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An Acid-Catalyzed Cyclialkylation that Provides Rapid Access to a Twisted Molecular Basket

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Dedicated to Professor Leo Paquette

The inspiration for creating molecules with concave topology[1] comes from nature in which chemical processes are conducted in confined environments. In the early eighties,[2] D. J. Cram noted a paucity of synthetic compounds possessing a cavity and contemplated about the potential of encircling a guest species with such hosts. In the years that followed, numerous studies of various cavitands[3] as well as self-assembled capsules[4] have shown some benefits of molecular encapsulation. For example, 1) the modulation of the outcome of chemical reactions,[5] 2) the enhancement of the persistence of unstable reactive intermediates,[6] and 3) the control of the conformational dynamics of molecules.[7] In spite of much advancement in the area,[8] the utility of cavity-containing compounds for routine separation,[9] sensing,[10] and catalysis[11] remains limited. We suggest that cavitands with useful topological features and functionalities are still difficult to come by,[12] which impedes the expansion of the field into more practical areas of science.[13] Although one can use the tools of kinetic and thermodynamic templation for preparing capsules,[14] there are often other reactions competing with the desired macrocyclization. In this vein, our report delineates an effective macrocyclization strategy that can be used for the rapid preparation of hosts resembling gated molecular baskets.[15] In particular, we have used methods of experimental and computational chemistry for investigating the formation of cup-shaped $\mathbf{1}_{syn}$ possessing a twisted framework and chiral inner space (Figure 1).

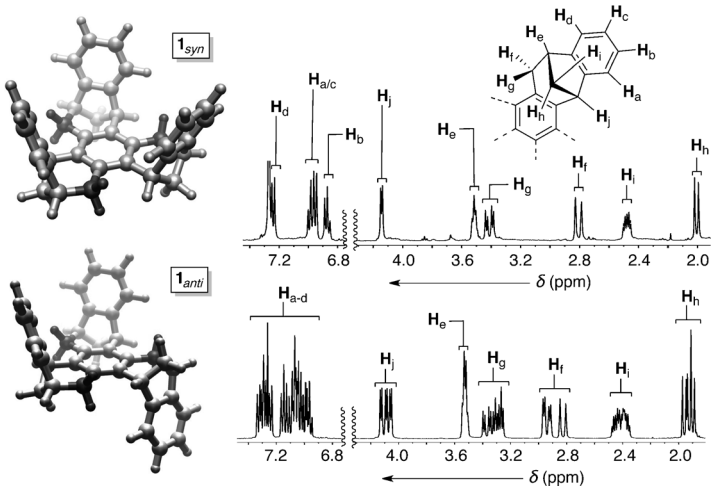
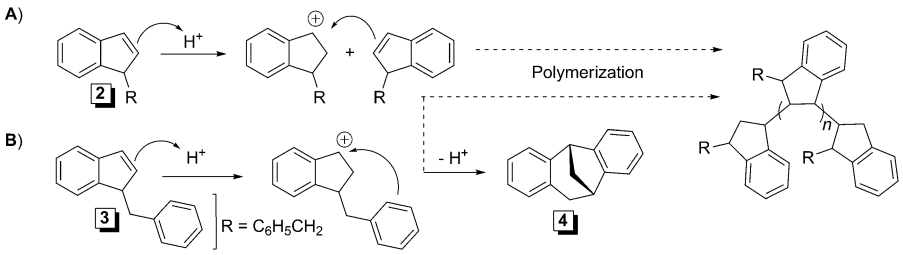


Figure 1. Top: Energy-minimized structure (B3LYP/6-31G*)[18] of basket $\mathbf{1}_{syn}$ and its ^{1}H NMR spectrum (400 MHz, $CDCl_3$). Bottom: Energy-minimized structure (B3LYP/6-31G*)[18] of compound $\mathbf{1}_{anti}$ and its ^{1}H NMR spectrum (400 MHz, $CDCl_3$).



Scheme 1. A) In the presence of acids, indene (**2**, R = H) undergoes a cationic polymerization to give polymeric products. B) In the presence of CH_3SO_3H, compound **3** gives dibenzobicyclo[3.2.1]octadiene **4** in 10–77% yield (Table 1).

