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Multiple Hindered Rotators in a Gyroscope-Inspired Tribenzylamine Hemicryptophane

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Abstract

A gyroscope-inspired tribenzylamine hemicryptophane provides a vehicle for exploring the structure and properties of multiple *p*-phenylene rotators within one molecule. The hemicryptophane was synthesized in three steps in good overall yield using mild conditions. Three rotator-forming linkers were cyclized to form a rigid cyclotrimeratrylene (CTV) stator framework, which was then closed with an amine. The gyroscope-like molecule was characterized by ¹H NMR and ¹³C NMR spectroscopy and the structure was solved by X-ray crystallography. Rigidity of the two-component CTV-trimethylamine stator was investigated by ¹H variable temperature (VT) NMR experiments and molecular dynamics simulations. These techniques identified gyration of the three *p*-phenylene rotators on the millisecond time scale at −93 °C, with more dynamic but still hindered motion at room temperature (27 °C). The activation energy for the *p*-phenylene rotation was determined to be ~10 kcal mol^{−1}. Due to the propeller arrangement of the *p*-phenylenes, their rotation is hindered but not strongly correlated. The compact size, simple synthetic route and molecular motions of this gyroscope-inspired tribenzylamine hemicryptophane make it an attractive starting point for controlling the direction and coupling of rotators within molecular systems.

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Supporting Information Available: X-ray structures (selected bond lengths and angles), ¹H NMR and ¹³C NMR spectra, NMR experiments investigating guest binding, analysis of molecular dynamics simulations and computational modeling are included in the supporting information. This material is available free of charge via the internet at <http://pubs.acs.org>.

Introduction

Synthetic chemical systems provide means to explore complex phenomena in biological machines¹⁻⁸ and also to create novel molecular mechanical components.⁹ Designs based on macroscopic devices include brakes, gears, propellers, ratchets, turnstiles, rotors, scissors, and most recently gyroscopes.^{3,10-14} These molecular systems have been extensively studied in solution, in solid phases, on surfaces and in polymers.¹⁵ One challenge in designing these systems is the required restriction of some molecular degrees of freedom, while allowing specific motions of targeted molecular components.⁹ Synthesis of such molecules can also be challenging. Criteria for the construction of molecular gyroscopes have been identified and generally applied: rotary elements (rotators) are attached to a static framework (stator); steric contacts, internal rotation barriers, and interaction with solvent should be minimized to allow low-friction, low-barrier rotary motion; rotating groups are isolated and/or well-separated from each other. To expand upon these criteria, we designed a gyroscope-inspired framework with cyclotrimeratrylene (CTV) and trimethylamine as the 2-component stator, bridged by three *p*-phenylene rotators (Scheme 1). This creates a new application for CTV, which has been used previously for the synthesis of cryptophanes in host-guest chemistry (with biosensing and chiroptical properties),¹⁶⁻³¹ supramolecular assemblies, gels and organic microporous polymers:³² CTV provides a rigid hemicryptophane framework for the synthesis of a novel gyroscope-inspired molecule. Our design incorporates a novel combination of features: (i) efficient, high-yielding synthetic scheme, (ii) multiple, proximate rotators in one covalently bonded molecular system, (iii) exclusion of other molecules and ions from the stator interior that may impede rotator motion, and (iv) hindered rotators experiencing friction through exposure to solvent.

Gyroscope-inspired molecular systems have focused largely on approaching barrierless rotation of isolated or sequestered rotors. One of the first examples (also referred to as a molecular turnstile) was synthesized by Moore and Bedard.³³⁻³⁴ The creative design included a rigid hexa(phenylacetylene) framework that preserved the low barrier of rotation about the 1,4-axis of the substituted *p*-phenylene moiety. Garcia-Garibay and coworkers extended these ideas in the construction of amphidynamic crystals,^{11,15,35-54} where the introduction of bulky substituents creates sufficient space in the lattice framework to allow near barrierless rotation of the central *p*-phenylene group. Furthermore, the *p*-phenylene moiety can be functionalized to create a dipole moment that could be used for controlling motion with an external electric field.^{11,36-38,42} Following a different approach, Gladysz and coworkers prepared a series of metal-centered molecular gyroscopes in which the rotator is protected by three-spoke structures as part of the stator. The rotational dynamics of these gyroscopes were studied in solution and their crystal structures indicated sufficient free volume around the rotator to allow low-barrier rotation.^{9,55-59} Most recently, Kitagawa *et al.* designed a self-assembled supramolecular gyroscope where the stator is a heterocapsule formed by noncovalent interactions and the rotator is an encapsulated guest.⁶⁰

