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Molecular Gyroscope with a *trans*-Cyclohexane-1,4-diimine Rotor Unit: Isolation and Characterization of a Geometric Isomer as a Formal Intermediate of Hindered Rotation

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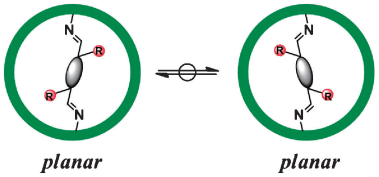
Condensation reactions of macrocyclic diamines **1** and cyclohexane-1,4-dicarbaldehydes **2** with the substituents at 1,4-positions gave a series of macrocage molecules that can be considered molecular gyroscopes. The gyro-rotational behavior of the cyclohexane rotor is largely affected by the degree of steric requirement of the substituents, and isolation of *syn*-isomer suggests stepwise motion in the macrocages attached with bulky substituents on the rotor.

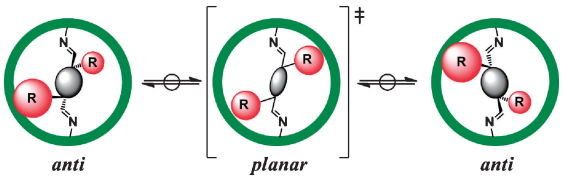
Macrocyclic molecules having a rotating unit in the center have attracted much attention in terms of their unique structures, dynamics, and functions.[1] Such macrocages are often called molecular gyroscopes or turnstiles as first proposed by Garcia-Garibay[2] and Moore,[3] respectively. Such cage molecules can serve as a useful motif for studying the internal motion of molecules, since the way and ease of the motion can be modified by the macrocycle/rotor structures.[1–3] Here we describe a new series of macrocyclic compounds bridged with a *trans*-cyclohexane-1,4-diimine unit, which exhibit characteristic rotational behavior (gyro-rotaion) depending on the steric bulkiness of the substituents on the cyclohexane rotor unit.

As shown in Scheme 1, the substituents on the rotor are accommodated in the macrocyclic cavity to adopt the *planar*-conformation as an energy-minimized geometry when the substituents are small enough (type-1). Very small activation energy is expected for the gyro-rotation for this class. As the substituents on the rotor become larger, the rotation of the cyclohexane unit is gradually slowed. The macrocages are prone to prefer another conformation, in which the substituents are directed to the opposite sides of the macrocycle (*anti*-conformation) (Scheme 2). The rotational motion of the cyclohexane unit in these type-2 compounds occurs via the *planar*-conformation, which corresponds to the transition state of gyro-rotation. Due to the limitation of the cavity size, much larger substituents can no longer go through the cavity (Scheme 3), and the *syn*-conformation would be involved as the intermediate of the rotational motion in type-3, in which the substituents are located on the same side of the macrocycle. The system undergoing stepwise partial-rotations is interesting from the viewpoint of unique intramolecular motion such as unidirectional rotation.[4]

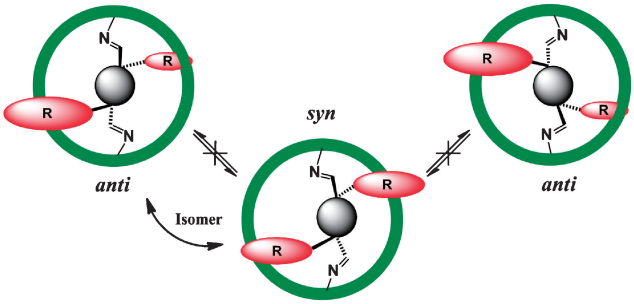
In this work, bis(*m*-terphenyl)-type diamines **1A** and **1B**[5] are chosen as the macrocyclic outer rings to study the rotational behavior depending on the substituent bulkiness as depicted above. We have succeeded in isolating both *anti*- and *syn*-conformations as stable species by attaching large enough substituents such as biphenyl-4-ylmethyl at the 1,4-positions of cyclohexane rotor units (type-3). In contrast, a cyclohexane rotor unit with smaller substituents such as methoxycarbonyl is freely rotating within the same macrocycle to exhibit gyro-rotation (type-1). The details are described herein (Figure 1).



Scheme 1. Gyro-rotation in molecular gyroscope with small substituents (Type-1).



Scheme 2. Gyro-rotation in molecular gyroscope with medium-sized substituents (Type-2).