In the presence of Lewis- or Brønsted acids, indene **2** undergoes a cationic polymerization to give polyindenes (Scheme 1A).[16] The propagation step of the addition includes the formation of the indanyl cation,[17] which enables the chain growth. In light of this mechanism, we reasoned that in the presence of an acid, indene derivative **3** should undergo a cationic polymerization in competition with a Friedel–Crafts annulation to give dibenzobicyclo-[3.2.1]octadiene **4**[19] (Scheme 1B); the hypothesis was based on earlier studies of electrophilic ring closures of aryl-substituted compounds (cyclialkylations).[20] Interestingly, we found that **3** (1.0 mM, CH_2Cl_2), in the presence of methane-

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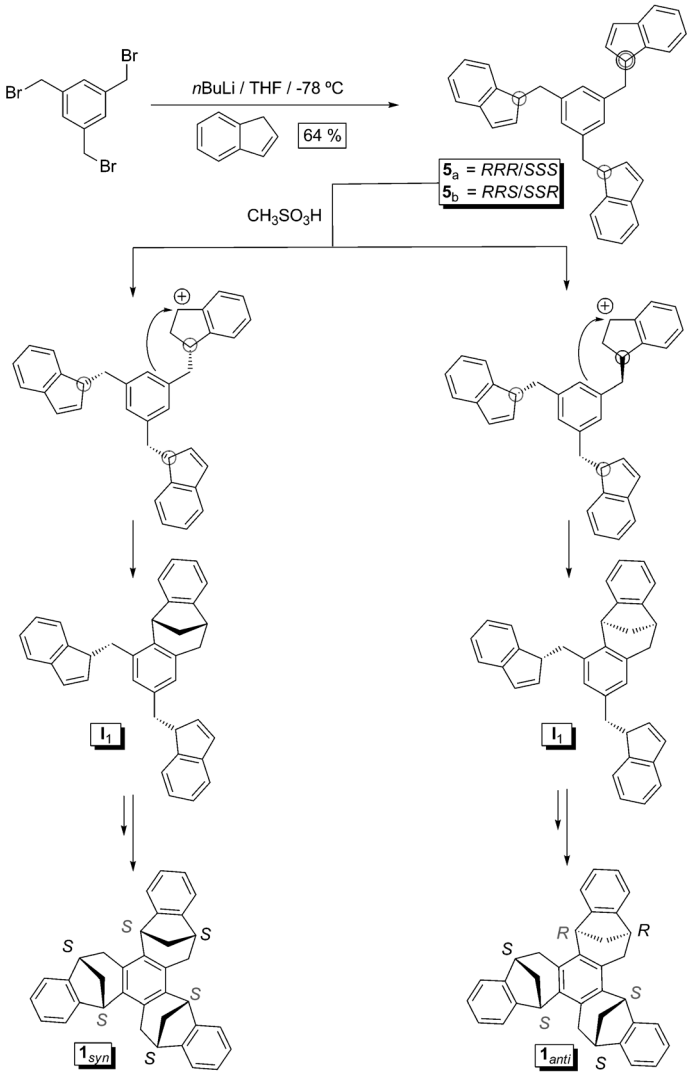
Table 1. The annulation of compound **3** (1.0 mM) into **4** and of $\mathbf{5}_{a/b}$ into $\mathbf{1}_{syn/anti}$ was promoted with CH_3SO_3H (50.0 mM), as determined after HPLC separation.

Substrate	Solvent	T [K]	Yield [%]
3	CH_2Cl_2	298	≈10
3	$ClCH_2CH_2Cl$	344	62
3	$ClCH_2CH_2Cl$[a]	344	77
$\mathbf{5}_{a/b}$	CH_2Cl_2	298	47
$\mathbf{5}_{a/b}$	CH_2Cl_2	313	57
$\mathbf{5}_{a/b}$	$ClCH_2CH_2Cl$	344	75
$\mathbf{5}_{a/b}$	$ClCH_2CH_2Cl$[a]	344	85

[a] The substrate was added by a syringe pump over a period of 2 h.

sulfonic acid (CH_3SO_3H, 50.0 mM), would give **4** in a rather low yield (10%, Table 1), with the polymerization reaction dominating the conversion of starting material, compound **3**. There arose an intriguing question: would trivalent $\mathbf{5}_{a/b}$ give any of cup-shaped $\mathbf{1}_{syn}$ through a tandem of such cyclialkylation reactions (Scheme 2)?