Herein, we report a streamlined synthesis of a gyroscope-inspired tribenzylamine hemicryptophane (**5**, Scheme 2) involving multiple hindered rotators, where fast rotation is observed by ¹H NMR spectroscopy above a critical temperature. Rotations about the 1,4-axis of the three *p*-phenylene rotators encased in a rigid CTV-trimethylamine stator were investigated using ¹H variable temperature (VT) NMR spectroscopy and molecular dynamics (MD) simulations.

Results and Discussion

Synthesis and X-ray crystal structure of hemicryptophane **5**

In order to synthesize the gyroscope-inspired tribenzylamine hemicryptophane **5**, the linkers (including the rotators) were first cyclized in the rigid CTV framework and then closed with an amine to form the final three-dimensional structure (Scheme 2). Reaction of commercially available vanillyl alcohol **1** and dibromo-*p*-xylene **2** gave the versatile linker **3** in 65% yield. Cyclization of **3** was achieved with a catalytic amount of Sc(OTf)₃ in acetonitrile to afford the “gyroscope scaffold intermediate” **4** in 29% yield. This reaction was based on previous protocols where various 3,4-disubstituted benzyl alcohols were treated with catalytic Sc(OTf)₃ to prepare CTV and cryptophane derivatives.¹⁸ Compound **4** was reacted with 7 N NH₃ in MeOH to give **5** in 67% yield, with an overall yield of 13% for the three steps. Compound **5** was characterized by solution ¹H NMR and ¹³C NMR spectroscopy, high-resolution mass spectrometry (using electrospray ionization method) and X-ray crystallography. This short synthetic scheme utilizes mild conditions and results in high overall yields. Moreover, this route provides ample versatility by increasing the number of methylene spacer units or introducing new functional groups on **3** to form rotators with different conformations, rotation barriers, and dipole moments.

The X-ray crystal structure of **5** indicates the three rotators adopt a propeller conformation (Figure 1). **5** crystallizes in the monoclinic space group P2₁/c and each unit cell consists of four molecules with two of each enantiomer (Figure 1; Figure S1, Supporting Information). In both enantiomers the *p*-phenylene rotators are oriented edgewise into the interior (angled away from the methoxy group ortho to them) with an average dihedral angle of ~ 88.1° for *O*-C_{benzylic}-C_{phenyl}-C_{phenyl}, ~ -68.6° for *N*-C_{benzylic}-C_{phenyl}-C_{interior-phenyl} and ~ 107.5° for *N*-C_{benzylic}-C_{phenyl}-C_{exterior-phenyl} (see Figure 1c). The minimal distance from the phenylic proton on C44 (pointing into the cage) to the plane described by the next aryl ring (C10 to C15) is relatively small at 3.22 Å. After the van der Waals radii for hydrogen and carbon are included,⁶¹ the “clearance” distance is approximately 0.32 Å. The distance from the same proton to the nitrogen atom was even shorter at 2.97 Å, with clearance distance of 0.22 Å when van der Waals radii are included, as the nitrogen is oriented into the interior with an average C–N–C bond angle of 114.42° (see Figure 1c). This propeller-shaped conformation with a pyramidal nitrogen atom where the lone pair is pointed into the cage is similar to the crystal structure of tribenzylamine, where the rigid CTV is not present.⁶² It is believed that this conformation is primarily favored due to steric hindrance.⁶² Despite the propeller conformation of the rotators and the positioning of the nitrogen atom into the interior of the cage, rotator motion is expected given the observed clearance distances (Figure 1).

