to 0.56mM. Concentration as shown: 0.09mM.
Model compound 8a has a red color in dichloromethane. It shows a broad charge-transfer (CT) band around 475 nm with low extinction coefficient. The presence of a CT band becomes clearer in the difference spectrum. (Figure 2.6, Top) A previous report on the intermolecular complex between s-trinitrobenzene and N,N-dimethylaniline supports the assignment of the 475 nm absorption as a CT band. A CT band for the complex was reported to be centered on 487 nm. We have not observed a CT band for any other model compounds.

![Absorption spectra of 8a in CH2Cl2. Top: difference spectrum (0.08 mM); bottom: 8a and its precursor (0.15 mM).](image)

**Figure 2.6** Absorption spectra of 8a in CH2Cl2. Top: difference spectrum (0.08 mM); bottom: 8a and its precursor (0.15 mM).

As shown in Table 2.1 (entries 1-6), for compounds with pentafluorobenzoate at C(1), the attractions of arene-arene increases from the compound with the strongest EWG (CF3) to the compound with the strongest EDG (NMe2). However, compounds 9a-f, 10a-d, and 11a-d, (entries 10-23, Table 2.1), which have a single arene substituent exhibit an opposite trend. These compounds exhibit the “normal” substituent effects, i.e., a stronger EWG leads to a higher population of the syn conformation. The population of the syn isomer for these compounds is
dependent on the X-substituent in the following order: CF₃>F>H>Me>MeO>NMe₂. Compounds 9a-f (entries 10-15) have a nitrobenzoate group at C(1). For compound 9f, the highest syn/anti ratio (12.7, X = CF₃) was observed, and the lowest was observed for compound 9a (5.2, X = NMe₂) in CDCl₃. The same trend was observed for compound 10a-d and 11a-d. When X changes from a Me group to a CF₃ group (entries 16-23, Table 2.1), the syn/anti ratios are between 2.6 to 6.4.

Compounds 12a-d play as control compounds by replacing the C(1) benzoate group with the cyclopentane carboxylate group. When the X substituent changes to CF₃, the preference for the syn conformations is much less distinct as you can see from the syn/anti ratios (2.2-2.9). The substituent effects for this series are not obvious since there are no arene-arene interactions. The relatively weak preference for the syn isomer is mainly ascribed to a lone pair-π* interactions between the phenolic oxygen and the C(1) arene.31

The rotation of the benzyl group at C(9) around the C₃sp-C₃sp bond gives rise to three rotational minima, one anti and two syn conformations as shown in Figure 1.2. In each of these three conformations, the phenyl ring of the benzyl group should be able to rotate around the C₃sp(phenyl)-C₃sp(benzylic) bond. However, the phenyl rotation is hindered by the triptycene

Figure 2.7 Minimum energy conformation for compound 7a (X = NMe₂) found by MacroModel using MM2 force field.32 (a) Space-filling model and (b) ball-and-stick model. The distance between the arenes is labeled in angstrom.
scaffold hydrogen atoms at C(8) and at C(11) and the oxygen atom at C(1). Therefore it is clear that both the anti and the syn isomer have only one minimum conformation in which the phenyl group bisects the two blades of the triptycene skeleton with regard to the benzyl group at C(9). This shows a symmetrical anti conformation in which, although no forced contact, the C(9) phenyl group is fit snugly between the triptycene blades. In the syn isomer, the stable conformation of the ester function places the pentafluorobenzoate ring parallel to the C(9) benzyl group.\textsuperscript{31,33} The minimum configuration of compound 7a generated by Macromodel with an interplanar distance is about 3.5 Å, which is shown in Figure 2.7. As indicated in the space-filling model, the pentafluorobenzoate ring and the N,N-dimethylaminobenzyl ring assume the parallel-displaced configuration.

Conformations calculated from Macromodel indicate that the two arenes lie parallel to each other in a stable conformation allowing potential electronic interactions. An \textit{ab initio} electronic structure calculation on an appropriate model is necessary to study the electronic effects involved in these aromatic interactions. However, the Macromodel structures allow one to visualize the interacting aromatic rings and to have a better understanding of the model system. The rigid structure of the triptycene skeleton should leave little room for structure errors even with simple molecular mechanics calculations.

Opposite trends are observed in substituent effects for compounds (7a-f) with pentafluorobenzoate at C(1) and for compounds with a mononitrobenzoate (9a-f) or with other singly substituted benzoate groups (10a-d or 11a-d). We assume that the preference for the syn conformation arises from attractive interactions between the two attached arenes because the anti conformation is free from steric repulsion. The two opposite trends and the non-linearity in substituent effects for compounds 7a-f are differentiated by plotting the free energies of attractions vs. $\sigma_{\text{para}}$ for two series of compounds (7a-f and 9a-f) in Table 2.1 (Figure 2.8).

A straight line and a curve are obtained for compound 9a-f and 7a-f respectively. These opposite trends (Figure 2.8) can be rationalized by the electrostatic model proposed by Hunter and Sanders.\textsuperscript{13,26} A straight line for compounds 9a-f demonstrates that the electrostatic forces are dominant in controlling arene-arene interactions. The arene interactions in compounds 7a-f are
Figure 2.8  Plot of free energy of attraction (-\(\Delta G^\circ\)) vs. \(\sigma_{\text{para}}\) for compounds 7a-f (♦) and 9a-f (Δ). Non-linearity in substituent effects was observed for compounds 7a-f. Experiments were conducted in C\(_6\)D\(_3\)Br.

affected by charge transfer interactions while other compounds with a mono-substituted benzoate group are controlled mainly by electrostatic interactions. As described in the monograph by Foster,\(^1\) organic charge transfer complexes are structures involving mainly dispersion, dipole and similar forces together with a usually small contribution from a covalent dative structure in which one electron has been transferred from the donor to the acceptor component of the complex. This small contribution from the covalent dative structure appears to operate and to produce an attractive interaction that is stronger than a simple electrostatic interaction for compounds 7a and 8a. Smaller contribution from electron-density transfer might be plausible since its attractive interaction is also higher than the Hammett plot predicted for compound 7b with a C(9) methoxybenzyl group. From this study, we can suggest that there is a threshold for charge-transfer effects to occur in aromatic interactions. The aromatic system must be strongly perturbed with substituents of opposite polarity on each interacting arene in order to reach this threshold.

This study shows that two mechanisms are operating in the parallel-stacked aromatic interactions. Electrostatic forces are important when the monocyclic arenes on C(1) are substituted with a single substituent. However, charge-transfer interactions are the dominant force when multiple EWG are present on a monocyclic arene. Due to the fact that the intensity of charge-transfer interactions is inversely proportional to the difference between the ionization
potential \((\text{IP})\) of the donor and the electron affinity \((\text{EA})\) of the acceptor, only the model compound with a C(1) pentafluorobenzoate \((7\text{a})\) and dinitrobenzoate \((8\text{a})\) and a C(9) dimethylaminobenzyl group exhibit the charge transfer bands as these electron-acceptors have relatively high EA. From our study, we suggest that in order for charge transfer interaction to occur, the two interacting arenes must be able to adopt a nearly perfect parallel-stacked arrangement in addition to being strong electron acceptors and donors. Any deviation from this configuration may prevent the HOMO-LUMO interactions between the arenes. These promising results will be very helpful in both chemical and biological recognition.

2.3 Additional Study

We have also synthesized compounds \(7\text{g}, 8\text{d}, \text{and} 9\text{g}\) from the starting material 9-Bromoanthracene \(2\) (Scheme 2.2). Variable temperature NMR experiments was performed for each compound in CDCl\(_3\) and C\(_6\)D\(_5\)Br to find out the effect of increasing one more aromatic ring at the C(9) carbon on the \(\text{syn/anti}\) ratio with different acceptors at the C(1) carbon. We have used 6-Methoxy-2-napthaldehyde group at the C(9) carbon to study this effect. As methoxy group is a little weak electron donor, we have thought that these series of compound should show higher \(\text{syn/anti}\) ratio.

To our disappointment, we were not able to assign the \(\text{syn/anti}\) ratio from the variable temperature NMR studies because of the two \(\text{syn}\) and one \(\text{anti}\) conformation at lower temperature. At the lower temperature we have observed two sets of a doublet and a singlet around the chemical shift of 4.7 ppm. All signals overlapped with each other, which made it impossible for us to calculate the \(\text{syn/anti}\) ratio at different temperature. We have also not observed any charge-transfer(CT) band for the these compounds.
2.4 Experimental Section

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. Reagents were purchased from commercial sources and used without further purification. Compounds 6c-f and 9c-f (X = CH₃, H, F, CF₃) have been reported recently from our laboratories.¹ Flash column chromatographic separations were performed using silica gel 40 – 63 μm. Reactions were monitored by TLC with UV light and stain detection. NMR spectra (¹H, ¹³C,


\[ ^{19}\text{F} \] were recorded on 200, 300, and 500 MHz spectrometers with CDCl\(_3\), Acetone-d\(_6\), or DMSO-d\(_6\) as the solvents and (CH\(_3\))\(_4\)Si as the internal reference. Melting points were not corrected.

![Diagram](image)

**General Synthetic Procedure for 9-(4'-Substitutedphenyl)anthracenylmethanol (3).**

9-Bromoanthracene 2 (4.0 g, 15.6 mmol) was dissolved in dry THF (60 ml) and the solution was cooled to \(-78^\circ\text{C}\). A solution of n-butyl lithium (1.6 M in hexane, 9.7 ml, 15.6 mmol) was added. The mixture was stirred at \(-78^\circ\text{C}\) for 1 h. A solution of 4-substitutedbenzaldehyde (15.6 mmol) in 20 ml of THF was then added. After 0.5 h, the mixture was allowed to warm up to room temperature and the stirring was continued for another 1.5 h. Water (150 ml) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined and dried over anhydrous magnesium sulfate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography to give 3 as a solid.

**9-(4'-Dimethylaminophenyl)anthracenylmethanol (3a):** yield 80%; yellow solid, m.p. 66-67 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.56 (1 H, d, J = 3.8 Hz), 2.88 (6 H, s), 6.63 (2 H, d, J = 8.8 Hz), 7.19-7.42 (7 H, m), 7.99-8.03 (2 H, m), 8.38-8.45 (3 H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 40.6, 70.7, 112.4, 124.8, 125.3, 125.7, 127.0, 128.3, 129.1, 129.9, 131.6, 131.8, 134.4, 149.6; LCMS caled for C\(_{23}\)H\(_{21}\)NO + H 328.2, found 328.3.

**9-(4'-Methoxyphenyl)anthracenylmethanol (3b):** yield 80%; yellow solid, m.p. 92-93 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.64 (1 H, d, J = 3.8 Hz), 3.74 (3 H, s), 6.79 (2 H, d, J = 8.8 Hz), 7.24-7.28 (2 H, m), 7.39-7.44 (5 H, m), 7.8-8.03 (2 H, m), 8.35-8.38 (2 H, m), 8.46 (1 H, s); \(^{13}\)C
NMR (50 MHz, CDCl₃) δ 55.2, 70.1, 113.6, 124.9, 125.1, 125.9, 127.1, 128.5, 129.2, 129.8, 131.7, 134.1, 135.8, 158.4; LCMS calcd for C₂₂H₁₈O₂ + Na 337.1, found 337.2.

![Chemical structure](image)

General Synthetic Procedure for 9-(4’-Substitutedbenzyl)anthracene (4).³⁶ To a solution of sodium borohydride (1.5 g, 39.5 mmol) in TFA (50 ml) was added dropwise a solution of alcohol 3 (6.1 mmol) in dichloromethane (22 ml) at 0 ºC. The mixture was allowed to stir at 0 ºC for 5 min and at room temperature for 1 h. Then it was poured into 250 ml of 10% NaOH solution, extracted with ether and dried over anhydrous magnesium sulfate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography to afford anthracene 4 as a solid.

9-(4’-Dimethylaminobenzyl)anthracene (4a): yield 85%; yellow solid, m.p. 126-127 ºC; ¹H NMR (200 MHz, CDCl₃) δ 2.83 (6 H, s), 4.90 (2 H, s), 6.58 (2 H, d, J = 8.7 Hz), 6.98 (2 H, d, J = 8.6 Hz), 7.40-7.45 (4 H, m), 7.98-8.03 (2 H, m), 8.21-8.26 (2 H, m), 8.39 (1 H, s); ¹³C NMR (75 MHz, CDCl₃) δ 32.5, 40.7, 112.9, 124.8, 125.0, 125.7, 126.2, 128.7, 129.0, 130.5, 131.7, 132.8, 149.0; LCMS calcd for C₂₃H₂₁N + H 312.2, found 312.3.

9-(4’-Methoxybenzyl)anthracene (4b): yield 50%; yellow solid, m.p. 136-137 ºC; ¹H NMR (300 MHz, CDCl₃) δ 3.72 (3 H, s), 4.96 (2 H, s), 6.77 (2 H, d, J = 8.6 Hz), 7.06 (2 H, d, J = 8.6 Hz), 7.45-7.51 (4 H, m), 8.04-8.07 (2 H, m), 8.23-8.27 (2 H, m), 8.45 (1 H, s); ¹³C NMR (75 MHz, CDCl₃) δ 32.6, 55.1, 113.8, 124.8, 124.9, 125.8, 126.4, 129.0, 129.1, 130.4, 131.7, 132.2, 132.9, 157.8; LCMS calcd for C₂₂H₁₈O + H 299.1, found 299.2.
General Synthetic Procedure for 9-(4'-Substitutedbenzyl)-1,4-dionetriptycene (5). The 9-(4'-substitutedbenzyl) anthracene 4 (4.6 mmol) and p-benzoquinone (0.6 g, 5.5 mmol) in 23 ml of toluene were heated in a sealed tube at 115 °C for 48 h. The solvent was removed under reduced pressure and the crude product was used for the next step without further purification as we found out that the Diels-Alder adduct decomposes during its purification via column chromatography hence the low yields.

