The Folding and Assembly of Stereoisomeric Twisted Baskets

DISSERTATION

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Abstract

The chirality of organic building blocks is of great importance for creating a variety of useful materials and drugs. The production of enantio-enriched molecules thus constitutes an integral part of many organic processes. Cavitands are concave organic compounds that can be used for trapping smaller guest molecules. While chiral cavitands exist, there still remains a need to design and develop hosts that are complementary in size and shape to numerous chiral guests for their detection, resolution and/or facile conversion into other useful compounds. Examples of such chiral molecules, and of interest to this work, include many pharmaceuticals, commodity chemicals and chemical warfare agents. In line with a need for developing novel chiral hosts, we recently described a synthetic method for the preparation of cup-shaped cavitands possessing a nonfunctional hydrocarbon framework and a twisted (chiral) inner space. In particular, a tandem of cycloalkylation reactions was promoted with strong acids to, via general-acid catalysis, give rise to baskets (akin to \((P/M)-1\)\textsubscript{syn}, Figure 1.23) comprising six stereogenic centers of the same kind \((R\) or \(S\)) embedded in the host's bicyclic platform. In this study, we expanded the scope of our preliminary investigation by: (a) optimizing a procedure for obtaining functionalized and twisted baskets with either right-\((P)\)-1\textsubscript{syn} or left-handed \((M)\)-1\textsubscript{syn} sense of twist (Figure 1.23) and (b) resolving such racemic host into pure enantiomers. These modular and easily accessible cavitands are \(C_3\) symmetric, possessing: (a) six esters at the
rim for additional functionalization, (b) unique chiroptical characteristics, (c) photochemically sensitizing sidewalls for promoting photochirogenesis and (d) deep and twisted inner space for discriminating chiral guests.

Upon obtaining enantiopure twisted basket \((P)-1\) or \((M)-1\), we modified the rim of the baskets to obtain gated baskets of type \((P)-13\), \((S_3, M)-15\), and \((P)-17\). Basket \((P)-13\) possesses three quinoline gates tethered to the twisted platform via \(\text{CH}_2\) hinges. This chiral cavitand was found to fold quinoline gates at the rim of its twisted platform in acetonitrile and give molecular capsules that assemble into large unilamellar vesicles. In less polar dichloromethane, cup-shaped \((P)-13\) packed into vesicles as well, although with the quinoline gates unfolded. The orientation of quinoline gates in folded \((P)-13\) in acetonitrile was found to be in both clockwise (+) and counterclockwise (−) directions, denoting the absence of chirality transfer from the chiral platform to the gates. In order to produce a twisted basket with unidirectionally folded gates, we introduced an \(S\) stereogenic center to each hinge position, generating \((S_3, M)-15\). In line with our previous study,\(^1\) we found that such \(\text{CH}(\text{CH}_3)\) stereogenic center with \(S\) configuration in \((S_3, M)-15\) directed the twisting of its quinoline gates at the rim in a counterclockwise orientation (−). The coordination of \((S_3, M)-15\) to \(\text{Cu(II)}\) was found to give 1:1 stoichiometric complex. The coordination of quinoline nitrogens to \(\text{Cu(II)}\) in the center above the basket cavity drives the conformational equilibrium of \((S_3, M)-15\) in acetonitrile toward a folded structure, with quinoline gates oriented in counterclockwise (−) fashion.

Gated basket \((P)-17/(M)-17\) contains three amidopyridine gates at the rim. With racemic \((P/M)-17\), it was found that this host (\(^1\)H NMR and IR spectroscopy) stayed
monomeric in CDCl$_3$ at 298.0 K with the gates forming a seam of intramolecular N–H⋯N hydrogen bonds. In particular, the amidopyridine gates assume a unidirectional orientation, as directed by the twisted platform, to either clockwise (+) or counterclockwise (−) orientation of intramolecular N–H⋯N hydrogen bonds. The results of computational studies suggested a small energy difference ($\Delta E_p = 1.07$ kcal/mol) content between $(P)$-17(+) and $(P)$-17(−), with $(P)$-17(−) possessing less energy. The experimental results with enantiopure $(P)$-17 (Circular Dichroism) suggested that the P-shaped cup sets the amidopyridine gates in a clockwise (+) orientation of intramolecular N–H⋯N hydrogen bonds. The folded form of spacious (355 Å$^3$) and chiral (P/M)-17 undergoes an unfolding process in the presence of the polar [D$_6$]DMSO or CF$_3$CH$_2$OH solvent; specifically, with around 25 vol.-% of these solvents, the N–H⋯N hydrogen bonds at the rim are broken, thereby allowing a stochastic rotation of the amidopyridine gates about the rim. Interestingly, the thermal stability of folded (P/M)-17 is good with only a small fraction of unfolded state(s) forming at 104 °C in o-xylene.
Dedication

To my mother Patrapond Pratumyot
To my father Jaran Pratumyot
For their unconditional love
And
To my family
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Chapter 1: Chiral Basket: the Mimic of Chiral Enzyme Receptors

1.1 Background and significance

Enzymes catalyze various types of biochemical reactions that take place in living organisms. Compared to chemical catalysts, enzymes frequently exhibit higher rates, and specificities of the reaction and could be carried out in aqueous solution under mild conditions. Due to the complementary in size and shape of enzyme and substrate, along with geometric placement of catalytic functional groups within the enzyme-substrate complex, superior reaction catalytic performance is achieved.\(^2\) Shapes of various enzymes active sites are asymmetric and thus the chirality become a significant role in molecular recognition and enzymatic catalysis.\(^3,4\) An example of such enzymes is lipase. It is widely used as an enantioselective catalyst for the kinetic resolution of racemic mixtures of secondary alcohol in hydrolysis and transesterification.\(^5\) Another example is sulfatase which catalyzes the enantioselective hydrolysis of sulfate esters, generating alcohol and hydrogen sulfate.\(^6,7\) Fascinated by the nature of enzymes that produce highly effective catalysis, scientists are inspired to mimic them. Enzyme mimics have been studied extensively\(^8-13\) with two major purposes. One purpose is to understand the enzymatic mechanisms, both kinetically and thermodynamically, from chemical reactions generated in the artificial enzyme model system. Another purpose is to utilize the existing knowledge about the properties and architectures of enzymes in designing novel chemical
catalysts that aim to have as high selectivity and rate characteristics as enzymes do, or even possess some special characteristics that make them better than enzymes.²

![Diagram](image)

Figure 1.1. The “Three point” interaction model of chiral recognition proposed by Easson and Stedman.¹⁴

According to Easson and Stedman (1933), enzyme receptors possess three nonequivalent binding sites in order to distinguish between enantiomers.¹⁴ This statement was later supported by Ogston (1948) when the enzymatic decarboxylation of L-serine to glycine was explained.¹⁵ The stereoselective decarboxylation of the prochiral intermediate aminomalonic acid was the key step of this conversion. Aligned with the “three point” interaction model by Easson and Stedman (Figure 1.1), the interaction between aminomalonic acid and enzyme resulted in inequivalence of its carboxylic moieties (Figure 1.2) because they were placed in different binding sites of the enzyme, one of which was responsible for the decarboxylation. This model also explained the biological enantioselectivity and was used in other disciplines including enantioselective separation
of chiral compounds by chromatographic stationary phases. The molecular chirality of enzymes is thereby the determining factor in the molecular recognition and differentiation process.

Figure 1.2. The “three point” interaction for enzymatic conversion of aminomalonic acid by Ogston.

Realizing the importance of chirality in enzyme architectures, scientists design and synthesize chiral artificial hosts and explore their potentials in catalysis, separation science, sensor applications, and drug delivery. Artificial hosts with an enforced cavity, (cavitands) have been studied for resolving chiral compounds such as drugs, metabolites, and commodity chemicals. In line with a need for developing novel chiral hosts, we recently described a synthetic method for the preparation of novel cavitands possessing a hydrocarbon framework with twisted (Figure 1.23) inner space. In particular, a tandem of cycloalkylation reactions was promoted with strong acids to give baskets (akin to (P/M)-\textit{1}_{\text{syn}} in Figure 1.24) comprising six stereogenic centers of the same kind (R or S) embedded
in the host's bicyclic platform. In this study, we focused on developing a preparative procedure for obtaining enantiopure functionalized baskets with right (P)-$\mathbf{1}_{\text{syn}}$ and left (M)-$\mathbf{1}_{\text{syn}}$ handed twisted frameworks (Figure 1.23) as they would present dissymmetric basket platforms for further modification. Notably, chiral baskets of type 1 are $C_3$ symmetric and modular, possessing: 1) six esters at the rim for additional functionalization, 2) unique chiroptical characteristics, 3) photochemically sensitizing sidewalls for promoting photochirogenesis, and 4) deep and twisted hydrophobic pockets for discriminating chiral guests (Figure 1.23).

1.2 Artificial chiral receptors and their applications

Artificial chiral receptors are man-made enzyme mimics and have been extensively explored for their action in asymmetric catalysis. Due to the ability of chiral hosts to differentiate enantiomers, their use is also spread to the area of chiral resolution, separation, and sensor technology. In most cases, binding of substrates and chiral receptors is driven by hydrophobic inclusion inside a cavity. However, metal-ligand coordination in receptor-substrate complexes may also render the recognition process.

Cyclodextrins are attractive in the first construction of artificial receptors due to their ready availability. Native cyclodextrins contain six to eight glucose monomers connected in a ring, creating a cone shape with a hydrophobic interior and water soluble hydroxyl groups on the exterior. The chiral recognition by native β-CDx was first reported by Cramer and Dietsche who studied the resolution of mandelic acid derivatives. Later on, researchers devoted much effort in developing chemically modified CDx variants in
order to improve their chiral resolution properties. In 1995, Breslow reported that more rigid cyclodextrin dimers, compared to more flexible cyclodextrin monomers, better recognize substrates such as cis- and trans-stilbene derivatives in a stereoselective manner. The authors claimed that the cyclodextrin dimer host (Figure 1.3) binds to substrates more tightly than simple cyclodextrin. The better defined structure of cyclodextrin dimer • substrat complex should lead to better catalysts. In 2002, Inoue and coworkers investigated the complexation and chiral recognition of 6-amino-6-deoxy-β cyclodextrin (Figure 1.4) towards anionic, cationic, and neutral chiral guests. They discovered that this cationic β-CDx enhanced chiral discrimination of anionic guests, compared to native β-CDx but not that for neutral and cationic guests.

![a) β-Cyclodextrin](image)

![b) examples of cyclodextrin dimers studied by Breslow and co-workers.](image)

Figure 1.3. The structure of a) β-cyclodextrin and b) examples of cyclodextrin dimers studied by Breslow and co-workers.
Recently, Yuan and co-workers\textsuperscript{35} reported that zinc(II)-dipicolylamine conjugated \( \beta \)-CDx (Figure 1.5) acts as a synthetic receptor toward the recognition of carboxy-terminal domain of RNA polymerase II (CTD) peptide with association constants of \( 6.52 \times 10^3 \) to \( 1.49 \times 10^5 \), which are 16 to 72 times higher than that of ZnDpa, suggesting the role of \( \beta \)-CDx in the molecular recognition.

Other platforms of chiral artificial receptors have been designed and constructed by many researchers in order to improve molecular recognition of substrates with different
sizes, shapes and functional groups. In the early 1980s, Collet and co-workers introduced a new class of molecular platforms containing a cavity called “cryptophanes” which could be described as a hollow sphere enclosed by two cyclotribenzylene caps and three linkers. Their syn and anti-structures are defined by the position of the linker (Figure 1.6) and the chirality of of cryptophanes (C₁, C₂, C₃ of D₃ symmetry) depends on the substitutions on cyclotribenzylene or the linkers.

As various substitutions on cyclotribenzylene are possible, many types of cryptophanes have been created (Figure 1.7). The first generation of cryptophanes is cryptophane-A whose recognition with methane and Xenon was explored. Cryptophane-C was used for the chiral discrimination of bromochlorofluoromethane, whereas cryptophane-O was modified to recognize acetylcoline. The most interesting work on cryptophanes is concerned with their chiroptical and binding properties. The synthesis of cryptophanes often times leads to a mixture of anti and syn isomers, the
separation of the enantiomers\textsuperscript{42} is thus important for applications in biosensing and chiral recognition.

![Chemical structures of cryptophanes A, C, and O](image)

Figure 1.7. The chemical structures of cryptophane-A, C and O.\textsuperscript{37}

In 2011, Buffeteau and co-workers developed an enantiopure water-soluble cryptophane (PP-1 and MM-1) composed of two cyclotrimeratrylene bowls bearing five hydroxyl groups and three ethoxy linkers. Its complexation with propylene oxide (PrO) was proved to be enantioselective (Figure 1.8) in LiOH and KOH solutions.\textsuperscript{43}

![Structure of enantiopure water-soluble cryptophane PP-1 and its enantioselective encapsulation](image)

Figure 1.8. The structure of enantiopure water-soluble cryptophane PP-1 and its enantioselective encapsulation toward (R)-propylene oxide.\textsuperscript{43}
In 1985, Donald Cram won a Nobel Prize on his work involving host-guest chemistry which prompted the creation of many container molecules categorized into two types; carcerands and hemicarcerands (Figure 1.9 and Figure 1.10 respectively). Carcerands trap guest molecules during their synthesis, forming host-guest complexes called carceplexes. Once they are formed, guests cannot leave the carceplexes without breaking covalent bonds. Hemicarcerands, in contrast, release guests from host-guest complexes, called hemicarceplexes, at high temperature. The guest release and capture in hemicarceplexes is occurring via gating mechanisms.

Figure 1.9. The structure of first carcerand created by Cram and co-workers.

Chiral hemicarceplexes were developed and were reported to exhibit good enantioselectivity towards halogenocompounds. Host \((R_4)\)-1 was thus prepared in the form of host-solvent complex \((R_4)\)-1·CHCl₃ (Figure 1.10) and guest exchange occurred to give \((R_4)\)-1·G, in a one to one ratio. The author mentioned that differences in steric
repulsions and dipole-dipole alignment in the diastereomeric transition states played a role in decomplexations. In fact, one stereoisomer of the guest was found to escape the complex at a faster rate than another.

Figure 1.10. The schematic represents the structure of \((R)_4\cdot \text{CHCl}_3\).

Rebek and co-workers\(^{47}\) introduced systems in which capsules with asymmetric inner space were generated via dimerization of monomer components (Figure 1.11). The direction of a seam of hydrogen bonds that holds the host together is determined by the chirality of the chiral guest molecules. This means chiral guests force their assembly with host into one favorable host-guest assembled structure. The capture of chiral guests inside hosts with dissymmetric confined cavities, discovered in this work, provides an ideal model for asymmetric catalysis. The term chiral “tennis ball”\(^{48}\) or chiral “softball”\(^{49}\) are used to name these capsules. They were also reported to achieve enantioselective encapsulation of various small chiral guests including camphor derivatives.
1.3 Molecular baskets and their development toward chiral cavity

To create artificial receptors mimicking the role of enzymes in controlling the trafficking of substrates, products or solutes from the active sites, the Badjic group has developed a number of cavitands called “molecular baskets” and investigated their conformational dynamics, aggregation, and kinetic and thermodynamic encapsulation of small guest molecules. Molecular baskets are composed of two major units; a platform that provides the cavity to accommodate guest molecules and gates that control the dynamics of the molecular basket and regulate the traffic of guests in and out of the cavity. (Figure 1.12) The gates of these baskets are connected to the platform at CH₂ or CHR hinge.
positions that allow the gates to rotate, thus controlling the encapsulation of guests by rapid opening and closing of the cavity.

Figure 1.12. The structure of basket 1.1 (left) and solid state structure of basket 1.1 with a molecule of chloroform in its interior (right).

The gates may be folded by two means; intramolecular hydrogen bonding\textsuperscript{50,51} and ligand to metal chelation\textsuperscript{52,53,54,55}. The main platforms of baskets developed by our group contain a $C_3$ axis of symmetry and are constructed to be varied in size and shape in order to assist the complementary binding of guests with various geometries. The platform of our first generation of baskets has benzene as the floor, connected to three bicyclohexane rings that provide the curvature and extend into phthalimide walls, giving rise to a bowl-shaped structure of baskets (Figure 1.12). Gates are attached to the platform via condensation reactions of their amine forms with a common intermediate “tris-anhydride” (Figure 1.13), generating baskets with a cavity size ranging from 136.6 Å$^3$ - 339 Å$^3$ in volume.\textsuperscript{56,57,58,59,60}
Baskets 1.1, which has three phenol gates at the rims (Figure 1.12), was first synthesized.\textsuperscript{56} Both experimental and theoretical studies showed that basket 1.1 was closed by intramolecular hydrogen bonding of three phenol rings. However, the encapsulation of guests was not observed. It was reasoned that gates were too dynamic and the host was less preorganized, thereby preventing the encapsulation. To improve the stability of host-guest complexes, gates were modified to have stronger intramolecular interactions, thus favoring a closed conformation. It was found that basket 1.2 (Figure 1.14) enclosed its cavity by chelation of its pyridine gates to Cu(I) with $K_a$ of $1.8 \times 10^5$ M$^{-1}$ at 298 K. In addition, the encapsulation of acetonitrile and methyl isocyanide inside the enclosed cavity was observed.\textsuperscript{54}
Figure 1.14. The chemical structure of basket 1.2 (left) and its folded structure upon binding to Cu(II) (right).