Scheme 3. Hindered rotation in molecular gyroscope with very large substituent (Type-3).

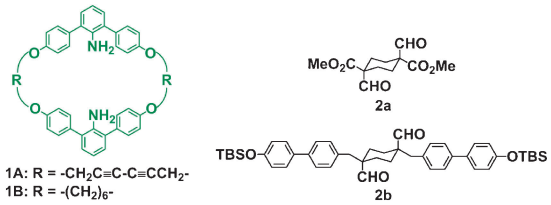
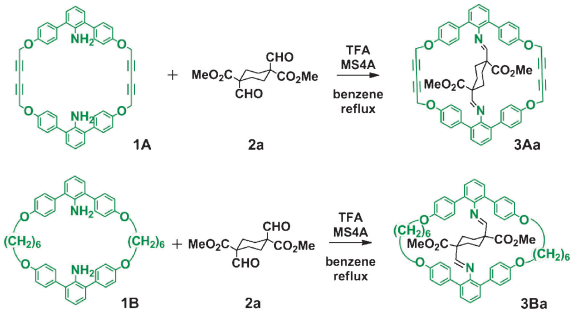


Figure 1. Structures of macrocycles **1A** and **1B** and cyclohexane units **2a** and **2b**.



Scheme 4. Synthesis of macrocyclic diimines **3Aa** and **3Ba**.

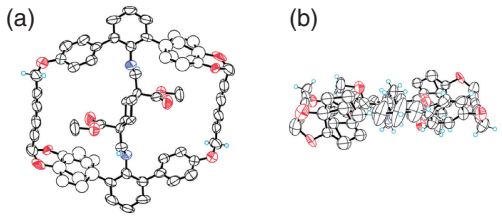


Figure 2. X-ray structure of diimine **3Aa**. (a) Front view and (b) top view.

Upon condensation of *trans*-dimethyl 1,4-diformylcyclohexane-1,4-dicarboxylate (**2a**)[6] with rigid macrocycle **1A** with hexadiyne parts connecting two aminoterphenyl units under acidic dehydrating conditions (refluxing benzene, TFA), macrocage diimine **3Aa**[7] was obtained in 15% yield,[8] which is sensitive to hydrolysis (Scheme 4).

According to the X-ray analysis on **3Aa**,[9] the molecule adopts the characteristic geometry of a type-1 molecular gyroscope and the two ester groups are accommodated within the cavity (Figure 2). A noteworthy structural feature is that ester groups larger than the imine units are located at the axial positions of cyclohexane. Such conformation is not favorable in terms of 1,3-diaxial interactions[10] but is suitable to connect the two amine groups of the outer macrocycle with a greater separation (N–N: 7.24 Å) than in the case of another conformation in which the two ester groups adopt the equatorial positions. Yet, the separation is still much narrower than the free macrocycle **1A** (8.52 Å) or benzene solvate (**1A**·(benzene)$_3$) (8.45 Å) determined by the X-ray analyses (Figures S1 and S2),[9,11] and the strain in the outer macrocycle of **3Aa** could account for its high sensitivity toward hydrolysis.

When another macrocycle **1B**, in which two aminoterphenyl units are connected by flexible hexamethylene chains, is condensed with the cyclohexane unit **2a**,[7] the ester groups may be located at the equatorial positions to reduce 1,3-diaxial interactions in molecular cage **3Ba** (Scheme 4).[7] This is the case, and the X-ray analysis[9] revealed the geometry in which two nitrogen atoms are connected by much smaller separation (6.00 Å) by locating the imine groups at the axial positions (Figure 3). Accordingly, the cyclohexanedicarboxylate unit in **3Ba** is more voluminous than in **3Aa**, but the ester groups can be still be accommodated in the cavity thanks to the flexible nature of the hexamethylene chains in the outer ring.

