ORGANIC LETTERS

2007
Vol. 9, No. 18
3559−3561

Synthesis of a Triply-Bridged Molecular Gyroscope by a Directed Meridional Cyclization Strategy

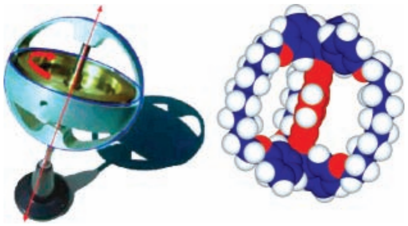
Jose E. Nuñez, Arunkumar Natarajan, Saeed I. Khan, and Miguel A. Garcia-Garibay*

Department of Chemistry and Biochemistry, University of California,
Los Angeles, California 90095-1569

mgg@chem.ucla.edu

Received June 11, 2007

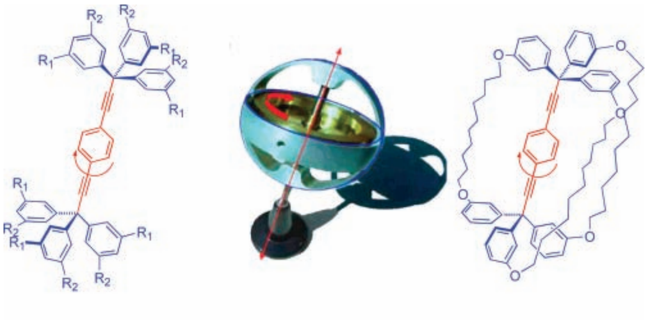
ABSTRACT



A crystalline triply bridged molecular gyroscope has been prepared and analyzed by single-crystal X-ray diffraction. A convergent synthetic strategy was developed to control the direction of the three bridges, from the preferred two zonal and one meridional arrangement of a one-step cylclization process to the directed three meridional bridges achieved by a north–south desymmetrization.

Growing interest in artificial molecular machinery[1] has led to the design and exploration of amphidynamic crystals as a new class of materials with physical properties that depend on the internal dynamics of mobile molecular components.[2] Our initial contributions have centered on molecules with shapes and functions analogous to those of macroscopic gyroscopes,[2a−e,3] such as compounds **1a−c** (Figure 1). They consist of an intrinsically barrierless[4] 1,4-dialkynylbenzene *rotator* as the dynamic component (red) and two triarylmethyl (trityl) or triptycyl groups acting as a *stator* (blue). In addition to providing steric shielding, the stator serves as a frame of reference to define the dynamics of the rotator in the crystal.[2a−e]

While steric hindrance in crystals results in rotational frequencies slower than those expected in the gas phase (~10^{12} s^{-1}),[2e] 2-fold flipping frequencies measured by solid-state NMR depend on the structure of the stator. At 298 K,



1a: R_1 = H, R_2 = H
1b: R_1 = OMe, R_2 = H
1c: R_1 = *t*-Bu, R_2 = *t*-Bu

Figure 1. Gyroscope consisting of a rotating mass (rotator) linked by an axle to a shielding enclosure (stator). Molecular analogues consist of a phenylene *rotator*, a dialkyne *axle* (red), and a bis-trityl *stator* (blue).