Scheme 2. The synthesis of $\mathbf{5}_{a/b}$ and an electron-pushing mechanism to describe the first cyclialkylation with $\mathbf{5}_{a/b}$ transforming into $\mathbf{1}_{syn/anti}$.

First, we synthesized $\mathbf{5}_{a/b}$ by completing the coupling of 1,3,5-tris(bromomethyl)benzene with indene (Scheme 2).[18] Although the separation of diastereomeric $\mathbf{5}_a$ and $\mathbf{5}_b$ was an arduous task, ^{1}H NMR spectroscopic measurements suggested that two species (C_3 symmetric $\mathbf{5}_a$ and C_1 symmetric $\mathbf{5}_b$) formed in an approximate 1:5 ratio (see the Supporting Information, Figure S6). Indeed, the result of HPLC separation corroborated this proportion of $\mathbf{5}_a/\mathbf{5}_b$ stereoisomers (see the Supporting Information, Figure S16).

We tested various acids for catalyzing the conversion of $\mathbf{5}_{a/b}$ into $\mathbf{1}_{syn/anti}$ in CH_2Cl_2 and at 298 K (see the Supporting Information, Table S1). Markedly, triflic- (CF_3SO_3H, $pK_a = -14$) and methanesulfonic acids (CH_3SO_3H, $pK_a = -2.6$) promoted the reaction giving the desired cyclotrimer as a mixture of *syn*/*anti* diastereomers in a 1:5 ratio and 47% overall yield (Scheme 2). The cationic polymerization of $\mathbf{5}_{a/b}$ (Scheme 1B) is a bimolecular process with, perhaps, a negative entropy of activation characterizing the chain extension. In line with this premise, we increased the reaction's temperature to assist the intramolecular annulation at the expense of the intermolecular polymerization. Indeed, the overall yield of $\mathbf{1}_{syn/anti}$ (Table 1) improved in refluxing CH_2Cl_2 (57%), and the yield increased to 75% with the higher boiling $ClCH_2CH_2Cl$. In fact, when the cyclialkylation of $\mathbf{5}_{a/b}$ was completed with a slow addition of the substrate (using a syringe pump), the yield of desired $\mathbf{1}_{syn/anti}$ increased to 85% (Table 1).

Compounds $\mathbf{1}_{syn}$ and $\mathbf{1}_{anti}$ were separated by column chromatography (SiO_2, hexanes/acetone = 10:1). The full assignment of their ^{1}H NMR resonances (Figure 1) was accomplished with the assistance of ^{1}H-^{1}H COSY and NOESY correlations (see the Supporting Information, Figure S9–S12). Importantly, C_3 symmetric $\mathbf{1}_{syn}$ comprises three [3.2.1] bicyclic rings twisted in the same direction so that the molecule is helical with either right (*P*) or left-handed (*M*) sense of twist (Figure 2A). Indeed, the HPLC chromatogram of $\mathbf{1}_{syn}$

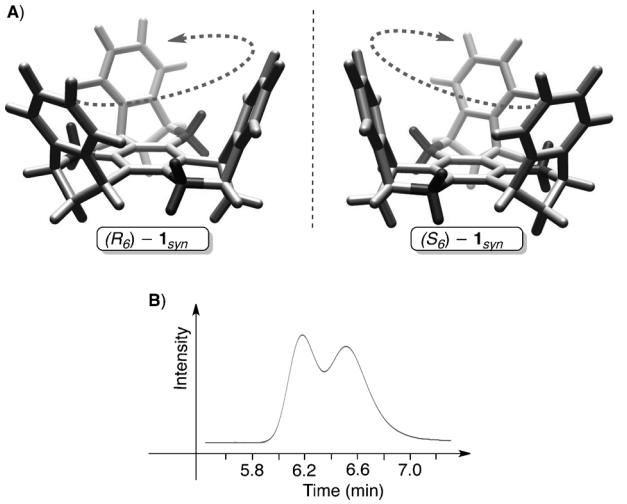


Figure 2. A) C_3 symmetric $\mathbf{1}_{syn}$ has a screw-shaped structure with either a right ((R_6)-$\mathbf{1}_{syn}$) or left-handed ((S_6)-$\mathbf{1}_{syn}$) sense of twist. B) HPLC chromatogram of $\mathbf{1}_{syn}$ (hexane/isopropanol = 93:7, Chiracel OD-H) shows two signals corresponding to a racemic mixture of (R_6/S_6)-$\mathbf{1}_{syn}$ baskets.