General Synthetic Procedure for 9-(4’-Substitutedbenzyl)-1,4-dihydroxytriptycene (6). A mixture of the adduct 5 (1 mmol) and KOAc (0.26 g, 2.7 mmol) in methanol (11 ml) was refluxed for 3 h. After cooling to room temperature, the solution was poured into water, and solid was collected by filtration. Further purification via flash column chromatography afforded 9-(4’-substitutedbenzyl)-1,4-dihydroxytriptycene (6) as a solid.
9-(4’-Dimethylaminobenzyl)-1,4-dihydroxytriptycene (6a): yield 71% from 4a; white solid, m.p. 161-162 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.91 (6 H, s), 4.53 (3 H, br), 4.78 (1 H, s), 5.87 (1 H, s), 6.27 (1 H, d, J = 8.6 Hz), 6.38 (1 H, d, J = 8.6 Hz), 6.68 (2 H, br), 6.89-7.00 (5 H, m), 7.24-7.42 (5 H, m); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 33.2, 40.4, 47.4, 52.4, 112.7, 114.2, 117.2, 123.4, 124.1, 124.5, 124.9, 130.3, 132.7, 134.6, 144.4, 145.6, 146.4, 149.3; LCMS calcd for C\(_{29}\)H\(_{25}\)NO\(_2\) + H 420.2, found 420.3.

9-(4’-Methoxybenzyl)-1,4-dihydroxytriptycene (6b): yield 69% from 4b; white solid, m.p. 178-179 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.77 (3 H, s), 4.39 (1 H, s), 4.45 (1 H, s), 4.61 (2 H, br), 5.86 (1 H, s), 6.24 (1 H, d, J = 8.6 Hz), 6.38 (1 H, d, J = 8.5 Hz), 6.70-7.43 (12 H, m); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 33.6, 47.4, 52.6, 55.2, 113.7, 114.1, 114.2, 116.7, 123.5, 124.5, 125.0, 129.7, 130.0, 130.6, 144.5, 145.5, 146.4, 158.0; LCMS calcd for C\(_{28}\)H\(_{22}\)O\(_3\) – H 405.1, found 405.0.

General Synthetic Procedure for 9-(4’-Substitutedbenzyl)-1,4-di(substitutedbenzoyl) triptycene (7-9).\(^38\)

9-(4’-Dimethylaminobenzyl)-1,4-di(pentafluorobenzoyl)triptycene (7a): Pentafluorobenzoyl chloride 13 (0.06 ml, 0.4 mmol) was added to a solution of 9-(4’-dimethylaminobenzyl)-1,4-dihydroxytriptycene 6a (71 mg, 0.2 mmol) in dichloromethane (3 ml) and pyridine (1.5 ml) at 0 °C. The mixture was allowed to stir at 0 °C for 10 min and at room temperature for 6 h. 20 ml of water was added to quench the reaction. The precipitate was collected by filtration and washed with water. The crude product was then dissolved in a minimum amount of dichloromethane and precipitated with hexanes to afford the pure product 7a as a yellow solid (68 mg, 50%). m.p. 270-271 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.85 (6 H, s), 4.43 (2 H, m), 5.61 (1 H, s), 6.35 (2 H, br), 6.70-7.59 (12 H, br); \(^19\)F NMR (188 MHz, CDCl\(_3\)) \(\delta\) -136.38 (2 F, br), -138.41 (2 F, ddd, J = 5.6, 17.0, 20.7 Hz), -148.13 (1 F, tt, J = 5.6, 20.7 Hz), -149.09 (1 F, br), -160.33 (2 F, ddt, J = 5.6, 15.1, 20.7 Hz), -162.66 (2 F, br); HRMS calcd for C\(_{43}\)H\(_{23}\)F\(_{10}\)NO\(_4\) + H 808.1545, found 808.1549.
\(^{19}\)F NMR spectra were recorded for compounds 7a-f (Ar = pentafluorophenyl), and 8c in which 
CF\(_3\)CO\(_2\)H was used as a standard (\(\delta = -76.20\), s). Due to the limited solubility of compounds 
7a-f, and 8a-c in various solvents, we found it was more efficient in the identification of these 
compounds by \(^{19}\)F NMR than \(^{13}\)C NMR.

\[
\begin{array}{cccc}
6a, X = \text{NMe}_2 \\
6b, X = \text{MeO} \\
6c, X = \text{CH}_3 \\
6d, X = \text{H} \\
6e, X = \text{F} \\
6f, X = \text{CF}_3 \\
7a, X = \text{NMe}_2 (50\%) \\
7b, X = \text{MeO} (50\%) \\
7c, X = \text{CH}_3 (73\%) \\
7d, X = \text{H} (75\%) \\
7e, X = \text{F} (78\%) \\
7f, X = \text{CF}_3 (67\%) \\
8a, X = \text{NMe}_2 (55\%) \\
8b, X = \text{MeO} (53\%) \\
8c, X = \text{CF}_3 (70\%) \\
9a, X = \text{NMe}_2 (50\%) \\
9b, X = \text{MeO} (67\%) \\
9c, X = \text{CF}_3 (67\%)
\end{array}
\]

9-(4'-Methoxybenzyl)-1,4-di(pentafluorobenzoyl)triptycene (7b): yield 50\%; light yellow 
solid, m.p. > 280 \(^\circ\)C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.72 (3 H, s), 4.45 (2 H, m), 5.62 (1 H, s), 
6.55 (2 H, br), 6.84-7.59 (12 H, br); \(^{19}\)F NMR (188 MHz, CDCl\(_3\)) \(\delta\) -132.60 (2 F, br), -134.33 
(2 F, ddd, \(J = 5.6, 17.0, 20.7\) Hz), -144.01 (1 F, tt, \(J = 5.6, 20.7\) Hz), -144.58 (1 F, br), -156.24 
(2 F, ddt, \(J = 5.6, 15.1, 20.7\) Hz), -158.34 (2 F, br); HRMS calcd for C\(_{42}\)H\(_{20}\)F\(_{10}\)O\(_5\) + Na 817.1049, 
found 817.1061.
9-(4'-Methylbenzyl)-1,4-di(pentafluorobenzoyl)triptycene (7c): yield 73%; white solid, m.p. > 280 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.24 (3 H, s), 4.48 (2 H, m), 5.62 (1 H, s), 6.81-7.06 (11 H, m), 7.37-7.52 (3 H, m); $^{19}$F NMR (188 MHz, CDCl$_3$) δ -136.12 (2 F, br), -137.84 (2 F, ddd, J = 5.6, 17.0, 20.7 Hz), -147.50 (1 F, tt, J = 5.6, 20.7 Hz), -148.13 (1 F, br), -159.77 (2 F, ddt, J = 5.6, 15.1, 20.7 Hz), -162.02 (2 F, br); HRMS calcd for C$_{42}$H$_{20}$F$_{10}$O$_4$ + Na 801.1100, found 801.1098.

9-Benzyl-1,4-di(pentafluorobenzoyl)triptycene (7d): yield 75%; white solid, m.p. > 280 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 4.52 (2 H, m), 5.63 (1 H, s), 6.89-7.17 (12 H, m), 7.31-7.59 (3 H, m); $^{19}$F NMR (188 MHz, CDCl$_3$) δ -133.49 (2 F, br), -135.57 (2 F, ddd, J = 5.6, 17.0, 20.7 Hz), -145.23 (1 F, tt, J = 5.6, 20.7 Hz), -145.71 (1 F, br), -157.49 (2 F, ddt, J = 5.6, 15.1, 20.7 Hz), -159.23 (2 F, br); HRMS calcd for C$_{41}$H$_{18}$F$_{10}$O$_4$ + Na 787.0943, found 787.0943.

9-(4'-Fluorobenzyl)-1,4-di(pentafluorobenzoyl)triptycene (7e): yield 78%; white solid, m.p. > 280 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 4.48 (2 H, m), 5.63 (1 H, s), 6.74-7.08 (11 H, m), 7.33-7.37 (3 H, m); $^{19}$F NMR (188 MHz, CDCl$_3$) δ -114.76 (1 F, s), -133.65 (2 F, br), -133.65 (2 F, ddd, J = 5.6, 17.0, 20.7 Hz), -144.70 (2 F, tt, J = 5.6, 20.7 Hz), -144.70 (2 F, tt, J = 5.6, 20.7 Hz), -157.04 (2 F, ddt, J = 5.6, 15.1, 20.7 Hz), -159.23 (2 F, br); HRMS calcd for C$_{41}$H$_{17}$F$_{11}$O$_4$ + Na 805.0849, found 805.0873.

9-(4'-Trifluoromethylbenzyl)-1,4-di(pentafluorobenzoyl)triptycene (7f): yield 67%; white solid, m.p. > 280 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 4.55 (2 H, m), 5.64 (1 H, s), 6.87-7.59 (14 H, m); $^{19}$F NMR (188 MHz, CDCl$_3$) δ -63.19 (3 F, s), -136.12 (2 F, br), -137.77 (2 F, ddd, J = 5.6, 17.0, 20.7 Hz), -146.80 (1 F, br), -146.80 (1 F, br), -147.24 (1 F, tt, J = 5.6, 20.7 Hz), -159.67 (2 F, ddt, J = 5.6, 15.1, 20.7 Hz), -159.67 (2 F, ddt, J = 5.6, 15.1, 20.7 Hz), -160.80 (2 F, br); HRMS calcd for C$_{42}$H$_{17}$F$_{13}$O$_4$ + Na 855.0817, found 855.0806.

9-(4'-Dimethylaminobenzyl)-1,4-di(3',5'-dinitrobenzoyl)triptycene (8a): yield 55%; red solid, m.p. > 280 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.73 (6 H, s), 4.44 (2 H, dd, J = 17.3 Hz), 5.47 (1 H, s), 5.92 (1 H, br), 6.32 (1 H, br), 6.67-6.82 (3 H, m), 6.96-7.15 (6 H, m), 7.33 (2 H, br), 7.61 (1 H, br), 8.74 (2 H, br), 9.14 (1 H, br), 9.41-9.50 (3 H, m); HRMS calcd for C$_{43}$H$_{29}$N$_5$O$_{12}$ + H 808.1891, found 808.1919.
9-(4'-Methoxybenzyl)-1,4-di(3',5'-dinitrobenzoyl)triptycene (8b): yield 53%; light yellow solid, m.p. > 280 ºC; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.66 (3 H, s), 4.44 (2 H, dd, J = 16.1 Hz), 5.48 (1 H, s), 6.22 (1 H, br), 6.65 (1 H, br), 6.83-7.1 (9 H, m), 7.37 (2 H, br), 7.59 (1 H, br), 8.74 (2 H, br), 9.19 (1 H, br), 9.41-9.50 (3 H, m); HRMS calcd for C$_{42}$H$_{26}$N$_4$O$_{13}$ + Na 817.1394, found 817.1371.

9-(4'-Trifluoromethylbenzyl)-1,4-di(3',5'-dinitrobenzoyl)triptycene (8c): yield 70%; white solid, m.p. > 280 ºC; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.63 (2 H, dd, J = 17.7 Hz), 5.50 (1 H, s), 6.77-7.11 (10 H, m), 7.29-7.40 (3 H, m), 7.60 (1 H, br), 8.76 (2 H, br), 9.21 (1 H, br), 9.39-9.51 (3 H, m); $^{19}$F NMR (188 MHz, CDCl$_3$) $\delta$ -63.04 (3 F, s); HRMS calcd for C$_{42}$H$_{23}$F$_3$N$_4$O$_{12}$ + Na 855.1162, found 855.1166.

9-(4'-Dimethylaminobenzyl)-1,4-di(4'-nitrobenzoyl)triptycene (9a): yield 50%; orange solid, m.p. > 280 ºC; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.88 (6 H, s), 4.38 (2 H, m), 5.48 (1 H, s), 6.41 (2 H, br), 6.79-7.73 (13 H, m), 7.91 (2 H, br), 8.46-8.56 (5 H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 33.8, 40.7, 48.8, 48.9, 112.1, 119.9, 121.7, 123.1, 123.7, 124.1, 125.4, 130.2, 131.2, 131.5, 134.3, 134.6, 143.0, 144.0, 148.6, 150.7, 151.2, 163.0; HRMS calcd for C$_{43}$H$_{31}$N$_3$O$_8$ + Na 740.2009, found 740.2000.