---

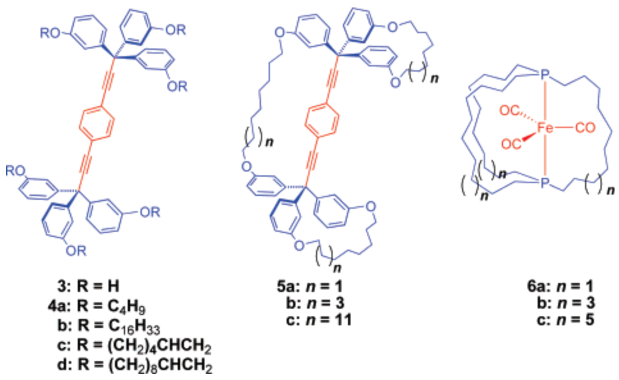
[1] (a) Balzani, V.; Credi, A.; Raymo, F.; Stoddart, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348. (b) Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. *Chem. Rev.* **2005**, *105*, 1281. (c) Bedard, T.C.; Moore, J. A. *J. Am. Chem. Soc.*, **1995**, *117*, 10662. (d) Kay, E. R.; Leigh, D. A.; Zerbetto, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 72. (e) Feringa, B. L.; Koumura, N.; Delden, R. A.; TerWiel, M. K. *J. Appl. Phys. A*, **2002**, *75*, 301. (f) Sestelo, J. P.; Kelly, T. R. *Appl. Phys. A* **2002**, *75*, 337. (g) Shirai, Y.; Morin, J.-F.; Sasaki, T.; Guerrero, J. M.; Tour, J. M. *Chem. Soc. Rev.* **2006**, *35*, 1043. (h) Marsella, M. J.; Rahbarnia, S.; Wilmont, N. *Org. Biomol. Chem.* **2007**, *5*, 391.

10.1021/ol071379y CCC: $37.00

they vary from ca. 800 Hz for **1a** ($R_1 = R_2 = H$)[2d] and 5 kHz for **1b** (R_1 = OMe, R_2 = H),[5a,b] up to >100 MHz for **1c** ($R_1 = R_2$ = tBu).[5c] Now, in order to better emulate the structure and function of a macroscopic gyroscope, we set out to synthesize compound **2** (Figure 1). It is anticipated that fully encapsulated rotators with polar groups (−F, NO_2, etc.) will exhibit interesting dielectric properties, as these are expected to respond to electric, magnetic, and optic stimuli.[2a−c,3,6]

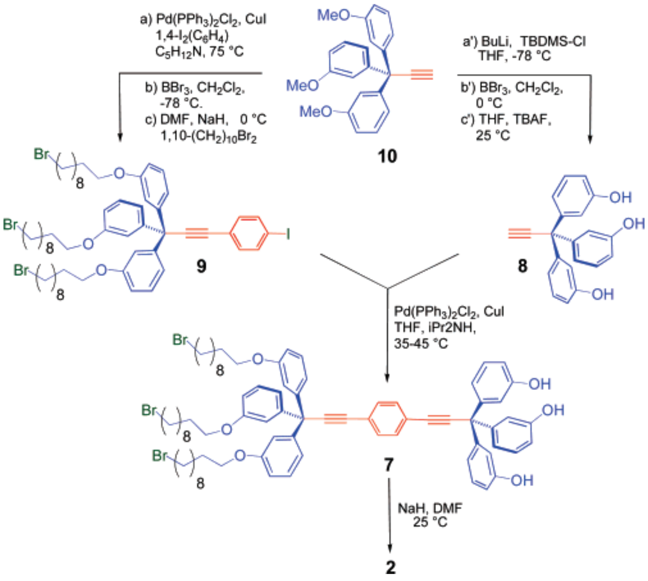
As a first step toward a general synthesis of triply bridged structures, we explored the functionalization of hexa-*m*-phenol **3**. We noticed that reaction of the hexaphenolate with 6 equiv of *n*-bromobutane or *n*-bromohexadecane in DMSO at 363 K produced derivatives **4a** and **4b** in ca. 80% yield within 15 min (Scheme 1). Encouraged by this and by molecular models suggesting that 8- and 10-carbon chains should have no obvious strain, we explored a one-pot reaction with 3.0 equiv of 1,8- and 1,10-dibromoalkanes. While the reactions proceeded rapidly and cleanly, triple cyclization led to the "open" structures **5a** and **5b**, with one meridional (north-south) and two zonal (east-west) bridges. These compounds were characterized by NMR and mass spectrometry, and the structure was confirmed by single-crystal X-ray diffraction in the case of **5b** (Scheme 1).[7]

Scheme 1



Recognizing the success of Gladysz et al.[8] on the synthesis of metal-centered gyroscopes (**6a**−**c**, Scheme 1) through metathesis reactions,[9] we decided to synthesize the *ω*-alkenyloxy derivatives **4c** and **4d**. We selected 6 and 10 *ω*-alkenyl carbon chains to explore the effect of the ring closing metathesis reaction on the formation of 10 and 18 carbon bridges to form the required 28- and 36-membered macrocyles. Unfortunately, metathesis reactions with $PhCH{=}RuCl_2(PCy_3)_2$ or $PhCH{=}RuCl_2(ImesH_2)(PCy_3)$[9] followed by PdC-catalyzed hydrogenation yielded compounds **5b** and **5c**, respectively, with zonal and meridional bridges. Given the drawbacks of the symmetrically functionalized precursor, next we investigated a directed meridional approach with the asymmetric precursor **7** (Scheme 2).