In solution, free rotation of the cyclohexane unit in molecular cages **3Aa** and **3Ba** is expected from the above X-ray structures, which was confirmed by ^{1}H NMR spectroscopy

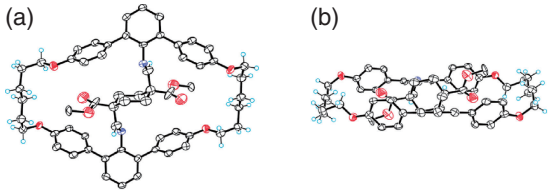


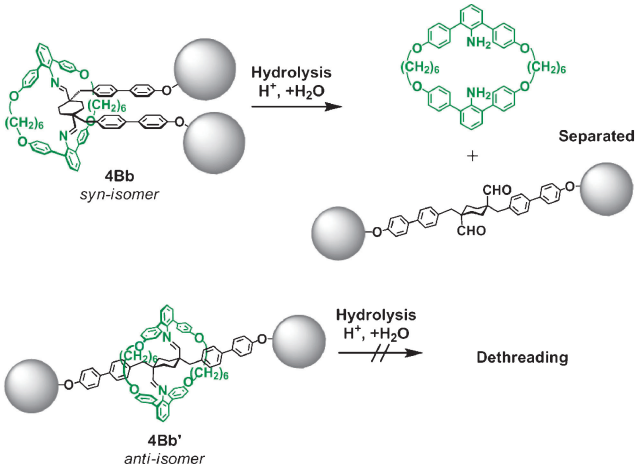
Figure 3. X-ray structure of diimine **3Ba**. (a) Front view and (b) top view.

(298 K, $CDCl_3$). For example, the 8 protons assigned as Ar–O–CH_2– units are observed as a sharp singlet (4.80 ppm) in **3Aa** or as a triplet (4.02 ppm, $J = 6.0$ Hz) in **3Ba**, which can be accounted for only by assuming the time-averaged higher symmetry. Thus, it can be concluded that the gyro-rotation in **3Aa** and **3Ba** is faster than the NMR time-scale at 298 K in solution (Figures S3 and S4[11]).

Next we turned our attention to generate the macrocyclic cage **3Ab** and **3Bb**, in which gyro-rotation is hindered due to the bulkiness of biphenyl-4-ylmethyl groups at the 1,4-positions of the cyclohexane unit. To further modify the terminal group of biphenyl unit later, 4′-TBSO groups are installed on the rotor precursor **2b**. As expected from Scheme 3, condensation of macrocycle **1A** and **2b** (refluxing benzene, TFA) afforded a mixture of two isomeric products **3Ab**/**3Ab′** (1:1)[7] in a combined yield of 37%. By starting with flexible macrocycle **2B**, isomeric mixture of **3Bb**/**3Bb′** were formed in about 2:1–3:1 ratio, which were separated by chromatography on Al_2O_3 (y. 31% and 12%, respectively).[7] At this moment, it is not clear which component of **3Bb**/**3Bb′** corresponds to the *syn*- or *anti*-isomer. However, the structural identity was unambiguously determined by the end-capping/hydrolysis technique[5] as follows.

The key feature we focused on is that only the *anti*-isomer has the structure in which the long rotor unit is threaded through the macrocyclic outer ring. Both of the *syn*- or *anti*-isomers **3Bb**/**3Bb′** could be hydrolyzed under the acidic conditions to regenerate **1B** and **2b**. In contrast, after attaching end-caps at the biphenyl termini, which is large enough to prevent dethreading, only *syn*-isomer can be hydrolyzed into the two components (**1B** and terminal-modified-**2b**), since the interlocked structure would be formed upon hydrolysis of *anti*-isomer (Scheme 5).

By the reaction of **3Bb** (major) and **3Bb′** (minor) with α-bromo-α'-{4-[tris(4′-*tert*-butylbiphenyl-4-yl)methyl]phenoxy}-*p*-xylene (**5**)[5] in the presence of TBAF/Cs_2CO_3, the terminal-modified compounds **4Bb** (major) and **4Bb′** (minor) were obtained (See Supporting Information). In the case of **4Bb**, the 8 protons assigned as Ar–O–CH_2– units are observed as four multiplet signals around 4.15, 4.00, 3.47, and 3.25 ppm, whereas the same 8 protons are observed as one multiplet signal (3.72 ppm) in **4Bb′**. These results can be accounted for by supposing that cyclohexane units in **4Bb** and **4Bb′** do not rotate. The ^{1}H NMR spectral changes under acidic hydrolytic conditions clearly indicate that **4Bb** derived from the major component **3Bb** gave **1B** and terminal-modified-**2b** (Figure 4), thus **3Bb** is the *syn*-isomer. On the other hand, the minor component **3Bb′** is proven to be the *anti*-isomer, since **4Bb′** derived from **3Bb′** showed only marginal spectral changes under hydrolytic conditions (Figure 5). Isolation of *syn*-isomer **3Bb** along with *anti*-



Scheme 5. Hydrolysis of (a) *syn*-isomer and (b) *anti*-isomer in wet $CDCl_3$. Shaded circles indicate 4-{4-[tris(4′-*tert*-butylbiphenyl-4-yl)methyl]phenoxymethyl}benzyl groups.