9-(4'-Methoxybenzyl)-1,4-di(4'-nitrobenzoyl)triptycene (9b): yield 67%; white solid, m.p. > 280 ºC; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.74 (3 H, s), 4.40 (2 H, m), 5.49 (1 H, s), 6.57 (2 H, br), 6.79-7.04 (9 H, m), 7.34 (3 H, m), 8.20 (2 H, br), 8.43-8.56 (6 H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 33.9, 48.8, 48.9, 55.2, 113.1, 119.6, 120.0, 121.7, 123.2, 123.8, 124.0, 124.1, 124.2, 125.7, 130.5, 131.1, 131.5, 134.5, 143.0, 143.8, 151.2, 157.6, 163.0; HRMS calcd for C$_{42}$H$_{28}$N$_2$O$_9$ + Na 727.1693, found 727.1697.
Synthetic Procedure for 9-(6’-Methoxy-2’-napthyl)anthracenyl methanol (14). \(^{35}\)

9-Bromoanthracene 2 (4.0 g, 15.6 mmol) was dissolved in dry THF (60 ml) and the solution was cooled to –78 °C. A solution of n-butyl lithium (1.6 M in hexane, 9.7 ml, 15.6 mmol) was added. The mixture was stirred at –78 °C for 1 h. A solution of 6-methoxy-2-naphthaldehyde (2.9 g, 15.6 mmol) in 20 ml of THF was then added. After 0.5 h, the mixture was allowed to warm up to room temperature and the stirring was continued for another 1.5 h. Water (150 ml) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined and dried over anhydrous magnesium sulfate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography to give 14 as a yellow solid (4.53 g, 80%). m.p. 99-100 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.74 (1 H, d, \(J = 3.7\) Hz), 3.87 (3 H, s), 7.06-7.1 (2 H, m), 7.35-7.46 (5 H, m), 7.52 (1 H, d, \(J = 3\) Hz), 7.59-7.63 (2 H, m), 7.83 (1 H, s), 8.02-8.05 (2 H, m), 8.40 (1 H, s), 8.43 (1 H, s), 8.50 (1 H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 55.3, 70.4, 105.6, 118.8, 124.1, 124.8, 124.9, 125.0, 126.0, 126.9, 128.7, 128.8, 129.2, 129.6, 130.0, 131.8, 133.5, 134.0, 139.1, 157.6; LCMS calcd for C\(_{26}\)H\(_{20}\)O\(_2\) + Na 387.1, found 387.3.
Synthetic Procedure for 9-(6’-Methoxy-2’-napthyl)anthracene (15).\(^{36}\) To a solution of sodium borohydride (1.5 g, 39.5 mmol) in TFA (49 ml) was added a solution of alcohol 14 (2.2 g, 6.1 mmol) in THF (50 ml) at 0 °C. The mixture was heated under reflux for 16 h. Then it was poured into 250 ml of 10% NaOH solution, extracted with ether and dried over anhydrous magnesium sulfate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography to afford anthrace 15 as a yellow solid (1.37 g, 65%). m.p. 144-145 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.85 (3 H, s), 5.12 (2 H, s), 7.02 (2 H, m), 7.32 (2 H, m), 7.40-7.49 (5 H, m), 7.60 (1 H, m), 8.05 (2 H, m), 8.24 (2 H, m), 8.45 (1 H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 33.6, 55.3, 105.6, 118.6, 124.9, 124.9, 125.9, 126.2, 126.6, 126.9, 127.4, 129.0, 129.1, 129.2, 130.6, 131.7, 131.9, 133.1, 136.1, 157.2; LCMS calcd for C\(_{26}\)H\(_{20}\)O + H 349.2, found 349.3.

\[ \text{H}_3\text{CO} \quad \text{Toluene, reflux} \quad 48 \text{ h} \]

\[ \text{O} \quad \text{O} \]

\[ \text{OCH}_3 \]

15

16

Synthetic Procedure for 9-(6’-Methoxy-2’-napthyl)-1,4-dionetriptycene (16).\(^6\) The 9-(6’-methoxy-2’-napthyl)anthracene 15 (0.45 g, 1.3 mmol) and \(p\)-benzoquinone (0.17 g, 1.6 mmol) in 6.5 ml of toluene were heated in a sealed tube at 115 °C for 48 h. The solvent was removed under reduced pressure and the crude product was used for the next step without further purification.
Synthetic Procedure for 9-(6’-Methoxy-2’-napthyl)-1,4-dihydroxytriptycene (17). A mixture of the adduct 16 and KOAc (0.26 g) in methanol (11 ml) was refluxed for 4 h. After cooling to room temperature, the solvent was evaporated in vacuo. 20 ml of water was added, and the solids were collected by filtration. Further purification via flash column chromatography afforded the desired product 17 as a white solid (0.38 g, 65% from 15). m.p. 188-189 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.89 (3 H, s), 4.36 (1 H, br), 4.69 (3 H, m), 5.90 (1 H, s), 6.17 (1 H, br), 6.34 (1 H, br), 6.89-7.11 (6 H, m), 7.29-7.64 (8 H, m); ¹³C NMR (75 MHz, CD₃CN) δ 48.3, 48.4, 53.9, 55.5, 106.4, 113.9, 114.6, 115.4, 119.0, 126.2, 128.5, 129.6, 129.7, 130.3, 133.7, 135.8, 145.9, 146.1, 147.0, 147.6, 147.9, 158.1; LCMS calcd for C₃₂H₂₄O₃ + Na 479.2, found 479.3.

General Synthetic Procedure for 9-(6’-Methoxy-2’-napthyl)-1,4-di(substitutedbenzoyl) triptycene (7g, 8d, 9g): ³⁸

9-(6’-Methoxy-2’-napthyl)-1,4-di(pentafluorobenzoyl)triptycene (7g): Pentafluorobenzoic chloride 13 (0.06 ml, 0.4 mmol) was added to a solution of 9-(6’-methoxy-2’-napthyl)-1,4-dihydroxytriptycene 17 (91 mg, 0.2 mmol) in dichloromethane (3 ml) and pyridine (1.5 ml) at 0 °C. The mixture was allowed to stir at 0 °C for 10 min and at room temperature for 6 h. 20 ml of water was added to quench the reaction. The precipitate was collected by filtration and washed with water. The crude product was then dissolved in a minimum amount of dichloromethane and precipitated with hexanes to afford the pure product 7g as a light yellow solid (84 mg, 50%).
m.p. > 280 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.91 (3 H, s), 4.70 (2 H, m), 5.66 (1 H, s), 6.79 (1 H, m), 6.95-7.08 (10 H, m), 7.37 (4 H, m), 7.62 (1 H, br); \(^{19}\)F NMR (188 MHz, CDCl\(_3\)) \(\delta\) -136.39 (2 F, m), -137.93 (2 F, ddd, \(J = 5.6, 17.0, 20.7\) Hz), -147.56 (1 F, tt, \(J = 5.6, 20.7\) Hz), -148.18 (1 F, br), -160.16 (3 F, ddt, \(J = 5.6, 15.1, 20.7\) Hz), -162.20 (1 F, br); LCMS calcd for C\(_{46}\)H\(_{22}\)F\(_{10}\)O\(_5\) + Na 867.1, found 867.3.

\(^{19}\)F NMR spectrum was recorded for compound 7g (Ar = pentafluorophenyl) in which CF\(_3\)CO\(_2\)H was used as a standard (\(\delta = -76.20\), s). Due to the limited solubility of compounds 7g, 8d, and 9g in various solvents, it was impossible to record \(^{13}\)C NMR.

9-(6'-Methoxy-2'-napthyl)-1,4-di(3,5-dinitrobenzoyl)triptycene (8d): yield 55%; yellow solid, m.p. > 280 °C; \(^1\)H NMR (300 MHz, Pyridine-\(d_5\)) \(\delta\) 3.78 (3 H, s), 4.97 (2 H, m), 6.31 (1 H, s), 6.91-7.82 (16 H, m), 8.41-9.54 (6 H, m); LCMS calcd for C\(_{46}\)H\(_{28}\)N\(_4\)O\(_{13}\) + Na 867.2, found 867.3.
9-(6’-Methoxy-2’-napthyl)-1,4-di(4-nitrobenzoyl)triptycene (9g): yield 71%; light yellow solid, m.p. > 280 ºC; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.93 (3 H, s), 4.56 (2 H, m), 5.53 (1 H, s), 6.76-7.96 (20 H, m), 8.37-8.58 (4 H, m); LCMS calcd for C\(_{46}\)H\(_{30}\)N\(_2\)O\(_9\) + Na 777.2, found 777.2.

**Variable Temperature NMR Experimental Procedure**

The \(^1\)H NMR spectra were recorded on a Bruker 300 or 500 MHz instrument with a variable temperature probe. A 0.05 M solution of the sample in a deuterated solvent such as bromo-benzene and chloroform was placed in a high quality NMR tube. All samples were degassed using a needle to bubble nitrogen through the sample for \(\sim\)1 minute. The NMR tube was then capped with a cap and sealed with parafilm. The sample tube was placed into the NMR probe and the airline to the probe was replaced with liquid nitrogen transfer line. The desired temperature was set on the variable temperature unit and the sample was allowed to equilibrate for 10 ~ 15 minutes at each set temperature. Then the \(^1\)H NMR spectrum at each temperature was recorded. The ratios of rotamers were obtained through the integrations of selected peaks.

**Calibration of the Variable Temperature NMR probe.**

The calibration of the probe’s temperature was established by recording the \(^{13}\)C NMR spectrum of tris(trimethylsilyl)methane, a \(^{13}\)C internal thermometer immediately before or after a \(^1\)H NMR spectrum was recorded. Actual probe temperature was determined from the equation below, in which \(\Delta\delta\) is the chemical shift difference in ppm between two peaks, methane and methyl carbons. To balance these two peaks, 10% \(^{13}\)C-enriched tris(trimethylsilyl)methane was employed and it was added directly to the sample to prepare a 0.3 % (v/v) solution. The \(^{13}\)C signals were recorded in 64 scans.

\[
T \,(^\circ C) = 84.71(\Delta\delta) - 36.5 \, (\text{in CDCl}_3)
\]
Standard Error Calculation by Linear Regression Analysis

After computer simulation, Eyring equation \( \ln(k/T) = -(\Delta H^\neq/RT) + (\Delta S^\neq/R) + 23.76 \) can be obtained by plotting \( \ln(k/T) \) vs \( 1/T \) through linear regressions (Micro Excel). For compound 7f, Eyring equation is \( \ln(k/T) = -7.1811(1000/T) + 23.673 \) (See Figure 2.4). Therefore, \( \Delta H^\neq \) and \( \Delta S^\neq \) can be calculated by the expressions: \( \Delta H^\neq = -R(\text{slope}) \) and \( \Delta S^\neq = R(\text{intercept-23.76}) \). The errors for \( \Delta H^\neq \) and \( \Delta S^\neq \) can be determined by the method discussed below. Assuming the equation obtained is \( y = a + bx \) (\( a \) and \( b \) are intercept and slope respectively), the standard errors \( S(a) \) and \( S(b) \), which define plus and minus uncertainties in \( a \) and \( b \), are expressed as:

\[
S(a) = \text{ESE } \left[ \frac{\Sigma x_i^2}{D} \right]^{1/2} \\
S(b) = \text{ESE } \left( \frac{m}{D} \right)^{1/2}
\]

where \( m \) is the number of observations and \( \text{ESE} \) is the estimated standard error in \( y \). \( \text{ESE} \) and \( D \) are defined by the equations:

\[
\text{ESE} = \left( \frac{\Sigma [(y_i - y_{\text{calc}})^2]{}}{\nu} \right)^{1/2} \\
D = m \Sigma x_i^2 - (\Sigma x_i)^2
\]

where \( \nu \), the degrees of freedom, is \( m \) minus the number of adjustable parameters; \( y_{\text{calc}} = a + bx_i \).

For our case, \( x = 1000/T, y = \ln(k/T), a = 23.673, b = -7.1811 \), \( m = 8 \) and \( \nu = 8-2 = 6 \). Therefore, the standard errors for slope and intercept can be determined by above equations. \( S(a) = 0.15 \) and \( S(b) = 0.55 \), so \( \Delta H^\neq = -R(\text{slope}) = -1.987 (-7.1811 \pm 0.55) \text{ kcal/mol} = 14.27 \pm 1.1 \text{ kcal/mol} \); \( \Delta S^\neq = R(\text{intercept-23.76}) = 1.987 [(23.673 \pm 0.15)-23.76] \text{ cal mol}^{-1} \text{ K}^{-1} = -0.17 \pm 0.3 \text{ cal mol}^{-1} \text{ K}^{-1} \).
Chapter 3. Preliminary Study of C-H···O Hydrogen Bonding Interactions

3.1 Introduction

The hydrogen bond is a unique phenomenon in structural chemistry and biology. Research in this area is an evergreen challenge and hydrogen bonds continue to manifest themselves in indefinite ways. Its role in molecular association has attracted many researchers to study the hydrogen bonding interactions. The hydrogen bond is able to control and direct the structures of molecular assemblies in supramolecular chemistry.

Hydrogen bonds are typically defined as the intermolecular interaction between a hydrogen, bonded to an electronegative atom, and another electronegative atom such as N, O, or F. Sutor proposed the existence of the C-H···O hydrogen bond in the early 1960s. Because of the relatively low electronegativity of carbon, a carbon-hydrogen group is not a typical hydrogen bond donor but situations do exist where a CH group can act as a hydrogen bond donor, this phenomenon usually occurs with particularly acidic hydrogens. Vibrational spectroscopy data suggests that the ability of a C-H group to act as a proton donor depends on the carbon hybridization as C(sp)-H>C(sp$^2$)-H>C(sp$^3$)-H, and increases with the number of electron withdrawing groups. Carbons with adjacent nitrogen atoms form particularly strong hydrogen

![Geometrical parameters used in the description of C-H···O hydrogen bonds. The hydrogen bond distance $d_{H}$ is approximately 2.2-2.5 Å; C···O distance $d_{CO}$ is 3.0-4.0 Å; the C-H···O angle $\zeta$ is between 90 and 180 °C. The elevation angles $\theta$ and $\xi$ are small.](image)
bonds. Early crystallographic data suggests some donor potential even for the weakly polarized methyl groups. The magnitude of the interactions typically ranges between 2 and 15 kcal.mol$^{-1}$ and the D-H---A distance is 2.0-3.0Å (where D and A are electronegative atoms). These interactions are very important in the structure and function of proteins. The strongest hydrogen bond is the C-H⋯O contact, which exhibits typical directional and electrostatic features (Figure 3.1).

C-H⋯O hydrogen bonds determine crystal packing especially when stronger hydrogen bonding is absent. Many structures simply cannot be rationalized unless C-H⋯O hydrogen bonding is actively invoked. The structure and function of biological molecules is to a large degree determined by hydrogen bonding, e.g. in proteins, nucleic acids, carbohydrates, membranes and also the aqueous medium in which these components are held. The three-dimensional architecture of proteins and nucleic acids is stabilized by hydrogen bonds; biological recognition mainly operates by this mechanism.

