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The Entrapment of Chiral Guests with Gated Baskets: Can a Kinetic Discrimination of Enantiomers Be Governed through Gating?

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Abstract: The capacity of gated hosts for controlling a kinetic discrimination between stereoisomers is yet to be understood. To conduct corresponding studies, however, one needs to develop chiral, but modular and gated hosts. Accordingly, we used computational (RI-BP86/TZVP//RI-BP86/SV(P)) and experimental (NMR/CD/UV/Vis spectroscopy) methods to examine the transfer of chirality in gated baskets. We found that placing stereocenters of the same kind at the rim ($R^1 = CH_3$, so-called bottom) and/or top amide positions ($R^2 = sec$-butyl) would direct the helical arrangement of the gates into a *P* or *M* propeller-like orientation. With the assistance of ^1H NMR spectroscopy, we quantified the intrinsic (thermodynamic) and constrictive (kinetic) binding affinities of (*R*)- and (*S*)-1,2-dibromopropane **5** toward baskets (S_{3b}/*P*)-**2**, (S_{3t}/*M*)-**3**, and (S_{3bt}/*P*)-**4**. Interestingly, each basket has a low ($|\Delta G°| \leq$ 1.3 kcal mol^{-1}), but comparable ($de <$ 10%) affinity for entrapping enantiomeric (*R*/*S*)-**5**. In terms of the kinetics, basket (S_{3b}/*P*)-**2**, with a set of *S* stereocenters at the bottom and *P* arrangement of the gates, would capture (*R*)-**5** at a faster rate ($k_{in}{}^R/k_{in}{}^S = 2.0 \pm 0.2$). Basket ($S_{3t}$/*M*)-**3**, with a set of *S* centers at the top and *M* arrangement of the gates, however, trapped (*S*)-**5** at a faster rate ($k_{in}{}^R/k_{in}{}^S = 0.30 \pm 0.05$). In light of these findings, basket (S_{3bt}/*P*)-**4**, with a set of *S* stereocenters installed at both top and bottom sites along with a *P* disposition of the gates, was found to have a lower ability to differentiate between enantiomeric (*R*/*S*)-**5** ($k_{in}{}^R/k_{in}{}^S = 0.8$). Evidently, the two sets of stereocenters in this "hybrid" host acted concurrently, each with the opposite effect on the entrapment kinetics. Gated baskets are hereby established to be a prototype for quantifying the kinetic discrimination of enantiomers through gating and elucidating the electronic/steric effects on the process.

Keywords: chirality transfer · encapsulation · equilibrium · kinetics · NMR spectroscopy · stereoselective recognition

Introduction

There has been growing interest in understanding the amplification of chirality within supramolecular systems[1] for applications in separation and materials science,[2] as well as asymmetric catalysis.[3] To transfer chirality, one typically relies on steric and electronic communication[4] between groups in close proximity to a stereocenter, with stereochemical information propagating throughout the entire molecule,[5] and/or dynamic assembly;[2,6] an example of the effective transmission of chiral information in synthetic systems is given by the "sergeants and soldier" principle.[1c] Cavitands with or without a symmetry axis possess so-called inherent chirality[7] (Figure 1A) that may be changed through reversal of their curved surface[8] and/or other dynamic processes.[9] Indeed, the inner space of such concave hosts could serve as a medium for promoting enantioselective reactions[10] or detection of important analytes,[11] although little is known about the principles that guide the chirality transfer or the kinetics/thermodynamics[11b,12] of stereoselective encapsulation in such asymmetric environments. In fact, self-assembled and covalent capsules could differentiate enantiomers, although with poor diastereoselectivity[11b,11f,11g,11k,13] relative to modern standards of asymmetric catalysis. The symmetric characteristics[12a,14] of hosts have been suggested to play a role in the recognition by reducing the number of diastereomeric substrate–host interactions and thereby improving the selectivity. Accordingly, two-[15] and threefold[15c,16] receptors have been employed for differentiating enantiomers. In terms of the stereoselective encapsulation kinetics, however, the characteristics of the host's aperture were claimed to have an effect on the energy of the process.[11b,12b,17] Despite these advances, there is a need to elucidate the details of the stereoselective encapsulation and, in particular, learn about controlling the constrictive (kinetic)[18] and intrinsic (thermodynamic)[19] binding energies that characterize the process.

Our gated baskets regulate the movement of molecules to and from their interior with a set of hydrogen-bonded gates revolving from a *P* to an *M* orientation, and vice versa

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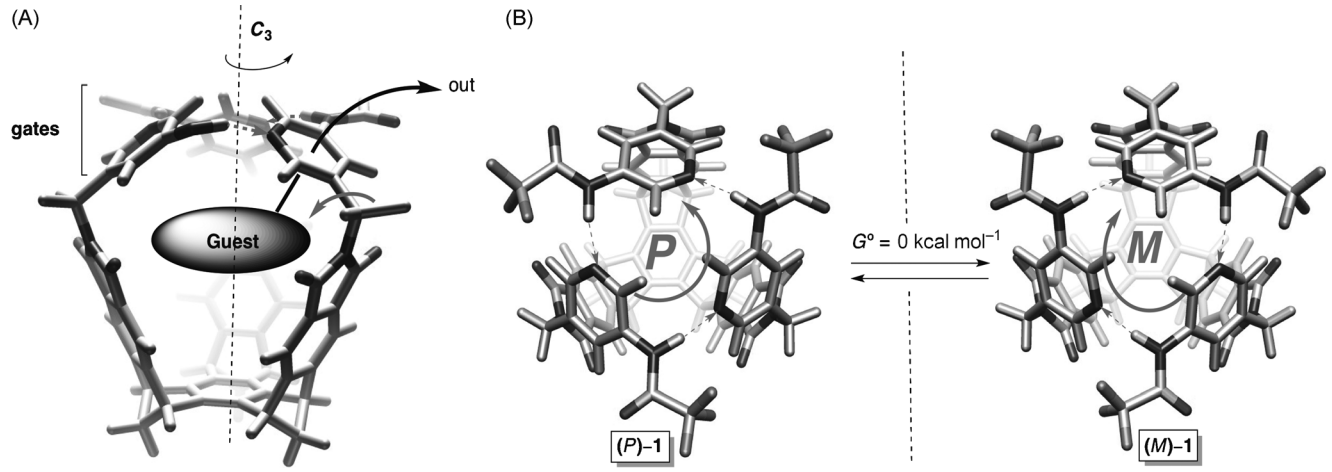

Figure 1. A) Gated molecular baskets are, at the top, lined with three intramolecular hydrogen bonds (dotted arrow) for holding pyridine-based gates. The C_3-symmetric baskets possess inherent chirality, which is switched upon 180° rotation of each gate at the rim (solid arrows). B) Top view of energy minimized (*M*)-**1** and (*P*)-**1** (RI-BP86/SV(P)) forms of basket **1**.