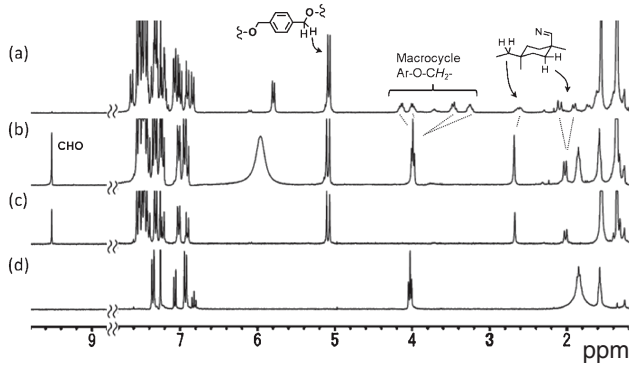


Figure 4. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of diimine **4Bb** (a) and its hydrolyzed mixture (b). (c) and (d) were measured after GPC separation of the hydrolyzed sample, which corresponds to (c) terminal-modified-**2b** and (d) macrocycle **1B**, respectively.

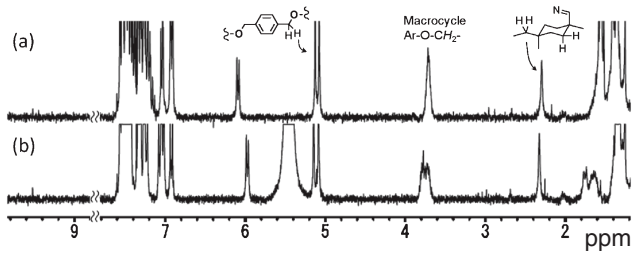


Figure 5. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of diimine **4Bb′** (a) before and (b) after an addition of TFA.

isomer **3Bb′** clearly shows that the hindered gyro-rotation of *anti*-**3Bb′** would occur, if at all, in a stepwise manner by involving *syn*-isomer **3Bb** as the intermediate.

In summary, the rotational motion of macrocage molecules, that mimic gyroscopes/turnstiles, are largely affected by the steric requirement of the rotor unit. By attaching the substituents with a different size, the mechanism of gyro-rotation would be divergent. The large substituents require the system to adopt the intermediate for the gyro-rotation as in type-3, for which the isomer can be isolated when the rotation is completely hindered.

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7 Experimental procedures and selected spectral data are given in the Supporting Information.

8 Although *trans*-**2a** used in the above reaction contains 20% of *cis*-isomer due to the less selective reduction of the tetraester precursor by DIBALH,[6] no product was isolated having the *cis*-diimine substructure.

9 **1A**: triclinic, $P\bar{1}$, $a = 7.751(10)$, $b = 12.548(15)$, $c = 19.64(2)$ Å, $\alpha = 71.35(4)$, $\beta = 78.69(5)$, $\gamma = 90.10(6)°$, $V = 1771(3)$ A^3, $Z = 2$, $R = 0.0929$; **1A·(benzene)$_3$**: triclinic, $P\bar{1}$, $a = 10.028(5)$, $b = 10.661(5)$, $c = 13.261(7)$ Å, $\alpha = 102.519(5)$, $\beta = 109.719(7)$, $\gamma = 101.017(7)°$, $V = 1247.8(11)$ A^3, $Z = 1$, $R = 0.0723$; **3Aa**: orthorhombic, *Pccn*, $a = 30.06(12)$, $b = 17.33(8)$, $c = 8.98(4)$ Å, $V = 4678(37)$ A^3, $Z = 4$, $R = 0.0615$; **3Ab**: triclinic, $P\bar{1}$, $a = 8.635(3)$, $b = 10.814(3)$, $c = 14.111(5)$ Å, $\alpha = 71.45(2)$, $\beta = 80.22(3)$, $\gamma = 75.87(3)°$, $V = 1205.2(6)$ A^3, $Z = 1$, $R = 0.109$.

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