Many experimental techniques, such as X-ray and neutron diffraction analysis, vibrational spectroscopy, gas-phase rotational spectroscopy, and computational chemistry have been used to study C-H⋯O hydrogen bond. X-ray crystallography is the most common technique used to detect this kind of interactions. Theoretical calculations have been published for weakly polarized C-H groups, estimating C-H⋯O hydrogen bond energies to be around 0.5 to 1 kcal mol$^{-1}$. Despite this wealth of experimental and theoretical work, the strength of the C-H⋯O hydrogen bond, and that of the weak hydrogen bond in general, has not been experimentally determined.

We have already used the triptycene based model system to measure arene-arene interactions in our lab. Based on the results from our previous work, once again we have used a triptycene based model system to investigate the C-H⋯O hydrogen bonding. The system is designed in such a way that the C-H can form hydrogen bonding with O through a six-membered ring. The strong electron-withdrawing group activates the C-H group. As stated before, the thermodynamic parameters for the C-H⋯O hydrogen bond has been determined based on the equilibrium constants between the syn and the anti isomers at different temperatures. Figure 3.2 shows the model compound, which we have used to study this project.
Figure 3.2  The equilibrium between *syn* and *anti* conformations of model compound for C-H…O hydrogen bonding study

3.2 Results and Discussion

Again, we have used triptycene based model compounds to study the C-H…O hydrogen bonding interactions (Figure 3.2). These compounds are designed in such a way that, splitting of C(9) protons at lower temperature is clearly observed, i.e. we should be able to assign the *syn/anti* ratio from the variable temperature NMR experiments. More credit should go to Xiaowen Xue, who has spent much more time behind designing such model compounds.

I have synthesized model compounds 24a-d and 26 with *p*-Methoxyphenol group at C(9) (Figure 3.2). The C-H group in this compounds are activated by strong electron-withdrawing group such as CF₃, CO₂CH₃, CN, & CHO. A synthetic scheme for these compounds is shown in Scheme 3.1 and Scheme 3.2.
We have performed variable temperature NMR experiments from –75 to 25°C to obtain thermodynamic and kinetic parameters with these model compounds 24a-c and 26 in hand. Due to the Cl₃C-H–O hydrogen bonding with oxygen in chloroform-d, we have used toluene-d₈ as the solvent for this study. As predicted, the C(9) protons changed from a singlet at room temperature to two sets of signals, an AB quartet and a singlet, indicative of the syn and the anti conformers at temperature between -45 to -55°C between the chemical shift of 4.6-5.0 ppm, respectively (Figure 3.6). A statistical 2:1 syn/anti ratio is expected when there is no interaction
between C(1)-hydrogen and C(9)-oxygen. A greater than 2:1 syn/anti ratio indicates an attractive interaction while a smaller ratio is indicative of a repulsive interaction. The syn/anti ratio increases as the temperature decreases. The syn/anti isomeric ratios at different temperature in toluene-d8 are shown in Table 3.1,3.2, & 3.3 for compounds 24a-c. We were unable to assign the syn/anti ratio for compound 26 due to the overlapping of all signals at lower temperature. The highest syn/anti ratio is found for compound 24a at -62°C (211K) as shown in Table 3.1. Compound 24c should give the higher syn/anti ratio (due to the higher value of substituents constant; $\sigma_p, \sigma_m = 0.660, 0.56$ respectively) than compound 24a ($\sigma_p, \sigma_m = 0.54, 0.43$ respectively). We have yet to find out the observed difference in substituents effects for these compounds.

### Table 3.1 Ratio of syn/anti isomers at different temperature for compound 24a

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<th>T(K)</th>
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<th>$K_{eq}$</th>
<th>Ratio of syn/anti</th>
<th>ln($K_{eq}$)</th>
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<td>4.264</td>
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<td>2.100</td>
<td>4.200</td>
<td>0.742</td>
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<td>4.608</td>
<td>2.065</td>
<td>4.130</td>
<td>0.725</td>
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</table>
Table 3.2 Ratio of \textit{syn/anti} isomers at different temperature for compound 24b

<table>
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<th>T(K)</th>
<th>1000/T</th>
<th>$K_{eq}$</th>
<th>Ratio of \textit{syn/anti}</th>
<th>ln($K_{eq}$)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.106</td>
<td>2.212</td>
<td>0.101</td>
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<tr>
<td>211</td>
<td>4.739</td>
<td>1.104</td>
<td>2.208</td>
<td>0.099</td>
</tr>
<tr>
<td>217</td>
<td>4.608</td>
<td>1.102</td>
<td>2.204</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Table 3.3 Ratio of \textit{syn/anti} isomers at different temperature for compound 24c

<table>
<thead>
<tr>
<th>T(K)</th>
<th>1000/T</th>
<th>$K_{eq}$</th>
<th>Ratio of \textit{syn/anti}</th>
<th>ln($K_{eq}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>198</td>
<td>5.051</td>
<td>1.728</td>
<td>3.456</td>
<td>0.547</td>
</tr>
<tr>
<td>205</td>
<td>4.878</td>
<td>1.709</td>
<td>3.418</td>
<td>0.536</td>
</tr>
<tr>
<td>212</td>
<td>4.717</td>
<td>1.691</td>
<td>3.382</td>
<td>0.525</td>
</tr>
<tr>
<td>218</td>
<td>4.587</td>
<td>1.670</td>
<td>3.340</td>
<td>0.513</td>
</tr>
<tr>
<td>225</td>
<td>4.444</td>
<td>1.651</td>
<td>3.302</td>
<td>0.501</td>
</tr>
</tbody>
</table>

From the thermodynamic relationship:

\[ \Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \]
\[ = -RT\ln K_{eq} \]

Therefore,

\[ \ln K_{eq} = -\Delta H^\circ/RT + \Delta S^\circ/R \]

$\Delta H^\circ$ and $\Delta S^\circ$ can be obtained by plotting ln$K_{eq}$ vs. 1/T (Figure 3.3, 3.4, & 3.5) for compounds 24a-c.

![Figure 3.3](image_url)

\textbf{Figure 3.3} ln($K_{eq}$) vs. 1000/T for the equilibrium between \textit{anti} and \textit{syn} conformation for compound 24a.
Figure 3.4 ln(Keq) vs. 1000/T for the equilibrium between anti and syn conformation for compound 24b.

Figure 3.5 ln(Keq) vs. 1000/T for the equilibrium between anti and syn conformation for compound 24c.

$$\Delta H^\circ = -R \text{ slope} = -1.987 \times 0.1165 = -0.23 \pm 0.04 \text{ kcal mol}^{-1} \text{ for compound 24a}$$

$$= -1.987 \times 0.0140 = -0.03 \pm 0.01 \text{ kcal mol}^{-1} \text{ for compound 24b}$$

$$= -1.987 \times 0.0815 = -0.16 \pm 0.01 \text{ kcal mol}^{-1} \text{ for compound 24c}$$

$$\Delta S^\circ = R(y\text{-int}) = 1.987 \times 0.1894 = 0.38 \pm 0.22 \text{ cal mol}^{-1} \text{ K}^{-1} \text{ for compound 24a}$$

$$= 1.987 \times 0.0327 = 0.06 \pm 0.06 \text{ cal mol}^{-1} \text{ K}^{-1} \text{ for compound 24b}$$

$$= 1.987 \times 0.1393 = 0.28 \pm 0.10 \text{ cal mol}^{-1} \text{ K}^{-1} \text{ for compound 24c}$$
Based on this study, the C-H⋯O hydrogen bond in compounds 24a, 24b, 24c, have strengths of $\Delta H^\circ = -0.23 \pm 0.04, -0.03 \pm 0.01, -0.16 \pm 0.01$ kcal mol$^{-1}$, respectively. Errors were calculated using linear regression analysis (see Chapter 2).

In addition, the slow exchange process has also been studied by dynamic NMR. The rotational rate constants about the C-C bond at C(9) have been determined by line shape analysis at each temperature using the WinDNMR$^{28}$ program for compound 24a. The barrier for rotation around this C-C bond has been calculated using the Eyring equation based on the rotational rate constants.

![Figure 3.6](image)

**Figure 3.6** Temperature-dependent $^1$H NMR signals (left column) and computer simulated signals (right column) for the C(9) protons of model compound 24a. The syn conformers give rise to the AB quartet and the anti isomer gives rise to the small singlet at low temperatures. The large sharp singlet is due to the C(10) proton. The experiments were carried out in toluene-$d8$ and the temperatures are calibrated using a $^{13}$C internal thermometer.$^{29}$
The Eyring equation:

\[ \Delta H^\neq - T\Delta S^\neq = -RT\ln K^\neq = -RT\ln[(h/k_B)(k/T)] \]

\[ \ln(k/T) = -\frac{\Delta H^\neq}{RT} + \left(\frac{\Delta S^\neq}{R}\right) - \ln(h/k_B) \]

\( \Delta H^\neq \) and \( \Delta S^\neq \) can be extracted by plotting \( \ln(k/T) \) vs. (1/T).

**Table 3.4** Sample rate constants at various temperatures measured for compound 24a.

<table>
<thead>
<tr>
<th>T(K)a</th>
<th>1000/T</th>
<th>k(sec^-1)b</th>
<th>ln(k/T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>205</td>
<td>4.88</td>
<td>0.87</td>
<td>-5.46</td>
</tr>
<tr>
<td>211</td>
<td>4.73</td>
<td>1.98</td>
<td>-4.67</td>
</tr>
<tr>
<td>217</td>
<td>4.60</td>
<td>4.26</td>
<td>-3.93</td>
</tr>
<tr>
<td>240</td>
<td>4.17</td>
<td>28</td>
<td>-2.15</td>
</tr>
<tr>
<td>248</td>
<td>4.03</td>
<td>133</td>
<td>-0.62</td>
</tr>
<tr>
<td>262</td>
<td>3.82</td>
<td>292</td>
<td>0.11</td>
</tr>
<tr>
<td>298</td>
<td>3.36</td>
<td>7238</td>
<td>3.19</td>
</tr>
</tbody>
</table>

*Temperature calibrated with \(^{13}\)C internal thermometer.²⁹* Rotational rate constants obtained by computer simulations using the program WinDNMR.²⁸

**Figure 3.7** \( \ln(k/T) \) vs. 1000/T for the equilibrium between *anti* and *syn* conformations for compound 24a. The rate constants were determined by line shape analysis around the coalescence temperature (-40°C).

\[ \Delta H^\neq = -R \text{ (slope)} = -1.987x(-5.5931)x1000 \text{ cal mol}^{-1} = 11.11 \pm 0.47 \text{ kcal mol}^{-1} \]

\[ \Delta S^\neq = R \text{ (y-int – 23.76)} = 1.987x(21.71 – 23.76) = -4.07 \pm 2.00 \text{ cal mol}^{-1} \text{ K}^{-1} \]
Based on this study, the rotational barrier for compound 24a has $\Delta H^\neq = 11.11 \pm 0.47$ kcalmol$^{-1}$, and $\Delta S^\neq = -4.07 \pm 2.00 \text{ cal mol}^{-1} \text{ K}^{-1}$.

A diagram of energy as a function of dihedral angle is shown in Figure 3.8 from the data we have obtained for this dynamic process. The Newman projection of 24a is drawn in such a way that Y represents C(9) p-Methoxyphenyl and X represents the aromatic ring attached with two adjacent electron-withdrawing groups.

![Energy Level Diagram](image)

**Figure 3.8.** An energy level diagram for the rotamers of compound 24a as a function of dihedral angle.

In summary, the results from our study have addressed the main concern about whether the weak C-H···O interactions could be determined experimentally using this model system. This model system is capable, although not perfect, of producing quantitative measurements of the
weak C-H–O hydrogen bonds. The measured magnitude of C-H–O hydrogen bond is in good agreement with theoretical calculations. The current results provide us with a tool to fully expand the study to different types of C-H hydrogen bond donor and to various heteroatom hydrogen bond acceptors. These results will also be useful for organic chemists, structural biologist, and computational chemists in developing new biological and chemical recognition systems.

3.3 Experimental Section

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. Reagents were purchased from commercial sources and used without further purification. Compound 18 was prepared according to the literature procedures. Flash column chromatographic separations were performed using silica gel 40 – 63 μm. Reactions were monitored by TLC with UV light and stain detection. NMR spectra (1H, 13C, 19F) were recorded on Bruker 200, 300 and 500 spectrometers with CDCl3, Acetone-d6 or DMSO-d6 as the solvents and (CH3)4Si as the internal reference. Melting points are not corrected.