To expand the scope of guests, basket 1.3, whose amidopyridine gates could form stronger intramolecular hydrogen bonding than phenol gates by performing two-point interactions, was synthesized (Figure 1.15). It appeared that this basket is less dynamic, thereby increasing stability of host-guest complexe. This allowed a study of the encapsulation of various guests including haloalkanes.\textsuperscript{59,61} The results showed that the binding affinity of halomethanes with the basket is a function of guest’s size.\textsuperscript{59} The largest, CBr\textsubscript{4}, exhibited the highest affinity, while the smallest, CCl\textsubscript{3}H, showed the lowest affinity (Figure 1.16). This observation is also in agreement with Rebek’s 55% rule,\textsuperscript{62} as the guests having the volume of 84-110 \(\text{Å}^3\) could be entrapped inside the host possessing the cavity’s volume of 221\(\pm\)9 \(\text{Å}^3\).
Figure 1.15. Chemical structure of basket 1.3 with the seam of intramolecular hydrogen bonding showing two-point interaction (red line) (left), and the energy optimized (DFT, B3LYP) top and side views of its conformer folded via hydrogen bonding (right).59

Figure 1.16. Van’t Hoff plot(s) for the encapsulation of halomethane guests inside basket 1.3.59

To be able to fine-tune the guest’s kinetic lability, the gates with different R groups at amido units were installed onto the platform, generating basket 1.3 – 1.8 (Figure 1.17) and
their effects on the conformational dynamic of the baskets were examined. The results showed that the electron-withdrawing CF$_3$ group at R position slows the gate’s dynamics while the electron-donating group CH$_3$ increase its dynamics. Therefore, guest t-BuBr was retained longer in the basket 1.8 with lifetime $t$ (1/$k_{out}$) of 14, while it spent less time in basket 1.3 with a lifetime $t$ (1/$k_{out}$) of 0.2 (Figure 1.18).$^{61}$
Figure 1.18. Schematic represents basket 1.3-1.8 capable of controlling time ($t$) that $t$-BuBr spends in their cavity.$^{61}$

The water-soluble baskets were also created by having amino acid connected to the basket’s rim (Figure 1.19). The encapsulation of DMMP guest (118 Å$^3$), which has a similar size to chemical nerve agent sarin (132 Å$^3$), into basket 1.9 – 1.15 was studied in aqueous phosphate buffer at pH 7. It was found that the substituent (R) groups on amino acids (Figure 1.19) affected the binding interaction of host-guest complexes. The degree of branching at the first carbon of each substituent influences the host-guest interaction the most, while the branching at the remote carbons has less of an effect. The glycine functionalized basket 1.9, which has the smallest degree of branching (substituent “-H”) showed the strongest binding toward DMMP guest ($K_a = 465\pm10 \text{ M}^{-1}$), whereas the isoleucine functionalized basket 1.14, which has the greatest degree of branching (substituent “-CH(CH$_3$)CH$_2$CH$_3$”), has the lowest binding affinity toward DMMP ($K_a = 4.23\pm0.09 \text{ M}^{-1}$).$^{63}$
The second generation of baskets was created to provide a larger inner space (318 - 477 Å³). This family of baskets is different from the previous one as its walls are composed of quinoxaline units instead of phthalimide units (Figure 1.20). The extension of one more aromatic ring enlarges the basket’s cavity (Figure 1.20). However, the longer distance between each basket’s arm might prevent the formation of intermolecular hydrogen bonding at the gates. Considering this, we choose to connect this more spacious basket to the amidopyridine gates with a CF₃ substituent, creating basket 1.16 (Figure 1.20). Due to a great difference in electrostatic potential energy between the hydrogen bond donor (N-H) and the hydrogen bond acceptor (Pyr-N) of an amidopyridine gate containing a CF₃ substituent, a strong electronic interaction to form hydrogen bonding between the reacting gates is expected to compensate their far distance. The encapsulation study of 1.16 with solvent molecules such as CD₂Cl₂ (61 Å³), CDCl₃ (75 Å³), CFCl₃ (81 Å³) and CCl₄ (89 Å³) showed that the population of the basket’s inner space (PC) affected the mechanism of gates’ folding. The spacious basket was also prepared in a water-soluble form.
(amphiphilic basket) by introducing three polar ammonium caps at the rims, generating basket 1.17 (Figure 1.21). This basket was calculated to have an inner space of 477 Å³. The basket could entrap dimethyl phenylphosphonate guest, possessing the volume of 184 Å³, akin to soman in size (186 Å³) (Figure 1.22), with $K_{\text{app}}$ of $(1.97 \pm 0.02) \times 10^3$ M$^{-1}$.27

Figure 1.20. Chemical structures of basket 1.8 and 1.16 forming intramolecular N–H⋯N hydrogen bonds and their corresponding energy-minimized forms (PM6). The volume of each basket’s cavity was computed by the 3 V computational method while their van der Waals surfaces are visualized using UCSF Chimera software.57
Figure 1.21. Chemical structure (left) and van der Waals surface (right) of amphiphilic basket $1.17$ (MMFFs, Spartan).

Figure 1.22. Structure of $[1.17 \subset \text{DMPP}]$ complex, computed with molecular dynamics.

It was evident that baskets in both first and second generations have a propensity to entrap small guest molecules including haloalkanes and nerve agent mimics. However, the enantioselective encapsulation, which is proved to be very useful for separation, detection or transformation of chiral compounds, has not been explored yet in our lab.
Therefore, we designed and constructed the third generation of baskets called “twisted basket” that possess a twisted framework and chiral inner space, and have a larger volume than the ones in the first two basket families; there will be a discussion about these baskets in the next section.

1.4 Methodology toward the synthesis and separation of chiral twisted baskets

This part of the chapter was adopted from a previously published paper: Hermann, K.; Pratumyot, Y.; Polen, S.; Hardin, A. M.; Dalkilic, E.; Dastan, A.; Badjić, J. D. Twisted Baskets. Chem. A Eur. J. 2015. 21, 3550–3555. My contribution to this publication was a part of synthesis and NMR characterization.

Twisted baskets are cavitands possessing $C_3$ axis of symmetry and a chiral inner space. The platform of these, third generation, baskets has a benzene as the floor, connected to three bicycloheptane rings that provide the curvature and the twist, and extended into naphthalimide walls giving twisted bowl-shaped structure to baskets (Figure 1.23). In order to ease the modification, twisted baskets were prepared by having six methyl ester moieties at the rims, as appeared in basket ($P$)-1 and ($M$)-1. In this section, the synthesis and purification to obtain enantiopure basket ($P$)-1 and ($M$)-1 will be described (Figure 1.23).
To obtain a twisted basket with a chiral inner space, the cycloalkylation of a trivalent system composing of three side wall arms and one benzene floor in the center, was exploited (Figure 1.24).\textsuperscript{24} To prepare a trivalent compound 4, commercially available 5-indanol was converted to compound 2 following known procedures (Figure 1.24).\textsuperscript{64,65,66,67} The free-radical bromination of indane derivative 2, followed by E1 elimination of bromoalkane intermediate in aprotic solvent toluene gave indene derivative 3. Compound 3 was then deprotonated with a strong base nBuLi at low temperature to generate an indene nucleophile that underwent S\textsubscript{N}2-like substitution with triiodomesitylene 5, giving the trivalent compound 4 with both homochiral ($4^{RRR}/4^{SSS}$) and heterochiral ($4^{RRS}/4^{SSR}$) diastereomers. The ratio of homochiral and heterochiral was 1:4 when the optimized equimolar quantities of substrates were used. The cycloalkylation of
diasteremomeric mixture 4 was then performed under methanesulfonic acid catalytic condition to give twisted basket \((P/M)-1_{syn}\) and \(1_{anti}\) in the same 1:4 proportion. According to our earlier study, the substitution reaction to give compound 4 is under kinetic control.\(^{24}\) To optimize the yield of cup shaped \((P/M)-1_{syn}\), the stereoselectivity of the conversion of 3 into 4 was examined. To study this, the substitution reaction of triiodomesityline 5 with indene derivatives 3, 6, and 7 was performed. The results showed that the more nucleophilic indene 6 \((pK_a = 20)\) gave the highest quantity of desired homochiral product \(8_{RRR/SSS} : 8_{RRS/SSR} = 1:3\), while the less nucleophilic indene 7 \((pK_a = 18-20)\) and 3 \((pK_a < 18)\) generated lower quantity of homociral product \(9_{RRR/SSS} : 9_{RRS/SSR} = 1:4\) and \(4_{RRR/SSS} : 4_{RRS/SSR} = 1:5\) respectively. This evidence confirmed that this substitution reaction is kinetically controlled with stronger nucleophiles promoting faster reaction. In line with this logic, the excess amount of nucleophile \([3]\) compared to electrophile triiodomesityline was used in the substitution reaction in order to increase the reaction’s kinetic rate. Six equivalents of nucleophile was found to be optimal for this reaction, and as expected, gave higher yield of homochiral product \(4_{RRR/SSS}\) with the ratio of \(4_{RRR/SSS} : 4_{RRS/SSR}\) being 1:4 (Figure 1.25).
Figure 1.24. The scheme represents the synthesis of twisted basket \((P/M)\)-1\textsubscript{syn}.

Figure 1.25. The reaction of indene derivatives 3, 6, 7 with triiodomesitylene 5 to give a diastereomeric mixtures of products in different ratios. Reactions were run with 3 equivalents of the indene derivative. \(^a\)This reaction used 6 molar equivalents of indene derivative.
To resolve racemic \((P/M)\)-1\textsubscript{syn}, the transesterification\textsuperscript{69} of \((P/M)\)-1\textsubscript{syn} with (1\textit{R},2\textit{S},5\textit{R})-(−)-menthol in the presence of titanium (IV) catalyst 10 was performed\textsuperscript{70,71} (Figure 1.26). To ensure a complete transformation of the hexaester reactant into sterically hindered \((P)\)-11 and \((M)\)-11, with six menthol groups at the rim, menthol was used as solvent and the reaction was run at high temperature (180 °C) for a long period of time.\textsuperscript{72} Importantly, the chromatographic separation of diastereomeric \((P)\)-11/(\textit{M})-11 was facile with each compound having a distinct \(R_f\) value (\(R_f = 0.37\) and 0.50, Figure 1.26).

Figure 1.26. The transesterification of enantiomeric \((P/M)\)-1\textsubscript{syn} promoted by Titanium (IV) catalyst produced diastereomeric \((P/M)\)-11 that was separated on a thin-layer chromatographic plate (SiO\(_2\), hexanes : diethyl ether = 2:1). Spectroscopic analyses of the chromatographic fractions indicated the correspondence of the bottom band to \((P)\)-11 and that of the top band to \((M)\)-11.
$^1$H NMR spectra (400 MHz, CD$_2$Cl$_2$) of isolated (P)-11 and (M)-11 (Figure 1.27a) showed a single set of resonances corresponding to, in each case, a $C_3$ symmetric compound. The decoalescence of $^1$H NMR signals of each spectra was not observed at lower temperatures, suggesting that the menthol moieties at the rim rotate faster than NMR time scale. (Figure 1.28) $^1$H NMR assignments of 12, (M)-11, and (P)-11 were completed by $^1$H-$^1$H COSY NMR and the reported spectroscopic assignment for (1R,2S,5R)-(-)-menthol. Comparing $^1$H NMR spectra of compound 12, (M)-11, and (P)-11, it was apparent that there was an upfield shift of: 1) two doublets corresponding to H$_{a/b}$ nuclei, and 2) multiplet corresponding to the juxtaposed H$_m$ proton, all as a part of the menthol substituents. (Figure 1.27a) This suggested that menthol moieties on (M)-11 and (P)-11 were shielded by the basket environment and those on (P)-11 experienced a greater effect than (M)-11.
Figure 1.27. a) $^1$H NMR spectra (400 MHz, CD$_2$Cl$_2$) of model compound 12 (top) and twisted baskets (M)-11 (middle) and (P)-11 (bottom). b) Chemical structures of 12 and (P)-11 with selected protons labeled from H$_a$ to H$_n$. c) Energy-minimized (MMFFs, Monte Carlo conformational search; 1000 steps) structures of (M)-11 and (P)-11, representing the most abundant conformers (>95%) obtained in the calculation; note that C-H-π centroid distances are shown, while some hydrogen atoms are removed for clarity.

Figure 1.28 Figure A segment of variable temperature $^1$H NMR (400MHz, CDCl3) spectra of compound a) (M)-11 and b) (P)-11.
To explain this observation, the Monte Carlo conformational study (MMFFs force field, Spartan) of \((P)-11/(M)-11\) with the calculation was completed. The results suggested that structures closely resembling those shown in Figure 1.27c were the predominantly populated conformation. This means both \((P)-11\) and \((M)-11\) diastereomers place one of its menthol isopropyl groups in the cavity of the basket so that \(H_a/H_b\) and \(H_m\) nuclei reside in the shielding region of the surrounding naphthalene rings. However, the one in \((P)-11\) was placed deeper inside the cavity than the one in \((M)-11\), which resulted in \(H_a/H_b\) and \(H_m\) nuclei of \((P)-11\) being more diamagnetically shielded by the basket’s aromatics. According to the different folding characteristics of \((P)-11\) and \((M)-11\), we surmise that the separation of \((P)-11\) and \((M)-11\) on silica is due to \((P)-11\) being more compact and thus attaching on the silica better than \((M)-11\).

Upon the separation of \((P)-11\) and \((M)-11\) with column chromatography, we assigned their absolute configurations using exciton-coupled circular dichroism (ECCD)\textsuperscript{74} spectroscopy (discussed in the next section). The diastereomeric \((P)-11\) and \((M)-11\) were then individually transformed to enantiopure \((P)-1\text{_{syn}}\) and \((M)-1\text{_{syn}}\) which each contain six methyl ester groups, providing access for further functionalization. The reaction was performed with a strong acid (\(\text{CH}_3\text{SO}_3\text{H}\)) to promote the substitution of six (-)-menthol groups in \((P)-11\) (or \((M)-11\)) with methanol (Figure 1.29).
1.5 The optical properties of diastereomeric and enantiomeric chiral twisted baskets

The exciton chirality method (exciton coupled circular dichroism spectroscopy, ECCD) was used to probe the absolute configuration of compounds \((P)-\text{11}/(M)-\text{11}\), encompassing right- and left-handed twists. Upon absorbing light at 220 nm (naphthalene’s \(^1\text{B}_\text{b}\) transition in the Platt’s notation), three naphthalene chromophores were excited and each generated a strong electric dipole along its axis, with each one lying at an acute angle with respect to the next one (Figure 1.30a). In line with ECCD, an exciton coupling of these three \(^1\text{B}_\text{b}\) transition dipole moments gave a bisignate spectrum with the rotational strengths and sign being a function of their interchromophoric distance \((d)\) and orientation \((\Omega)\). Diastereomeric basket \((P)-\text{11}/(M)-\text{11}\) showed the opposite CD spectrum. According to the semi-empirical exciton chirality rule, the negative couplet from the blue spectrum (Figure 1.30a, bottom left) reflects the counter clockwise rotation of dipole moment’s axes,
which is corresponding to the rotational twist in \((P)-11\) that is of isolated chromatographic fraction with \(R_f\) of 0.37 (Figure 1.26). On the other hand, the positive couplet from the red spectrum (figure 1.30a, bottom left) indicates the clockwise rotation of the dipole moment’s axes, which corresponds to the rotational twist in \((M)-11\), whose isolated chromatographic fraction has \(R_f\) of 0.50 (Figure 1.26). Model compound 12, which was not in a chiral environment, exhibited no CD couplet (black spectrum in Figure 1.30a, bottom left). Furthermore, the large \(A\) value \((|\Delta\varepsilon_1|+|\Delta\varepsilon_2|)\) of 535 shows a through-space interaction of the naphthalene chromophores in \((P)-11\) with a contribution from all three ECCD couplets,\(^1\) thereby following the pair-wise additivity principle.\(^77\) The UV/Vis and CD spectra of energy-minimized \((M)-1_{\text{syn}}\) (Figure 1.30b) using time-dependent density functional theory (TD-B3LYP/ TZVP)\(^79\) were also computed. Remarkably, the observed positive exciton chirality of \((M)-11\) centered at 242 nm is in an agreement with the computed ECCD couplet of \((M)-1_{\text{syn}}\). The absolute configuration of \(P/M\) twisted baskets is in this way confirmed.
Figure 1.30. a) Absorption (UV/Vis, top left) and circular dichroism (CD, bottom left) spectra of (P)-11 (blue, 2.5 µM), (M)-11 (red, 2.5 µM) and 12 (black, 5.0 µM) in hexane at 298 K. Energy-minimized structure of model compound 12 (MMFFs, Spartan) with the $^1B_b$ transition dipole moment along the naphthalene chromophore (top right). The negative exciton chirality characterizes twisted basket (P)-11 since its three naphthalene chromophores (only two are shown) are positioned in space so that a counterclockwise rotation of the front electric dipole moment (blue) by an acute angle brings it onto the exciton axis in the back (bottom right).b) Computed DFT: B3LYP/TZVP (black) UV/Vis (top) and CD (bottom) spectra of basket (M)-1$_{syn}$; for comparison, UV/Vis (top) and CD (bottom) spectra of (M)-11 (red) are included. The blue sticks are computed electronic transitions that were subjected to Gaussian broadening (0.25 eV) and wavelength shift (-0.2 eV) for generating the computed spectra.

Upon obtaining the enantiopure (P)-1$_{syn}$ and (M)-1$_{syn}$, the resolved baskets were subjected to ECCD study. The CD spectrum of (P)-1$_{syn}$ (blue, Figure 1.31) is a mirror image of the one corresponding to (M)-1$_{syn}$ (red, Figure 2) with a negative CD couplet centered at 247 nm and in accord with the counter clockwise (−) position of three degenerate $^1B_b$ transitions from the naphthalene chromophores (Figure 1.31). Interestingly, the positive Cotton effect at 239 nm ($\Delta \varepsilon_1 = 60 \, \text{M}^{-1} \text{cm}^{-1}$) is accompanied with a negative CE at
256 nm (Δε₂ = -112 M⁻¹cm⁻¹): the A value |Δε₁| + |Δε₂| = 172) is for (P)-1_syn substantially smaller than for (P)-11 (A = 535). The interaction of naphthalene chromophores through space, as being a function of their distance (d) and orientation (Ω), is clearly different for twisted hosts having the same sense of helicity (P) but different ester groups at the rim. We reason that the inclusion of one (-) menthol in the cavity of (P)-11, as discerned in our prior work, could play a role in enhancing the rotational strengths of the bisignate spectrum.