Scheme 2



We envisioned the synthesis of compound **7** by Pd(0)-catalyzed coupling of terminal alkyne **8** with iodophenylene

---

(2) (a) Khuong, T.-A.; Nuñez, J. E.; Godinez, C. E.; Garcia-Garibay, M. A. *Acc. Chem. Res.* **2006**, *39*, 413. (b) Garcia-Garibay, M. A. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10771. (c) Garcia-Garibay, M. A. *Top. Curr. Chem.* **2006**, *262*, 179. (d) Dominguez, Z.; Dang, H.; Strouse, M. J.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 7719. (e) Godinez, C. E.; Zepeda, G.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 4701. (f) Gardinier, J. R.; Pellechia, P. J.; Smith, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 12448. (g) Zhu, H. F.; Wang, X. F.; Okamura, T. A.; Sun, W. Y.; Ueyama, N. *J. Coord. Chem.* **2006**, *59*, 429. (h) Vaughan, O. P. H.; Williams, F. J.; Bampos, N.; Lambert, R. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3779. (i) Setaka, W.; Sato, K.; Ohkubo, A.; Kabuto, C.; Kira, M. *Chem. Lett.* **2006**, *35*, 596. (j) Horike, S.; Matsuda, R.; Tanaka, D.; Matsubara, S.; Mizuno, M.; Endo, K.; Kitagawa, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7226. (k) Sato, D.; Akutagawa, T.; Takeda, S.; Noro, S.; Nakamura, T. *Inorg. Chem.* **2007**, *46*, 363.

(3) Analogous structures with polar rotators have properties analogous to macroscopic compasses: (a) Dominguez, Z.; Khuong, T.-A. V.; Dang, H.; Sanrame, C. N.; Nuñez, J. E.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 8827. (b) Horansky, R. D.; Clarke, L. I.; Price, J. C.; Khuong, T.-A. V.; Jarowski, P. D.; Garcia-Garibay, M. A. *Phys. Rev. B* **2005**, *72*, 014302. (c) Horansky, R. D.; Clarke, L. I.; Winston, E. B.; Price, J. C.; Karlen, S. D.; Jarowski, P. D.; Santillan, R.; Garcia-Garibay, M. A. *Phys. Rev. B* **2006**, *74*, 054306.

(4) (a) Abramenkov, A. V.; Almenningen, A.; Cyvin, B. N.; Cyvin, S. J.; Jonvik, T.; Khaikin, L. S.; Roemming, C.; Vilkov, L. V. *Acta Chem. Scand.* **1988**, *A42*, 674. (b) Sipachev, V. A.; Khaikin, L. S.; Grikina, O. E.; Nikitin, V. S.; Traettberg, M. *J. Mol. Struct.* **2000**, 523, 1.

(5) (a) Nuñez, J. E.; Khuong, T.-A. V.; Campos, L. M.; Farfan, N.; Dang, H.; Karlen, S. D.; Garcia-Garibay, M. A. *Cryst. Growth Des.* **2006**, *6*. 866. (b) Khuong, T.-A. V.; Dang, H.; Jarowski, P. D.; Maverick, E. F.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 839. (c) Khuong, T.-A. V.; Zepeda, G.; Ruiz, R.; Khan, S. I.; Garcia-Garibay, M. A. *Cryst. Growth Des.* **2004**, *4*, 15.

(6) Rozenbaum, V. M. *Sov. Phys. JETP* **1991**, *72*, 1028.