9-(4'-Methoxy-phenoxyethyl)-11,12-(furan-1",3"-dione)-10-hydro-9,10-ethanoanthracene (19). The 9-(4'-methoxy-phenoxyethyl)-anthracene 18 (10.58 g, 33.7 mmol) and maleic anhydride (3.96 g, 40.4 mmol) in 168 ml of benzene were refluxed under a nitrogen atmosphere for 15 h. The mixture was allowed to cool to room temperature, and the solvent was removed under reduced pressure to obtain crude product. The crude product was then dissolved in a minimum amount of dichloromethane and precipitated with hexanes to afford the pure product as a light yellow solid (12.26 g, 85%). 1H NMR (300 MHz, CDCl3) δ 3.62 (1 H, dd, J = 3.3, 9.2 Hz), 3.81 (3 H, s), 3.85 (1 H, d, J = 9.6 Hz), 4.81 (1 H, d, J = 3.3 Hz), 5.19 (1 H, d, J = 9.5 Hz),
5.32 (1 H, d, J = 9.5 Hz), 6.94 (2 H, d, J = 9.0 Hz), 7.10-7.47 (10 H, m); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 45.71, 47.241, 48.50, 48.78, 55.83, 65.56, 114.96, 116.19, 122.36, 124.00, 124.13, 125.55, 126.99, 127.02, 127.70, 127.75, 138.31, 140.84, 141.38, 152.58, 154.71, 169.30, 170.40.

\begin{align*}
\text{LiAlH}_4, \text{THF, reflux, 5 h} & \rightarrow \text{80\%} \\
\begin{array}{c}
\text{OPMP} \\
\text{O}
\end{array}
\begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\rightarrow
\begin{array}{c}
\text{OPMP} \\
\text{OH}
\end{array}
\begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\end{align*}

\(9-(4'-\text{Methoxy-phenoxy)methyl)-11,12\text{-dimethanol-10-hydro-9,10-ethanoanthracene (20).}\)\textsuperscript{54}

The anhydride \(19\) (1 g, 2.3 mmol) in THF (44 ml) was added dropwise to a suspension of lithium aluminum hydride (0.4 g, 9.4 mmol) in THF (6.4 ml) over 30 min under nitrogen at room temperature. Stirring was continued at room temperature for 0.5 h. Then the reaction mixture was heated to reflux for 4.5 h. The mixture was cooled in an ice-bath and a ground mixture of sodium sulfate decahydrate (2.7 g) and celite (1.5 g) was added. The mixture was stirred overnight. The solution was then filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography giving a white solid (0.75 g, 80\%). m.p. 90-91 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 2.50 (1 H, br), 2.66 (1 H, br), 2.94 (2 H, br), 3.30 (1 H, t, J = 10.2 Hz), 3.45 (1 H, t, J = 10.2 Hz), 3.64 (1 H, dd, J = 7.5, 11.6 Hz), 3.78-3.85 (4 H, m), 4.23 (1 H, d, J = 2 Hz), 4.98 (2 H, dd, J = 9.8, 17.3 Hz), 6.97 (2 H, d, J = 9.0 Hz), 7.10-7.34 (10 H, m); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 43.80, 44.36, 48.12, 48.48, 55.80, 61.18, 64.77, 66.84, 114.86, 115.58, 121.99, 122.48, 123.18, 124.78, 125.72, 125.83, 125.91, 125.96, 140.42, 141.68, 143.33, 143.96, 152.74, 154.32.

\begin{align*}
\text{Cl-SO} & \rightarrow \text{OTs} \\
\begin{array}{c}
\text{OPMP} \\
\text{OH}
\end{array}
\rightarrow
\begin{array}{c}
\text{OPMP} \\
\text{OH}
\end{array}
\begin{array}{c}
\text{OTs} \\
\text{H}
\end{array}
\end{align*}

\(53\%\)
9-(4'-Methoxy-phenoxy)methyl)-11,12-ditosylate-10-hydro-9,10-ethanoanthracene (21). To a solution of diol 20 (1.2 g, 3 mmol) in dry pyridine (27.5 ml) was added a solution of p-toluene sulfonyl chloride in dry pyridine at 0 °C under nitrogen. After stirring at 0 °C for 6 h, the mixture was slowly poured into cold water (80 ml) and extracted three times with dichloromethane. The combined extracts were washed once with water, brine and dried over MgSO₄. The solution was then filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography giving a white solid (1.12 g, 53%). m.p. 149-150 °C; ¹H NMR (500 MHz, CDCl₃) δ 2.37 (3 H, s), 2.46 (3 H, s), 2.6 (1 H, br), 2.68 (1 H, br), 3.44 (1 H, t, J = 10.3 Hz), 3.69 (1 H, dd, J = 6.6, 10.5 Hz), 3.82 (3 H, s), 3.94 (1 H, dd, J = 3.7, 10.7 Hz), 4.09 (1 H, dd, 4.3, 8.8 Hz), 4.36 (1 H, d, J = 1.9 Hz), 4.71 (1 H, d, J = 9.8 Hz), 4.87 (1 H, d, J = 9.7 Hz) 6.90-7.79 (20 H, m); ¹³C NMR (125 MHz, CDCl₃) δ 21.65, 21.69, 40.19, 40.28, 45.30, 47.63, 55.79, 65.97, 67.27, 70.13, 114.76, 115.61, 122.01, 122.40, 123.89, 125.79, 126.00, 126.17, 126.25, 127.74, 128.07, 129.80, 130.01, 132.19, 132.59, 139.67, 140.24, 142.61, 143.05, 144.91, 144.95, 152.35, 154.43.

9-(4'-Methoxy-phenoxy)methyl)-11,12-dimethylene-10-hydro-9,10-ethanoanthrace (22). To a solution of tosylate 21 (77 mg, 0.1 mmol) in dimethylsulfoxide (0.7 ml) and THF (0.2 ml) was added potassium tert-butoxide (36 mg, 0.3 mmol) under nitrogen atmosphere. After stirring at room temperature for 18 h, the reaction mixture was poured into ice-water and extracted three times with ether. The organic layer was washed with brine and dried over MgSO₄. The solution was then filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography giving a light yellow solid (34 mg, 86%). m.p. 148-149 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.83 (3 H, s), 4.89 (1 H, s), 5.02 (1 H, br), 5.11 (1 H, s), 5.19(2 H, s), 5.28 (1 H, s), 5.45 (1 H, s), 6.94-6.97 (2 H, m), 7.1-7.35 (10 H, m); ¹³C NMR (50 MHz, CDCl₃)
δ 51.90, 55.09, 55.81, 66.67, 104.61, 114.87, 115.48, 123.23, 126.28, 126.46, 140.74, 142.53, 144.63, 152.79, 154.27.

9-(4'-Methoxy-phenoxy)methyl)-1,4-dihydro-2,3-ditrifluoromethane-triptycene (23a). \(^5^7\)
Hexafluoro-2-butyne (0.18 g, 1.1 mmol) was condensed to a 15 ml pressure tube by a dry ice/acetone cooling bath. A solution of diene 6 (0.2 g, 0.6 mmol) in 3 ml of toluene was slowly added through a septum. The pressure tube was then capped and heated at 115 °C for 72 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography giving a yellow solid (77 mg, 27%). m.p. 71-72 °C; \(^1^H\) NMR (300 MHz, CDCl\(_3\)) δ 3.29 (2 H, br), 3.82-3.84 (4 H, m), 4.05 (1 H, br), 4.83 (1 H, s), 5.28 (2 H, dd, J = 9.7, 21.7 Hz), 6.95-7.33 (12 H, m); \(^1^3^C\) NMR (75 MHz, CDCl\(_3\)) δ 21.55, 53.91, 54.15, 55.85, 66.14, 115.07, 115.48, 120.02, 122.29, 122.79, 122.99, 124.79, 124.82, 124.87, 140.22, 142.68, 145.56, 145.94, 145.98, 146.55, 152.54, 154.63; \(^1^9^F\) NMR (188 MHz, CDCl\(_3\)) CF\(_3\)CO\(_2\)H used as a reference δ 76.2 (S), -59.64 (3 F, q, J = 13.9 Hz), -62.78 (3 F, q, J = 14.1 Hz).

\(^1^9^F\) NMR spectra were recorded for compounds 23a, and 24a in which CF\(_3\)CO\(_2\)H was used as a standard (δ = -76.20, s).
9-(4'-Methoxy-phenoxy)methyl)-1,4-dihydro-2,3-dicarboxylic acid dimethyl ester-triptycene (23b). The diene 22 (0.2 g, 0.6 mmol) and dimethylacetylenedicarboxylate (0.16 g, 1.1 mmol) in 3 ml of toluene were heated in a sealed tube at 115 °C for 72 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography giving a mixture of the desired product 23b, and the aromatized product 24b (0.26 g). This mixture was used for the synthesis of 24b.

![Chemical reaction](image)

9-(4'-Methoxy-phenoxy)methyl)-1,4-dihydro-2,3-dicarbonitrile-triptycene (23c). The diene 22 (200 mg, 0.6 mmol) and dicyanoacetylene (84 mg, 1.1 mmol) in 3 ml of toluene were heated in a sealed tube at 115 °C for 72 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography giving a white solid (110 mg, 46%). m.p. 215-216 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 3.35-3.51 (4 H, m), 3.83 (3 H, s), 4.79 (1 H, s), 5.15 (2 H, s), 6.91-7.33 (12 H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 29.35, 31.64, 53.75, 54.18, 55.86, 65.82, 115.15, 115.23, 115.31, 121.45, 122.59, 123.04, 124.22, 125.03, 125.14, 136.46, 139.11, 144.67, 145.50, 152.13, 154.75.
General Synthetic Procedure for the 9-(4'-Methoxy-phenoxy)methyl-2,3-disubstituted-triptycene (24a-c). 

A solution of Diels-Alder adduct 23a-c (0.2 mmol) in 7 ml of xylene containing 20 mg of 10% Pd/C was heated at reflux for 48 h. The hot solution was filtered and Pd/C residue was washed with dichloromethane. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography to produce the corresponding desired product as a solid.

24a: yield 85%; yellow solid, m.p. 72-74 °C; \( ^1 \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 3.85 (3 H, s), 5.50 (2 H, s), 5.55 (1 H, s), 6.98-7.00 (6 H, m), 7.19 (2 H, m), 7.41-7.48 (4 H, m), 7.85 (1 H, s), 7.91 (1 H, br); \(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \( \delta \) 53.48, 53.84, 55.82, 65.96, 115.05, 115.76, 122.65, 124.02, 125.81, 125.95, 142.97, 144.85, 149.09, 150.70, 152.40, 154.74; \(^{19}\)F NMR (188 MHz, CDCl\(_3\)) -59.38 (3 F, q, J = 14.0 Hz), -59.48 (3 F, q, J = 14.0 Hz); HRMS calcd for C\(_{30}\)H\(_{20}\)F\(_6\)O\(_2\) + Na 549.1265, found 549.1271.

24b: yield 83%, white solid, m.p. 113-114 °C; \( ^1 \)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 3.80 (3 H, s), 3.84 (6 H, d, J = 1.4 Hz), 5.48 (3 H, s), 6.97-7.04 (6 H, m), 7.19 (2 H, d, J = 9.1 Hz), 7.34 (4 H, m), 7.74 (2 H, s); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 52.54, 53.45, 54.04, 55.86, 66.18, 115.03, 115.82, 122.68, 123.82, 125.57, 125.69, 129.08, 129.27, 143.31, 145.16, 148.12, 149.79, 152.71, 154.64, 167.83, 168.12; HRMS calcd for C\(_{32}\)H\(_{26}\)O\(_6\) + Na 529.1627, found 529.1641.
24c: yield 88%, white solid, m.p. 253-254 °C; ¹H NMR (300 MHz, CDCl₃) δ 3.85 (3 H, s), 5.46 (2 H, s), 5.54 (1 H, s), 6.97-7.18 (8 H, m), 7.39-7.46 (4 H, m), 7.78 (1 H, s), 7.87 (1 H, s); ¹³C NMR (50 MHz, CDCl₃) δ 53.56, 53.69, 55.82, 65.44, 112.90, 112.94, 115.10, 115.50, 115.80, 122.76, 124.22, 126.14, 126.27, 127.72, 142.11, 143.96, 150.81, 152.00, 152.14, 154.83.

9-(4'-Methoxy-phenoxy)methyl)- 2,3-dimethanol-triptycene (25). The diester 24b (0.44 g, 0.87 mmol) in THF (17 ml) was added dropwise to a suspension of lithium aluminum hydride (0.14 g, 3.58 mmol) in THF (3 ml) over 30 min under nitrogen at room temperature. Stirring was continued at room temperature for 0.5 h. Then the reaction mixture was heated to reflux for 4.5 h. The mixture was cooled in an ice-bath and a ground mixture of sodium sulfate decahydrate (1.4 g) and celite (0.7 g) was added. The mixture was stirred overnight. The solution was then filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography giving a white solid (0.27 g, 70%). ¹H NMR (300 MHz, CDCl₃) δ 2.75 (2 H, br), 3.83 (3 H, s), 4.56 (4 H, d, J = 7.1 Hz), 5.41 (1 H, s), 5.47 (2 H, s), 6.97-7.01 (6 H, m), 7.18-7.24 (2 H, m), 7.37-7.40 (6 H, m); ¹³C NMR (75 MHz, CDCl₃) δ 53.09, 53.96, 55.86, 63.9, 64.29, 66.44, 115.03, 115.64, 123.55, 125.05, 125.20, 125.34, 136.10, 136.59, 144.16, 144.94, 146.11, 147.05, 152.81, 154.51.