![Figure 1.31. Circular dichroism (left) and UV-Vis (right) spectra of enantiopure (P)-1_syn (blue, 10 µM) and (M)-1_syn (red, 10 µM) at 298.0 K in CH₃CN. The coupling of π−π* transition dipole moments, along the long axis of each naphthalene chromophore at 247 nm, contributes to the observed negative (blue) and positive (red) CD couplets.](image)

1.6 Conclusion

In conclusion, we have completed the preparation of a novel cavitand comprising a twisted concave platform (P or M) and six ester groups at the rim. This host is modular, and prone to additional functionalizations, with a deep and chiral hydrophobic pocket made of three photochemically active naphthalene rings. The functional and twisted baskets can now be used for: 1) building chiroptical sensors capable of reporting on the presence of
minute quantities of chiral substances in the environment, 2) resolving useful drugs and drug intermediates, and/or 3) developing novel stereo-selective supramolecular catalysts.
Chapter 2: The Folding and Assembly of Stereoisomeric Twisted Baskets

2.1. Background and significance

The inner space of cavitands and molecular capsules provides a unique environment for accommodating complementary guest molecules \(^{80,81}\) and allowing fine-tuning of their physical and chemical characteristics. Indeed, the study of molecules within molecules has, in the last few decades, revealed ways to (a) prolong the lifetime of reactive intermediates, \(^{82}\) (b) stabilize transition states of chemical reactions, \(^{83,84}\) (c) create new forms of stereoisomerism, \(^{85}\) (d) permit crystallographic characterization of compounds, \(^{86}\) (e) allow detection of molecules \(^{87}\) and (f) enable controlling the outcome of chemical reactions. \(^{88,89,90}\) Interestingly, folded aromatic oligomers (foldamers) \(^{91,92}\) have also been examined for trapping molecules \(^{93,94}\) with their conformational dynamics affecting the rate by which guests enter/exit such structures, \(^{95}\) the process in which conformational dynamics of a host directs the kinetics of molecular encapsulation (i.e. constrictive binding) is referred to as gating. \(^{96}\) Furthermore, calix[4]arene with four cholic acids at the rim has been found to reversibly fold polar and nonpolar faces of cholates as a function of the solvent polarity. \(^{97}\) This type of host, possessing the characteristics of both foldamers and cavitands, was put to work in controlling the transfer of glucose molecules across a lipid membrane. \(^{98}\)
In line with these studies, we hereby describe the capacity of twisted and enantiopure basket \((P)-13\) (Figure 2.6)\textsuperscript{99} to form nanosized vesicles\textsuperscript{100} in dichloromethane and acetonitrile.\textsuperscript{101} In more polar acetonitrile, the basket folds its quinoline gates\textsuperscript{96} to give molecular capsules (c.a. 355 Å\textsuperscript{3})\textsuperscript{102} (Figure 2.14). In non-polar dichloromethane, however, the quinoline gates separate from one another to give unfolded baskets still assembled into vesicles (Figure 2.14).\textsuperscript{103} We note that here described findings pave a way for obtaining gated vesicles capable of regulating constrictive binding\textsuperscript{96,104} within nanostructured materials for various applications.\textsuperscript{105,106}

\subsection*{2.2 Foldamers}

Foldamers are artificial structures that fold into specific and stable conformations akin to those seen in the living organisms such as proteins and nucleic acids. These biomacromolecules are capable of regulating sophisticated chemical processes in nature; therefore, many scientists have sought to create unnatural oligomers that could fold into conformationally ordered state, such as helices, turns and sheets, in solution and perform functions mimicking those in nature. The structures of folded oligomers are stabilized by noncovalent interactions between nonadjacent monomer units and solvent effects.\textsuperscript{107} Indeed, the folding of foldamers is influenced by both internal and external properties. The former factor includes shape and rigidity of molecules, along with the ability to form noncovalent interactions, all of which facilitate folding by reducing the entropic cost of forming such organized conformation. The later factors consist of solvent effects such as
the hydrophobic effect, aggregation, host-guest complexation and contacts with interfaces.\textsuperscript{92} According to Jeffrey Moore, foldamers are divided into two families; “biotic” and “abiotic”.\textsuperscript{92} Biotic foldamers are synthetic oligomers whose backbones mimic those seen in biopolymers, thus their folding is guided by the same principles as biopolymers. The hydrogen bonding between appropriate units along the backbone is usually responsible for their folding. Nucleotidomimetic foldamers and peptidomimetic foldamers are examples of biotic foldamers. Abiotic foldamers, on the other hand, have backbones and folding modes different from those of biopolymers. They are created in a diverse range of structures; however, they share similar aromatic rich sequence characteristic such as oligophenylene-ethynlenes,\textsuperscript{103} aromatic electron donors and acceptors in alternating positon,\textsuperscript{108} aza-heterocycles,\textsuperscript{109} aromatic tertiary amide, imide or urea oligomers and aromatic oligomides.\textsuperscript{110,111,112,113} Abiotic foldamers have been explored extensively because their folded structures are highly stable, predictable, and their structures can be elucidated by crystallography. The discovery of foldamers could lead us to developments in therapeutic and material chemistry. Some of foldamers show biological activity even they are not similar to their naturally occurring counterpart.

2.3 Solvophobic based foldamers\textsuperscript{91}

Solvents provide a medium which reactants can interact with each other at a fast rate. In covalent reactions, solvent choice has a great effect on reaction rates and mechanisms. For example, polar protic solvents retard $S_N2$ reactions due to their solvation
of nucleophiles. In supramolecular chemistry, noncovalent interactions are responsible for the assembly and spatial organization of a number of discrete components. Noncovalent interactions involved in supramolecular chemistry include both solvent-solute and solvent-solvent interaction; therefore, solvents are considered in supramolecular chemistry as reactants, as well as media. There are two kinds of solvent effects involved in noncovalent interaction; direct and indirect. A direct effect is the competition of solvents with substrates for a reactive site, e.g., the perturbation of intramolecular hydrogen bonding between two subunits of a macromolecule by water or DMSO. An example of an indirect effect is the hydrophobic effect, which plays a role in the self-assembly of nonpolar solutes in aqueous solutions. In the classical hydrophobic effect, the aggregation of nonpolar molecules in water is entropically driven. The hydrophobic collapse of nonpolar molecules in water creates cavities in water and disturbs the orientation of water molecule at the nonpolar-water interfaces, thus increasing the entropy of the system. In opposite to hydrogen bonding interactions, which are specific and directional, solvophobic interactions occurs randomly and have no direction. Therefore, synthetic foldamers whose intramolecular self-organization is guided by nonspecific forces alone are geometrically manipulated to have moieties responsible for hydrophobic collapse at the appropriate position. The complementary solvophobic surface generated in such system prevents random aggregation and directs the self-association into well-defined structure. The introduction of geometric constrain by incorporating rigid aromatic rings in to foldamers results in more
effective aromatic interaction between reacting subunits. This statement was supported by the work of Peter G. Wolynes and co-workers\textsuperscript{103} on the discovery of the solvophobically driven folding of a phenylacetylene oligomer into a compact helix with a well-defined tubular cavity capable of binding to useful substrates (Figure 2.1). The hydrophobic collapse of oligomers occurs in acetonitrile, a polar solvent, when the chain length of an oligomer involves more than 8 monomer units. The folded structure in acetonitrile can be destroyed by chloroform, a less polar solvent, and temperature as evidenced by the increased intensity ratio of UV absorption maxima at 290 and 303 nm (chromophores involved in hydrophobic collapse) when the percent (volume) of chloroform in acetonitrile or temperature increases (Figure 2.2). Furthermore, the $^1$H-NMR spectrum of oligomers with different chain lengths in acetonitrile showed an upfield shift of the average $^1$H-NMR chemical shift ($\delta_A$) with an increase in chain length, which was not observed in chloroform (Figure 2.3). This confirmed a helix formation in acetonitrile when monomer units (n) > 8.

Intramolecular aromatic stacking resulted in the upfield shift of the average $^1$H-NMR chemical shift ($\delta_A$) and is responsible for the helix’s hydrophobic collapse by maximizing aromatic-aromatic contacts and minimizing interactions of the hydrocarbon backbone with the solvent.
Figure 2.1. a) Phenylacetylene oligomers 1 to 9 (upper left) when n is the number of monomers. Octadecamer 9 is also shown in a random coil conformation. b) Helical conformation of octadecamer 9 where R and end groups have been removed for clarification.¹⁰³

Figure 2.2. The change in the intensity ratio of the UV absorption maxima at 290 and 303 nm (I₃₀₃/I₂₉₀) upon a) increment addition of chloroform into the solution of octadecamer 9 in acetonitrile at 25 °C and b) increasing the temperature of the solution of octadecamer 9 in 60 vol.-% chloroform.¹⁰³
In 2005, Shigeo Kohmoto and co-workers synthesized naphthalene-based foldamers possessing naphthalene rings connected at their \( \alpha \)-position with iminodicarbonyl linkers (Figure 2.4). \(^{1}H\)-NMR spectra showed an upfield shift of \( H_a \) as the number of naphthalene rings increased due to multiple interactions between intramolecular naphthalene rings. An NOEs between the protons \( H_a-H_d \) and \( H_a-H_j \) (Figure 2.5) was also observed, suggesting a folded conformation in solution. The introduction of a chiral auxiliary at the imide nitrogen atom regulates helicity control of the foldamer. The \((S)\)-1-((1-naphthyl)ethyl substituent at the nitrogen atom was bulky enough to cause the helicity, resulting in chiral foldamers.
Figure 2.4. The chemical structure of naphthalene-based foldamers with “n” number of monomers (top left) and the structure of the folded conformation when n = 5 (bottom right).

Figure 2.5. a) $^1$H-NMR spectra illustrated the upfield shift of H$_a$ as the number of naphthalene units oligomer chains increase from 1 to 5 (1a, 2a, 3a, and 5a). b) NOE correlations observed in the folded conformation of oligomer 3. 

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2.4 Experimental design and the preparation of quinoline gated basket


In Chapter 1, we described a synthetic method for obtaining enantiopure \((P/M)-1\) baskets, each possessing a bicyclo [3.2.1] hydrocarbon platform with right- or left-handed sense of twist and six methyl esters at the rim (Figure 1.23). To deepen the cavity of enantiopure \((P)-1\) and functionalize its portal, we reacted this compound with quinolin-3-ylmethanamine to obtain \((P)-13\) (Figure 2.6). We then investigated the folding characteristics of this gated basket. The quinoline gates of \((P)-13\) is aromatic moieties which are hydrophobic and thus has a propensity to adopt a folded conformation in polar solvent by the solvophobic effect. In this line, NMR (Nuclear Magnetic Resonance spectroscopy), ECCD (Exciton-Coupled Circular Dichroism) and UV-Vis (Ultraviolet-Visible spectroscopy) were used to investigate whether \((P)-13\) has self-folding properties in polar solvent. Regardless of self-folding property, three quinoline gates at \(C_3\) symmetrical positions could adopt a folded conformation by coordinating their nitrogen atoms to a metal, creating folded structure of metal \(\subset\) basket complexes.\(^1\) To reveal this ability, NMR, ECCD, UV, and EPR (Electron Paramagnetic Resonance spectroscopy) was utilized. As the platform of basket \((P)-13\) possesses a right handed sense of twist, we speculated that the platform could transfer its chirality information to the folded gates at top, providing gates arrange themselves in a counterclockwise (–) fashion. In this regard, chirality transfer has been followed using ECCD. The assembly of \((P)-13\) was also studied
by TEM (Transmission Electron Microscopy), SEM (Scanning Electron Microscopy), and DLS (Dynamic Light Scattering). To better understand and interpret the phenomena observed with \((P)-13\), we synthesized \((P)-14\) (Figure 2.6) which lacks the ability to fold by replacing quinoline gates with n-butyl gates.

![Chemical structures](image)

Figure 2.6. The scheme represents the transformation of basket \((P)-1\) to basket \((P)-13\) and \((P)-14\).

### 2.5 The folding of quinoline gated basket and the chirality transfer

Firstly, \((P)-13\) is a \(C_3\) symmetric host containing three 2,3-naphthalimide chromophores embedded in the twisted framework carrying three quinoline “gates” at the rim. The CD spectrum of enantiopure \((P)-13\) in acetonitrile reveals a negative CD couplet centered at 270 nm (Figure 2.7a). Allegedly, the observed absorptions originate from the interaction of \(\pi\) to \(\pi^*\) transition dipole moments (270 nm) in the naphthalimide chromophores, along each of their long axis and situated in the counterclockwise fashion (Figure 2.7b).\(^{115}\) The sense of the framework’s helicity in \((P)-13\) is, as expected, the same
as in \((P)\)-11. Secondly, three quinoline chromophores in \((P)\)-13 possess a strong transition electric moment (\(\lambda = 233\, \text{nm}, \varepsilon = 57,000\, \text{M}^{-1}\text{cm}^{-1}\)), polarized along each of their long axis (Figure 2.7b).\(^1\) In line with this, we noted a complete absence of any cotton effect or exciton coupling around 230 nm; note that UV-Vis spectrum of \((P)\)-13 reveals the presence of the quinoline chromophores (Figure 2.7a). The CD spectrum of \((P)\)-14 (Figure 2.7b), containing three n-butyl chains instead of quinoline rings (Figure 2.6), was in acetonitrile almost identical to the one corresponding to \((P)\)-13. On the basis of these results, we presume that three quinoline rings (a) revolve about the rim of \((P)\)-13 in a stochastic manner to adopt various orientations or (b) assemble into left- and right-handed propellers to nullify the difference in the absorption of the circularly polarized light.

To additionally probe the conformational characteristics of quinoline containing baskets, we titrated a standard solution of Cu\((\text{BF}_4)\)_2\(\cdot\)6\(\text{H}_2\text{O}\) to enantiopure \((P)\)-13 in acetonitrile and monitored the process with CD spectroscopy (Figure 2.8a). In line with an earlier study,\(^1\) the hypothesis was that the coordination of Cu(II) to the quinoline nitrogen atoms would join the heterocycles and place them into a propeller like orientation (Figure 2.11b). Indeed, the formation of Cu(II)\(\subset\)\((P)\)-13 complex ensued: the CD binding isotherm (Figure 2.8b) in addition to \(^1\)H NMR spectroscopy (Figure 2.9) and mass spectrometry (Figure 2.10), was in line with the formation of 1:1 coordination complex.
The titration of (P)-13 in CH$_3$CN with Cu(BF$_4$)$_2$·6H$_2$O did not give much change in the shape of ECCD spectra especially at about 233 nm where the exciton coupling of quinolone gates would appear (Figure 2.8); however, the change in molar circular dichroism $\Delta \varepsilon$ (M$^{-1}$ cm$^{-1}$) was obvious at 280 nm and the sigmoidal curve is drawn to guide the eye, showing 1:1 binding isotherm of Cu(II)⊂(P)-13 (Figure 2.8b).
Figure 2.8. Selected circular dichroism spectra of \((P)\text{-13}\) in CH\(_3\)CN (20 µM, 298 K) (left) obtained upon an incremental addition of a standard solution of Cu(BF\(_4\))\(\cdot\)6H\(_2\)O (1.0 mM) in acetonitrile. A change in molar circular dichroism \(\Delta\varepsilon\) (M\(^{-1}\) cm\(^{-1}\)) of a solution of \((P)\text{-13}\) (20 µM) in acetonitrile at 280 nm (right).

Figure 2.9. A series of \(^{1}\)H-NMR spectra (600 MHz, CD\(_3\)CN; 298 K) recorded on the addition of 1.45 mM standard solution of Cu(BF\(_4\))\(\cdot\)6H\(_2\)O (molar equivalents are shown on the left) to 36.2 µM solution of \((P)\text{-13}\) in CD\(_3\)CN.
Figure 2.10. High resolution ESI mass spectrum of Cu(II)⊂(P)-13.

A series of $^1$H-NMR spectra (600 MHz, CD$_3$CN; 298 K) obtained upon the addition of standard solution of 1.45 mM Cu(BF$_4$)·6H$_2$O to 36.2 µM solution of (P)-13 in CD$_3$CN (Figure 2.9) showed that as the quantity of Cu(BF$_4$)·6H$_2$O increases, the proton signals corresponding to the quinoline gates become broad and eventually disappear at approximately equimolar host:guest ratio thereby in line with 1:1 stoichiometry. High resolution ESI mass spectrum of Cu(II)⊂(P)-13 (Figure 2.10) also shows the parent signal
at 1305.3407 corresponding to the base ion (M+Cu)^+ (m/z calcd for C_{84}H_{54}CuN_{6}O_{6}: 1305.3395 [M+Cu]^+) which supports the formation of Cu(II)⊂(P)-13.

Figure 2.11. a) Electron paramagnetic resonance spectrum of Cu(II)⊂(P)-13 in CH$_3$CN at 100 K. b) Side and top views of square pyramidal Cu(II)⊂(P)-13 (DFT: M06/6-31G*).

Electron paramagnetic resonance spectrum of Cu(II)⊂(P)-13 in CH$_3$CN at 100 K (Figure 2.11a) showed a normal/axial EPR signature with equivalent x and y axes and two g tensor values ($g_{\parallel} = g_z > 2.1 > g_\perp = g_x, g_y > 2.0$ and $A = 177$ G), suggesting a square-pyramidal coordination geometry about the Cu(II) center (Figure 2.11b).$^{116}$ Importantly, the DFT conformational study of Cu(II)⊂(P)-13 (DFT: M06/6-31G*) showed the
propeller-like orientation of three quinoline gates at the rim (Figure 2.11b). For the calculation, we assumed that two acetonitrile molecules would coordinate to Cu(II) while the counter ions (BF$_4^-$) were not considered. Interestingly, the CD spectrum of Cu(II)$\subset (P)$-13 was almost identical to the one corresponding to (P)-13. The absence of an exciton couplet at c.a. 230 nm (originating from quinolines) was apparent (Figure 2.7b) despite the square-pyramidal coordination geometry of Cu(II)$\subset (P)$-13 in which the quinolines adopt helical orientations (Figure 2.11b). It follows that Cu(II)$\subset (P)$-13 ought to have an equal population of right (–)- or left (+)-handed quinolines at top of its cavity! Does basket (P)-13 encompass similar conformational characteristics as Cu(II)$\subset (P)$-13)?

In this regard, a variety of aromatic oligomers has been known to undergo a solvophobically driven folding in polar solvents (acetonitrile)$^{117}$ and unfolding in nonpolar solvents (dichloromethane)$^{103}$ Accordingly, $^1$H NMR spectrum of (P)-13 in CD$_3$CN and CD$_2$Cl$_2$ showed a set of resonances corresponding to, in each case, a $C_3$ symmetric molecule (Figure 2.12a). We used cross-correlations, from two-dimensional $^1$H-$^1$H COSY (Figure A.2-A.3) and NOESY spectra (Figure A.4-A.5), to assign all of the signals. Notably, diastereotopic H$_{g/h}$ protons emerged as an AB quartet in CD$_3$CN (4.8 ppm, Figure 2.12a) but were a singlet in CD$_2$Cl$_2$ (5.0 ppm, Figure 2.12a).
Figure 2.12 a) Selected regions of $^1$H NMR spectra (800 MHz, 298 K) of (P)-13 in CD$_3$CN and CD$_2$Cl$_2$. b) The assignment of proton nuclei in (P)-13. c) Energy-minimized forms of (P)-13 (DFT: M06-2x/6-31G*) with quinoline gates adopting helical (–) and (+) orientations.