revealed two peaks corresponding to a racemic mixture of (R_6/S_6)-$\mathbf{1}_{syn}$ basket (Figure 2B).

To investigate the mechanism of the macrocyclization of $\mathbf{5}_{a/b}$, we used methods of both experimental and computational chemistry (Figures 3 and 4). First, the electron-pushing formalism suggests that the formation of the indanyl-cation intermediate is followed by an intramolecular Friedel–Crafts reaction to close the seven-membered ring (Scheme 2); the process is then repeated twice to give $\mathbf{1}_{syn/anti}$. If the proton transfer(s) governs the rate law of the reaction (Figure 3), then the general-acid catalysis (A-S_E2 type mechanism) takes place.[21] Alternatively, if the formation of the σ complex is rate-controlling, then the specific-acid (A1 type, Figure 3) mechanism operates.[21] We monitored the depletion of reactant $\mathbf{5}_{a/b}$ with time to find that the reaction is first order in this compound (Figure 3). Additionally, we found that the reaction is of a higher order in methanesulfonic acid (Figure 3); note that the excessive amounts of the acid (10–80 equiv) were used to secure the pseudo-first order conditions. Importantly, a higher rate order in acid was previously observed in electrophilic additions[22] occurring in nonpolar solvents, thereby suggesting the involvement of multiple CH_3SO_3H molecules in the protonation. In fact, the rate law pertaining to the cyclization of monomeric **3** (Scheme 1) was also found to be higher order in acid ($v = k_{obs}$ [**3**] $[CF_3SO_3H]^2$, the Supporting Information, Figure S17). Furthermore, we observed the formation of two reactive intermediates during the conversion of $\mathbf{5}_{a/b}$ into $\mathbf{1}_{syn/anti}$ (HPLC, the Supporting Information, Figure S18), which is in line with the sequential nature of the transformation (Figure 3). Since the experimental rate law ($v = k_{obs}$ $[\mathbf{5}_{a/b}]$ $[CF_3SO_3H]^n$, $n = 2$ or 3) could be fit to both general and specific-acid mechanistic scenarios, we examined the addition of CD_3SO_3D to $\mathbf{5}_{a/b}$. In particular, we hypothesized that a preequilibrium step would cause for deuterium atoms to be incorporated into the reactant upon the initiation of the reaction. In line with this premise, we found no deuterium atoms (^{1}H NMR spectra, the Supporting Information, Figure S15) in $\mathbf{5}_{a/b}$ after ≈40% completion of the reaction. Moreover, we found a primary kinetic isotope effect of $k_H/k_D = 2.2$ (the Supporting Information, Figure S19) suggesting that the proton transfer step(s) are rate limiting;[23]