Unlike some previously reported porous gyroscopes,⁵⁸ which encountered barriers to rotation due to the intercalation of solvent molecules (or neighboring molecules in solid state), the small internal volume in **5** should prevent guest encapsulation. Indeed, X-ray crystallography indicated an empty tribenzylamine hemicryptophane, lacking solvent molecules. Small molecules such as helium, dihydrogen, dinitrogen and xenon were not observed to bind to **5** at 1 atm over a range of temperatures, 47 °C to -93 °C (see Supporting Information for experimental details). Molecular dynamics simulations were also in agreement with the experimental findings and suggest that these small molecular species should be excluded from the interior (Figure S2, Supporting Information). Computational modeling was used to explore effects due to rotation of the *p*-phenylene rotators. GRASP⁶³ was employed in order to investigate whether a potential interior cavity within **5** emerges with rotation of the rotators. With a probe radius of 1.4 Å, only in improbable, high-energy structures (ΔE > 30 kcal mol⁻¹, where ΔE is the energy relative to the X-ray structure) where the angle of each *p*-phenylene rotator increased by 90° relative to the crystal structure was a cavity identified (Figure S3, Supporting Information). This suggests that a cavity of

sufficient volume to accommodate small guest molecules is essentially nonexistent, thereby preventing the inclusion of small molecules that may hinder *p*-phenylene rotation.

¹H VT-NMR experiments with hemicryptophane **5**

In order to investigate the energy barrier of the rotators in solution phase, we performed a ¹H VT-NMR study of **5** in CD₂Cl₂ from −93 °C to 27 °C. The NMR spectra in Figure 2 indicate that the rotational rate of the *p*-phenylene rotators became slow on the NMR timescale as the temperature was decreased. At 27 °C, the four protons (labeled H₂, H₃, H₄ and H₅ in Figure 2a) on each of the three rotators were split into two doublets at 6.1 ppm (average signal from H₂ and H₄) and 6.9 ppm (average signal from H₃ and H₅). Upon cooling, these doublets became broader and the energy barrier for *p*-phenylene rotation was estimated from equations (1) and (2),⁶⁴ see Experimental Procedures, to be 9.2 kcal mol^{−1} from the coalescence temperature (ca. −70 °C; *k*_{coalesce} ≈ 2300 Hz). As the temperature was further reduced to −93 °C, a new pair of doublets of equal intensity (3 protons each) arose for each doublet that coalesced. This led to splitting of the doublet for H₂ and H₅ and also H₃ and H₄, where H₂ and H₃ shift upfield as they are pointed into the cavity while H₄ and H₅ are oriented away from the cavity. The H₃-H₅ splitting pattern (Figure 2b) evidences that *p*-phenylene rotation at −93 °C is slow on the NMR timescale, *t*_{rot} > 3 ms. Similar temperature-dependent behavior was recently reported for a 2,3-dichlorophenylene rotator caged within a polysilaalkane stator.⁶⁵ In line with our design, the stator remained rigid throughout the ¹H VT-NMR dataset as indicated by the fact that the integration and splitting pattern of all CTV-trimethylamine proton peaks were constant. It is also interesting to note that protons H_{A1} and H_{A2} remained diastereotopic throughout the ¹H VT-NMR series (Figure 2b). All peaks were assigned by ¹H-¹H NOESY experiment (Figure 3).