9-(4'-Methoxy-phenoxy)methyl)- 2,3-dimethanol-triptycene (25). The diester 24b (0.44 g, 0.87 mmol) in THF (17 ml) was added dropwise to a suspension of lithium aluminum hydride (0.14 g, 3.58 mmol) in THF (3 ml) over 30 min under nitrogen at room temperature. Stirring was continued at room temperature for 0.5 h. Then the reaction mixture was heated to reflux for 4.5 h. The mixture was cooled in an ice-bath and a ground mixture of sodium sulfate decahydrate (1.4 g) and celite (0.7 g) was added. The mixture was stirred overnight. The solution was then filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography giving a white solid (0.27 g, 70%). ¹H NMR (300 MHz, CDCl₃) δ 2.75 (2 H, br), 3.83 (3 H, s), 4.56 (4 H, d, J = 7.1 Hz), 5.41 (1 H, s), 5.47 (2 H, s), 6.97-7.01 (6 H, m), 7.18-7.24 (2 H, m), 7.37-7.40 (6 H, m); ¹³C NMR (75 MHz, CDCl₃) δ 53.09, 53.96, 55.86, 63.9, 64.29, 66.44, 115.03, 115.64, 123.55, 125.05, 125.20, 125.34, 136.10, 136.59, 144.16, 144.94, 146.11, 147.05, 152.81, 154.51.
9-(4′-Methoxy-phenoxymethyl)- 2,3-dicarbaldehyde-triptcene (26). Dry DMSO (0.18 ml, 1.33 mmol) in CH$_2$Cl$_2$ (0.14 ml) was added dropwise over 10 min to a -78°C solution of oxalyl chloride (0.12 ml, 0.67 mmol) in CH$_2$Cl$_2$ (0.64 ml) under nitrogen. After 5 min, diol 25 (0.07 g, 0.16 mmol) in CH$_2$Cl$_2$ (1.8 ml) was added dropwise to this clear solution over 15 min. The mixture was rigorously stirred for 45 min at -78°C followed by the addition of triethylamine (0.74 ml, 2.67 mmol) over 10 min. After 10 min, the mixture was allowed to warm up to room temperature and the stirring was continued for another 75 min. Ice-cold water (1.6 ml) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted twice with CH$_2$Cl$_2$. The combined organic layer was washed with water, brine and dried over anhydrous MgSO$_4$. After the solvent was removed under reduced pressure, the residue was purified by flash column chromatography using a short column of silica gel to give 26 as a white solid (0.05 g, 67%). Column was run fast due to a labile nature of the product 26. $^1$H NMR (300 MHz, CDCl$_3$) δ 3.84 (3 H, s), 5.53 (2 H, s), 5.60 (1 H, s), 6.99-7.08 (6 H, m), 7.19-7.24 (2 H, m), 7.41-7.46 (4 H, m), 7.99 (2 H, s), 10.36 (1 H, s), 10.51 (1 H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 53.75, 54.22, 55.86, 66.07, 115.12, 115.75, 122.76, 124.05, 124.97, 125.85, 125.98, 134.23, 134.31, 142.83, 144.71, 150.87, 152.48, 154.78, 191.66, 191.87.

Variable Temperature NMR Experimental Procedure.

The $^1$H NMR spectra were recorded on a Bruker 300 MHz instrument with a variable temperature probe. A 0.05 M solution of the sample in a deuterated solvent such as toluene was placed in a high quality NMR tube. All samples were degassed using a needle to bubble nitrogen through the sample for ~1 minute. The NMR tube was then capped with a cap and sealed with parafilm. The sample tube was placed into the NMR probe and the air line to the probe was replaced with liquid nitrogen transfer line. The desired temperature was set on the variable temperature unit and the sample was allowed to equilibrate for 10 ~15 minutes at each set temperature. Then the $^1$H NMR spectrum at each temperature was recorded. The ratios of rotamers were obtained through the integrations of selected peaks.
Calibration of the Variable Temperature NMR probe.  

The calibration of the probe’s temperature was established by recording the $^{13}$C NMR spectrum of tris (trimethylsilyl) methane, a $^{13}$C internal thermometer immediately before or after a $^1$H NMR spectrum was recorded. Actual probe temperature was determined from the equation below, in which $\Delta \delta$ is the chemical shift difference in ppm between two peaks, methane and methyl carbons. To balance these two peaks, 10% $^{13}$C-enriched tris (trimethylsilyl) methane was employed and it was added directly to the sample to prepare a 0.3% (v/v) solution. The $^{13}$C signals were recorded in 64 scans.

$$T \quad (^\circ \text{C}) = 77.931(\Delta \delta) - 24.9 \quad (\text{in Toluene-} \ d_8)$$
Chapter 4. An Attempt to Study the $\pi$-Stacking Effect in Asymmetric Induction

4.1 Introduction

The field of asymmetric synthesis evolved from the study of diastereoselectivity in reactions of chiral compounds, through auxiliary-based methods for the synthesis of enantiomerically pure compounds (diastereoselectivity followed by isomer separation and auxiliary cleavage), to asymmetric catalysis. Asymmetric synthesis is a reaction or reaction sequence that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate.

Asymmetric induction achieved with chiral auxiliaries and chiral catalysts can be enhanced by $\pi$-stacking effects, which lock one conformation of a reactant preferentially in a given transition state assembly. In organic synthesis, $\pi$-stacking effect has been used successfully for some of the most C-C bond forming reactions with unparalleled selectivity in many cases. $\pi$-stacking effect have been encouraged for control of asymmetric bond forming reactions, under both stoichiometric (chiral auxiliaries) and catalytic conditions, and for the purpose of assisting in molecular recognition.60,61

In 1972, Corey postulated the first synthetic application of a $\pi$-stacking interactions for the chiral reduction of the C-15 ketone (a) to the C-15 (S)-alcohol (b) (Figure 4.1, R = 4-biphenylcarbamoyl) in the synthesis of prostaglandins.62 In this example $\pi$-stacking interaction between a carbonyl and an arene lock the functional groups into what would otherwise be unfavorable reactive conformation. Binger has used the (-)-8-phenylmenthol derivatives in asymmetric [3 + 2] cycloadditions catalyzed by Ni(COD)$_2$ as shown in Figure 4.2.63 Treatment of the (-)-8-phenylmenthol acrylate (c) with methylenecyclo-propane (d) gave the methylenecyclopentane ester (e) in 90% yield and 64% de.
Figure 4.1 Protecting group directed reduction en route to prostaglandins

Figure 4.2 [3 + 2] cycloaddition of (-)-8-phenylmenthol

To study the sigma donor effects in the aromatic portion that may affect π-attractive interactions, we are trying to design the ideal model compounds bearing an electron donor or acceptor. As shown in Figure 4.3, the model compound can exist in two different conformation: a straight chain or a chair like conformation. If there are π-attractive interactions taking place, then it should exist as a chair like conformation. Based on our previous study, we assume that

Figure 4.3 Model Compounds for π-Stacking in Asymmetric Induction
when substituent X is a strong electron-donating group, there will be a strong $\pi$-attractive interaction between a carbonyl carbon atom and an arene, which will result in the chair like conformation. With the model compounds in hand, we are going to perform the Diels-Alder reactions to obtain the difference in product diastereoselectivity with different substituents.

4.2 Results and Discussion

![Scheme 4.1](image)

We have synthesized our model compound 33a ($X = \text{NMe}_2$) using the following pathway (Scheme 4.1). 4-Bromo-N,N dimethyl aniline 27a was used as a starting material to synthesize racemic alcohol 29a ($X = \text{NMe}_2$) (Scheme 4.2). Enzymatic resolution of the racemic alcohol

![Scheme 4.2](image)
using Lipase AK and Vinyl acetate followed by the removal of acetate, gave us the optically pure (R)-29a (Scheme 4.3). Absolute configuration of alcohol (R)-29a was confirmed by preparing the O-Methylmandelate ester (Scheme 4.4), since an enantiopure form of this alcohol has not been reported so far.

**Scheme 4.3**

![Scheme 4.3 Diagram]

rac-29a $\rightarrow$ rac-29a (62%) (R)-30a (31%)  
$[\alpha] = +8.8$, 41 % ee

![Scheme 4.4 Diagram]

(R)-30a $\rightarrow$ (R)-29a  
$[\alpha] = -19.0$, 88% ee
4.3 Experimental Section

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. Reagents were purchased from commercial sources and used without further purification. Flash column chromatographic separations were performed using silica gel 40–63 μm. Reactions were monitored by TLC with UV light and stain detection. NMR spectra (1H, 13C) were recorded on 300, and 500 MHz spectrometers with CDCl3 as the solvent.

4-(4-Dimethylamino-phenyl)-4-methyl-pentan-2-one (28a). 4-Bromo-N,N dimethyl aniline 27a (3.0 g, 15 mmol) was dissolved in dry THF (58 ml) and the solution was cooled to −78 °C. A
solution of n-butyl lithium (1.6 M in hexane, 22.5 ml, 36 mmol) was added. The mixture was stirred at −78 °C for 30 min and at 0 °C for 1 h. This reaction mixture was added to a solution of dimethylaluminium chloride (1 M in hexane, 15 ml, 15 mmol) at −20 °C. The mixture was stirred for 10 min at −20 °C. A solution of mesityl oxide (1.6 ml, 13.5 mmol) in 18 ml of THF was added dropwise at −20 °C followed by 0.15 g (0.59 mmol) of [Ni(acac)₂]. The reaction mixture was stirred at 0 °C for 4 h. Aqueous ammonium chloride was added to quench the reaction and it was stirred more for 15 min. The product was then extracted twice using ethyl acetate and dried over anhydrous magnesium sulfate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography to give 28a as a yellow oil (1.9 g, 58%).

\[ \text{1H NMR (300 MHz, CDCl₃)} \delta \text{1.39 (6 H, s), 1.77 (3 H, s), 2.67 (2 H, s), 2.92 (6 H, s), 6.69-6.72 (2 H, m), 7.22-7.25 (2 H, m);} \]

\[ \text{13C NMR (75 MHz, CDCl₃)} \delta \text{29.0, 31.9, 36.5, 40.6, 57.3, 112.5, 126.1, 135.9, 148.8, 208.8.} \]

\[ \text{NaBH₄, MeOH 0 °C to rt, 2 h} \]

\[ \text{90%} \]

\[ \text{28a} \]

\[ \text{rac-29a} \]

4-(4-Dimethylamino-phenyl)-4-methyl-pentan-2-ol (rac-29a). To a 0 °C solution of 4-(4-Dimethylamino-phenyl)-4-methyl-pentan-2-one 28a (1.8 g, 8.20 mmol) in 100 ml of MeOH was added portionwise NaBH₄ (0.47 g, 12.31 mmol). After 1 h, the mixture was allowed to warm up to room temperature and the stirring was continued for another 1 h. Saturated NH₄Cl was added to quench the reaction. The solution was extracted three times with EtOAc and the combined organic layers were washed with water, brine and dried over anhydrous magnesium sulfate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography to give rac-29a as a colorless liquid (1.6 g, 90%).

\[ \text{1H NMR (300 MHz, CDCl₃)} \delta \text{1.03 (3 H, d, J = 6.2 Hz), 1.23 (1 H, d, J = 7.3 Hz), 1.32 (6 H, s), 1.66 (1 H, dd, J = 2.6, 11.8 Hz), 1.83 (1 H, dd, J = 5.6, 8.4 Hz), 2.92 (6 H, s), 3.77 (1 H, m), 6.75-6.80 (2 H, m), 7.25-7.29 (2} \]
Enzymatic resolution of racemic 4-(4-Dimethylamino-phenyl)-4-methyl-pentan-2-ol (rac-29a). To a round bottom flask was added 1.6 g of molecular sieves (ground, activated 4 Å), 0.8 g of lipase AK in 17 ml of vinyl acetate, followed by 4-(4-Dimethylamino-phenyl)-4-methyl-pentan-2-ol 29a (1.6 g, 7.23 mmol), and the reaction mixture was stirred at room temperature. Progress of the reaction was monitored by TLC and 1H NMR. After 4 days, the reaction mixture was filtered through a pad of celite and washed with hexanes. The solvents were removed under reduced pressure and the crude mixture was purified using silica gel chromatography to give (R)-30a (31%), and rac-29a (62%) as a colorless liquid. Characterization of the acylated product: 1H NMR (300 MHz, CDCl3) δ 1.04 (3 H, d, J = 6.2 Hz), 1.30 (6 H, s), 1.68 (1 H, dd, J = 3, 11.7 Hz), 1.73 (3 H, s), 2.02 (1 H, dd, J = 6.1, 8.5 Hz), 2.89 (6 H, s), 4.89 (1 H, m), 6.67-6.71 (2 H, m), 7.16-7.20 (2 H, m); 13C NMR (75 MHz, CDCl3) δ 21.1, 21.8, 29.1, 29.4, 35.0, 40.8, 50.1, 68.6, 112.6, 126.3, 136.8, 148.6, 170.4.
4-(4-Dimethylamino-phenyl)-4-methyl-pentan-2-ol ((R)-29a). To the solution of ester (R)-30a (0.15 g, 0.57 mmol) in 6.4 ml of MeOH was added the K$_2$CO$_3$ (0.20 g, 1.43 mmol) at rt. The reaction mixture was stirred at room temperature for 24 h. 10 ml of water was added followed by 25 ml of CH$_2$Cl$_2$. The organic layer was separated and the aqueous layer was extracted two times with 25 ml portions of CH$_2$Cl$_2$. The combined organic layers were washed with brine and dried over MgSO$_4$. The solvents were removed under reduced pressure and the crude mixture was purified using silica gel chromatography to give (R)-29a (0.12 g, 96%) as a colorless liquid. $[\alpha]_D = -19.0^\circ$ (10 mM in MeOH), 88% ee; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.03 (3 H, d, J = 6.2 Hz), 1.23 (1 H, d, J = 7.3 Hz), 1.32 (6 H, s), 1.66 (1 H, dd, J = 2.6, 11.8 Hz), 1.83 (1 H, dd, J = 5.6, 8.4 Hz), 2.92 (6 H, s), 3.77 (1 H, m), 6.75-6.80 (2 H, m), 7.25-7.29 (2 H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 28.4, 30.7, 36.2, 41.1, 45.5, 53.6, 65.7, 113.4, 126.7, 137.4, 148.1.