(Figure 1).[20] We have shown that the *P*/*M* racemization is, in this C_3-symmetric system (Figure 1), somewhat synchronized with the in/out transfer of the guest, that is, the gates must assume the "open" state, without internal hydrogen bonding, before the departure/entrance of a guest molecule takes place.[21] The conformational changes in the host, that is, the revolving of the gates, controlling the encapsulation kinetics are referred to as gating.[20a,22] In this vein, we reasoned that by restricting the orientation of the gates to either a *P* or *M* propeller-like form[23] (Figure 1B), the capsule would develop a chiral inner space. Given the modular nature of such a chiral cavitand,[24] an opportunity for investigating the enantioselective encapsulation of guests would arise and, in particular, their kinetic discrimination (the rates by which molecules become entrapped) through gating. Indeed, cryptophans were recently shown[17] to encapsulate one enantiomeric guest at a faster rate than another ($k_{in}^{fast}/k_{in}^{slow} < 2$) with, perhaps, steric strain directing the difference in the measured activation energies, although no form of "gating" was part of the process.[12b,25]

In this study, we utilized computational and experimental methods to investigate the transfer of chirality in baskets **1**–**4** (Figure 2). Next, we measured binding constants (K) and rate coefficients ($k_{in/out}$) that characterize the entrapment and release of the enantiomers of 1,2-dibromopropane by a number of chiral baskets. The utility of the gating process for a kinetic discrimination of enantiomers is yet to be understood, and this study will quantify the phenomenon and then set the stage for elucidating the fine details of the process.

Results and Discussion

Transfer of chirality:

Research hypothesis and nomenclature: Gated basket **1** is, in CD_2Cl_2, a racemic mixture of two C_3-symmetric species in a dynamic equilibrium,[20b] each assuming a left- or right-handed helical orientation of the gates (Figure 1B). On the basis of our earlier studies of metal-containing baskets,[23] we hypothesized that the placement of an alkyl group at the hinge position ($R^1 = CH_3$, Figure 2) could bias the helicity of this system. That is to say, the stereogenic CH_3CH center (*R* or *S*) may force the pyridine gates to adopt either a *P* or *M* orientation. In addition, the placement of stereogenic centers at the amide positions (R^2 = *sec*-butyl, Figure 2) could also have an effect on the orientation of the gates. With this in mind, we synthesized baskets **1**–**4** by following established protocols (Figure 2 and Scheme S1 in the Supporting Information). Basket **1** has no stereogenic centers, whereas (S_{3b})-**2** has three *S* stereogenic groups at the hinge (bottom) positions, compound (S_{3t})-**3** has an *S* stereogenic center at each amide group (top), and basket (S_{3bt})-**4** has three *S* stereocenters at both the bottom and top sites (Figure 2).

*Compound (S_{3b})-**2***: The computed structure of basket (*P*)-**1** (RI-BP86/SV(P), Figure 1B) shows three pyridine gates somewhat shifted to the right, driving one of the "hinge" hydrogen atoms ($\mathbf{H}_I$, Figure 3A) away from the adjacent carbonyl oxygen atom. We surmised that a more sizeable group (CH_3, Figure 3B) would create less van der Waals strain if placed at this particular position (*S* stereocenter), thereby stabilizing the *P* helical stereoisomer. In contrast, through this same mechanism, the substitution of $\mathbf{H}_{II}$ in (*M*)-**1** with a CH_3 group (Figure 3A) should give rise to an *M* helical structure (Figure 3B). Indeed, we computed (RI-BP86/TZVP//RI-BP86/SV(P), Figure 3C) that the (S_{3b}/*P*)-**2** diastereomer is 2.19 kcal mol^{-1} (ΔG at 298.0 K) more stable than (S_{3b}/*M*)-**2**, with CH_3 groups pivoting the three pyridine gates into a right-handed helix (Table 1).

The ^{1}H NMR spectrum of (S_{3b})-**2** in CD_2Cl_2 showed one set of signals corresponding to a C_3-symmetric species (Figure 2). The N–H resonance at approximately 12.15 ppm was shifted downfield, denoting the formation of N–H···N intramolecular hydrogen bonds.[20b] Evidently, there was no