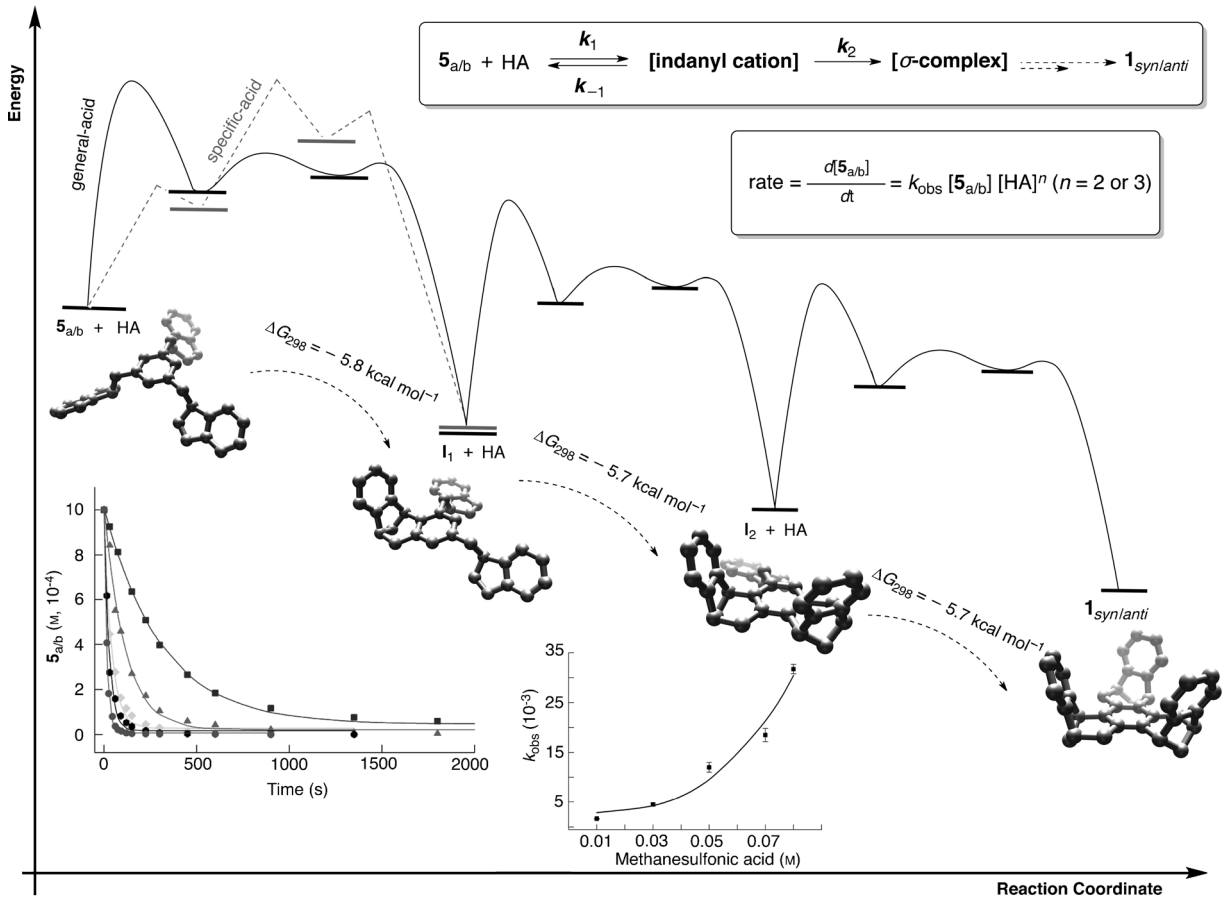


Figure 3. Top: A potential energy diagram for the conversion of $\mathbf{5}_{a/b}$ into $\mathbf{1}_{syn/anti}$ with CH_3SO_3H (HA). Bottom: The change in the concentration of $\mathbf{5}_{a/b}$ (1.0 mM) with CH_3SO_3H (10–80 mM) was monitored by HPLC (334 K, $ClCH_2CH_2Cl$). The data were analyzed by a nonlinear least-square analysis (SigmaPlot 12.0) and fitted to a first-order kinetic model to give k_{obs} ($R^2 > 0.99$). When pseudo-first-order coefficients k_{obs} were plotted against the concentration of CH_3SO_3H, a second ($R^2 > 0.96$) or third-order dependence ($R^2 > 0.97$, see the fitted line) on this reactant appeared. The calculated thermodynamic ΔG values (in kcal mol^{-1}) were computed at the TPSSh/6-311+G**//B3LYP/6-31G* level of theory.

note that discerning a complete role of the acid, in promoting the formation of $\mathbf{1}_{syn/anti}$, would necessitate additional experimentation.