Molecular dynamics simulations

To investigate the conformational fluctuations of the rotators and stator, MD simulations were carried out on **5** (Figure 4). One of the crystal structures was used as the initial structure, and the length of the simulations was 50 ns. Equilibration was confirmed by monitoring relaxation of structural parameters (Figure S4, Supporting Information). Three dihedral angles that reflect the conformations of the rotators were selected: ($\alpha \equiv N1-C16-C13-C14$, $\beta \equiv N1-C32-C29-C30$ and $\gamma \equiv N1-C48-C45-C44$). The symmetry of the structure yields nearly identical average values of these angles that are in agreement with the values observed in the crystal structure: $\alpha = -72.3^\circ \pm 10^\circ$, $\beta = -71.8^\circ \pm 10^\circ$ and $\gamma = -72.8^\circ \pm 10^\circ$; the uncertainties (fluctuations) are one standard deviation (Figure S5, Supporting Information). The MD simulations at 25 °C indicated limited fluctuations within the structure on the nanosecond time scale (Figure 4), and the CTV unit that forms the stator remains highly rigid, in agreement with the NMR results noted above. The *p*-phenylene units are not observed to rotate and instead librate in a manner consistent with a hindered rotor that rotates on a time scale > 100 ns. Therefore, simulations, X-ray, and NMR structural data all agree that the propeller-shaped conformation is highly favored in **5**. High temperatures were artificially employed to observe rotation in the simulations: at 527 °C, rotations of the three *p*-phenylenes are frequent, conformations where the rotators are directed edgewise into the interior (similar to what is seen in the crystal structure) are preferentially populated, and no preferred rotational direction in the three *p*-phenylenes is observed.

To investigate further the *p*-phenylene rotation and interactions among the rotators, the crystal structure of **5** was minimized, and the dihedral angle α was systematically varied (Figure 5). The structure was then relaxed via energy minimization, constraining the coordinates of all atoms but those in the two remaining β and γ *p*-phenylene rings. The β -

ring is essentially invariant during the rotation. The γ -ring only rotates at most 19.7° to accommodate the 180° rotation of the α -ring. An energy barrier arises due to the steric interaction between the α -ring and γ -ring. Interestingly, the rotational energy barrier estimated from this simplistic and highly-constrained calculation ($\sim 12 \text{ kcal mol}^{-1}$) is consistent with the experimental value inferred from the ^1H VT-NMR experiments ($\sim 10 \text{ kcal mol}^{-1}$). The modeling results suggest that, although not entirely independent, the rotations of the α - and γ -rings are only weakly coupled.

Conclusions

In summary, a novel gyroscope-inspired tribenzylamine hemicryptophane **5** was synthesized in three steps in good overall yield using mild conditions. This synthetic route offers the possibility of preparing hemicryptophanes with multiple, proximate rotators, where the molecular properties of the rotators can be varied by changing the length and composition of the linkers used to cyclize the “gyroscope scaffold intermediate” **4**. The compact size of the cavity in this system helps to avoid the inclusion of solvent and gaseous molecules that have the potential to inhibit rotation. ^1H VT-NMR data indicate a critical temperature for the onset of rotation on the sub-millisecond time scale and a hindered, dynamic motion of these three rotators at room temperature. The desired rigidity of the CTV stator and the rotator properties of the *p*-phenylenes were corroborated by ^1H VT-NMR spectroscopy and MD simulations. As a *p*-phenylene ring rotates, it encounters one of the neighboring *p*-phenylenes, leading to a steric barrier that hinders rotation. Rotation of the rings appears not to be strongly correlated with one another.

The compact size and molecular motions of **5** make it a compelling initial motif from which to engineer unidirectional, potentially coupled rotators for molecular locomotion or transmitting torque. Towards this goal, it may be possible to introduce sterically bulky substituents on the linkers to control the temperatures at which rotation becomes accessible and to favor one direction of rotation. Different substituent groups can also be introduced to create a dipole moment on the rotators, thereby allowing the use of electric fields to explore rapid conformational response in these systems and to control the direction of rotation.

Experimental Procedures

Reagents

All reactions were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Column chromatography was performed using 60 Å porosity, 40-75 μm particle size silica gel from Sorbent Technologies. Thin layer chromatography (TLC) was performed using silica gel plates with UV light at 254 nm for detection. ^1H NMR (360 and 500 MHz) and ^{13}C NMR (125 MHz) spectra were acquired on Bruker DMX 360 and AMX 500 spectrometers. Electrospray ionization (ESI) mass spectrometry was performed in high-resolution mode on a Micromass Autospec instrument. All reagents were commercially available and used without further purification, unless otherwise stated.