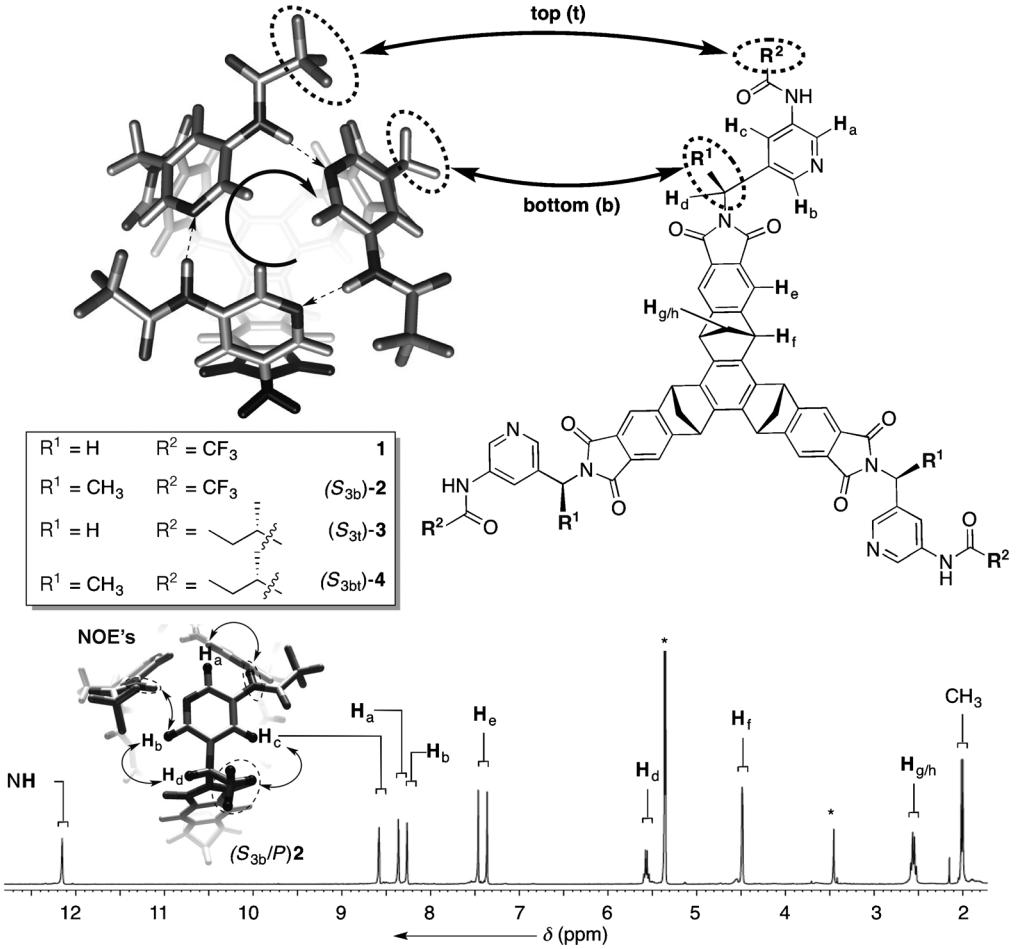

Figure 2. Chemical structure of the four baskets used in this study. Chiral baskets **2**–**4** contain "bottom" (R^1) and/or "top" (R^2) sites, each comprising a stereogenic center. A ^{1}H NMR spectroscopic study of (S_{3b})-**2** (500 MHz, CD_2Cl_2) suggests the exclusive formation of diastereomer (S_{3b}/P)-**2** in solution (see also Figure S1 in the Supporting Information); the * corresponds to the residual signal from methanol used in the preceding chromatographic separation.

Table 1. Computed thermodynamic parameters (RI-BP86/TZVP//RI-BP86/SV(P)) for the interconversion of the *M* and *P* stereoisomers for each basket and the Boltzmann-weighted population [%] of such states at 298 K ($\Delta G_{M/P}$).

Basket	$\Delta H_{M/P}$ [kcal mol^{-1}]	$\Delta G_{M/P}$ [kcal mol^{-1}]	*M* [%]	*P* [%]
(S_{3b})-**2**	−2.72	−2.19	2	98
(S_{3t})-**3**	0.15	−0.40	34	66
(S_{3bt})-**4**	−2.53	−4.06	0	100

decoalescence of the ^{1}H NMR signals at lower temperatures (210.0–300.0 K, Figure S3 in the Supporting Information), suggesting the exclusive formation of either the (*P*)- or (*M*)-diastereomer of (S_{3b})-**2**; note that the racemization of basket **1** has previously been found to occur with a free energy of activation barrier of 10.6 kcal mol^{-1} at 250.0 K.[26] Furthermore, the 2D ^{1}H NMR NOESY spectrum of (S_{3b})-**2** exhibited cross-peaks corresponding to the saturation transfer between N–H/H_a and H_b (from the adjacent ring), CH_3/H_c and H_d/H_b protons (Figure 2 and Figure S1 in the Supporting Information). These protons were computed to reside within 2.70 Å of each other in the (S_{3b}/P)-**2** diastereomer (Figure 3 C). To further verify the formation of (S_{3b}/P)-**2**, we measured the electronic (UV/Vis) and circular dichroism (CD) spectra of this compound in CH_2Cl_2 at 273.0 K (Figure 4). Three prominent Cotton effects were observed at 280 (**I**), 257 (**II**), and 237 nm (**III**).[23b] On the basis of an earlier study,[23b] we formally ascribe band **I** to the pyridine, and transitions **II** and **III** are assigned to the phthalimide chromophores. Importantly, the CD spectrum of (S_{3b})-**2** is akin to the one corresponding to the previously studied Ag^I folded basket containing the *S* stereogenic CH_3CH center at the hinge and the *P* sense of twist of unsubstituted pyridines.[23b] The CD measurements therefore suggested a greater quantity of the *P* basket in the mixture (Figure 3 B), and variable-temperature ^{1}H NMR spectroscopy experiments (Figure S3 in the Supporting Information) revealed a *de* > 95 % for (S_{3b}/P)-**2**.

Compounds (S_{3t})-***3*** *and* (S_{3bt})-***4***: As stated earlier, we were also interested to find whether a set of stereogenic centers at the top of basket (S_{3t})-**3** (Figure 2) would have an effect on the helicity of its pyridine-based stereogenic unit. One