Along with the kinetic measurements, we utilized a computational approach with density functional theory,[24] and optimized various geometries of $\mathbf{5}_{a/b}$, $\mathbf{I}_1$–$\mathbf{I}_2$ and $\mathbf{1}_{syn/anti}$ at the B3LYP/6-31G* level of theory and then completed a single-point energy calculation at the TPSSh/6-311+G** level of theory (Figure 2).[18] We noted that there is a considerable difference in thermodynamic stability of these constitutional isomers. In brief, the conversion $\mathbf{5}_{a/b}\rightarrow\mathbf{I}_1\rightarrow\mathbf{I}_2\rightarrow\mathbf{1}_{syn/anti}$ follows a "downhill" trajectory in which the stability of the product is 17.2 kcal mol^{-1} (ΔG_{298}, Figure 3) greater than that of the reactant. The two diastereomeric products $\mathbf{1}_{syn}$ and $\mathbf{1}_{anti}$, however, have a comparable energy content ($\Delta G_{298}^{syn/anti} = -0.8$ kcal mol^{-1}).[18]

Importantly, a mixture of diastereomeric $\mathbf{5}_{a/b}$ ($\approx$1:5) was found under all reaction conditions give $\mathbf{1}_{syn/anti}$ in the same $\approx$1:5 ratio (Table 1). In line with the computational results, we deduce that the reaction is under a kinetic control with two reaction pathways occurring simultaneously (Scheme 2): the *RRR*/*SSS* stereoisomer (compound $\mathbf{5}_a$) converts into $\mathbf{1}_{syn}$ basket whereas the other *RRS*/*SSR* stereoisomer (compound $\mathbf{5}_b$) turns into $\mathbf{1}_{anti}$. In line with such a proposition, we treated $\mathbf{1}_{syn/anti}$ with CH_3SO_3H (50.0 mM) to find no change in the quantity or the proportion of the two compounds after a prolonged period of time (24 h). Furthermore, the intermediate indanyl cation must be a subject of rapid hydride-shifts (Figure 4A), which may cause the "crossover" between two parallel reaction pathways. First, we completed the annulation of tris-indene $[D_6]\mathbf{5}_{a/b}$ (with the isotopes installed at positions 1 and 4, Figure 4A) to find product $[D_6]\mathbf{1}_{syn/anti}$ carrying deuterium atoms at the original sites (see also the Supporting Information, Scheme S3). Evidently, the Wagner–Meerwein rearrangements (Figure 4A) were not occurring in the reaction. This experimental observation is also in agreement with computational results (TPSSh/6-311+G**//B3LYP/6-31G*, Figure 4B) showing a considerable activation barrier of 21.2 kcal mol^{-1} for the 1,2-hydride shift. The suprafacial 1,4-sigmatropic shift of hydride (Figure 4B) was found to be even more energy-demanding ($\Delta G^{\ddagger}_{298} = 53.8$ kcal mol^{-1}).[18] In fact, the conversion of the indanyl cation into the σ complex appears to be the lowest energy pathway ($\Delta G^{\ddagger}_{298} = 9.9$ kcal mol^{-1}, Figure 4B)[18] available to this high-energy intermediate.

A rapid access to concave compounds is critical for obtaining useful quantities of hosts capable of trapping smaller molecules, for application in the area of sensing and catalysis.[11,25] Our study describes an effective cyclialkylation reaction that one can use for obtaining cavitands with a chiral inner space. The stage is now set for exploring the scope and characteristics of these concave hosts.