Preparation of the O-Methylmandelate ester (31a).$^{67}$ DMAP (3 mg, 0.025 mmol) was added to a solution of the title alcohol (R)-29a (58 mg, 0.25 mmol), (R)-Methoxyphenyl acetic acid (42 mg, 0.25 mmol) and DCC (52 mg, 0.25 mmol) in 3 ml of CH$_2$Cl$_2$. After 24 h, the dicyclohexylurea was removed by filtration, the filter cake was washed with hexane, and the combined filtrate was washed twice with water and once with NaHCO$_3$, and saturated brine. The organic phase was then dried over anhydrous MgSO$_4$. The solvents were removed under reduced pressure and the crude mixture was purified using silica gel chromatography to give 31a (69 mg, 72%) as a colorless liquid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.85 (3 H, d, J = 8.3 Hz), 0.95 (6 H, s), 1.70 (1 H, dd, J = 2.6, 11.8 Hz), 1.79 (1 H, dd, J = 5.6, 8.4 Hz), 2.88 (6 H, s), 3.34 (3 H, s), 4.60 (1 H, s), 4.76 (1 H, m), 6.60-6.62 (2 H, m), 6.98-7.01 (2 H, m), 7.33-7.41 (5 H, m).
Acrylic acid 3-(4-dimethylamino-phenyl)-1,3-dimethyl-butyl ester (33a).\textsuperscript{68} 4-(4-Dimethylamino-phenyl)-4-methyl-pentan-2-ol -29a (0.2 g, 0.90 mmol) was dissolved in 9 ml of THF. The solution was brought to 0 °C in an ice-bath. TEA (0.15 ml, 1.08 mmol) was added, and the mixture was stirred for 1 h. 0.1 ml (1.36 mol) of acryloyl chloride was added dropwise at 0 °C. After 1.5 h at 0 °C, the solid was removed by filtration and the solvents were removed under reduced pressure. The crude mixture was purified using silica gel chromatography to give 33a (0.23 g, 94%) as a colorless liquid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.07 (3 H, d, J = 6.2 Hz), 1.30 (6 H, s), 1.74 (1 H, dd, J = 3.3, 14.6 Hz), 2.04 (1 H, dd, J = 8.2, 14.6 Hz), 2.89 (6 H, s), 4.93 (1 H, m), 5.67 (1 H, dd, J = 1.6, 10.3 Hz), 5.89 (1 H, dd, J = 10.4, 17.3 Hz), 6.21 (1 H, dd, J = 1.6, 17.3 Hz), 6.66-6.69 (2 H, m), 7.16-7.24 (2 H, m); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 21.7, 28.7, 29.7, 36.1, 40.8, 50.3, 69.2, 112.7, 126.3, 129.1, 129.7, 136.9, 148.6, 165.5.
Chapter 5. Preparation of a 2-Bromoglucoside to Study the One-Pot Synthesis of the Tetrasaccharide unit of Durhamycin A

5.1 Introduction

A group of natural products including olivomycin A, chromomycin A, mithramycin and durhamycin A belong to the discrete group of aureolic acid anticancer antibiotics. Durhamycin A (32) is a potent inhibitor in both Tat-dependent in vitro transcription and Tat-dependent cell-based assays. It was shown that the deoxysaccharide moieties and the highly functionalized pentyl side chain play major roles in the DNA binding of mithramycin. This information coupled with the anti-HIV activity of durhamycin suggest that the polysaccharide chain is important for the biological activity of the aureolic acid natural products.

![Durhamycin A (32) and Tetrasaccharide (33)](image)

**Figure 5.1** Tetrasaccharide unit (33) of the anti-HIV agent Durhamycin A (32).

A major difficulty in the synthesis of polysaccharides is the glycosidation step, which involves the preparation of glycosyl donors, activation, and coupling to acceptors. Usually glycosidation is carried out between a donor and an acceptor one step at a time. After a disaccharide is made, usually a few steps of functional group manipulation is required before another sugar unit can be coupled to the disaccharide. Stereoselectivity (α or β anomeric bond formation) in glycosidation is difficult to control in the case of 2-deoxy donors.
In order to explore the possibility of chemically synthesizing the tetrasaccharide unit (33) of the anti-HIV agent duramycin A (32) by a one-pot glycosidation reaction, the relative reactivity of the individual glycosyl donors needed to be studied first. Previous studies have established that 2-halogen can be used in glycosyl donors as a removable control element for achieving glycosidation stereoselectivity.\textsuperscript{74-76} To study the reactivity of the 2-deoxy-2-substituted glycopyranosyl donors, we have synthesized the 2-Bromoglucoside.

5.2 Results and Discussion

2-Bromoglucoside 42 was synthesized starting from tri-O-acetyl-D-glucal 34 (Scheme 5.1 & 5.2). Anhydro sugar 35 was prepared by methanolysis of 34 followed by intramolecular

![Scheme 5.1](image_url)

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61
bromoetherification (NBS, (Bu₃Sn)₂O, CH₃CN) in a 60% yield.⁷⁵ The protection of the C(3) &
C(4)-OH with TESCl gave the TES ether 36 in an 80% yield. Acetolysis of the anhydro linkage
of 36 followed by deprotection of the anomeric acetate and then activation of the pyranose using
DAST gave the 38.⁷⁵,⁷⁶ At this point we were able to separate the β and α anomer. The ratio of β:
α was found as 83: 17. Treatment of β anomer of 38 with K₂CO₃ in MeOH at rt provided the
desired β anomer of 39 in 50% yield as well as β anomer of 40 with the loss of TES group at
C(3)-OH in a 39% yield. Our attempt to perform this reaction at 0 °C in order to improve the
yield of the desired 39(β) did not help at all. It gave the same product yield ratio with longer
reaction time. Protection of C(6)-OH of 39(β) with tosylate gave 41 in 70% yield, which was
subjected to the S_N2 reaction with NaBr in dry DMF to furnish the 2,6-dibromoglycal 42 in 93%
yield.⁷⁷ The final step was the glycosidation reaction of the donor 42 with the acceptor benzyl
alcohol. This reaction took place smoothly with the help of a Lewis acid SnCl₂ as an activator in
1h with 76% product yield.⁷⁸ This indicates that the 2-Bromoglucoside is a moderately strong
reactive donor.
5.2 Experimental Section

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. Reagents were purchased from commercial sources and used without further purification. Compound 35 was prepared according to the literature procedures.\textsuperscript{75} Flash column chromatographic separations were performed using silica gel 40 – 63 μm. Reactions were monitored by TLC with UV light and stain detection. \textsuperscript{1}H NMR spectra were recorded on Bruker 200, 300 and 500 spectrometers with CDCl\textsubscript{3} as the solvent.

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {35};
  \node (B) at (2,0) {36};
  \draw[->] (A) -- (B) node[midway, above] {TESCl, imidazole, DMF, CH\textsubscript{2}Cl\textsubscript{2}; -60 0 °C to rt, 1 h; 80%};
\end{tikzpicture}
\end{center}

\textbf{4-Bromo-2,3-bis-triethylsilanyloxy-6,8-dioxa-bicyclo[3.2.1]octane (36).}\textsuperscript{76} 1.0 ml (6.14 mmol) of Triethylsilyl chloride was added dropwise over a period of 10 min to a stirred –60 °C solution of 0.55 g (2.45 mmol) of 6-Bromoglucal 35 and 0.5 g (7.34 mmol) of imidazole in CH\textsubscript{2}Cl\textsubscript{2} (6.0 ml) and DMF (1.5 ml). After 40 min at –60 °C the reaction mixture was brought up to rt. After 20 min at rt, sat. NaHCO\textsubscript{3} was added. The organic layer was separated and washed with H\textsubscript{2}O. The aqueous layer was extracted twice with EtOAc, and washed with H\textsubscript{2}O. The combined organic layers were dried over MgSO\textsubscript{4}. The solution was then filtered and the solvent removed under reduced pressure, and purified over silica gel column giving 36 as a colorless oil (0.89 g, 80%). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) δ 0.59 (12 H, m), 0.94 (18 H, m), 3.57 (1 H, d, J = 17.3 Hz), 3.67 (2 H, d, J = 6.5 Hz), 4.00 (1 H, s), 4.16 (1 H, d, J = 6.9 Hz), 4.38 (1 H, d, J = 5.3 Hz), 5.52 (1 H, s).

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {36};
  \node (B) at (2,0) {37};
  \draw[->] (A) -- (B) node[midway, above] {CF\textsubscript{3}CO\textsubscript{2}H, Ac\textsubscript{2}O, rt, 4 h; 60%};
\end{tikzpicture}
\end{center}
Acetic acid 6-acetoxy-5-bromo-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-ylmethyl ester (37).\textsuperscript{77} To a solution of 4-Bromo-2,3-bis-triethylsilanyloxy-6,8-dioxo-bicyclo[3.2.1]octane 36 (0.4 g, 0.89 mmol) in acetic anhydride (4.5 ml) at rt was added TFA (0.21 ml, 1.78 mmol). After 4 h the reaction mixture was diluted with ether, and sat. NaHCO\textsubscript{3} was added dropwise. The resulting mixture was stirred overnight. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, and dried over MgSO\textsubscript{4}. The solution was then filtered and the solvent removed under reduced pressure, and purified over silica gel column giving 37 as a colorless oil (0.3 g, 60%). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) \(\delta\) 0.69 (12 H, m), 0.94 (18 H, m), 2.06 (3 H, s), 2.12 (3 H, s), 3.66-4.12 (5 H, m), 4.34 (1 H, d, J = 12.1 Hz), 5.86-6.22 (1 H, d, J = 3.0, 8.5 Hz).

![Chemical structure of 37 and 38](image)

Acetic acid 5-bromo-6-fluoro-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-ylmethyl ester (38).\textsuperscript{78} To a 0.5 g (0.9 mmol) solution of Acetic acid 6-acetoxy-5-bromo-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-ylmethyl ester 37 in 11.3 ml MeOH:Et\textsubscript{2}O (2:1) at 0 °C was added hydrazine (11 M in H\textsubscript{2}O, 0.14 ml). The reaction mixture was warm up to the rt. After 3 h, water was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, and dried over MgSO\textsubscript{4}. The solution was then filtered and the solvent removed under reduced pressure. The crude yellow oil was dissolved in 2.3 ml of CH\textsubscript{2}Cl\textsubscript{2}, and 0.15 ml (1.29 mmol) of DAST was added dropwise at 0 °C. After 20 min, the reaction mixture was poured into a saturated aqueous solution of NaHCO\textsubscript{3}. The organic layer was separated, and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were washed with brine, and dried over MgSO\textsubscript{4}. The solution was then filtered and the solvent removed under reduced pressure, and purified over silica gel column giving 38 as a yellow oil (0.23 g, 50%). \textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) for \(\beta\) isomer: \(\delta\) 0.65 (12 H, q, J = 9.7 Hz), 0.96 (18 H, t, J = 7.4 Hz), 2.07 (3 H, s), 3.78–4.25 (5 H, m),
4.41–4.47 (1 H, m), 5.49-5.77 (1 H, d, J = 2.6, 4.3 Hz); α isomer: δ 0.72 (12 H, m), 0.95 (18 H, m), 2.09 (3 H, s), 3.59-4.17 (5 H, m), 4.43 (1 H, d, J = 12.4 Hz), 5.49-5.75 (1 H, s).

β: α 83:17

5% K₂CO₃, MeOH
rt, 1.5 h

39β (50%) 40β (39%)

(5-Bromo-6-fluoro-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-yl)-methanol (39). To a stirred solution of Acetic acid 5-bromo-6-fluoro-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-ylmethyl ester 38 and 4 mg (0.03 mmol) of K₂CO₃ was dissolved in 2.5 ml of absolute methanol at rt. After 1.5 h, the solids were removed by filtration and the solvent removed under reduced pressure. Column chromatography using silica gel gave 39 (0.14 g, 50%) and 40 (0.12 g, 39%) as yellow oil.

(5-Bromo-6-fluoro-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-yl)-methanol (39): ¹H NMR (200 MHz, CDCl₃) δ 0.72 (12 H, m), 0.96 (18 H, m), 3.61-4.03 (7 H, m), 5.51-5.78 (1 H, d, J = 1.6, 2.3 Hz).

3-Bromo-2-fluoro-6-hydroxymethyl-5-triethylsilanyloxy-tetrahydro-pyran-4-ol (40): ¹H NMR (200 MHz, CDCl₃) δ 0.69 (6 H, q, J = 7.3 Hz), 0.97 (9 H, t, 7.9 Hz), 2.79 (1 H, br), 3.43-3.95 (7 H, m), 5.16-5.55 (1 H, d, J = 7.3, 7.2 Hz).

To a stirred solution of (5-Bromo-6-fluoro-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-ylmethyl ester (41). Toluene-4-sulfonic acid 5-bromo-6-fluoro-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-ylmethy
tetrahydro-pyran-2-yl)methanol 39 (0.32 g, 0.68 mmol) in pyridine (1.7 ml) and CH₂Cl₂ (1.7 ml) cooled at 0 °C, was added tosyl chloride (0.14 g, 0.75 mmol). The cooling bath was removed, and the stirring was continued at ambient temperature. After 4 h the reaction mixture was cooled again to 0 °C, and quenched with water. The organic layer was separated and washed with sat CuSO₄ solution (3 x 5 ml), water (3 x 5 ml). The combined aqueous phases (excluding the first water layer) were extracted with CH₂Cl₂ (2 x 5 ml) and those organic extracts were washed with water (2 x 3 ml). The combined organic layers were washed with brine, and dried over MgSO₄. The solution was then filtered and the solvent removed under reduced pressure, and purified over silica gel column giving 41 as a yellow oil (0.3 g, 70%). ¹H NMR (300 MHz, CDCl₃) δ 0.62 (12 H, q, J = 5.3 Hz), 0.94 (18 H, t, J = 5.2 Hz), 2.43 (3 H, s), 3.72-3.81 (2 H, m), 3.95 (1 H, m), 4.04 (1 H, m), 4.17 (1 H, dd, J = 5.7, 10.4 Hz), 4.34 (1 H, m), 5.52-5.71 (1 H, d, J = 3.7, 3.7 Hz), 7.32 (2 H, d, J = 8.0 Hz), 7.78 (2 H, d, J = 7.9 Hz).