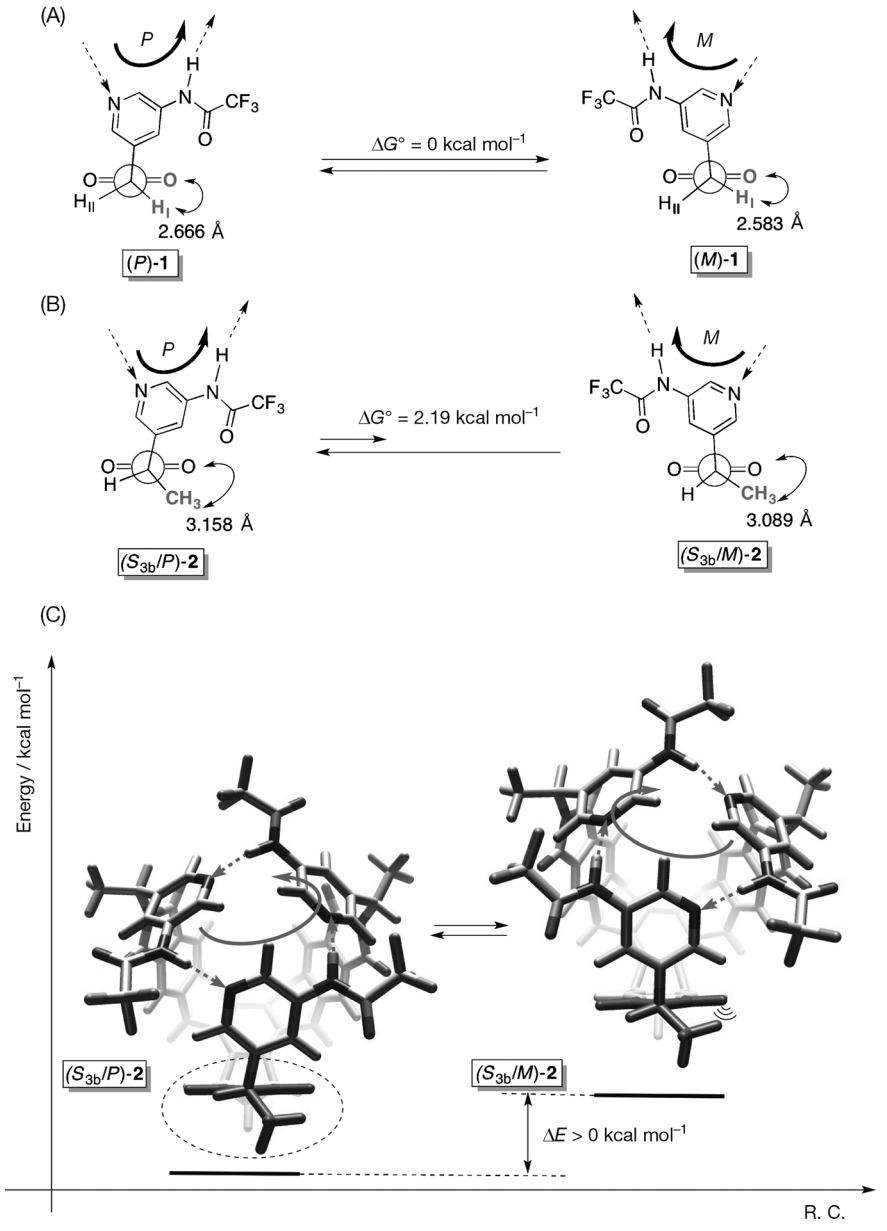

Figure 3. A) Newman projections of *P* (left) and *M* (right) stereoisomeric forms of basket **1**. B) Newman projections of (S_{3b}/*P*)-**2** and (S_{3t}/*M*)-**2** stereoisomeric forms of basket **2**. C) Energy-minimized (DFT: RI-BP86/SV(P)) structures of more-stable (S_{3b}/*P*)-**2** and less-stable (S_{3b}/*M*)-**2** (Table 1).

reason to place *sec*-butyl groups (R^2 = *sec*-butyl, Figure 2) at the amide positions is related to the availability of the proper synthetic precursor ((*S*)-2-methylbutanoic anhydride, see Scheme S1 in the Supporting Information). With the assistance of density functional theory (DFT: RI-BP86/TZVP//RI-BP86/SV(P)), we first computed that diastereomeric baskets (S_{3t}/*P*)-**3** and (S_{3t}/*M*)-**3** are comparable in energy ($\Delta G_{M/P} = -0.4$ kcal mol^{-1} at 298.0 K, Table 1). Variable temperature ^{1}H NMR spectra (400 MHz, 300.0–210.0 K) of (S_{3t})-**3**, however, showed no decoalecence of proton resonances (see Figure S4 in the Supporting Information), whereas the CD spectrum of this compound (Figure 4) suggested an *M* orientation of the pyridine moieties! Evidently, the chirality amplification occurred in this system and the *S* stereogenic centers at the top drove the formation of the (S_{3t}/*M*)-**3** basket. The computational results were not in complete agreement with the experiments as the calculated enthalpy at 298 K indicated only a slight preference for the observed *M*-isomer (0.15 kcal mol^{-1}), whereas the calculated free energy indicated a preference for the *P*-isomer (0.40 kcal mol^{-1}). This discrepancy could be due to a greater degree of freedom of *sec*-butyl moieties and/or a differential solvation effect.

Nevertheless, we examined the chiral characteristics of (S_{3bt})-**4**, having *S* chiral centers at both bottom and top sites (Figure 2). Variable-temperature ^{1}H NMR spectroscopic measurements of (S_{3bt})-**4** in $CDCl_3$ (400 MHz, 210.0–300.0 K) showed the presence of one C_3-symmetric diastereomer at all temperatures (Figure S5 in the Supporting Information), with CD spectroscopic results indicating the formation of the *P* helix (Figure 4). That is to say, diastereomer (*S*$_{3bt}$/*P*)-**4** is now dominating the *P*/*M* equilibrium! Note that the ^{1}H–^{1}H NOESY spectrum of (S_{3bt})-**4** (see Figure S2 in the Supporting Information) was also in line with the formation of (S_{3bt}/*P*)-**4**. In this case, the computational results suggested an effective transfer of chirality with (S_{3bt}/*P*)-**4** being 4.1 kcal mol^{-1} ($\Delta\Delta G$ at 298 K, Table 1) more stable than (S_{3bt}/*M*)-**4**. It appears that the hinge group ($R^1 = CH_3$, Figure 2) takes precedence over the amide unit (R^2 = *sec*-butyl, Figure 2) in setting up the chirality of gated baskets.