[4-(4(bromomethyl)benzyl)oxy-3-methoxyphenyl]methanol (**3**)

A mixture of vanillyl alcohol **1** (2.5091 g, 16.276 mmol, 1.0 equiv.), dibromo-*p*-xylene **2** (6.4033 g, 24.259 mmol, 1.5 equiv.), and K_2CO_3 (2.2511 g, 16.288 mmol, 1.0 equiv.) dissolved in acetone (24.0 mL, 0.786 g/mL, 18.9 g) was heated at 70°C overnight with stirring. The reaction solvent was removed by rotary evaporation. The resulting residue was rinsed in a separatory funnel with a 1:1 mixture of H_2O (60 mL) and CH_2Cl_2 (60 mL). The phases were separated and the aqueous layer extracted three times with CH_2Cl_2 (100 mL). The combined organic layer was washed once with 1 M NaOH (100 mL) and once with

saturated NaCl (100 mL). The organic layer was dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (5:95 Acetone:CH₂Cl₂ → 20:80 Acetone:CH₂Cl₂) to give **3** as white powder (3.5422 g, 65%); m.p. 86–88 °C; ¹H NMR (500 MHz, CDCl₃, 25 °C) δ = 7.42–7.38 (m, 4H), 6.96 (s, 1H), 6.85–6.81 (m, 2H), 5.14 (s, 2H), 4.60 (s, 2H), 4.49 (s, 2H), 3.89 (s, 3H), 1.86 (s, 1H); ¹³C NMR (125 MHz, CDCl₃, 25 °C) δ = 149.9, 147.6, 137.6, 137.5, 134.5, 129.4, 127.7, 119.4, 114.1, 111.1, 70.8, 65.4, 56.1, 33.36; HRMS (ESI) calculated for C₁₆H₁₇BrO₃ (M+Na⁺) 359.0259; found 359.0239.

2,7,12-Tris-(4-bromomethylbenzyloxy)-3,8,13-trimethoxy-10,15-dihydro-5H tribenzo[a,d,g]cyclononene (**4**)

A mixture of **3** (2.0232 g, 6.0210 mmol, 1.0 equiv.) and Sc(OTf)₃ (0.0295 g, 0.0599 mmol, 0.01 equiv.) dissolved in MeCN (5.9 mL, 0.786 g/mL, 4.7 g) was heated at 65 °C overnight with stirring. The reaction solvent was removed by rotary evaporation. The resulting residue was extracted twice with CH₂Cl₂ (150 mL) and washed three times with sat. NaCl (150 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (CH₂Cl₂ → 2:98 THF:CH₂Cl₂) to give **4** as white powder (0.5571 g, 29%); m.p. 91–93 °C; ¹H NMR (360 MHz, CDCl₃, 25 °C) δ = 7.39–7.37 (m, 12H), 6.85 (s, 3H), 6.72 (s, 3H), 5.09 (s, 6H), 4.73 (d, 3H, *J* = 13.7 Hz), 4.50 (s, 6H), 3.76 (s, 9H), 3.50 (d, 3H, *J* = 13.8 Hz); ¹³C NMR (125 Hz, CDCl₃, 25 °C) δ = 148.6, 147.2, 137.9, 137.5, 132.9, 131.9, 129.4, 127.6, 116.4, 114.0, 71.4, 56.4, 36.6, 33.3; HRMS (ESI) calculated for C₄₈H₄₅Br₃O₆ (M⁺) 954.0766; found 954.0724. The NMR spectra matched the reported literature data.⁶⁶

Tribenzylamine Hemicryptophane (**5**)