To explain this observation, we invoke our recent results$^{118}$ whereby the splitting of H$_{g/h}$ resonances into a quartet occurred with aromatic gates forming a unidirectional seam of hydrogen bonds but showed a singlet when the hydrogen bonds were broken. Accordingly, we reason that the quinoline gates from (P)-13 adopt clockwise and/or
counterclockwise orientations in acetonitrile while remain randomly oriented in dichloromethane. In fact, energy-minimized (DFT: M06-2x/6-31G*)35 structures of diastereomeric (P)-13 with (−) and (+) helical gates were found to possess a comparable energy content (ΔE = 0.54 kcal/mol, Figure 2.12c). Furthermore, the singlet corresponding to H$_a$ from (P)-13 was in CD$_3$CN (8.82 ppm, Figure 2.12a) found at a higher field than in CD$_2$Cl$_2$ (8.95 ppm, Figure 2.12a). To explain the observation, we note that each of the energy-minimized (P)-13 encompasses three aromatic gates at top of the juxtaposed H$_a$ protons (Figure 1.12b); in fact, these protons are less than 3.05 Å from the closest sp$^2$ hybridized carbon of the quinoline ring, i.e., within the cut-off distance for forming the attractive C–H–π interactions. Allegedly, the anisotropic effect from quinolines is, in acetonitrile but not dichloromethane, magnetically shielding H$_a$ nuclei to reduce their chemical shift. At last, the CD spectra of folded and unfolded forms of (P)-13 are, in CH$_3$CN and CH$_2$Cl$_2$, almost identical (Figure 2.7b) and similar to Cu(II)⊂(P)-13 in CD$_3$CN (Figure 2.8a). The observation could be explained with the notion that folded structures of (P)-13 and Cu(II)⊂(P)-13 encompass the quinoline rings residing both clockwise (+) and counterclockwise (−) at the rim to cancel their exciton coupling. The unfolded form of (P)-13 is, however, lacking the Cotton effects from the quinoline chromophores as these groups are residing further away from one another and also randomly oriented about the portal of the host. In line with the interpretation, the twisted framework of basket (P)-13 is clearly not transferring the stereochemical information to
To examine the aggregation of twisted baskets in organic media, we completed a series of dynamic light scattering (DLS) and electron microscopy measurements (Figure 2.13). Evidently, basket (P)-13 assembles into nanosized vesicles with the size distribution centered at ~ 240 nm in both dichloromethane (Figure 2.13a, PDI = 0.39) and acetonitrile (Figure 2.13b, PDI = 0.36). In addition, Cu(II)⊂(P)-13 gives rise to a somewhat larger vesicles with hydrodynamic radii centered at ~ 310 nm (Figure 2.13c, PDI = 0.32). On the basis of the propensity of earlier examined baskets to form nanosized vesicles in water, we reason that cup-shaped (P)-13 are likely to populate the vesicular membrane by packing “tail-to-tail” (Figure 2.13). In this way, the non-polar cages reside in the interior of the lipid-like bilayer and away from polar acetonitrile, while quinoline groups stay in contact with the bulk solvent. In the case of dichloromethane, the packing of host molecules is, we posit, comparable (Figure 2.13) since $^1$H NMR spectra of the aliphatic region of the host are in these two solvents almost identical (Figure 2.12a).
Figure 2.13. Size distribution of (a) 4.9 mM \((P)-\textbf{13}\) in CD\(_2\)Cl\(_2\) (b) 50 \(\mu\)M \((P)-\textbf{13}\) in CD\(_3\)CN and (c) 50 \(\mu\)M Cu(II)\(\subset\)(\((P)-\textbf{13}\) in CD\(_3\)CN was obtained from dynamic light scattering measurements at 298.0 K. (a) Transmission electron microscopy (TEM) image of \((P)-\textbf{13}\) (4.9 mM in CH\(_2\)Cl\(_2\)) deposited on a copper grid and stained with uranyl acetate. Scanning electron microscopy (SEM) images of (b) \((P)-\textbf{13}\) (50 \(\mu\)M in CD\(_3\)CN) and (c) Cu(II)\(\subset\)(\((P)-\textbf{13}\) (50 \(\mu\)M in CD\(_3\)CN) deposited on a silicon wafer and coated with gold.
Figure 2.14. Basket \((P)-13\) folds its quinoline gates in acetonitrile (left) while unfolds them (right) in dichloromethane (MMFFs, Spartan). The host assembles in both solvents to give nanosized vesicles (see Figure 2.13).

2.7 Conclusion

In conclusion, we discovered that the hydrocarbon framework of twisted baskets has a capacity to direct the folding of three aromatic gates at top of the cavity in acetonitrile. In nonpolar dichloromethane solvent, however, the quinoline gates unfold by assuming random positions about the rim. Importantly, both folded and unfolded baskets form nanosized vesicles with the mode of aggregation directed by the solvophobic effect\(^{91}\) and shape of these hosts.\(^{100}\) At present, we aim to employ the results of our findings toward investigating the assembly and recognition characteristics of twisted baskets in water.
Chapter 3: On the controlling of dynamic stereoisomerism of twisted baskets

3.1 Background and significance

The unique dynamic stereoisomerism of chiral supramolecules plays an important role in the control of asymmetric induction, selective encapsulation and stereoselective release of molecules. The existence of a chirality center in a close proximity to the reaction site results in the selection toward a more favorable energy pathway, leading to stereoselective activation\textsuperscript{120} in asymmetric catalysis, kinetic resolution, and encapsulation. In line with the potential of chirality control, we attempted to create chiral capsules with gates whose folding is taking place in a stereoselective fashion. Transition metal coordination of multidentate nitrogen-containing ligands such as tripodal tris(2-pyridylmethyl)amines (TPA) generates propeller-like coordination complexes\textsuperscript{121,122,123}. In the TPA system, the helical arrangement of three pyridine rings can be controlled by introducing a chiral center into one of the pyridine arms\textsuperscript{121}. This chirality control strategy worked very well with our previous study with transition-metal (Ag(I), Cu(I), Cu(II)) folded baskets\textsuperscript{1,124}. The introduction of \textit{R} stereogenic center at the “hinge” position of baskets directed the folding of gates in (−) propeller-like fashion and \textit{vice versa}. (Figure 3.3) In the previous work (chapter 2), we discovered that three quinoline gates at the rims
of twisted basket \((P)-13\) fold in acetonitrile by way of solvophobic effect. However, the helicity of the gates at top ought to be in both clockwise (+) and counterclockwise (−) orientation at an equal population. The incremental addition of \(\text{Cu(BF)}_4\cdot\text{H}_2\text{O}\) into a solution of \((P)-13\) in acetonitrile showed 1:1 coordination complex of \(\text{Cu(II)}\subset\!(P)-13\) (Figure 2.8); however, the cooperation of Cu(II) to the folded structure of \((P)-13\) does not drive the equilibrium of folded complex toward one with preferred helical orientation. In order to explore the potential of chiral molecular capsule type \(\text{Cu(II)}\subset\!(P)-13\) as the transition metal Lewis acid catalyst in asymmetric reactions such as Diels-Alder, chirality near the transition metal, where the coordination of substrates occurs, should be specified. Thereby, in this study, we attempted to control the helicity of quinoline gates on top of the twisted basket using a previous strategy.\(^1\) We hypothesized that by introducing \(S\) stereogenic centers at the hinge positons of the baskets, the three quinoline gates would adopt unidirectional orientation. As the chirality of the twisted basket platform does not affect the chirality of the gates, we, in this study, use the twisted basket possessing a clockwise \((M)\) twist only.

3.2 Metal-mediated control of axial/propeller chirality in organic molecules

Chiral ligands have been used extensively in asymmetric synthesis and catalysis, as well as supramolecular chemistry due to their ability to create an asymmetric environment around the metal center.\(^{121}\) The coordination geometry of metal·ligand complex determines
the shape and asymmetric environment around the metal center where the reaction occurs. Therefore, it is important to be able to control the coordination geometry of ligands when bound to a metal center in order to achieve high asymmetric induction to the reaction substrates. $C_3$-symmetric chiral ligands have shown great potential for chiral recognition and enantioselective reactions.\textsuperscript{125,126,127,128} The ligand tris(pyridylmethyl)-amine (TPA) have been used extensively in the coordination chemistry of metal such as copper and iron.\textsuperscript{129} The coordination of the nitrogen pyridines in TPA to a metal provides a propeller-like, $C_3$-symmetric complex display. The attempt to control the direction of the propeller twist, by way of the generation of coordination complexes with highly asymmetric environment, was achieved by placing sterically bulky substituents on one arm of the ligand (Figure 3.1).\textsuperscript{121}

![Figure 3.1. The chemical structure of the tripodal Tris(2-pyridylmethyl)amine Derivative Bn-CDPy3 (left) and the ORTEP diagram of its complex with Co(I) (right).](image)

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In this vein, the Badjic group has utilized this existing strategy to control the twist of the $C_3$ symmetric gates that are located on top of the molecular basket’s cavity. Silver (I) was shown to mediate the folding of the three pyridine gates situated on top of basket 3.1 (Figure 3.2a). The gates were brought together by the coordination of the nitrogen pyridine to the Ag(I) at the middle on top of the cavity and arranged themselves in a propeller-like geometry with either a (−) or (+) sense of twist (Figure 3.2b). The racemic conformations were suggested by the Density functional theory (DFT, BP86 functional) calculation which showed a low activation barrier of the interconversion between $[\text{Ag(I)} \subset 3.1]^P$ and $[\text{Ag(I)} \subset 3.1]^M$ (2.7 kcal mol$^{-1}$), as well as the low temperature $^1$H NMR experiment that showed a complete coalescence of $H_e/H_f$ signals, even at 183 K ($\text{CD}_2\text{Cl}_2/\text{CD}_3\text{OD}$, 9:1) (Figure 3.2b).

![Figure 3.2](image.png)

Figure 3.2. a) The chemical structure of basket 3.1. b) Energy minimized (DFT, BP86) conformations of $[\text{Ag(I)} \subset 3.1]^P$ and $[\text{Ag(I)} \subset 3.1]^M$; calculated potential energy diagram for $[\text{Ag(I)} \subset 3.1]^P$ and $[\text{Ag(I)} \subset 3.1]^M$ interconversion via synchronized rotation of pyridine flaps about their N-C-C-C dihedral angle.
In order to obtain predominantly one twisted enantiomer, a CH(CH)₃ stereogenic center was introduced to the hinge positions of basket 3.1, creating either basket (R₃)-3.2 or basket (S₃)-3.2 (Figure 3.3). In line with the previous report of TPA ligands, the alkyl substituents at the hinge positions successfully directed the twisting of pyridine rings in which R configuration in Ag(I)-(R₃)-3.2 controlled the twisting of the pyridine rings in a clockwise (+) orientation, while S configuration in Ag(I)-(S₃)-3.2 controlled the twisting of the pyridine ring in a counterclockwise (–) orientation (Figure 3.3). The absolute configuration of the gates was determined using ECCD method. A series of ECCD spectra obtained from incremental addition of Ag(I) to a solution of basket (R₃)-3.2 (Figure 3.4) showed an enhanced positive cotton effect at 260 nm, suggesting the induction of chirality to the quinoline gates in a clockwise (+) fashion. On the other hand, the titration of Ag(I) to (S₃)-3.2 gave the ECCD spectra having a negative cotton effect at 260 nm, indicating the counterclockwise (–) orientation of the quinoline gates. The DFT (RI-BHLYP/SV(P),TZVP) geometry optimizations of Ag(I)-(R₃)-1 are in agreement with the experimental data in which the clockwise (+) diastereomer is more stable (ΔE = 6.6 kcal mol⁻¹) than the corresponding counterclockwise (–) orientation.
Figure 3.3. The chemical structure of basket (R$_3$)-3.2 and DFT energy minimized structures (RI-BHLYP/SV(P),TZVP) of two conformational diastereomers [Ag(I)–(R$_3$)-3.2]$^M$ and [Ag(I)–(R$_3$)-3.2]$^P$.

\[^{124}\]
In order to expand the scope of the gating property in molecular baskets, we sought out to examine the coordination of Cu(II) to basket \((S_3)-3.3\) that possesses three quinoline gates at the rim (Figure 3.5). The ECCD spectra collected upon incremental addition of (0.1-4.0 molar equivalents) of Cu(BF\(_4\))\(_2\cdot6\)H\(_2\)O (Figure 3.6b) showed that the basket \((S_3)-3.3\) was capable of binding to Cu(II). In line with the earlier study, the coordination of Cu(II) to the quinoline gates in \((S_3)-3.3\) directed the chromophores in a counterclockwise
(−) twist as evidenced by an increased negative excitonic couplet centered at 239 nm with the incremental addition of Cu(BF₄)₂·6H₂O. The negative CD couplet observed originated from the interaction through space of the transition electric moment (λ ≈ 233 nm) of the quinoline chromophores (Figure 3.6a). The coordination geometry of Cu(II)-(S₃)-3.3 complexe was predicted by geometry minimizations, with DFT at the RI-BHLYP/SV(P),TZVP level of theory, and thus the square-pyramidal complex B was shown to have a greater thermodynamic stability (2.0 kcal mol⁻¹) than the trigonal bipyramidal complex A (Figure 3.7b). In an agreement with the calculation, the EPR spectrum of Cu(II) (d⁹ electronic state, S = ½), within the Cu(II)-(S₃)-3.3 complex revealed a normal/axial EPR signature with g‖ = 2.31 > g┴ = 2.07 and A‖ = 166 G (Figure 3.7a), suggesting the sole formation of complex B in solution.

Figure 3.5. The chemical structure of basket (S₃)-3.3.
Figure 3.6. a) The interaction of the transition electric moments from the quinoline arms should give a negative ECCD couplet in Cu(II)-(S₃)-3.3. b) Circular dichroism spectra of (S₃)-3.3 (2.63 mM) obtained upon an incremental addition (0.1–4.0 molar equivalents) of Cu(BF₄)₂·6H₂O.

Figure 3.7. a) EPR spectrum of square-pyramidal complex Cu(II)⊂(S₃)-3.3 in CH₃CN at 77 K. b) Five-coordinate complexes A and B (M=Cu²⁺) were energy minimized with density functional theory (RI-BHLYP/SV(P), TZVP) to reveal a greater thermodynamic stability of square-pyramidal B.
3.3 Experimental design and the preparation of (S)-quinoline gated twisted basket

Upon obtaining enantiopure (M)-1 by following the strategy established in chapter 1, (S)-1-(quinolin-3-yl)ethan-1-amine was coupled to tris-anhydride intermediate generated in situ from the reaction of the hydrolyzed (carboxylic acid) form of (M)-1 in acetic acid at 110 °C (Figure 3.8). The resulting (S3, M)-15 (Figure 3.8) was then studied by ECCD in order to investigate the effect of the S stereogenic centers at the basket’s hinges to direct the helical orientation of the quinoline gates. ¹H-NMR and ¹H-¹H NOESY was used to study the self-folding properties of the gates. The assembled structure of (S3, M)-15 was also studied by TEM, SEM and DLS.

Figure 3.8. The scheme represents the synthesis of basket (S3, M)-15.
3.4. The folding of (S)-quinoline gated basket and the chirality transfer

The CD spectrum of (S₃, M)-15 in acetonitrile showed a positive CD couplet centered at 271.5 nm which at a shorter wavelength showed a negative cotton effect centered at 261 nm ($\Delta \varepsilon = -108 \text{ M}^{-1} \text{ cm}^{-1}$) and a longer wavelength showed a positive cotton effect centered at 282 nm ($\Delta \varepsilon = 36 \text{ M}^{-1} \text{ cm}^{-1}$). (red spectrum, Figure 3.9b) The CD spectrum originated from the interaction of $\pi$-$\pi^*$ transition dipole moments of naphthalimide chromophores about their long axis and situated in the clockwise (M) fashion. In addition, the CD spectrum revealed a negative CD couplet centered approximately at 239 nm which at a shorter wavelength showed a positive cotton effect at 228.5 nm and a longer wavelength was overlapped with the CD signal of naphthalene chromophores. Importantly, this additional CD bisignate signature was missing in the CD specturm of (P)-13 (blue spectrum, Figure 3.9b) whose hinge positions are achiral. According to the previous study by Stojanovic, et al.,¹ the CD couplet centered at 239 nm is in the area corresponding to quinoline chromophores whose transition electric moment at $\lambda = 233 \text{ nm}$ ($\varepsilon = 57,000 \text{ M}^{-1} \text{ cm}^{-1}$)¹ was prominent in the UV-Vis spectrum (Figure 3.9a). This means that the quinoline gates at the rim of (S₃, M)-15 preferably folded in a counterclockwise (−) helical orientation and thus the introduction of S stereogenic centers at the hinge positons of (S₃, M)-15 proved to direct the orientation of the gates!
Figure 3.9. UV-Vis (a) and circular dichroism (b) spectra of enantiopure \((S_3, M)-15\) in CH\textsubscript{3}CN (blue, 13.26 \(\mu\)M) and the inverse spectrum of \((P)-13\) in CH\textsubscript{3}CN (red, 15.5 \(\mu\)M) at 298.0 K.

In earlier study\(^1\), three quinoline gates at the rim of basket \((S_3)-3.3\) folded in a propeller like orientation by coordinating their nitrogen atoms to Cu(II) (Figure 3.7). To additionally probe the folding characteristics of \((S_3, M)-15\), we titrated a standard solution of Cu\((\text{BF}_4)\)\(_2\cdot6\text{H}_2\text{O}\) to the solution of \((S_3, M)-15\) in acetonitrile and followed its folding property using CD spectroscopy (Figure 3.10). Importantly, the enhancement of the molar ellipticity of quinoline chromophores at \(\lambda = 228.5\) nm was observed with the incremental addition of Cu\((\text{BF}_4)\)\(_2\cdot6\text{H}_2\text{O}\) until one equivalent was reached (\(\Delta\varepsilon = 40\ \text{M}^{-1}\ \text{cm}^{-1}\)) (Figure

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The pronounced positive cotton effect at a shorter wavelength of bisignate CD couplet belonging to the quinoline chromophores suggested that \((S_3, M)-15\) is capable of binding to Cu(II) in acetonitrile and its corresponding Cu(II) \(\subset (S_3, M)-15\) complexes adopted a counterclockwise \((-\)\) propeller-like conformation of quinoline gates at a higher population compared to the self-folded \((S_3, M)-15\). This means the coordination of Cu(II) to the nitrogen atom of quinoline gates in \((S_3, M)-15\) results in more stable folded conformation processing a counterclockwise \((-\)\) propeller-like conformation of the gates. The CD binding isotherm (Figure 3.11) suggested the formation of a 1:1 coordination complex.