Intrinsic binding of 1,2-dibromopropane ((*R*/*S*)-5): Previously, we have shown that numerous haloalkanes or small hydrocarbons ($V < 130$ Å^3) would occupy the inner space of gated baskets ($V = 221 \pm 9$ Å^3).[27] With the goal of investigating the stereoselectivity of such encapsulations, it seemed reasonable to begin our studies with small, but also chiral 1,2-dibromopropane ((*R*/*S*)-**5**, Figure 5 A). This compound

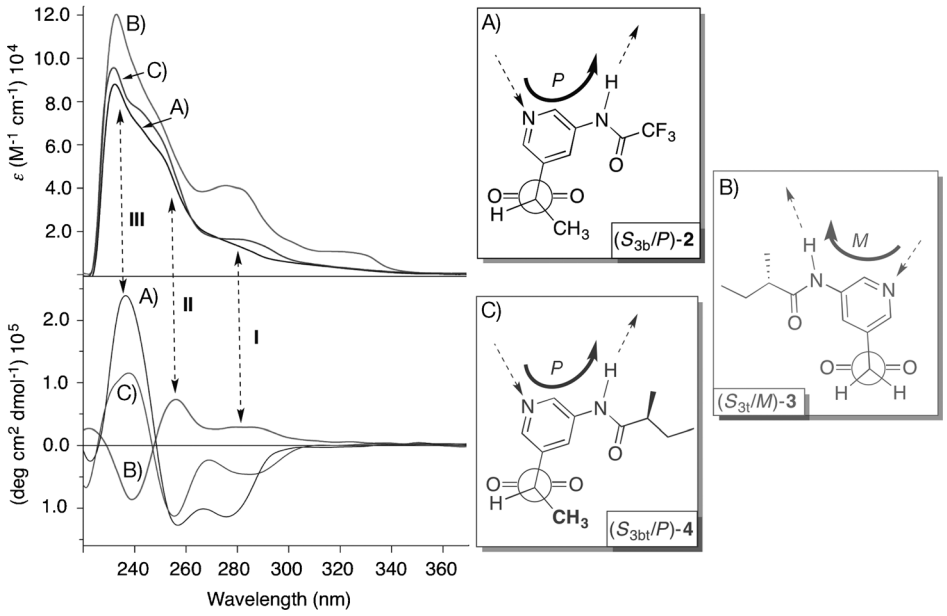

Figure 4. UV/Vis (top) and CD (bottom) spectra of A) (S_{3b}/P)-**2**, B) (S_{3t}/M)-**3**, and C) (S_{3bt}/P)-**4** in CH_2Cl_2 at 273.0 K.

has previously been found[28] to exist in three conformational states, of which the one with the bromine atoms in an antiperiplanar orientation (Figure 5A) is the most stable (population > 65%). Furthermore, the size ($V = 107$ A^3) and shape of (*R*/*S*)-**5** are complementary to the basket's interior (Figure 5A), and each stereoisomeric form of this guest could be prepared from commercially available (*R*)- or (*S*)-2-bromopropanoic acid (see Scheme S2 in the Supporting Information).

When racemic (*R*/*S*)-**5** (244.5 mM) was added to a solution of (*P*/*M*)-**1** (1.63 mM) in CD_2Cl_2, two sets of ^{1}H NMR signals appeared at 200.0 K, corresponding to the guest residing in two different environments (Figure 5B and Figure S6 in the Supporting Information). Since basket **1** is a racemic mixture of *P* and *M* stereoisomers (Figure 3A), we reasoned that two sets of ^{1}H NMR signals concur with the formation of two pairs of diastereomeric complexes: (*P*)-**1**⊂(*R*)-**5**/(*M*)-**1**⊂(*S*)-**5** as the first and (*P*)-**1**⊂(*S*)-**5**/(*M*)-**1**⊂(*R*)-**5** as the second pair (Figure 5B); in this analysis, we assumed rapid rotation of the guest within the host, which CPK models also support. When enantioenriched (*R*)-**5** (*ee* > 85%) was added to (S_{3b}/P)-**2**, only a single set of ^{1}H NMR resonances emerged at $\delta < 0$ ppm (Figure 5C), corresponding to this guest situated within the (S_{3b}/P)-**2** complex ((S_{3b}/P)-**2**⊂(*R*)-**5**; see also Figure S7 in the Supporting Information). Finally, the addition of enantioenriched (*S*)-**5** (*ee* > 85%) to the same basket, (S_{3b}/P)-**2**, led to the formation of (S_{3b}/P)-**2**⊂(*S*)-**5** with a single set of ^{1}H NMR resonances (Figure 5D).

Notably, a distinct set of ^{1}H NMR signals for either (*R*)-**5** or (*S*)-**5** within (S_{3b}/P)-**2** (Figure 5 C/D) denotes two diastereomeric complexes. In fact, these ^{1}H NMR signals can be further correlated with those found in the experiments with the racemic guest (Figure 5B): the doublet corresponding to the CH_3 group in (S_{3b}/P)-**2**⊂(*R*)-**5** at a higher field ($\delta = -2.41$ ppm, Figure 5C) is thus analogous to the CH_3 resonance in (*P*)-**1**⊂(*R*)-**5** ($\delta = -2.39$ ppm, Figure 5B). Thus, we conclude that the *P* basket has a somewhat greater thermodynamic affinity for the *R* stereoisomer of 1,2-dibromopropane (Table 2). The poor stereoselectivity of the recognition ($de \approx 10\%$), however, is not unexpected since the overall affinity of (*R*/*S*)-**5** for occupying the cavity of the basket is small ($|\Delta G°| \leq 0.9$ kcal mol^{-1}, Table 2).[9b,29] In another experiment, ^{1}H NMR chemical shifts of the same *R* guest inside the *M* basket ((S_{3t}/M)-**3**, Figure 5E) were as expected, with the CH_3 signal appearing at a lower field. Interestingly, ^{1}H NMR signals of (*R*)-**5** inside the (S_{3bt}/P)-**4** were broadened and difficult to discern (Figure 5F). We surmise that the hybrid nature of this basket, with two stereocenters having an opposite effect on the *P*/*M* propeller's chirality, could contribute to the formation of a "less-defined" encapsulation environment. The propensity of (*R*/*S*)-**5** for residing in (S_{3t}/M)-**3** and (S_{3bt}/P)-**4** was also small ($|\Delta G°| < 1.3$ kcal mol^{-1}, Table 2), with the encapsulation driven by enthalpy ($\Delta H° < 0$, Table 2). Interestingly, adverse entropy ($\Delta S° \approx -14$ to -17 cal mol^{-1} K) characterized such entrapments with perhaps restricted rotational mobility of the *sec*-butyl moieties and/or solvation effects preventing the complex's formation.