A mixture of **4** (0.0406 g, 0.0426 mmol, 1.0 equiv.) and K₂CO₃ (0.0869 g, 0.629 mmol, 15.0 equiv.) dissolved in MeCN (58 mL, 0.786 g/mL, 46 g) was heated at 90 °C with stirring as 7 N NH₃ in MeOH (0.0711 mL of 7 N NH₃, 0.5 mmol, ~12 equiv., in 4.7 mL of MeCN) was added by a syringe pump over 8 h. The reaction solvent was removed by rotary evaporation. The resulting residue was extracted with CH₂Cl₂ and transferred to a separatory funnel. The organic layer was washed once with a 1:1 mixture of H₂O (50 mL) and 1 M NaOH (50 mL) and then with 1 M NaOH (50 mL). The aqueous layer was extracted with CH₂Cl₂ (50 mL) and the combined organic layer was washed with sat. NaCl (50 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography (50:50 CH₂Cl₂: hexanes → 50:40:10 CH₂Cl₂: hexanes: EtOAc → 60:30:10 CH₂Cl₂: hexanes: EtOAc; all with 1% TEA) to give **5** as a white powder (0.0206g, 67%); m.p. (decom.) > 250 °C; ¹H NMR (360 MHz, CDCl₃, 25 °C) δ = 7.34 (s, 3H), 6.96–6.93 (m, 9H), 6.18 (d, 6H, *J* = 7.9 Hz), 5.41 (d, 3H, *J* = 12.1 Hz), 5.06 (d, 3H, *J* = 12.2 Hz), 4.83 (d, 3H, *J* = 13.7 Hz), 3.60 (d, 3H, *J* = 13.8 Hz), 3.58 (s, 9H), 3.54 (d, 3H, *J* = 13.2 Hz), 3.41 (d, 3H, *J* = 13.2 Hz); ¹³C NMR (125 MHz, CDCl₃, 25 °C) δ = 147.7, 143.0, 140.3, 132.9, 131.7, 130.8, 128.4, 127.4, 117.9, 113.9, 68.8, 55.5, 55.3, 34.9; HRMS (ESI) calculated for C₄₈H₄₅NO₆ (M+H⁺) 732.3326; found 732.3340.

Crystal growth and X-ray crystallography

Compound **5** was crystallized by vapor diffusion of diethyl ether or *n*-pentane into toluene. It crystallizes in the monoclinic space group P2₁/c (systematic absences 0k0: k = odd and h0l: l = odd) with *a* = 17.098(2) Å, *b* = 11.4592(9) Å, *c* = 21.096(2) Å, β = 113.539(2)°, *V* = 3789.3(6) Å³, *Z* = 4 and *d*_{calc} = 1.283 g/cm³. X-ray intensity data were collected on a Rigaku Mercury CCD area detector employing graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) at a temperature of −130 °C. Preliminary indexing was performed from a series of twelve 0.5° rotation images with exposures of 30 s. A total of 336 rotation images

were collected with a crystal to detector distance of 35 mm, a 2θ swing angle of -12° , rotation widths of 0.5° and exposures of 10 s: scan no. 1 was a ϕ -scan from 170° to 338° at $\omega = 0^\circ$ and $\chi = 0^\circ$. Rotation images were processed using CrystalClear,⁶⁷ producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the CrystalStructure⁶⁸ program package for further processing and structure solution on a Dell Pentium III computer. A total of 15571 reflections were measured over the ranges $5.2 \leq 2\theta \leq 50.02^\circ$, $-16 \leq h \leq 20$, $-13 \leq k \leq 12$, $-23 \leq l \leq 25$ yielding 6601 unique reflections ($R_{\text{int}} = 0.0261$). The intensity data were corrected for Lorentz and polarization effects and for absorption using REQAB⁶⁹ (minimum and maximum transmission 0.853, 1.000).