![CD binding isotherm](image)

Figure 3.10. Selected circular dichroism spectra of \((S_3, M)-15\) (13.26 \(\mu\)M) obtained upon an incremental addition (0.1–1.0 molar equivalents) of Cu(BF\(_4\))\(_2\) \(\cdot\) 6H\(_2\)O.
Figure 3.11. A change in molar circular dichroism $\Delta \Delta \varepsilon$ (M$^{-1}$ cm$^{-1}$) of a solution of $(S_3, M)$-15 (13.26 $\mu$M) upon an incremental addition (0.1–1.0 molar equivalents) of Cu(BF$_4$)$_2$·6H$_2$O in acetonitrile at 228.5 nm, 261 nm, and 282 nm (the sigmoidal curve is drawn to guide the eye).

3.5 The assembly of $(S)$-quinoline gated basket in organic solvents

Compared to the quinoline twisted basket $(P)$-13, basket $(S_3, M)$-15 which has additional stereogenic moieties at the hinge positions maintained the capability to assemble in nanosized vesicles in organic media. (Figure 3.12) This was evidenced by dynamic light scattering (DLS) and electron microscopy measurements. The aggregated vesicles of $(S_3, M)$-15 in dichloromethane was measured to have hydrodynamic radii centered at $\sim$ 360 nm (Figure 3.12a, PDI = 0.37). In acetonitrile, the aggregated size of vesicle is a little bit
smaller with size distribution centered at ~ 320 nm (Figure 3.12b, PDI = 0.40). The addition of Cu(II) into the solution of (\(S_3, M\))-15 in acetonitrile did not result in significantly change in the size of aggregated vesicle. Cu(II)⊂(\(S_3, M\))-15 in acetonitrile gave vesicles with hydrodynamic radii centered ~ 315 nm (Figure 3.12c, PDI = 0.67).

Figure 3.12. Size distribution of a) 44.2 μM (\(S_3, M\))-15 in CD\(_2\)Cl\(_2\) b) 44.2 μM (\(S_3, M\))-15 in CD\(_3\)CN and c) 44.2 μM Cu(II)⊂(\(S_3, M\))-15 in CD\(_3\)CN was obtained from dynamic light scattering measurements at 298.0 K. a) Transmission electron microscopy (TEM) image of (\(S_3, M\))-15 (44.2 mM in CH\(_2\)Cl\(_2\)) deposited on a copper grid and stained with uranyl acetate. Scanning electron microscopy (SEM) images of b) (\(S_3, M\))-15 (44.2 μM in CD\(_3\)CN) and c) Cu(II)⊂(\(S_3, M\))-15 (44.2 μM in CD\(_3\)CN) deposited on a silicon wafer and coated with gold.
Figure 3.12. Size distribution of a) 44.2 µM (S₃, M)-15 in CD₂Cl₂ b) 44.2 µM (S₃, M)-15 in CD₃CN and c) 44.2 µM Cu(II)⊂(S₃, M)-15 in CD₃CN was obtained from dynamic light scattering measurements at 298.0 K. a) Transmission electron microscopy (TEM) image of (S₃, M)-15 (44.2 µM in CH₂Cl₂) deposited on a copper grid and stained with uranyl acetate. Scanning electron microscopy (SEM) images of b) (S₃, M)-15 (44.2 µM in CD₃CN) and c) Cu(II)⊂(S₃, M)-15 (44.2 µM in CD₃CN) deposited on a silicon wafer and coated with gold (contd)

3.6 Conclusion

The twisted basket possessing quinoline gates with additional stereogenic centers at the hinge positions still maintained their self-folding property. The twisting of quinoline gates at the rim of basket (S₃, M)-15 successfully directed a counterclockwise (−) orientation when a S stereogenic alkyl center was introduced at the hinge positions. Moreover, the coordination of Cu(II) to quinoline nitrogens of (S₃, M)-15 resulted in Cu(II)⊂(S₃, M)-15 complexes whose population were prone to have a counterclockwise (−) conformation at the quinoline gates more than that of self-folded (S₃, M)-15. This is to say, the folding property of (S₃, M)-15 increases in the presence of Cu(II). The resulting
dynamic chirality at the northern rim, the existing static chirality at the southern rim, along with the dynamic chirality enhancement when bound to Cu(II) make molecular capsule type \((S_3, M)-15\) a potential catalyst in asymmetric conjugate addition reactions such as the Diels-Alder reaction, and Michael addition. Additionally, \((S_3, M)-15\) was shown to assemble into vesicles in both acetonitrile and dichloromethane. Its assembled structure still maintained after complexation with Cu(II) in acetonitrile. It would be interesting to investigate the effect of the basket’s aggregation state on catalysis in the future.
Chapter 4: On the Transfer of Chirality, Thermodynamic Stability, and Folding Characteristics of Stereoisomeric Gated Baskets

This chapter was adopted from: Hu, L.; Polen, S.; Hardin, A. M.; Pratumyot, Y.; Hadad, C. M.; Badjić, J. D. On the Transfer of Chirality, Thermodynamic Stability, and Folding Characteristics of Stereoisomeric Gated Baskets. European J. Org. Chem. 2015. 31, 6832–6840. Reproduced in part with permission. My contribution to this publication was a part of synthesis. In addition, a recent result about the folding of enantiopure basket was also incorporated.

4.1 Background and Significance

A precise tuning of the lifetime of supramolecular complexes\textsuperscript{130,131} is of interest for developing drug delivery systems\textsuperscript{132} with desired pharmacokinetic profiles,\textsuperscript{133,134} sequestering important substances,\textsuperscript{135,136} improving the efficiency of supramolecular catalysts,\textsuperscript{137,138,139} and controlling the outcome of parallel chemical reactions.\textsuperscript{89} Correspondingly, the persistence\textsuperscript{140} of encapsulation complexes\textsuperscript{141} has been found to rely on 1) the conformational dynamics of hosts\textsuperscript{142,143} and 2) the lability of self-assembled capsules.\textsuperscript{144,145} A dynamic change in the structure of concave hosts\textsuperscript{146,147} could create an aperture for permitting the trafficking of guests to and from their inner space. Thus, regulating the dynamics\textsuperscript{148,149} of encapsulation complexes by means of so-called gating\textsuperscript{96,150} could tune the length of time of a guest entrapped in the cavity.\textsuperscript{61} Indeed, gated
molecular baskets of the type \(18 (V = 226 \text{ Å}^3, \text{Figure 4.2a})\), with three amidopyridine gates at the rim, were designed in our laboratory to form a seam of intramolecular N–H···N hydrogen bonds.\(^{60}\) The disruption of these noncovalent contacts, characterized by an activation energy of about 10 kcal/mol,\(^{57,151}\) permits the substitution of solvent residing inside the basket’s cavity by a guest molecule from bulk solution.\(^{152}\) Accordingly, tuning the strength of the N–H···N hydrogen bonds in \(18\) by varying the electronic and steric characteristics of the amide’s R substituents (Figure 4.2a) enabled us to modulate the dynamics of the gates and therefore the time of the encapsulated guests in the basket.\(^{61}\) A rather low persistence (\(t_{1/2} \approx 1\) s or less at 250.0 K) of \([18 \subset \text{guest}]\) complexes, however, prevented us from 1) examining their utility in polar (aqueous) solvents,\(^{153,154,155,156}\) 2) controlling the outcome of chemical reactions,\(^{89}\) and 3) resolving enantiomeric guests.\(^{51}\) To further expand the scope of these gated hosts, we became interested in designing other baskets\(^{137,57}\) and investigating their mechanism of action as well as their dynamic characteristics.\(^{95}\) In that vein, we hereby describe the preparation of the deep \((V = 355 \text{ Å}^3)\)\(^{102}\) and stereoisomeric basket \((P/M)-17\) (Figure 4.2b). This gated host bears amidopyridine gates, as in \(18\) (Figure 4.2a), although attached to a larger bicyclo[3.2.1] platform possessing either \(P\) or \(M\) chirality (Figure 4.2b).\(^{99}\) We synthesized racemic \((P/M)-17\) and later on enantiopure \((P)-17\) and then showed that, in organic solvents, this concave compound forms a sizeable \(C_3\)-symmetric capsule (Figure 4.2b) with a unidirectional seam of three N–H···N hydrogen bonds.\(^{157,158}\) Interestingly, the
amidopyridine gates of \((P/M)-17\) remain folded at 104 °C in o-xylene without forming an appreciable quantity of unfolded state(s).

### 4.2 Experimental design and the preparation of amidopyridine gated basket

First, racemic basket \((P/M)-17\) was obtained by the base-promoted hydrolysis of the racemic hexa-ester \((P/M)-1\), followed by the condensation of the resulting hexa-acid product with amine 16 in acetic acid (Figure 4.1 and Figure 5.4). The folding characteristics of \((P/M)-17\) was investigated by NMR and density functional theory was used to predict the favorable stereoisomeric conformation of the basket. In order to better understand the transfer of chirality from the basket platform to amidopyridine gates in \((P/M)-17\), we ought to probe the folding of enantiopure \((P)-17\) using NMR and ECCD. The synthesis of enantiopure \((P)-17\) was carried out using enantiopure \((P)-1\) (follow the synthetic procedures in chapter 1) instead of racemic \((P/M)-1\) and then followed the same procedures as to obtained \((P/M)-17\).

### 4.3 The folding characteristic of amidopyridine gated basket

The \(^1\)H NMR spectrum (600 MHz, 298.0 K) of racemic \((P/M)-17\) in CDCl₃ shows a single set of resonances corresponding to a \(C_3\)-symmetric molecule (Figure 4.1). The \(^1\)H NMR signals were assigned with the assistance of cross-correlations in the two-
dimensional $^1$H-$^1$H COSY (Figure A.9), $^{13}$C-$^1$H HSQC (Figure A.10), and $^1$H-$^1$H NOESY NMR (Figure A.11) spectroscopic measurements. Notably, a large downfield shift of the N–H resonance ($\delta = 11.4$ ppm, Figure 4.1) suggests the formation of N–H···N hydrogen bonds, and is consistent with the single IR vibrational stretch of the hydrogen-bonded N–H at 3056 cm$^{-1}$ observed for ($P/M$)-17 in CD$_2$Cl$_2$ (Figure A12). The $^1$H NMR singlet arising from N–H was, furthermore, only slightly perturbed within a fifty-fold concentration range of ($P/M$)-17 (0.1–5.0 mm, Figure 4.1), which denotes the absence of complex intermolecular equilibria and the predominant formation of intramolecular aggregates in solution.
Figure 4.1. Basket (P/M)-17 obtained from racemic hexa-ester (P/M)-1 in an overall yield of 38% (top). $^1$H NMR spectrum (600 MHz, 298.0 K) of (P/M)-17 in CDCl$_3$ (middle). A small upfield shift of N–H resonances occurs upon 50-fold dilution (top to bottom) of a 5.0 mM CDCl$_3$ solution of (P/M)-17 (bottom).
In fact, diffusion-ordered NMR spectroscopic measurements (DOSY, see Figure A16) of a 1.25–5.0 mm solution of (P/M)-17 in CDCl₃ at 298K revealed that the apparent diffusion coefficient is relatively unaffected by concentration \( D_{\text{app}} = 5.2 - 6.3 \times 10^{-10} \text{m}^2/\text{s} \), see Table A.1), corresponding to an average hydrodynamic radius of \( R_{\text{H}} = 7.1 \ \text{Å} \). Because the radius of energy-minimized (P/M)-17 (ca. 7.6 Å, Figure 4.2b) is commensurate with this value, we deduced that the basket stays monomeric in CDCl₃ with its amidopyridine gates forming intramolecular N–H···N hydrogen bonds (Figure 4.2b). Given that (P/M)-17 is larger than 18 (Figure 4.2), the formation of hydrogen bonds came as a surprise because the amidopyridine gates should reside at a greater distance from one another (Table 4.1).

Table 4.1 Structural parameters for baskets (P)-17(+), (P)-17(−), and 18 in the gas phase. The results are shown as an arithmetic mean of the three values obtained from energy-minimized and \( C_1 \)-symmetric structures (M06-2X/6-31G*).

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<td>(P)-17(+)</td>
<td>0</td>
<td>2.997</td>
<td>159.340</td>
<td>9.705</td>
<td>2.453</td>
</tr>
<tr>
<td>(P)-17(−)</td>
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<td>2.990</td>
<td>158.912</td>
<td>9.548</td>
<td>2.436</td>
</tr>
<tr>
<td>18</td>
<td>n/a</td>
<td>2.975</td>
<td>157.907</td>
<td>8.983</td>
<td>2.492</td>
</tr>
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Figure 4.2. a) Energy-minimized structure of basket 18 (M06-2X/6-31G*) showing a seam of N–H···N hydrogen bonds at its rim. b) Energy-minimized structure of basket (P)-17 (M06-2X/6-31G*) in its folded (top) and unfolded form (bottom). In the unfolded state(s), the intramolecular N–H···N hydrogen bonds are absent with the amidopyridine gates undergoing a stochastic motion about $\chi_1$ and $\chi_2$ torsions. (Bottom) A coloured representation (Chimera) of the van der Waals surface of basket (P)-17, which has a diameter of around 1.6 nm and a spacious and chiral inner space (ca. 355 Å$^3$).
Importantly, the seam of hydrogen bonds could assume a clockwise (+) or counterclockwise (−) orientation at the basket’s rim (Figure 4.3).\textsuperscript{60} It follows that two conformational diastereomers \((P)-17(+)\) and \((P)-17(−)\), in addition to their enantiomers \((M)-17(−)\) and \((M)-17(+)\), should form in solution and primarily interconvert by rotation of the amidopyridine gates about the \(\chi^2\) torsion (Figure 4.2b). In accord with this hypothesis, we observe that the resonances corresponding to the \(\mathrm{H}_6/\mathrm{H}_8\) protons (from \(\mathrm{CH}_2\) groups, Figure 4.3) of folded \((P/M)-17\) give rise to an AB quartet at 298.0 K \((\delta = 4.80\ \text{ppm}, \text{Figure 4.1})\). This particular \(^1\text{H}\) NMR spectroscopic signature could, however, correspond to the formation of either one or both stereoisomeric pairs \((P)-17(+)/(M)-17(−)\) or \((P)-17(−)/(M)-17(+)\) (Figure 4.3), depending on their interconversion rate and population (see below: Figure 4.3).

To address this question, we recorded variable temperature \(^1\text{H}\) NMR spectra of \((P/M)-17\) in \(\text{CD}_2\text{Cl}_2\) (Figure 4.4a). Interestingly, lowering the temperature of the \(\text{CD}_2\text{Cl}_2\) solution of \((P/M)-17\) did not lead to the expected decoalescence of its \(^1\text{H}\) NMR signals: The AB quartet experienced increased line-broadening and the resonances corresponding to the aromatic protons shifted to a variable degree (Figure 4.4a). The absence of a prominent change in the AB quartet (193–298.0 K) with temperature is in line with the exclusive formation of either \((P)-17(+)/(M)-17(−)\) or \((P)-17(−)/(M)-17(+)\),\textsuperscript{51} that is, the existence of both stereoisomeric pairs should give rise to two AB quartets in the slow \(^1\text{H}\) NMR exchange regime, which does not correspond to our experimental observation,
Figure 4.3. Top views of energy-minimized baskets \((P)-17(+) / (M)-17(−)\) and \((P)-17(−) / (M)-17(+)\), with each enantiomeric pair forming a seam of intramolecular N–H···N hydrogen bonds.

(Figure 4.4a). With one stereoisomeric pair dominating the mixture, however, one would expect to observe a single AB quartet in both the slow and fast \(^1\)H NMR exchange regime, slightly changing as the interconversion rate varies. This particular scenario is in agreement with our observations and is also supported by dynamic NMR simulations (gNMR software\(^{161}\) of diastereotopic \(\text{CH}_2\) protons residing in different magnetic environments and described by two exchanging AB quartets. An apparent \(^1\)H NMR shift of aromatic and N–H resonances (Figure 4.4a) could be due to a rearrangement of solvent within the concave structure of the basket, as well as to some structural adjustments of the framework at lower
temperatures.

![H NMR spectra](image)

Figure 4.4. a) Variable-temperature $^1$H NMR spectra (600 MHz, CD$_2$Cl$_2$) of (P/M)-17. b) Variable-temperature $^{13}$C NMR spectra (150 MHz, CDCl$_3$) of basket 18 (left) and (P/M)-17 (right) showing $^{13}$C resonances corresponding to imide C=O groups.

Next, we recorded the $^{13}$C NMR spectra of baskets 18 and (P/M)-17 in CDCl$_3$ at 243.0 and 298.0K (Figure 4.4b). The hypothesis was that two carbon atoms, constituting six imide C=O groups within C$_3$-symmetric (P)-17(+) and (P)-17(−) (Figure 3), ought to reside in magnetically different environments. Thus, if both stereoisomers were present, there should be two pairs of $^{13}$C signals corresponding to the imide C=O groups given a slow exchange of stereoisomers on the $^{13}$C NMR timescale. In the fast exchange regime,
however, one would expect a pair of $^{13}$C signals shifting with temperature as the ratio of the two diastereomers changed. Basket ($P/M$)-17 exhibits two well-resolved $^{13}$C singlets for the imide C=O groups at both higher and lower temperatures at $\delta = 166.8$ and 167.3 ppm (Figure 4.4b). The appearance of only two $^{13}$C resonances having identical chemical shifts in the 55 K temperature range suggests the exclusive presence of a single stereoisomeric pair in solution: ($P$)-17(+)/(M)-17(−) or ($P$)-17(−)/(M)-17(+) (Figure 3). In contrast, the $^{13}$C NMR spectrum of basket 18 (Figure 4.2a) reveals two imide $^{13}$C resonances at 243.0 K and only one resonance at 298.0 K (Figure 4.4b). This indicates that the rate of interconversion between equally populated conformational enantiomers of basket 18, comprising amidopyridine gates residing in clockwise or counterclockwise (−) orientations at the rim, must change appreciably within the 55 K temperature range for it to be observed by NMR spectroscopy.$^{60}$ In conclusion, the experimental results are in line with the twisted framework of gated basket ($P/M$)-17 acting as a chiral auxiliary and transferring the stereochemical information to the gates at the rim by forcing them to assume a unidirectional, clockwise (+) or counterclockwise (−), orientation.$^{1}$ The remaining question, though, was which diastereomeric pair is more stable, ($P$)-17(+)/(M)-17(−) or ($P$)-17(−)/(M)-17(+)?