Table 2. Thermodynamic parameters for the encapsulation of (*R*)- and (*S*)-**5** with chiral baskets (CD_2Cl_2) were obtained from variable temperature ^{1}H NMR measurements and the corresponding van't Hoff plots (see Figures S7–S12 in the Supporting Information). The superscript (*R*) or (*S*) in the first column corresponds to the entrapment of (*R*)- or (*S*)-**5**.

Basket	$\Delta H°$ [kcal mol^{-1}]	$\Delta S°$ [cal mol^{-1} K]	$\Delta G°$ [kcal mol^{-1}]
(S_{3b}/P)-**2**$^{(R)}$	-1.72 ± 0.06	-4.0 ± 0.3	-0.92 ± 0.08[a]
(S_{3b}/P)-**2**$^{(S)}$	-1.88 ± 0.06	-5.1 ± 0.3	-0.86 ± 0.06[a]
(S_{3t}/M)-**3**$^{(R)}$	-3.5 ± 0.2	-16.7 ± 0.9	-0.3 ± 0.2[b]
(S_{3t}/M)-**3**$^{(S)}$	-3.5 ± 0.3	-15.9 ± 1.4	-0.5 ± 0.4[b]
(S_{3bt}/P)-**4**$^{(R)}$	-3.7 ± 0.3	-14 ± 1	-1.0 ± 0.3[b]
(S_{3bt}/P)-**4**$^{(S)}$	-4.0 ± 0.3	-14 ± 2	-1.3 ± 0.5[b]

[a] At 200 K. [b] At 189 K.

Constrictive binding of 1,2-dibromopropane ((*R*/*S*)-5): The encapsulation of guests with gated baskets was shown[21] to be first order in both basket and guest ($v_{in} = k_{in}$[basket]-[guest], whereas the departure of guests from the complex