NaBr, NaHCO₃
DMF, 70 ºC, 23 h
93%

3-Bromo-6-bromomethyl-2-fluoro-4,5-bis-triethylsilanyloxy-tetrahydro-pyran (42). A mixture of Toluene-4-sulfonic acid 5-bromo-6-fluoro-3,4-bis-triethylsilanyloxy-tetrahydro-pyran-2-ylmethyl ester 41 (0.11 g, 0.18 mmol), NaBr (0.18 g, 1.75 mmol) and NaHCO₃ (0.02 g, 0.21 mmol) in DMF (3.4 ml) was heated to 70 °C for 23 h. The mixture was diluted with EtOAc, followed by the addition of water. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, brine, and dried over MgSO₄. The solution was then filtered and the solvent removed under reduced pressure, and purified over silica gel column giving 42 as a yellow solid (87 mg, 93%). ¹H NMR (300 MHz, CDCl₃) δ 0.67 (12 H, q, J = 7.9 Hz), 0.99 (18 H, t, J = 4.8 Hz), 3.55 (1 H, dd, J = 4.5, 10.2 Hz), 3.81-3.87 (2 H, m), 3.96-4.03 (2 H, m), 4.10 (1 H, t, J = 3.6 Hz), 5.64-5.83 (1 H, d, J = 3.6, 3.6 Hz).
2-Benzylolxy-3-bromo-6-bromomethyl-4,5-bis-triethylsilanyloxy-tetrahydro-pyran (43). 3-Bromo-6-bromomethyl-2-fluoro-4,5-bis-triethylsilanyloxy-tetrahydro-pyran 42 (29 mg, 0.05 mmol) was dissolved in 1.1 ml of CH₂Cl₂ with 4Å MS (29 mg). The mixture was cooled to 0 °C. To this solution benzyl alcohol (0.01ml) along with SnCl₂ (0.03 g, 0.16mmol) and AgClO₄ (0.03 g, 0.16 mmol) was added. The reaction mixture was allowed to warm to rt. After 1 h, when the TLC shows no starting material, the reaction mixture was filtered with celite. The filtrate was washed with sat NaHCO₃. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, and dried over MgSO₄. The solution was then filtered and the solvent removed under reduced pressure, and purified over silica gel column giving 43 as a yellow solid (26 mg, 76%). 

\[
\begin{align*}
\text{42} & \quad \text{Benzyl Alcohol, SnCl₂, AgClO₄, 4Å MS} \\
\text{CH₂Cl₂, 0 °C to rt, 1 h} & \quad 76% \\
\text{43} & 
\end{align*}
\]

\[
\begin{align*}
\delta & \quad 0.70 (12 \text{ H, m}), 0.95 (18 \text{ H, m}), 3.46 (1 \text{ H, m}), 3.59 (1 \text{ H, m}), 3.64 (1 \text{ H, t, J = 10.1 Hz}), 3.69 (2 \text{ H, m}), 3.90 (1 \text{ H, t, J = 7.5 Hz}), 4.70 (2 \text{ H, dd, J = 15.0, 30.0 Hz}), 4.90 (1 \text{ H, d, J = 10.1 Hz}), 7.29 (1 \text{ H, m}), 7.33 (2 \text{ H, m}), 7.4 (2 \text{ H, m}). \\
\text{δ} & \quad 5.6, 5.8, 7.0, 7.1, 32.9, 54.4, 71.0, 74.4, 77.2, 80.0, 100.3, 127.9, 128.3, 128.4, 136.7.
\end{align*}
\]
Chapter 6. Attempted Preparation of a Molecular Receptor

6.1 Introduction

To expand our study in the area of weak noncovalent interactions, we have attempted to synthesise a molecular DNA base receptor. As discussed earlier, weak interactions, although small in magnitude, being numerous, are believed to provide stability to duplex DNA. The offset stacked orientation (Figure 2.1(b)) is also commonly found in proteins and is the geometry of base stacking in DNA. In this geometry, more surface area is buried, and the van der Waals and hydrophobic interactions are increased. Uracil-DNA glycosylase (UDG) is a key enzyme in the DNA repair system. The uracil molecule was found to be stacked over the aromatic ring of an invariant phenylalanine (Phe 101) and reported to be in van der Waals contacts with an invariant tyrosine.

The geometries of DNA duplexes are largely determined by hydrogen-bonded nucleobase pairing, offset base stacking at a vertical base distance of 3.4 Å, the conformation of the sugar backbond, the base sequence, the hydrophobic effect, and presumably specific solvation patterns in the minor and major grooves. The structure of the bases are shown in Figure 6.1. The polymeric chains of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are built of nucleotides, which consist of three distinct moieties; a purine or pyrimidine base, a ribose or 2’-deoxyribose and a monophosphate group.

The factors contributing to the thermodynamic stability of the DNA double helix have been the focus of intense scrutiny over many years. Hydrogen bonding and base stacking are important noncovalent interactions that stabilize the double helical structure. Of these two, hydrogen bonding is the better understood interaction; base stacking, however discussed at great lengths, is more complex and remains considerably less well understood. While π-π stacking is by consensus an important noncovalent interaction in DNA and proteins, the nature of this interaction remains debatable. To determine these weak interactions experimentally, we have initiated this project.
Figure 6.1 Constitution of purine and pyrimidine, the DNA and RNA bases adenine, guanine, cytosine, uracil and thymine, and definition of the terms nucleoside and nucleotide.

6.2 Results and Discussion

In order to study these interactions, we have attempted to synthesize the model compound 48 with R = C_{10}H_7 (Scheme 6.1). As a part of our plan, we were going to use another base, for example adenine as a guest molecule and perform the NMR experiments. If there is any hydrogen bonding interaction between two heterocyclic bases, then we were expecting to see a change in the chemical shift for N-H protons. We were also going to study the \( \pi \)-stacking interactions if it exists by changing the substituent R.
As shown in Scheme 6.2, we have β-D-Glucose pentacetate 44 as a starting material to synthesize the compound 48 (R = C\textsubscript{10}H\textsubscript{7}). A Vorbruggen condensation with uracil was carried out to obtain 2,3,4,6-tetraacetyl-β-D-glucopyranosyl-uracil 45. After deprotection to the corresponding β-D-glucopyranoside 46, we tried to introduce the 2-Napthoyl group selectively at the C(6)-OH. However to our disappointment, this reaction did not take place smoothly (Scheme 6.3). Also, at this point we had a solubility problem for compound 46. Due to these reasons, we decided to protect all of the remaining –OH group with the bulky TBS protecting group (Scheme 6.4), which indeed helped us to overcome the solubility problem. The final step was the selective
Scheme 6.3

\[
\text{Scheme 6.3}
\]

\[
\begin{align*}
\text{46} & \quad \xrightarrow{\text{Pyridine, } \text{Et}_3\text{N}} \quad \text{No Reaction} \\
\text{46} & \quad \xrightarrow{\text{DMF, imidazole, } \text{CH}_2\text{Cl}_2} \quad \text{No Reaction} \\
\text{46} & \quad \xrightarrow{\text{Pyridine, } -20 \degree \text{C to rt}} \quad \text{No Reaction}
\end{align*}
\]

Scheme 6.4

\[
\text{Scheme 6.4}
\]

\[
\begin{align*}
\text{46} & \quad \xrightarrow{\text{1. TBSCI, DMAP, imidazole, DMF}} \quad \text{TBSO} \\
& \quad \xrightarrow{\text{80 \degree C, 48 h}} \quad \text{49} \\
& \quad \xrightarrow{\text{2. TBSOTf, Pyridine, rt}} \quad \text{24 h} \\
& \quad \text{83%}
\end{align*}
\]
deprotection of TBS group at the C(6) (Scheme 6.5), followed by the introduction of the napthoyl group at C(6)-OH. Unfortunately, we did not succeed in this step due to the removal of the TBS group from the other carbons. As a result of these disappointing problems, we have abandoned this project temporarily.

6.3 Experimental Section

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. Reagents were purchased from commercial sources and used without further purification. Flash column chromatographic separations were performed using silica gel 40–63 μm. Reactions were monitored by TLC with UV light and stain detection. NMR spectra (1H, 13C) were recorded on 300 MHz spectrometers with CDCl3 or DMSO-d6 as the solvent.
2,3,4,6-tetraacetyl-β-D-glucopyranosyl-uracil (45). To the suspension of Uracil (1.15 g, 10.25 mmol) and β-D-Glucose pentacetate 44 (4 g, 10.25 mmol) in dichloroethane (50 ml) was added BSA (6.1 ml, 24.64 mmol). The mixture was stirred under nitrogen at ambient temperature for 40 min until a clear, colorless solution was obtained. TMSOTf (4.8 ml, 24.64 mmol) was added dropwise and the reaction mixture was heated at reflux for 2 h. After cooling to ambient temperature, the mixture was evaporated in vacuo. The resulting oil was diluted in ethyl acetate (240 ml) and washed with NaHCO₃, and brine. The solution was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give 45 as a white solid (4.0 g, 89%). ¹H NMR (300 MHz, CDCl₃) δ 1.97 (3 H, s), 1.99 (3 H, s), 2.03 (3 H, s), 2.06 (3 H, s), 3.92 (1 H, m), 4.09 (1 H, dd, J = 1.8, 12.6 Hz), 4.24 (1 H, dd, J = 4.9, 12.6 Hz), 5.13 (2 H, dd, J = 9.7, 19.4 Hz), 5.37 (1 H, t, J = 9.5 Hz), 5.80 (1 H, dd, J = 1.8, 8.2 Hz), 5.86 (1 H, d, J = 9.5 Hz), 7.31 (1 H, d, J = 8.2 Hz), 9.30 (1 H, br); ¹³C NMR (75 MHz, CDCl₃) δ 20.3, 20.5, 20.6, 20.7, 61.5, 67.7, 69.3, 72.6, 74.9, 80.2, 103.8, 139.0, 150.3, 162.5, 169.4, 169.5, 169.7, 170.4.

1-uracil-β-D-glucopyranoside (46). A solution of 2,3,4,6-tetraacetyl-β-D-glucopyranosyl-uracil 45 (2.76 g, 6.23 mmol) in NH₃/MeOH (12.5 ml) was stirred overnight at ambient temperature. After removal of the solvent in vacuo the precipitate was recrystallized from dichloromethane to give 46 as a white solid (1.67 g, 98%). ¹H NMR (300 MHz, DMSO) δ 3.15 (2 H, m), 3.24-3.33 (3 H, m), 3.40 (1 H, m), 4.58 (1 H, s), 5.08 (1 H, d, J = 5.5 Hz), 5.21 (1H, d,
J = 4.3 Hz), 5.29-5.36 (2 H, m), 5.60 (1 H, t, J = 6.6 Hz), 7.65 (1 H, d, J = 8.1 Hz), 11.32 (1 H, s); 13C NMR (75 MHz, CDCl3) δ 60.9, 69.5, 70.8, 76.9, 79.9, 82.4, 101.8, 141.4, 150.9, 163.0.

To a solution of 1-uracil-β-D-glucopyranoside 46 (0.25 g, 0.91 mmol) in DMF (7 ml) were added TBSCl (0.62 g, 4.10 mmol), imidazole (0.55 g, 8.12 mmol) and DMAP (0.06 g, 0.46 mmol). The solution was heated at 80 °C for 48 h, and allowed to return to rt. 3.5 ml of anhydrous pyridine and TBSOTf (3.71 g, 14.02 mmol) were added dropwise to the solution. After stirring at room temperature for 24 h and evaporation, the residue was taken up in toluene and the insoluble pyridinium triflate was removed by filtration. After washing with water, brine and drying over MgSO4, the residue was purified by column chromatography to give 49 as a white solid (0.55 g, 83%). 

1H NMR (300 MHz, CDCl3) δ 0.03 (24 H, m), 0.84 (36 H, m), 3.35 (1 H, m), 3.43 (1 H, t, J = 8.7 Hz), 3.54 (1 H, m), 3.63 (1 H, d, J = 9 Hz), 3.78 (2 H, m), 5.59 (1 H, d, J = 8.8 Hz), 5.74 (1 H, dd, J = 2.2, 8.1 Hz), 7.19 (1 H, d, J = 8.2 Hz), 8.42 (1 H, s).
7. References


(23) Carver Fiona, J.; Hunter Christopher, A.; Livingstone David, J.; McCabe James, F.; Seward Eileen, M. *Chemistry (Weinheim an der Bergstrasse, Germany)* **2002**, **8**, 2848-59. "Substituent effects on edge-to-face aromatic interactions"


(59) Farooq, O. Synthesis 1994, 1035-6. "Oxidation of aromatic 1,2-dimethanols by activated dimethyl sulfoxide"


(86) Detmer, I.; Summerer, D.; Marx, A. Chemical Communications (Cambridge, United Kingdom) 2002, 2314-2315. "DNA minor groove hydration probed with 4'-alkylated thymidines"


8. Spectroscopic Data

9-(6’-Methoxy-2’-napthyl)anthracenyl methanol 14

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9-(6’-Methoxy-2’-napthyl)anthracene 15

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1. $^1$H NMR
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2. \textsuperscript{13}C NMR
3. \textsuperscript{19}F NMR
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1. $^1$H NMR
2. $^{13}$C NMR
9-(4'-Methoxy-phenoxymethyl)- 2,3-ditrifluoromethane-triptycene 24a

1. $^1$H NMR
2. $^{13}$C NMR
3. $^{19}$F NMR
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9-(4′-Methoxy-phenoxymethyl)- 2,3-dicarbonitrile-triptcene 24c

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9-(4'-Methoxy-phenoxyethyl)- 2,3-dimethanol-triptcene 25

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