To probe the chirality transfer in ($P/M$)-17, we used density functional theory at the M06-2X/6-31G* level of theory to study ($P$)-17(+) and ($P$)-17(−) in the gas phase. The calculations indicate that basket ($P$)-17(−) is more stable than ($P$)-17(+) ($\Delta E_p = 1.07$
kcal/mol, Table 4.1), with the corresponding Boltzmann distribution ratio being around 0.9:0.1 at 298 K. The computed structural parameters of these two hosts are comparable (Table 4.1) with \((P)-17(-)\) having shorter N–H···N hydrogen-bonding contacts \([\Delta(N–H···N) = 0.007 \, \text{Å}, \text{Table 4.1}]\) and C–H···π contacts \([\Delta(C–H···π) = 0.017 \, \text{Å}, \text{Table 4.1}]\) between \(H_i\) of each amidopyridine gate and a benzene group from the juxtaposed gate (Figure 4.3).\(^{163}\) Presumably, the attractive noncovalent interactions between the atoms of \((P)-17(-)\) bring about a contraction of the naphthalimide side-walls \([\Delta(\text{imide N···N}) = 0.157 \, \text{Å}, \text{Table 4.1}]\). Because two diastereomeric concave hosts hold solvent molecules, a variation in the size of their interior could have an effect on the packing of the encapsulated solvents and affect the difference in thermodynamic stability; note that a computational study with explicit solvent molecules presents a challenging task because the positions and numbers of small solvent guests ought to be varied within this already sizeable host. On the basis of the results of the computational study and the relatively small energy differences between the diastereomeric baskets (Table 4.1), we surmise that \((P)-17(-)/(M)-17(+)\) dominate the conformational equilibrium in solution and therefore contribute to the observed \(^1\text{H}/^{13}\text{C} \) NMR spectra at various temperatures.

To probe the thermodynamic stability of folded \((P)-17(-)/(M)-17(+)\) in polar solvents,\(^{154,164}\) we incrementally added strong hydrogen-bond acceptor [D$_8$]DMSO \((\beta_s = 8.9)^{165}\) to the basket dissolved in CDCl$_3$ and monitored the process by \(^1\text{H} \) NMR spectroscopy (Figure 4.5a; see also Figure A.13). The chemical shift of the N–H resonance
moved upfield as the proportion of [D₆]DMSO solvating the amide groups in (P)-17(−)/(M)-17(+) increased (Δδ = 1.90 ppm, Figure 4.5a, b). In addition, the AB quartet corresponding to H₆/H₇ protons coalesced into a singlet (Figure 4.5a). Importantly, it required around 25 vol.-% of [D₆]DMSO to completely break the basket’s N–H···N hydrogen-bonding contacts, thereby attesting to the thermal stability of the folded host (Figure 4.5b); for comparison, basket 18 (Figure 4.2a) also required around 25 vol.-% of [D₆]DMSO for complete solvation of its hydrogen-bonding sites (Figure 4.5b; see also Figure A.14). As a corollary of the strong intramolecular contacts within (P)-17(−)/(M)-17(+), the sigmoidal titration curve (Figure 4.5b) denotes a cooperative unfolding of the basket with a small concentration of intermediate states. The two-state transition is accompanied by a conversion of folded into unfolded forms of the basket, comprising random and rapid rotations of non-interacting and solvated amidopyridine gates (about χ₁ and χ₂ torsions, Figure 4.2b). The proposed model of unfolding of (P)-17(−)/(M)17(+) is supported by a gradual conversion of the AB quartet into a singlet (Figure 4.5a). Thus, the hinge H₆/₇ protons of the unfolded host, having non-interacting amidopyridine gates rotating freely about χ₁/χ₂ torsions (Figure 4.2b), appear as a singlet due to an averaging of the corresponding resonances of the diastereotopic CH₂ protons when in different magnetic environments. Upon gradual addition of [D₆]DMSO to (P)-17(−)/(M)-17(+) (Figure 4.5a), the distance between the two doublets of the AB quartet decreases to give a singlet. We reason that this comes as a result of an increasing population of the unfolded state, which
shows a singlet for the H\textsubscript{s/t} protons, at the expense of the folded state, which shows an AB quartet for the H\textsubscript{s/t} protons, both exchanging rapidly on the \textsuperscript{1}H NMR timescale. As the unidirectional location of the three appended benzene chromophores (shown as mesh-like surfaces in Figure 4.5c) becomes randomized upon the unfolding of the host, there could be potential for turning these artificial hosts into switchable chemical sensors.\textsuperscript{167,168}

Figure 4.5. a) \textsuperscript{1}H NMR spectra (600 MHz, CDCl\textsubscript{3}) of (P)-17(-)/(M)-17(+) (1.90 mm) obtained upon an incremental addition of [D\textsubscript{6}]DMSO at 298.0 K; the quantity of [D\textsubscript{6}]DMSO increases from bottom to top. b) Chemical shift of the N–H resonance of baskets (P)-17(-)/(M)-17(+) (black) and 18 (red) obtained upon an incremental addition of CD\textsubscript{3}SOCD\textsubscript{3} to their 1.90 mM solution in CDCl\textsubscript{3} at 298.0 K. c) Folded and unfolded structures of basket (P)-17(-)/(M)-17(+) showing the different orientations of the side benzene groups.
Figure 4.6. a) Segments of the variable-temperature $^1$H NMR spectra (600 MHz) of a solution of $(P)$-$17(-)/(M)$-$17(+) (2.50 mM) in o-xylene. b) Variable-temperature $^1$H NMR spectra (600 MHz) of a solution of basket $18 (2.50 mM)$ in o-xylene; note that this host is poorly soluble in o-xylene.

Finally, the $^1$H NMR spectra of basket $(P)$-$17(-)/(M)$-$17(+) (2.50 mm)$, dissolved in o-xylene, show a small perturbation of the resonances at higher temperatures (300–377 K, Figure 4.6a; see also Figure A.15). In particular, the N–H signal exhibits an upfield shift ($\Delta \delta = 0.6$ ppm), which suggests a transformation of the basket from the folded into the unfolded form (Figure 4.6a). In addition, the doublets of the AB quartet, which correspond
to the H_{e1} protons in (P)-17(−)/(M)-17(+), maintain their shape as the distance between them decreases (Figure 4.6a). This result is in line with the formation of a small quantity of the unfolded host, thereby attesting to a thermal stability of the stereoisomeric and gated baskets. Similarly, basket 18 (Figure 4.2a) possesses great thermal stability towards unfolding in o-xylene, with a small quantity of unfolded states forming at higher temperatures (Figure 4.6b).

4.4 Probing the chirality transfer within enantiopure amidopyridine basket

On the basis of the experimental study described in the previous section with racemic (P/M)-17, we postulated the existence of chirality transfer within this basket. The twisted framework of (P/M)-17 transferred the stereochemical information to the gates at the rim by driving them to adopt a unidirectional, clockwise (+) or counterclockwise (−) orientation. The question remained to which diastereomeric pair would be more favorable, (P)-17(+)/(M)-17(−) or (P)-17(−)/(M)-17(+). In order to answer this question, we synthesized the enantiopure (P)-17 and examined the chirality at the amidopyridine gates of the folded structure using ECCD method.

From the previous study, basket (P/M)-17 was, in dichloromethane, shown to adopt a folded structure, where intramolecular hydrogen bonding of three quinoline gates occurred at two points. The ECCD spectrum of folded (P)-17 in dichloromethane (pink spectrum, Figure 4.7 b) showed a negative CD couplet centered at 272 nm with a negative cotton effect around 281 nm and a positive cotton effect around 262 nm. This electronic transition originated from the interaction of electric transition dipole moments generated.
along the long axis of the naphthalimide chromophores upon absorbing light at about 264 nm, as observed in the UV-Vis spectrum (Figure 4.7a). Comparing the CD spectrum of (P)-17 to the CD spectrum of (P)-13 (yellow spectrum, Figure 4.7b) and (P)-14 (blue spectrum, Figure 4.7b) which both have a CD signal originated from their naphthalimide chromophores but lack a CD couplet generated from their gates, the additional cotton effect at about 290 nm in the CD spectrum of (P)-17 is realized. If this additional CD signal originates from the unidirectional orientation of amidopyridine gates in (P)-17, it should disappear when the basket is unfolded. According to the previous study with (P/M)-17 (section 4.2), a polar solvent [D₆] DMSO was capable of disturbing intramolecular hydrogen bonding at the amidopyridine gates and unfolding the basket. Due to the high UV-cut off of DMSO, a polar solvent trifluoroethanol (TFE) was instead used as a folding antagonist in the ECCD method. The ¹H-NMR spectrum of (P)-17 in dichloromethane showed an AB quartet signal corresponding to H₄/H₅ proton which confirmed the folded conformation of (P)-17 in dichloromethane. Upon increment addition of TFE, that AB quartet coalesced and eventually turned into a singlet at about 25 vol.-% TFE, suggesting a completely unfolded conformation of the basket (Figure 4.8). In addition, the N-H resonance moved upfield with increased addition of TFE (Δε = 2.37 ppm, Figure 4.8). Importantly, similar to what was observed with DMSO, the titration curve (Figure 4.9) indicated that about 25 vol-% of TFE was required to completely break the basket’s N-H···H hydrogen-bonding contacts.
Figure 4.7. a) UV-Vis spectrum of enantiopure \((P)-17\) in \(\text{CH}_2\text{Cl}_2\) (14 \(\mu\)M), b) circular dichroism spectra of \((P)-17\) (pink, 14 \(\mu\)M), \((P)-14\) (blue, 18 \(\mu\)M), and \((P)-13\) (yellow, 13 \(\mu\)M) in \(\text{CH}_2\text{Cl}_2\), as well as \((P)-17\) (black, 11 \(\mu\)M) in 25 vol.-\% TFE in \(\text{CH}_2\text{Cl}_2\).

Figure 4.8. \(^1\text{H}\) NMR spectra (600 MHz, \(\text{CD}_2\text{Cl}_2\)) of \((P)-17\) (3.22 mM) obtained upon an incremental addition of TFE at 298.0 K.
As TFE was shown to act as a hydrogen-bond acceptor to solvate the hydrogen bonding sites and completely unfold the gates of (P)-17, we titrated (P)-17 in CD₂Cl₂ with TFE and followed the gates’ conformation through changes in the CD spectrum. As expected, there is a prominent decreased cotton effect around 290 nm upon incremental addition of TFE (Figure 4.10b). In line with this, UV-Vis spectra showed an increase in $\varepsilon$ at about 285 nm with an increasing proportion of TFE (Figure 4.10a). The observed change in electronic transition in both CD and UV-Vis was due to the change of the amidopyridine gates’ conformation upon unfolding. In addition, in line with the $^1$H NMR titration (Figure 4.9), the CD titration curve (Figure 4.11), showing the change in molar circular dichroism ($\Delta\varepsilon$ (M⁻¹ cm⁻¹)) at 290 nm of (P)-17 upon addition of TFE, demonstrated the requirement of about 25 vol.-% TFE to unfold the basket. In order to obtain the characteristic electronic transition of amidopyridine gates in the folded state, the CD spectrum of (P)-17 in CD₂Cl₂,
which corresponded to its folded conformation, was subtracted from the CD spectrum of 
(P)-17 in 25 vol.-% TFE in CD₂Cl₂, where it was completely unfolded. As a consequence, 
the bisignate ECCD curve centered at 280 nm, possessing a positive cotton effect at longer 
wavelength 290 nm and a negative cotton effect at shorter wavelength 270 nm, was shown 
to be an additional cotton effect upon the folding of (P)-17 (Figure 4.10c). According to 
the semi-empirical exciton chirality rule,⁷⁸ the positive cotton effect value at longer 
wavelength demonstrated the positive chirality. In line with this, the additional cotton 
effect at 290 nm observed with the folded (P)-17 corresponded to the clockwise orientation 
(+) of its amidopyridine gates. This indicated that the counterclockwise twisted framework 
of (P)-17 transferred its chirality to amidopyridine gates by forcing the twist of the gates 
into a clockwise direction. The results obtained from enantiopure basket (P)-17 clearly 
answer the remaining question in section 4.2 that (P/M)-17 adopts an opposite twist at the 
amidopyridine gates, compared to the twist of the basket’s platform; therefore, 
(P)-17(+)/(M)-17(−) is the major population in the solution of (P/M)-17 in 
dichloromethane.
Figure 4.10. a) UV-Vis and b) circular dichroism spectra of (P)-17 (14 µM, 298 K) obtained upon an incremental addition of TFE in CH₂Cl₂, c) a circular dichroism spectrum obtained after subtracting the circular dichroism of (P)-17 in CH₂Cl₂ with that in 25 vol.-% TFE in CD₂Cl₂.
Figure 4.11. The change in molar circular dichroism ($\Delta \varepsilon$) at 290 nm of basket $P$-17 obtained upon an incremental addition of TFE to its solution in CD$_2$Cl$_2$ at 298.0 K.

4.5 Conclusion

The amidopyridine gates of stereoisomeric basket ($P/M$)-17 form a seam of intramolecular N–H···N hydrogen bonds at the rim to enclose space (355 Å$^3$). The twisted platform of this concave host governs the orientation of the hydrogen-bonded gates with computational results suggesting that the $P$-shaped cup sets the gates into a counterclockwise (–) orientation whereas the $M$ platform induces a clockwise (+) orientation. However, the experimental results carried out with enantiopure basket ($P$)-17 (CD spectra) suggested that the $P$ basket’s framework drive the gates to arrange in a clockwise (+) direction! Perhaps the solvent plays a role in stabilizing one conformation of ($P$)-17 over another. The stereoisomeric basket ($P/M$)-17 undergoes a cooperative unfolding of its three amidopyridine gates, with a stochastic movement about the rim, in the presence of the polar solvent [D$_6$]DMSO or CF$_3$CH$_2$OH (TFE) and at high
temperatures. It requires around 25 vol.-% of [D₆]DMSO in CDCl₃ or 25 vol.-% of TFE in CH₂Cl₂/CD₂Cl₂ to promote a complete unfolding of (P/M)-17. Its thermal stability is also very good with a low degree of unfolding at higher temperatures (104 °C). The stage is now set for investigating the relationship between the folding/ dynamic characteristics of novel stereoisomeric baskets and the encapsulation of useful chiral molecules in both polar and nonpolar media with a view to their use in sensor design and catalysis.
Chapter 5: Synthetic Procedures

5.1 General procedures

All chemicals were purchased from commercial sources, and used as received unless stated otherwise. All solvents were dried prior to use according to standard literature protocols. Chromatography purifications were performed with silica gel 60 (Sorbent Technologies 40 – 75 µm, 200 x 400 mesh). Thin-layer chromatography (TLC) was performed with silica-gel plate w/UV254 (200 µm). $^1$H NMR spectra were recorded with Bruker AVIII 600 MHz and Bruker AVIII 850 MHz instruments. $^{13}$C NMR spectra were recorded with AVIII 700 MHz. All NMR spectra were referenced with the appropriate solvent residual signal as an internal standard. NMR samples were prepared with CD$_2$Cl$_2$ and CD$_3$CN solvents that were purchased from Cambridge Isotope Laboratories. The chemical shift values are expressed as δ values (ppm) while coupling constants (J) are given in Hertz (Hz). The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; dd, doublet of doublet t, triplet; qn, quintet; m, multiplet. High-resolution electrospray ionization mass (HRMS-ESI) spectra were recorded on a Bruker Micro-TOF ESI and Bruker 15 Tesla FT-ICR mass spectrometer using a sodium formate solution as an internal standard. Circular Dichroism (CD) measurements were completed.
with JASCO J-815.

5.2 Synthetic procedures

![Synthetic scheme](image)

Figure 5.1. Synthetic scheme for obtaining compound 5.

**Compound 5**: N-bromosuccinimide (11.747 g, 66.6 mmol) and mesitylene (2.783 mL, 20.0 mmol) were added to 150 mL of benzene in a 250 mL round-bottom flask. Azobisisobutyronitrile (821 mg, 5.0 mmol) was added and the reaction was brought to reflux for 10 hours. The reaction was removed from heat and filtered through a pad of silica. The solvent was then removed under reduced pressure and the remaining solid recrystallized (hexanes:dichloromethane = 1:1) to give 4.57 g of 1,3,5-tris(bromomethyl)benzene (79 %) as bright white needles. 1,3,5-tris(bromomethyl)benzene (4.57 g, 15.8 mmol) was suspended in 100 mL of acetone (dried over K$_2$CO$_3$) in a 250 mL round-bottom flask, and to the suspension sodium iodide (8.29 g, 55.3 mmol) was added and stirred at room temperature for one hour. The reaction mixture was then filtered through neutral alumina. The solvent was condensed and the crude solid was recrystallized (hexanes:dichloromethane = 3:2) to yield 3.97 g of 1,3,5-tris(iodomethyl)benzene (87 %) as a white solid, and stored in a flask protected from light.
$^1$H-NMR (400 MHz, CDCl$_3$): 7.25 (3H, s) and 4.37 (6H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): 140.90, 128.92, and 4.23. HRMS (ESI): calculated (M+Na)$^+$ = 520.7731, found: 520.7718.

$\text{Compound 3a:}$ 5-Indanol (10.0 g, 72.5 mmol) was dissolved in 350 mL of dichloromethane in a 500 mL round-bottom flask. The temperature was then lowered to $-95 \, ^\circ \text{C}$ by submersion into a hexanes/liquid nitrogen bath. Following, bromine (3.74 mL, 72.5 mmol) was added dropwise over 2 hours, with manual agitation of the flask due to the solidification of the reaction mixture. After complete addition, the reaction was stirred overnight as it slowly warmed to room temperature. The reaction mixture was extracted with a saturated solution of sodium dithionite (200 mL), followed by water (3 x 200 mL). The organic layer was dried over anhydrous sodium sulfate and removed under reduced pressure to yield 14.1 g (91%) of compound 3a as a clear oil. $^1$H NMR (400 MHz, CDCl$_3$):
7.28 (s, 1H), 6.89 (s, 1H), 5.39 (s, 1H), 2.83 (t, J = 7.4 Hz, 4H), 2.07 (p, J = 7.4 Hz, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): 150.75, 146.14, 138.03, 127.38, 112.17, 107.80, 33.10, 32.28, 26.23. The spectroscopic data are in an agreement with those reported in the literature (see J. Org. Chem. 1993, 58(15), 4023–4032). Note that we also detected a small quantity (~5%) of undesired regioisomer of the product, which was removed in the subsequent reaction.