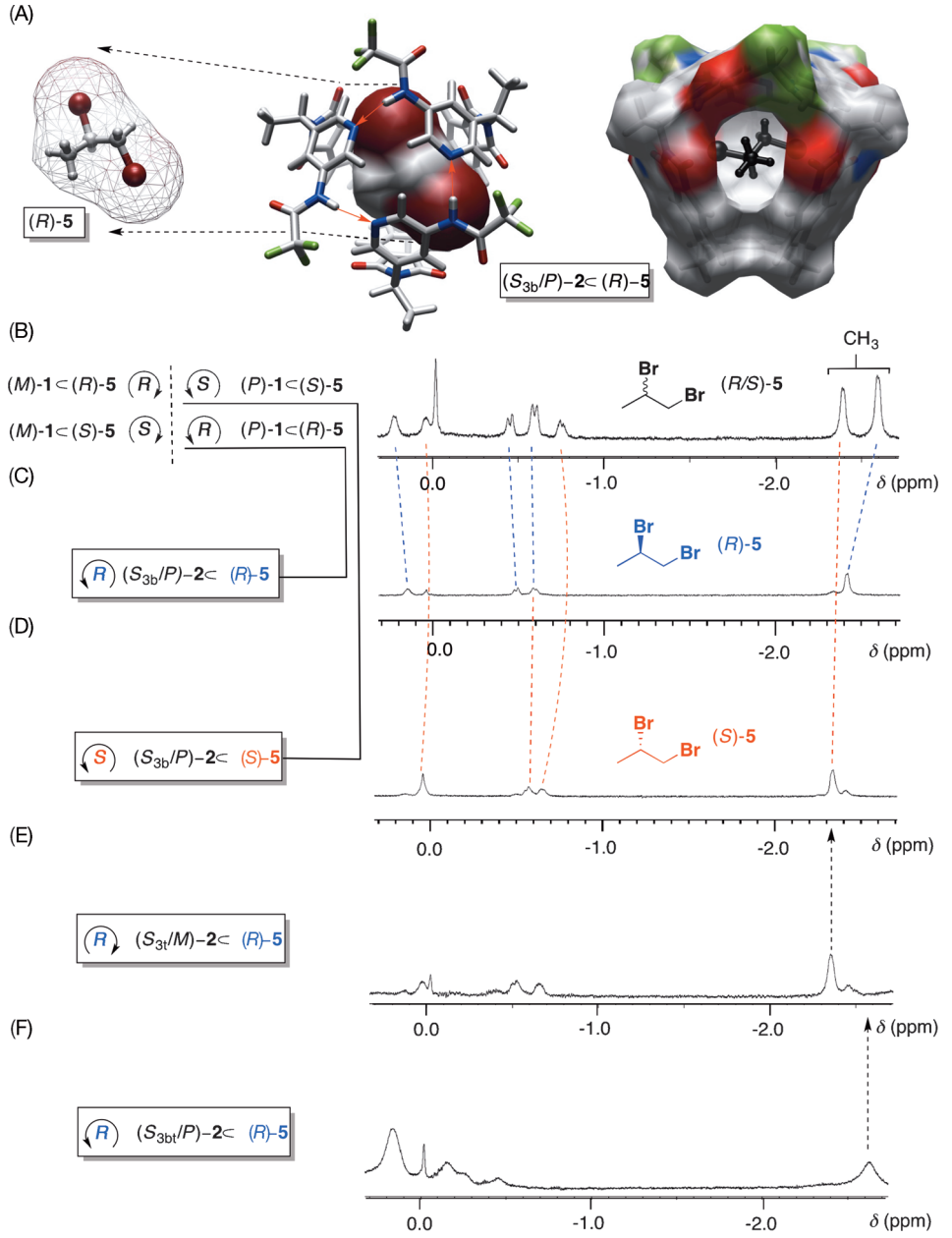

Figure 5. A) Energy-minimized structures of (*R*)-**5** and (S_{3b}/*P*)-**2**⊂(*R*)-**5** complexes (MMFFs, Spartan). B) A region of the ^{1}H NMR spectrum (400 MHz, 200.0 K) of a mixture of (*M*/*P*)-**1** (244.5 mM) and (*R*/*S*)-**5** (1.63 mM), revealing the presence of two diastereomeric complexes. C) A region of the ^{1}H NMR spectrum (400 MHz, 200.0 K) of a mixture of (S_{3b}/*P*)-**2** (3.92 mM) and (*R*)-**5** (62.7 mM), with signals corresponding to the (S_{3b}/*P*)-**2**⊂(*R*)-**5** complex. D) A region of the ^{1}H NMR spectrum (400 MHz, 200.0 K) of a mixture of (S_{3b}/*P*)-**2** (3.92 mM) and (*S*)-**5** (74.5 mM), with signals corresponding to the (S_{3b}/*P*)-**2**⊂(*S*)-**5** complex. E) A region of the ^{1}H NMR spectrum (400 MHz, 189.0 K) of a mixture of (S_{3t}/*M*)-**3** (3.34 mM) and (*S*)-**5** (734.8 mM), with signals corresponding to the (S_{3t}/*M*)-**3**⊂(*S*)-**5** complex. F) A region of the ^{1}H NMR spectrum (400 MHz, 189.0 K) of a mixture of (S_{3bt}/*P*)-**4** (5.04 mM) and (*R*)-**5** (302.4 mM), with signals corresponding to the (S_{3bt}/*P*)-**4**⊂(*S*)-**5** complex. For spectra in C, D, and E one can observe the presence of a small quantity of another diastereomeric complex as the guests were not enantiomerically pure (*ee* > 85 %).

was zeroth order in the guest ($v_{out} = k_{out}$[basket⊂guest]). In accord with this rate law, the basket "opens" its three aromatic gates, upon disruption of the internal hydrogen bonding, for guests to enter/exit its inner space.[30] The *P*/*M* revolving of the gates (Figure 3) could, to some extent, also occur without the in/out exchange of the entrapped compound.[21] For chiral baskets, however, the orientation of the gates is predominantly *P* or *M*. Presumably, the opening of such a basket is best described with the unidirectional motion of the gates starting from the most dominant stereoisomeric form as it is populated most of the time (Figure 6). That is to say, guests are expected to enter/exit the basket as the gates progress from the principal *P* or *M* stereoisomeric state. With two enantiomeric guests, this should lead to the formation of diastereomeric transition states, each with different free energies of activation ($\Delta G^{\ddagger}_{in/out}$, Figure 6) characterizing the process. Will chiral baskets (S_{3b}/*P*)-**2**, (S_{3t}/*M*)-**3**, and (S_{3bt}/*P*)-**4** have the capacity to kinetically discriminate between (*R*/*S*)-**5** despite a comparable thermodynamic affinity of the two enantiomers for occupying their interior? Since the thermodynamic stability of all host–guest complexes was low ($\Delta G°$, Table 2), we had to use an excess of guests to observe the encapsulation with ^{1}H NMR spectroscopy. This, in turn, required selective-inversion-transfer ^{1}H NMR methodology[31] to determine rate coefficients $k_{in}^{R/S}$ and $k_{out}^{R/S}$ characterizing (*R*/*S*)-**5** entering/exiting the (S_{3b}/*P*)-**2**, (S_{3t}/*M*)-**3**, and (S_{3bt}/*P*)-**4** baskets (Table 3, for more details see the Supporting Information). Importantly, at such high concentrations of (*R*/*S*)-**5**, there was an intense T_1 noise signal in the ^{1}H NMR EXSY spectrum of the mixture, thereby preventing an accurate determination of the rates with this methodology.[21] Hence, in this study, we can only compare the rates of guests entering baskets ($k_{in}^{R/S}$, Table 3) because the starting ground states are equivalent in energy (Figure 6). In fact, the constrictive decomplexation energies ($\Delta G^{\ddagger}_{out}$) comprise a contribution from the intrinsic binding ($\Delta G°$) making any comparison ambiguous and therefore difficult to analyze.

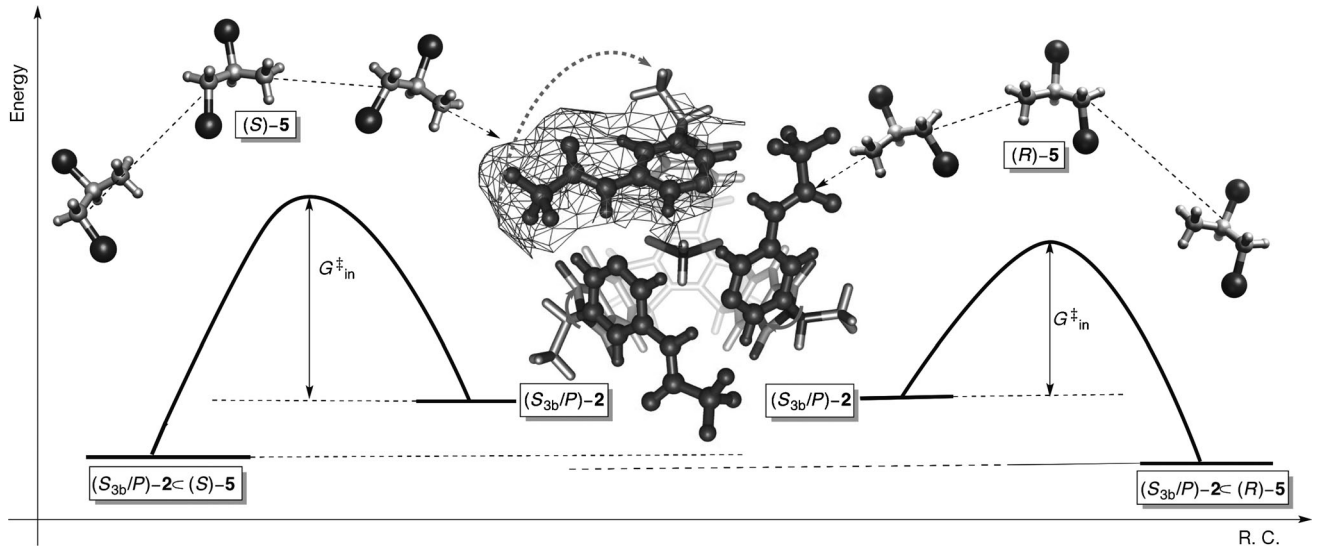

Figure 6. Energy-minimized structure of (S_{3b}/*P*)-**2** (RI-BP86/SV(P)) containing a molecule of CH_2Cl_2. The unidirectional opening of the basket will lead to the entrapment of enantiomeric (*R*)-**5** and (*S*)-**5**; the corresponding transition states are thus expected to be diastereomeric, and with different barriers of activation.