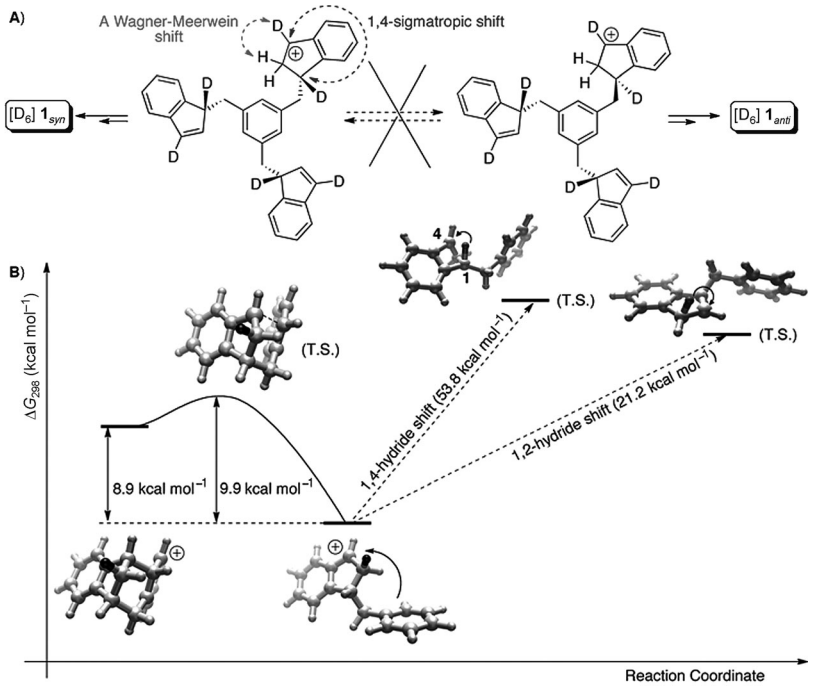


Figure 4. A) The occurrence of the Wagner–Meerwein shifts was tested with the $[D_6]\mathbf{5}_{a/b}$ substrate. B) The macrocyclization of the indanyl cation of **3** was found (TPSSh/6-311+G**//B3LYP/6-31G*) to have a low activation barrier ($\Delta G^{\ddagger} = 9.9$ kcal mol^{-1}) relative to possible hydride migrations.

Experimental Section

Preparative procedure for $\mathbf{1}_{syn/anti}$: Methanesulfonic acid (6.8 mmol, 442 μL) was added to a flame-dried flask containing anhydrous 1,2-dichloroethane (136 mL), and the mixture was brought to reflux. Compound $\mathbf{5}_{a/b}$ (656 mg, 1.42 mmol) was dissolved in anhydrous 1,2-dichloroethane (6 mL) and then added to the reaction mixture with a syringe pump over 2 h. After complete addition of the substrate, the reaction was allowed to reflux for an additional 2 h. The reaction mixture was then extracted three times with 50 mL of saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate and the solvent removed in vacuo. The crude product was purified by column chromatography (SiO_2, hexanes/acetone = 10:1) to yield 89.1 mg of $\mathbf{1}_{syn}$ (14%) and 467.2 mg of $\mathbf{1}_{anti}$ (71%).

$\mathbf{1}_{syn}$: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (3H, d), 7.02–6.93 (6H, m), 6.90–6.84 (3H, m), 4.14 (3H, d, J = 4.8 Hz), 3.52 (3H, m), 3.41 (3H, dd, J = 16.8 Hz, 4.8 Hz), 2.81 (3H, d, J = 16.8 Hz), 2.52–2.43 (3H, m), 2.01 ppm (3H, d, J = 10.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 146.65, 139.69, 126.92, 126.54, 122.91, 121.57, 41.00, 40.92, 40.25, 33.58 ppm; HRMS (ESI): m/z: calculated for $C_{36}H_{30}+Na^+$: 485.2240 $[M+Na]^+$; found: 485.2250.

$\mathbf{1}_{anti}$: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.20 (3H, m), 7.18–6.94 (9H, m), 4.13 (1H, d, J = 4.8 Hz), 4.09 (1H, d, J = 4.8 Hz), 4.06 (1H, d, J = 4.8 Hz), 3.57–3.48 (3H, m), 3.40–3.24 (3H, m), 3.00–2.76 (3H, m), 2.49–2.32 (3H, m) and 1.98–1.86 ppm (3H, m); ^{13}C NMR

(100 MHz, $CDCl_3$): $\delta = 150.46$, 150.26, 150.04, 146.80, 146.77, 146.51, 139.78, 139.72, 139.46, 126.73, 126.69, 126.64, 126.61, 126.57 (2C), 126.54, 126.34, 126.34, 123.25, 123.10 (2C), 121.44, 121.28, 121.12, 40.90, 40.81, 40.78, 40.77, 40.46, 40.32 (two signals), 40.28, 34.92, 33.74, 33.46, 33.41 ppm; HRMS (ESI): *m/z*: calculated for $C_{36}H_{30}+Na^+$: 485.2240 $[M+Na]^+$, found: 485.2221.

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Keywords: carbenium ions · cavitands · chirality · host–guest chemistry · kinetics

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