**Compound 3b:** Compound 3a (14.06 g, 66.0 mmol) was dissolved in 150 mL of anhydrous THF in a 250 mL round-bottom flask equipped with a reflux condenser and drying tube. Following, 14.7 mL (70.0 mmol) of hexamethyldisilazane (HMDS) was added and the reaction mixture was refluxed for 2 hours. After disappearance of the reactants (TLC, SiO2 hexane : ethyl acetate = 5:1), the reaction was removed from heat and the solvent/HMDS removed under reduced pressure (1 torr, 60 ºC for 30 minutes) to yield (6-bromo-2,3-dihydro-1H-inden-5-yl)oxy)trimethylsilane as a colorless oil in quantitative yield. $^1$H NMR (400 MHz, CDCl$_3$): 7.34 (s, 1H), 6.74 (s, 1H), 2.82 (q, J = 7.1 Hz, 4H), 2.07 (p, J = 7.5 Hz, 2H), 0.30 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$): 150.86, 145.11, 138.99, 128.73, 116.92, 113.13, 33.14, 32.39, 26.22, 0.74. ((6-Bromo-2,3-dihydro-1H-inden-5-yl)oxy)trimethylsilane (18.8 g, 66.0 mmol) was dissolved in 150 mL of anhydrous THF in a 250 mL round-bottom flask. The reaction mixture was brought to −95 ºC by submersion into a hexane/liquid N$_2$ bath. Freshly titrated n-BuLi (2.33 M, 66.0 mmol, 28.3 mL) was added slowly, ensuring the temperature remained constant. After addition, the reaction mixture was removed from the cold bath and allowed to warm to approximately −30 ºC. It was resubmersed into a hexanes/liquid N$_2$ bath and stirred for 20 minutes, followed by the
addition of 11.78 mL (70.0 mmol) of trifluoromethanesulfonic anhydride. The reaction was removed from the cold bath and stirred for an additional 10 minutes, followed by the addition of 15 mL of a saturated sodium bicarbonate solution and 15 minutes of stirring. The reaction was extracted with water (3 x 100 mL). The organic layer was dried over anhydrous sodium sulfate, and condensed to yield a purple oil which was purified via column chromatography (SiO$_2$, hexane) to yield 19.43 g of compound 3b as a colorless oil (87%). $^1$H NMR (400 MHz, CDCl$_3$): 7.36 (s, 1H), 7.20 (s, 1H), 2.93 (dt, $J$ = 13.4, 7.4 Hz, 4H), 2.14 (p, $J$ = 7.5 Hz, 2H), 0.37 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$): 154.29, 148.65, 143.98, 131.68, 129.81, 116.06, 116.04, 33.42, 32.49, 26.06, -0.35. The spectroscopic data are in an agreement with those reported in the literature (see J. Org. Chem. 2014, 79(10), 4757–4762).

**Compound 3c:** To a stirred solution of compound 3b (9.71 g, 28.7 mmol) in 150 mL of anhydrous CH$_3$CN, dimethyl furan-3,4-dicarboxylate (5.29 g, 28.7 mmol) and cesium fluoride (13.1 g, 86.1 mmol) were added. The reaction was placed under argon and stirred for 24 hours. Upon complete disappearance of the reactants (monitored by $^1$H NMR spectroscopy), the reaction mixture was filtered through a pad of silica, with a subsequent wash of acetonitrile (100 mL). The removal of the solvent at a reduced pressure yielded solid compound 3c (8.2g, 23.3 mmol) in a 95% yield, which was used without further purification. $^1$H NMR (400 MHz, CDCl$_3$): 7.28 (s, 2H), 5.90 (s, 2H), 3.80 (s, 6H), 2.83 (t, $J$ = 7.4 Hz, 4H), 2.09 (pd, $J$ = 7.7, 2.1 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): 163.30, 151.80, 145.05, 142.35, 118.45, 85.14, 52.65, 32.82, 25.91. HRMS (ESI): calculated (M+Na)$^+$ = 323.0842, found: 323.0880.
**Compound 2:** TiCl₄ (12.0 mL, 105 mmol) was slowly added to 180 mL of anhydrous THF at 0°C, followed by the addition of Et₃N (6.0 mL, 45.0 mmol) and LiAlH₄ (2.30 g, 60.0 mmol) under argon. The mixture was refluxed for 30 minutes and then allowed to cool to room temperature. A solution of compound 3c (8.2g, 23.3 mmol) in 20 mL of anhydrous THF was added. The reaction mixture was stirred for 2 hours at room temperature and was poured onto ice, followed by the addition of 1.0 M HCl (45 mL), after which the solution was filtered through a filter paper. The solution was extracted with dichloromethane (3 x 150 mL), dried over anhydrous sodium sulfate, filtered, and condensed. The crude product was purified further by column chromatography (SiO₂; hexane : ethyl acetate = 2:1) to yield 6.89 g of compound 2 as a white crystalline solid (85 %). $^1$H NMR (400 MHz, CDCl₃): 8.14 (s, 2H), 7.69 (s, 2H), 3.94 (s, 6H), 3.06 (t, $J = 7.3$ Hz, 4H), 2.15 (p, $J = 7.4$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl₃): 168.81, 147.11, 133.29, 130.05, 127.78, 123.31, 52.91, 33.06, 26.30. HRMS (ESI): calculated (M+Na)$^+$ = 307.0934, found: 307.0941.

**Compound 3:** Compound 2 (6.89 g, 24.2 mmol) was dissolved in 100 mL of benzene with stirring, followed by the addition of N-bromosuccinimide (4.31 g, 24.2 mmol) and azobisisobutyronitrile (198 mg, 1.21 mmol). The reaction was brought to reflux for 2 hours then cooled to room temperature. The solvent was removed under reduced pressure and the crude mixture was re-dissolved in 100 mL toluene, and the temperature raised to 115°C. The $^1$H NMR was checked after ~ 24 hours to determine the degree of conversion, as the reaction typically requires 36 – 48 hours for completion. The reaction mixture was subsequently removed from the heat bath and cooled to room temperature, diluted with 100 mL of toluene, and extracted with water (3 x 100 mL). The organic layer was dried over
anhydrous sodium sulfate, removed under reduced pressure and purified by column chromatography (SiO$_2$; hexanes:ethyl acetate = 2:1) in a dark hood with a foil-protected column to yield 4.32 g of compound 3 as an off-white crystalline solid (67%). $^1$H NMR (400 MHz, CDCl$_3$): 8.27 (s, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.86 (s, 1H), 7.04-7.01 (m, 1H), 6.79-6.76 (m, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.61-3.59 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): 146.87, 144.85, 138.05, 133.53, 132.15, 132.13, 130.59, 130.33, 123.23, 119.58, 77.68, 77.36, 77.04, 52.97, 52.93, 38.80. HRMS (ESI): calculated (M+Na)$^+$ = 305.0784, found: 305.0770.

Figure 5.3. Synthetic scheme for obtaining compounds (M)-11 and (P)-11.
Compounds $4^{RRR/SSS}$ and $4^{RRS/SSR}$: Compound 3 (1.40 g, 5.0 mmol) was added to a flame-dried flask containing 50 mL of anhydrous THF and 2.5 mL of freshly distilled HMPA (distilled from CaH$_2$ at a reduced pressure). The vessel was placed under an atmosphere of argon and cooled to $-78^\circ$C. n-BuLi (2.15 mL, 5.0 mmol; 2.33 M solution in hexane) was added dropwise and the mixture allowed to stir for an additional minute. A solution of 1,3,5-tris(iodomethyl)benzene (416 mg, 0.84 mmol) in 10 mL of anhydrous THF was then added rapidly (at once) and the mixture stirred for an additional 5 minutes. The reaction was quenched with 10 mL of water (at $-78^\circ$C) followed by the addition of 25 mL of ethyl acetate. The organic layer was extracted with 1 M HCl (2 x 25 mL), washed with water (25 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to yield an orange viscous oil. This crude oil was purified by column chromatography (SiO$_2$; hexane:ethyl acetate = 1:1) in a dark hood with a foil-protected column to yield 0.54 g (0.562 mmol, 67 %) of diastereomeric $4^{RRR/SSS}$ and $4^{RRS/SSR}$ in an approximate 1:4 ratio. $^1$H NMR (400 MHz, CDCl$_3$): 8.15 – 7.98 (m, 6H), 7.67 (d, $J = 11.6$ Hz, 3H), 7.60 (d, $J = 3.1$ Hz, 3H), 7.51 (s, 3H), 7.33 (s, 3H), 7.19 (s, 6H), 6.89 – 6.70 (m, 6H), 6.61 (dd, $J = 5.5$, 1.5 Hz, 3H), 6.38 (m, 3H), 6.21 (dd, $J = 5.6$, 2.0 Hz, 3H), 3.91 – 3.78 (m, 18H), 3.76 – 3.62 (m, 3H), 3.13 (m, 6H), 2.77 (m, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$): 171.12, 168.33, 168.25, 147.48, 147.37, 146.09, 146.04, 141.87, 141.72, 139.25, 139.15, 133.40, 133.34, 131.62, 131.51, 130.94, 130.84, 130.09, 129.93, 129.87, 128.39, 128.33, 127.97, 127.91, 127.34, 127.21, 122.54, 122.45, 119.51, 119.42, 77.34, 77.22, 77.02, 76.70, 60.38, 52.58, 52.55, 51.11, 38.07, 21.04, 14.20. HRMS (ESI): calculated (M+Na)$^+$ = 983.3038, found: 983.3023.
**Compound (P/M)-1**<sub>syn</sub>: Methanesulfonic acid (24.0 mL) and dry 1,2-dichloroethane (300 mL) were added to a 500 mL round-bottom flask equipped with a reflux condenser under an atmosphere of argon. The reaction mixture was stirred and heated to 100 °C. Compounds 4<sup>RRR/SSS</sup> and 4<sup>RRS/SSR</sup> (0.421 g, 0.437 mmol) were dissolved in 24 mL of dry 1,2-dichloroethane and added to the reaction mixture at once. After the addition, the reaction was heated for an additional 36 hours. Since some methyl esters would in (P/M)-1<sub>syn</sub> undergo hydrolysis, 50 mL of anhydrous methanol was added and the reaction temperature lowered to 80 °C for an additional two hours. Following, the reaction mixture was cooled, diluted with 150 mL of dichloromethane, and slowly added to a 2-liter beaker with a stirrer containing 50 g of sodium bicarbonate in an ice water solution (500 mL). The organic layer was extracted and washed with water (3 x 100 mL), dried over anhydrous sodium sulfate and condensed to yield a reddish crude oil, which was purified via column chromatography (SiO₂; dichloromethane:ethyl acetate = 10:1) to yield 62 mg (15 %) of racemic (P/M)-1<sub>syn</sub> as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl₃): 8.09 (s, 3H), 7.85 (s, 3H), 7.76 (s, 3H), 7.35 (s, 3H), 4.37 (d, <i>J</i> = 4.4 Hz, 3H), 3.86 (d, <i>J</i> = 14.7 Hz, 18H), 3.77 (t, <i>J</i> = 4.6 Hz, 3H), 3.62 (dd, <i>J</i> = 16.8, 5.7 Hz, 3H), 3.01 (d, <i>J</i> = 16.6 Hz, 3H), 2.60 – 2.51 (m, 3H), 2.14 (d, <i>J</i> = 10.7 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl₃): 168.32, 168.31, 150.09, 148.99, 139.38, 133.40, 133.24, 129.61, 127.70, 127.50, 127.27, 121.81, 120.15, 77.33, 77.22, 77.01, 76.70, 52.51, 52.48, 40.66, 39.96, 39.91, 34.63. HRMS (ESI): calculated (M+Na)<sup>+</sup> = 983.3038, found: 983.3046.

**Compounds (P)-11 and (M)-11**: Titanium isopropoxide (0.10 mL, 0.338 mmol) was added to a flame-dried 10 mL round-bottom flask, followed by addition of (1<sup>R</sup>, 2<sup>S</sup>, 5<sup>R</sup>)(-
)-menthol (1.692 g, 10.081 mmol). The flask was heated to 60 °C under a reduced pressure for 1 hour to remove any residual isopropanol. To such prepared titanium(IV) catalyst 10, racemic \( (P/M) \)-1syn (11 mg, 0.011 mmol) was added and the reaction mixture was placed under an atmosphere of argon. The mixture was heated to 180 °C for 72 hours, followed by cooling to room temperature. To the reaction mixture, 10 mL of ethyl acetate was added followed by 0.25 mL of water after which the mixture was stirred for 5 minutes. The solution was filtered through a filter paper and the resulting solution was removed under reduced pressure. The viscous oil was heated to 150 °C under a reduced pressure (~1 torr) on a Kugelrohr apparatus to remove any excess \((1R, 2S, 5R)\)-(-)-menthol. The crude solid product was purified by column chromatography (SiO\(_2\); hexane:diethyl ether = 2:1) to yield 5.7 mg of two diastereomeric products \((P)-11\) and \((M)-11\) in an approximate 1:1 ratio and 62 % overall yield.

**Compound \((M)-11\) \((R_f = 0.50)\):** \(^1\)H NMR (800 MHz, CDCl\(_3\)): 8.06 (s, 3H), 7.82 (s, 3H), 7.81 (s, 3H), 7.40 (s, 3H), 4.90 (td, \(J = 10.9, 4.3\) Hz, 3H), 4.85 (td, \(J = 10.9, 4.2\) Hz, 3H), 4.37 (d, \(J = 4.4\) Hz, 3H), 3.76 (m, \(J = 4.8\) Hz, 3H), 3.64 (dd, \(J = 16.8, 5.8\) Hz, 3H), 3.04 (d, \(J = 16.7\) Hz, 3H), 2.54 – 2.49 (m, 3H), 2.13 (d, \(J = 10.6\) Hz, 3H), 2.5 – 0.5 (menthol signals).

\(^{13}\)C NMR (200 MHz, CDCl\(_3\)): 14.48, 16.64, 16.86, 21.25, 21.28, 22.44, 22.47, 23.76, 23.86, 26.30, 26.61, 30.06, 31.81, 31.83, 34.71, 34.76, 40.35, 40.67, 40.84, 41.06, 47.48, 47.55, 75.41, 75.59, 120.56, 122.23, 127.70, 128.62, 129.49, 129.60, 129.75, 133.41, 133.56, 139.72, 149.06, 150.23, 166.97, 167.74. HRMS (ESI): calculated (M+Na)\(^+\) = 1729.0628, found: 1729.0596.
**Compound (P)-11 (Rf=0.37):** $^1$H NMR (800 MHz, CDCl$_3$): 8.07 (s, 3H), 7.81 (s, 3H), 7.77 (s, 3H), 7.39 (s, 3H), 4.92 (td, $J = 10.9$, 4.3 Hz, 3H), 4.82 (td, $J = 10.9$, 4.4 Hz, 3H), 4.38 (d, $J = 4.5$ Hz, 3H), 3.77 (m, $J = 4.8$ Hz, 3H), 3.64 (dd, $J = 16.9$, 5.6 Hz, 3H), 3.05 (d, $J = 16.6$ Hz, 3H), 2.57 – 2.40 (m, 3H), 2.13 (d, $J = 10.5$ Hz, 3H), 2.25 – 0.5 (menthol signals)

$^{13}$C NMR (200 MHz, CDCl$_3$) $\delta$ 14.55, 16.60, 16.72, 21.37, 22.45, 23.05, 23.67, 23.84, 26.27, 26.37, 29.72, 30.0, 31.82, 32.28, 34.68, 34.82, 40.35, 40.61, 40.82, 41.07, 47.34, 47.37, 75.63, 75.75, 120.54, 122.20, 127.71, 128.35, 129.36, 129.56, 129.85, 133.45, 133.63, 139.79, 149.05, 150.26, 167.17, 168.13. HRMS (ESI): calculated (M+Na)$^+$ = 1729.0628, found: 1729.0580.

**Compound (P)-1:** Compound (P)-11 (5 mg, 2.93 µmol) and methanesulfonic acid (0.1 mL) were dissolved in 1,2-dichloroethane/methanol (9:1, 3 mL) inside a sealed vessel (10 mL) and under an argon atmosphere. The reaction mixture was heated to 120 °C and stirred for 3 days. Subsequently, the mixture was diluted with 50 mL of dichloromethane, and washed with saturated sodium bicarbonate solution (50 mL). The organic layer was then washed with water (3 x 50 mL) and dried over anhydrous sodium sulfate. Upon the solvent removal (under a reduced pressure), the crude product was purified by column chromatography (SiO$_2$; dichloromethane:ethyl acetate = 4:1) to give 2.36 mg (83.5% yield) of enantiopure (P)-1 as a yellow solid. $^1$H NMR (600 MHz, CDCl$_3$, 298 K): $\delta$ (ppm) = 8.09 (1H, s), 7.85 (1H, s), 7.76 (1H, s), 7.35 (1H, s), 4.37 (1H, d, $J = 4.4$ Hz), 3.88 (3H, s), 3.84 (3H, s), 3.77 (1H, $m, J = 4.9$ Hz), 3.62 (1H, dd, $J = 16.9$, 5.7 Hz), 3.01 (1H, d, $J = 16.6$ Hz), 2.55 (1H, qn, $J = 5.4$ Hz), 2.14 (1H, d, $J = 10.6$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$, 298 K): $\delta$ (ppm) = 168.32, 168.31, 150.09, 148.99, 139.38, 133.40, 133.24, 129.61, 127.70,
127.50, 127.27, 121.81, 120.15, 77.33, 77.22, 77.01, 76.70, 52.51, 52.48, 40.66, 39.96, 39.91, 34.63; HRMS ESI: m/z calcd for C₆₀H₄₈O₁₂: 983.3038 [M + Na]+, found: 983.3046. The procedure for obtaining (M)-I is the same as for (P)-I with the spectroscopic data in full agreement.