The structure was solved by direct methods (SIR97).⁷⁰ Refinement was by full-matrix least squares based on F^2 using SHELXL-97.⁷¹ All reflections were used during refinement (F^2 values that were experimentally negative were replaced by $F^2 = 0$). The weighting scheme used was $w = 1 / [\sigma^2(F_o^2) + 0.0547P^2 + 0.9350P]$ where $P = (F_o^2 + 2F_c^2) / 3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a "riding" model. Refinement converged to $R_1 = 0.0479$ and $wR_2 = 0.1107$ for 5502 reflections for which $F > 4\sigma(F)$ and $R_1 = 0.0599$, $wR_2 = 0.1204$ and GOF = 1.078 for all 6601 unique, non-zero reflections and 500 variables

$$\left(R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|; wR_2 = \left\{ \Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2 \right\}^{1/2}; \text{GOF} = \left\{ \Sigma w(F_o^2 - F_c^2)^2 / (n - p) \right\}^{1/2} \right)$$

where n = the number of reflections and p = the number of parameters refined). The maximum Δ/σ in the final cycle of least squares was 0.001 and the two most prominent peaks in the final difference Fourier were $+0.173$ and $-0.253 \text{ e/\AA}^3$.

Calculating from ^1H VT-NMR data the energy barrier for *p*-phenylene rotation

Equation 1 was used to determine the *p*-phenylene rotation rate at the coalescence temperature:

$$k = \frac{\pi \Delta\nu_0}{\sqrt{2}} \quad (1)$$

where k is the rate coefficient, $\Delta\nu_0 = \nu_A - \nu_B$ is the chemical shift difference (in Hz) between the two separate signals at slow exchange (in this case at -93°C or 180 K). The Arrhenius equation (2) was used to determine the activation energy, E_a , at the coalescence temperature, T (in K):

$$\ln(k/H\text{z}) = -\frac{E_a}{R} \left(\frac{1}{T} \right) + \ln(A/H\text{z}) \quad (2)$$

where A is the pre-exponential factor and R is the universal gas constant.⁶⁴

Computational methods

All-atom MD simulations were carried out using NAMD2.⁷² The internal bonded parameters were obtained from AMBER-94⁷³ and the nonbonded parameters were proposed in previous studies.⁷⁴⁻⁷⁸ Simulations were performed in the absence of solvent at 25°C and temperature was controlled using Langevin dynamics with a damping coefficient of 5 ps^{-1} . The time step of the simulations was 0.5 fs. Relaxation calculations using energy minimization consist of up to 10,000 steps of the conjugate gradient algorithm as implemented in NAMD2; energy was monitored to confirm minimization.⁷²

GRASP⁶³ was employed to investigate a potential interior cavity within **5**. Different conformations were generated by manual rotations of the three *p*-phenylenes. The rotations were systematically performed in 10° increments using one of the crystal structures of **5** as reference. A probe radius of 1.4 Å was used for all calculations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 2.

(a) Schematic model of the molecular motion of **5**. (b) ¹H VT-NMR spectra of **5** measured in CD₂Cl₂ with a 500 MHz spectrometer.

Figure 3. ^1H - ^1H NOESY spectrum of **5** in CDCl_3 at 27°C with 500 MHz spectrometer to determine the assignment of protons.

Figure 4. Orthogonal views of 30 superimposed structures from the MD simulation of **5**. The dihedral angles are indicated: α (magenta), β (cyan) and γ (yellow).

Figure 5.

Minimized energy as a function of $\Delta\alpha$, which is rotation of the α dihedral angle relative to the energy minimized X-ray structure (gray). The crystal structure of **5** was minimized, and the angle α was varied in 10° increments, driving rotation of the α -ring (magenta). For each value of $\Delta\alpha$, the structure was energy minimized, constraining the coordinates of all atoms but those in the two remaining *p*-phenylene rotators: β -ring (cyan) and γ -ring (yellow). For clarity: the CTV moiety and hydrogens are not shown; two carbons of the α -ring are rendered black.

Scheme 1.

Gyroscope-inspired tribenzylamine hemicryptophane (**5**) possesses a rigid stator (a and c) and three rotator groups (b). Arrows illustrate rotation but are not intended to suggest unidirectionality.

Scheme 2.

Three-step synthesis of gyroscope-inspired tribenzylamine hemicryptophane **5**.