Table 3. Kinetic parameters for the entrapment/release of (*R*)-**5** (k_{in}^{R}, k_{out}^{R}) and (*S*)-**5** (k_{in}^{S}, k_{out}^{S}) with chiral baskets were obtained from ^{1}H NMR selective-inversion-transfer measurements (see Figure S13–S18 in the Supporting Information).[a]

Basket	k_{in}^{R} [$M^{-1}s^{-1}$]	k_{out}^{R} [s^{-1}]	k_{in}^{S} [$M^{-1}s^{-1}$]	k_{out}^{S} [s^{-1}]	k_{in}^{R}/k_{in}^{S}	k_{out}^{R}/k_{out}^{S}
(S_{3b}/*P*)-**2**	46±1	8.3±0.5	23±2	7.7±0.4	2.0±0.2	1.1±0.1
(S_{3t}/*M*)-**3**	4.6±0.6	17±1	15.5±1.3	19.7±0.3	0.30±0.05	0.86±0.05
(S_{3bt}/*P*)-**4**	56±3	28±3	81±4	29.5±0.5	0.70±0.04	0.95±0.02

[a] Spectral data for (S_{3b}/*P*)-**2** were collected at 200.0 K, whereas for (S_{3t}/*M*)-**3** and (S_{3bt}/*P*)-**4**, 189.0 K was used.

On the basis of our earlier studies, there should be a linear relationship between $\Delta G°$ and $\Delta G^{\neq}_{in}$ describing the encapsulation of isosteric guests;[30] thus the greater the intrinsic binding energy ($\Delta G°$) the faster the encapsulation ($\Delta G^{\neq}_{in}$). Interestingly, we found that compound (*R*)-**5** ($\Delta G° = -0.92 \pm 0.08$) enters basket ($S_{3b}$/*P*)-**2** twice as fast as (*S*)-**5** ($\Delta G° = -0.86 \pm 0.06$; $k_{in}^{R}/k_{in}^{S} = 2.0 \pm 0.2$, Table 3). That is, the *P* basket has a greater kinetic affinity toward the *R* stereoisomer of 1,2-dibromopropane. With (S_{3t}/*M*)-**3**, however, we found that the (*S*)-**5** guest enters the host at a faster rate ($k_{in}^{R}/k_{in}^{S} = 0.30 \pm 0.05$, Table 3). In this case, the *M* basket has a greater kinetic affinity toward the *S* stereoisomer of 1,2-dibromopropane.

Evidently, chiral and gated baskets discriminate between the enantiomers of **5** ($\Delta\Delta G^{\neq}_{in}{}^{(R/S)} = 0.3$ to 0.5 kcal mol^{-1}) regardless of their similar thermodynamic propensity ($\Delta G^{\circ(R/S)} = 0.06$ to 0.20 kcal mol^{-1}) for occupying the cavity of such dynamic hosts. The effect is noteworthy because basket **1** has a much poorer ability to differentiate between isosteric bromoalkanes; for five guests with a range of thermodynamic affinities ($\Delta\Delta G°$) of 2.83 kcal mol^{-1}, we found a relatively small difference in the encapsulation rates $\Delta\Delta G^{\neq}_{in} = 0.3$ kcal mol^{-1}![26] Furthermore, the unidirectional orientation of the aromatic gates at the basket's rim must be playing a role in governing the stereoselectivity of the transfer, with the *P* basket favoring (*S*)-**5**, and the *M* basket favoring the (*R*)-**5** enantiomer. This is reasonable because the two transition states for the encapsulation can, perhaps, be described as nearly "enantiomeric" in character. Basket (S_{3bt}/*P*)-**4** encompasses two stereocenters and is, in a way, a hybrid of the first two hosts, although with the *P* arrangement of the gates. On the basis of such a *P* disposition, we expected a greater kinetic/thermodynamic affinity for the (*R*)-**5** guest. However, the rate coefficients for the entrapment of enantiomeric guests turned out to be comparable ($k_{in}^{R}/k_{in}^{S} = 0.70 \pm 0.04$, Table 3), with the proportion k_{in}^{R}/k_{in}^{S} falling in comparison to those characterizing the other two hosts ($k_{in}^{R}/k_{in}^{S} = 0.30 \pm 0.05$ to 2.0 ± 0.2, Table 3). Thus, the "hybrid basket" acts as a composite host with two sets of spatially separated stereocenters operating simultaneously and having an opposite effect on the recognition event. In other words, the bottom (*S*)-CH*CH_3 center promotes the formation of the *P* basket and the encapsulation of the *R* guest, whereas the top (*S*)-$CH(CH_3)CH_2CH_3$ unit acts in the opposite way by assisting the entrapment of the *S* guest. Working together, the two centers imposed a modest kinetic/thermodynamic preference toward the *S* guest. Clearly, stereocenters at the amide functionality, in addition to the gates, are important for tuning the kinetics (Table 2) and thermodynamics (Table 3) of gated encapsulation. The results are encouraging because additional modifications of the steric characteristics[11b,17] of the amide moieties or even alterations to the bulk solvent[32] should lead to a greater kinetic selectivity k_{in}^{R}/k_{in}^{S}, which could be quantified with linear free energy relationships.

Conclusion

Gated molecular baskets can be transformed into chiral hosts by incorporating stereogenic[25] centers at the hinge (bottom) or amide (top) positions. Both stereocenters are important for directing the *P* or *M* helical disposition of the pyridine gates, and the bottom site seemingly dominates the process. Chiral baskets encapsulate enantiomeric 1,2-dibromopropane such that the orientation of the gates and the nature of the top amide functionality have an effect on the kinetic stereoselectivity. Notably, the stereodifferentiation of enantiomers is small ($k_{in}^{fast}/k_{in}^{slow} \approx 3.3$), but manageable. That is to say, governing a kinetic differentiation of stereoisomers with gated hosts should, in this environment, be possible by varying the steric and electronic characteristics of the top amide functionalities.

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