**Compound (P)-13:** To a solution of lithium hydroxide (4.46 mg, 105.60 µmol) in water (1.0 mL) was added the solution of enantiopure (P)-I (2.36 mg, 2.46 µmol) in 1.0 mL THF. The reaction mixture was brought to reflux for 2 hours. After cooling to room temperature, the organic solvent was removed under reduced pressure to give crude product in water. The aqueous solution was placed in an ice bath and its pH was adjusted to 1 using 2M HCl to cause the precipitation of yellow solid. The precipitate was washed with water (3 x 5 mL) and dried under the vacuum to give the hydrolyzed (carboxylic acid) form of (P)-13 1.89 mg (87.7% yield). This product (0.43 mg, 0.49 µmol) and 3-aminoquinoline (0.60 mg, 2.4 µmol) were dissolved in 1.0 mL acetic acid and the reaction mixture was heated at 110 °C for 12 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the solid residue was extracted with saturated sodium bicarbonate (20 mL) and dichloromethane (20 mL). The organic layer was washed with water (3 x 20 mL), dried over anhydrous sodium sulfate, condensed and the crude product purified by column chromatography (SiO₂; dichloromethane:methanol = 19:1) to give 0.44 mg (73.55 %) of (P)-13 as a yellow solid. ¹H NMR (600 MHz, CD₂Cl₂, 298 K): δ (ppm) = 8.92 (1H, d, J = 1.5 Hz), 8.17 (1H, s), 8.14 (1H, d, J = 1.9 Hz), 8.01 (1H, d, J = 8.5 Hz), 7.93 (1H, s), 7.93 (1H, s), 7.76 (1H, d, J = 7.8 Hz), 7.66 (1H, ddd, J = 8.46, 6.91, 1.28 Hz), 7.49 (1H, ddd, J = 7.85, 6.84, 1.1 Hz), 7.48 (1H, s), 4.94 (2H, s), 4.38 (1H, d, J = 4.3 Hz), 3.80 (1H, m, J =
\( \delta (\text{ppm}) = 168.06, 168.00, 151.77, 151.54, 150.23, 148.07, 139.51, 135.97, 135.70, 129.91, 129.76, 129.59, 128.18, 128.09, 127.55, 127.36, 127.31, 127.16, 124.73, 124.56, 124.08, 121.36, 41.18, 40.38, 40.20, 39.67, 34.92; \) HRMS ESI: m/z calcd for \( \text{C}_{84}\text{H}_{55}\text{N}_6\text{O}_6 \): 1243.4178 \([\text{M} + \text{H}]^+\),
found: 1243.4006.

**Compound (P)-14:** The hydrolyzed (carboxylic acid) form of \( P-(1) \) (0.43 mg, 0.49 µmol; see the previous procedure) and \( 1\)-aminobutane (40 µL, 0.40 mmol) were dissolved in 1 mL of acetic acid. The reaction mixture was heated at 110 °C for 12 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was extracted with saturated sodium bicarbonate (20 mL) and dichloromethane (20 mL). The organic layer was washed with water (3 x 20 mL), dried over anhydrous sodium sulfate, and after the removal of the solvent (under reduced pressure), the crude product was purified by column chromatography (SiO\(_2\); dichloromethane:methanol = 19:1) to give 0.44 mg (92.6 %) of compound (P)-14 as a yellow solid. \(^1\)H NMR (600 MHz, CDCl\(_3\), 298 K):
\( \delta (\text{ppm}) = 8.14 (1\text{H}, \text{s}), 7.89 (2\text{H}, \text{s}), 7.46 (1\text{H}, \text{s}), 4.40 (1\text{H}, \text{d}, J = 4.6 \text{ Hz}), 3.82 (1\text{H}, \text{m}, J = 4.9 \text{ Hz}), 3.65 (1\text{H}, \text{dd}, J = 12.38, 5.5 \text{ Hz}), 3.63 (2\text{H}, \text{t}, J = 7.4 \text{ Hz}), 3.04 (1\text{H}, \text{d}, J = 16.7 \text{ Hz}), 2.60 (1\text{H}, \text{qn}, J = 5.3 \text{ Hz}), 2.18 (1\text{H}, \text{d}, J = 10.7 \text{ Hz}), 1.60 (2\text{H}, \text{m}) 1.31 (2\text{H}, \text{m}), 0.89 (3\text{H}, \text{t}, J = 7.4 \text{ Hz}); \) \(^{13}\)C NMR (175 MHz, CDCl\(_3\), 298 K):
\( \delta (\text{ppm}) = 168.51, 168.27, 150.62, 149.56, 139.56, 135.78, 135.51, 127.50, 127.43, 124.04, 123.93, 123.57, 121.99, 40.80, 40.05, 38.04, 34.76, 30.75, 29.86, 20.26, 13.78; \) HRMS ESI: m/z calcd for \( \text{C}_{66}\text{H}_{57}\text{N}_3\text{NaO}_6 \): 1010.4140 \([\text{M} + \text{Na}]^+\),
found: 1010.4094.

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**Compound (S₃, M)-15**: The hydrolyzed (carboxylic acid) form of P-(1) (0.50 mg, 0.57 µmol; see the previous procedure) and (S)-1-(quinolin-3-yl)ethan-1-amine (0.98 mg, 5.7 µmol) which obtained by following the literature procedure reported in our earlier study *(Chem. Comm. 2012, 48, 4429-4431)* were placed in a round bottom flask containing 1 mL acetic acid. The reaction was heated at 110°C for 12 hours and then cooled down to room temperature. The solvent was then removed under reduced pressure and the residue was extracted with saturated sodium bicarbonate (20 mL) and dichloromethane (20 mL). The organic layer was washed with water (3 x 20 mL) and dried with anhydrous sodium sulfate. After removing the organic solvent, the remaining crude product was purified by column chromatography (SiO₂; dichloromethane:methanol = 19:1) to give 0.69 mg (94.5 %) of compound (S₃, M)-15 as a yellow solid. ¹H NMR (700 MHz, CD₂Cl₂, 298 K): δ (ppm) = 8.92 (1H, s), 8.26 (1H, s), 8.14 (1H, s), 8.01 (1H, d, J=8.3 Hz), 7.91 (1H, s), 7.87 (1H, s), 7.82 (1H, d, J=7.8 Hz), 7.66 (1H, m, J=7.6 Hz), 7.52 (1H, m, J=14.5 Hz), 7.47 (1H, s), 5.73 (1H, q, J=7.2 Hz), 4.37 (1H, d, J=4.3 Hz), 3.79 (1H, m, J=4.7 Hz), 3.63 (1H, d, J=5.6 Hz), 2.98 (1H, m, J=16.5 Hz), 2.55 (1H, d, J=10.8 Hz), 2.13 (1H, d, J=10.6 Hz), 1.95 (3H, d, J=7.3 Hz); ¹³C NMR (175 MHz, CD₂Cl₂, 298 K): δ (ppm) = 168.13, 168.05, 151.65, 151.00, 150.14, 147.98, 139.53, 136.00, 135.77, 134.37, 133.56, 129.71, 129.49, 128.37, 128.01, 127.57, 127.34, 127.18, 127.12, 124.55, 124.31, 124.03, 121.36, 47.76, 41.16, 40.37, 40.22, 34.91, 30.10; HRMS ESI: m/z calcd for C₈₇H₆₀N₆NaO₆: 1284.46 [M + Na]⁺, found: 1284.50.
Compound 16: Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), bidentate Xantphos ligand (18 mg, 0.03 mmol), and Cs$_2$CO$_3$ (180 mg, 0.56 mmol) were added to a solution of benzamide 16a (59 mg, 0.48 mmol) and 5-bromonicotinonitrile 16b (74 mg, 0.40 mmol) in dioxane. The reaction mixture was heated at reflux for 2 h, after which the solvent was removed in vacuo.

The crude product was purified by column chromatography (SiO$_2$, hexane/ethyl acetate, 3:2) to give intermediate 16c as a white solid (80 mg, 90%). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 8.22 (d, 1 H), 8.73 (t, 1 H), 8.65 (d, 2 H), 7.94 (s, 1 H), 7.89 (m, 2 H), 7.63 (m, 1 H), 7.54 (m, 2 H) ppm. $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 166.17, 147.56, 144.37, 134.97, 133.38, 132.84, 129.66, 129.08, 127.22, 116.28, 110.16 ppm.

Raney nickel (50% in water slurry, 1 mL) was added to a solution of compound 16c (50 mg, 0.22 mmol) in ethanol/NH$_4$OH (5 mL, 1:1). The reaction was stirred under H$_2$ for 10 h, after which it was filtered through Celite and washed with methanol (20 mL). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (CH$_2$Cl$_2$/CH$_3$OH, 6:1, containing 1% aqueous NH$_4$OH) to yield compound 16 as a white solid (37 mg, 74%). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 8.80 (d, 1 H), 8.33 (d, 1 H), 8.28 (t, 1 H) 7.96 (m, 2 H), 7.60 (m, 1 H), 7.53 (m, 2 H), 3.95 (s, 2 H) ppm. $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 167.68, 143.68, 140.50, 136.53, 136.04, 134.19, 133.38, 132.84, 129.66, 129.08, 127.22, 116.28, 110.16 ppm.
110.90, 128.34, 128.00, 127.35, 42.08 ppm. HRMS (ESI): calcd. for [M + H]^+ 227.1059; found 227.1062.

**Compound (P/M)-17:** Lithium hydroxide monohydrate (15.0 mg, 0.36 mmol) was added to a solution of hexa-ester (P/M)-1 (8.0 mg, 0.0083 mmol) in THF (0.5 mL) containing H_2O (0.5 mL). The mixture was heated at 80 °C for 2 h. THF was then removed under reduced pressure and 2 M HCl was added until the solution was acidic (litmus paper). The resulting solid precipitate was collected by centrifugation and dried under vacuum to give the fully hydrolyzed product as a white solid (7.2 mg). Next, the hexa-acid product (7.2 mg, 0.0083 mmol) was dissolved in glacial acetic acid (1 mL) and compound 16 (18.8 mg, 0.083 mmol) was added. The reaction was heated at 100 °C for 12 h. Acetic acid was then removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL), washed with a saturated aqueous solution of NaHCO_3 (2 x 5 mL) and brine (5 mL), and the organic layer dried with Na_2SO_4. The organic solvent was removed under reduced pressure and the crude product purified by preparative TLC (SiO_2; CH_2Cl_2/CH_3OH, 20:1) to yield compound (P/M)-17 as a white solid (4.6 mg, 38%). ^1H NMR (600 MHz, CDCl_3): δ = 11.38 (s, 1 H), 8.76 (s, 1 H), 8.64 (d, 1 H), 8.06 (s, 1 H), 8.03 (s, 1 H), 8.02 (d, 2 H), 7.78 (d, 1 H), 7.75 (s, 1 H), 7.66 (s, 1 H), 7.56 (t, 1 H), 7.45 (t, 2 H), 7.28 (s, 1 H), 4.82 (d, 1 H), 4.32 (d, 1 H), 3.77 (t, 1 H), 3.57 (dd, 1 H), 2.92 (d, 1 H), 2.59 (m, 1 H), 2.12 (d, 1 H) ppm. ^13C NMR (150 MHz, CDCl_3): δ = 168.03, 167.31, 166.75, 150.50, 149.47, 146.08, 142.08, 139.73, 136.03, 135.96, 135.41, 134.96, 134.21, 132.94, 131.95, 128.63, 128.14, 127.45, 126.90, 126.78, 124.72, 124.19, 123.56, 122.21, 40.61, 39.84, 39.79, 38.82, 34.80 ppm. HRMS (ESI): calcd. for [M + H]^+ 1450.4822; found 1450.4893.
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Appendix A: Supplementary Information

A.1 Supplementary information for chapter 2

Figure A.1. Proton assignment for compound \((P)-13\).
Figure A.2. $^1$H-1H COSY NMR spectrum (600 MHz, CD$_2$Cl$_2$, 298 K) of (P)-13.
Figure A.3. A region of $^1\text{H}^1\text{H}$ COSY NMR spectrum (600 MHz, CD$_2$Cl$_2$, 298 K) of (P)-13 showing the correlations from quinoline resonances.
Figure A.4. $^{1}H-{\textit{1}}H$ NOESY NMR spectrum (600 MHz, CD$_2$Cl$_2$, 298 K) of (P)-13.
Figure A.5. A selected region of $^1$H-$^1$H NOESY NMR spectrum (600 MHz, CD$_2$Cl$_2$, 298 K) of $(P)$-13, showing the correlations of quinoline resonances.
A.2 Supplementary information for chapter 4

Figure A.6. $^1$H NMR spectra (600 MHz) of basket \textbf{18} (5.0 mM) in CDCl$_3$ at 243 K (bottom) and 298 K (top).

Figure A.7. $^{13}$C NMR spectra (125 MHz) of basket \textbf{18} in CDCl$_3$ at 243 K (bottom) and 298 K (top).
Figure A.8. $^1$H NMR spectra (600 MHz, CDCl$_3$, 298 K.) of basket ($P/M$)-17 (the concentration of ($P/M$)-17 decreases from bottom to top: 5.0, 2.5, 1.0, 0.4 and 0.1 mM).

Figure A.9. $^1$H-$^1$H COSY NMR (600 MHz, CDCl$_3$, 298K) spectrum of basket ($P/M$)-17 (5.0 mM).
Figure A.10. Segments of $^1$H-$^{13}$C HSQC NMR spectrum (600 MHz, CDCl$_3$, 298 K) of basket ($P/M$)-17.
Figure A.11. Segments of $^1\text{H}-^1\text{H}$ NOESY NMR spectrum (600 MHz, CDCl$_3$, 298K) of basket ($P/M$)-17 (5.0 mM).
Figure A.12. Segments of FT-IR spectra of baskets 18 (red) and (P/M)-17 (blue), each dissolved in CH$_2$Cl$_2$ at 298 K; note that x axis corresponds to wavenumber (cm$^{-1}$) while y axis denotes transparency (%).
Figure A.13. $^1$H NMR spectra (600 MHz) of basket (P/M)-17 (1.9 mM) in CDCl$_3$ obtained upon an incremental addition of neat CD$_3$SOCD$_3$ at 298 K; note that vol.-% of CD$_3$SOCD$_3$ from bottom to top is: 0, 2.6, 7.5, 13.9, 17.8, 21.3, 22.9, 26.0, 28.8 and 31.5.

Figure A.14. $^1$H NMR spectra (600 MHz) of basket 18 (1.9 mM) in CDCl$_3$ obtained upon an incremental addition of neat CD$_3$SOCD$_3$ at 298 K; note that vol.-% of CD$_3$SOCD$_3$ from bottom to top is: 0, 0.7, 1.4, 4.0, 6.5, 10.1, 13.3, 17.4, 21.9, 25.9, 29.6 and 32.9.
Figure A.15. Variable temperature $^1\text{H}$ NMR spectra (600 MHz) of compound $\text{(P/M)}$-17 (2.5 mM) in o-xylene. Temperature from bottom to top is: 300, 315, 325, 343, 355 and 377 K.
Figure A.16. DOSY NMR spectra (600 MHz, 298 K) of variously concentrated solutions of basket \((P/M)-17\) in CDCl₃: (a) 5.0 mM, (b) 2.5 mM and (c) 1.25 mM.
Table A.1. Diffusion coefficients and hydrodynamic radii of basket ($P/M$)-17 in CDCl$_3$ at 298 K were obtained from DOSY NMR measurements.

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<th>Concentration (mM)</th>
<th>Diffusion coefficient (m$^2$/s)</th>
<th>Hydrodynamic radius (Å)</th>
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<td>6.7</td>
</tr>
<tr>
<td>2.5</td>
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<td>7.7</td>
</tr>
<tr>
<td>1.25</td>
<td>$5.9 \cdot 10^{-10}$</td>
<td>6.8</td>
</tr>
</tbody>
</table>
Appendix B: NMR Spectra

Figure B.1. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 5.
Figure B.2. $^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of compound 5.
Figure B.3. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 2.
Figure B.4. $^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of compound 2.
Figure B.5. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 3.
Figure B.6. $^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of compound 3.
Figure B.7. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of compounds $4^{RRR/SSS}$ and $4^{RRS/SSR}$. 
Figure B.8. $^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of compounds 4$^{RRR/SSS}$ and 4$^{RRS/SSR}$. 
Figure B.9. $^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound ($P/M$)-1$_{syn}$; note that residual solvent is ethyl acetate.
Figure B.10. $^{13}$C NMR (100 MHz, CDCl$_3$) spectrum of compound (P/M)-1$_{syn}$. 
Figure B.11. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) spectrum of compound (M)-11.
Figure B.12. $^{13}$C NMR (150 MHz, CDCl$_3$) spectrum of compound (M)-11.
Figure B.13. $^1$H NMR (400 MHz, CD$_2$Cl$_2$) spectrum of compound $(P)$-11.
Figure B.14. $^{13}$C NMR (200 MHz, CDCl$_3$) spectrum of compound ($P$)-11; note that the residual solvent is ethyl acetate.
Figure B.15. $^1$H NMR spectrum (600 MHz, CDCl$_3$) of compound (P)-1.
Figure B.16. $^1$H NMR spectrum (600 MHz, CD$_2$Cl$_2$) of compound (P)-13.
Figure B.17. $^{13}$C NMR spectrum (175 MHz, CD$_2$Cl$_2$) of compound (P)-13.
Figure B.18. $^1$H NMR spectrum (600 MHz, CDCl$_3$) of compound (P)-14.

Figure B.19. $^{13}$C NMR spectrum (175 MHz, CDCl$_3$) of compound (P)-14.
Figure B.20. $^1$H NMR spectrum (700 MHz, CD$_2$Cl$_2$) of compound (S, M)-15.

Figure B.21. $^{13}$C NMR spectrum (175 MHz, CD$_2$Cl$_2$) of compound (S, M)-15.
Figure B.22. $^1$H NMR spectrum (600 MHz, CDCl$_3$) of compound 16c.
Figure B.23. $^{13}$C NMR spectrum (600 MHz, CDCl$_3$) of compound 16c.

Figure B.24. $^1$H NMR spectrum (600 MHz, CD$_2$Cl$_2$) of compound 16.
Figure B.25. $^{13}$C NMR spectrum (150 MHz, CD$_2$Cl$_2$) of compound 16.

Figure B.26. $^1$H NMR spectrum (150 MHz, CD$_2$Cl$_2$) of compound (P/M)-17.
Figure B.27. $^{13}$C NMR spectrum (125 MHz, CDCl$_3$) of basket (P/M)$^{−}$17.