(7) Compound **2**: $C_{78}H_{88}O_6$, C_7H_8, 0.5 (C_7H_8), 0.15 (C_6H_6), colorless plates, MW = 1267.20, triclinic, $P\bar{1}$, a = 11.6972(16) Å, b = 18.1228(3) Å, c = 18.781(2)Å, α = 111.3840(16)°, β = 96.2430(3)°, γ = 90.9480-(3)°, Z = 2, F_000 = 1367, λ = 0.71073, T = 100(2) K, crystal size = 0.2 × 0.2 × 0.1, R_1 = 0.0621, wR_2 = 0.1639 (all data). **5b**. While plate-like crystals of **5b** from $CHCl_3$ failed to give good data refinement, we were able to obtain the connectivity and a reasonable packing arrangement: $C_{78}H_{88}O_6$, colorless plates, MW = 1121.48, tetragonal, P-4, a = 16.9165-(7) Å, b = 16.9165(7) Å, c = 11.7976(10) Å, α = 90.0°, β = 90.0°, γ = 90.0°, Z = 2, λ = 0.71073, T = 100(2) K, crystal size = 0.3 × 0.2 × 0.1.

(8) (a) Wang, L.; Hampel, F.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4372. (b) Narwara, A. J.; Shima, T.; Hampel, F.; Gladysz, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 4962. (c) Shima, T.; Hampel, F.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5537.

9, both being available from known tris(*m*-methoxy)trityl alkyne **10**.[5a] For the successful implementation of Scheme 2 we made the key observation that the BBr_3 removal of the methyl groups cannot be accomplished with a terminal alkyne. Therefore, **10** was reacted with a 2.5-fold excess of 1,4-diiodobenzene under Sonogashira conditions before it was submitted to demethylation with BBr_3[10] and subsequent alkylation with a large excess (18 equiv) of 1,10-dibromodecane. The desired tris(ω-bromoalkoxy) precursor **9** was obtained in 25% yield over three steps. Similarly, triphenol **8** was obtained by protection of **10** with TBDMS-Cl[11] prior to removal of the methyl groups with BBr_3[10] and removal of TBDMS with TBAF.[12] Sonogashira coupling of tribromide **9** with triphenol **8** gave compound **7**, a heavy oil, in 67% yield. Finally, reaction of **7** with 3 equiv of NaH in DMF for 19 h at 0−25 °C provided the desired meridional bridges of molecular gyroscope **2**. Satisfyingly, the three 28-membered macrocycles of the novel tricyclic structure are obtained in 27% isolated yield, for an average yield of 65% per cyclization step.

Molecular gyroscope **2** is a crystalline solid that dissolves well in boiling CH_2Cl_2 and $CHCl_3$ and only poorly in aromatic solvents. The solution ^1H and ^{13}C NMR of **2** are consistent with a rapidly equilibrating structure with a time-averaged C_{3h} point group. X-ray diffraction data from single crystals grown in mixtures of toluene and benzene were solved in the space group $P\bar{1}$ as a nonstoichiometric mixed clathrate.[7] The chemical formula of the asymmetric unit is $C_{78}H_{88}O_6$, $1.5C_6H_5CH_3$, $0.15C_6H_6$, with one molecule of **2**, one toluene molecule in a general position, and half of another toluene molecule at an inversion center[7] (Figure 2). One of the three bridges and the central phenylene are disordered over two positions with relative occupancies of 15% and 85% that correlate well with the presence or absence of substoichiometric benzene. The trityl groups of each molecule adopt propeller conformations of the same chirality but with aryl groups having different torsion angles for a molecular point group C_1. As illustrated in the right side of Figure 2, the steric shielding provided by three alkyl chains is not ideal. While the three bridges (in blue) curve away from the center to maximize the space around the rotator, bridges from neighboring molecules (in green) and included solvent molecules (in purple and magenta) reduce the free volume about the prospective rotator. The molecular and crystal structure of **2** suggests that bulkier chains will be required to create the shielding needed to prevent close packing interactions and the inclusion of solvent molecules. With a promising directed strategy now in place, a wide range of triply bridged derivatives are now in preparation for dynamic testing.

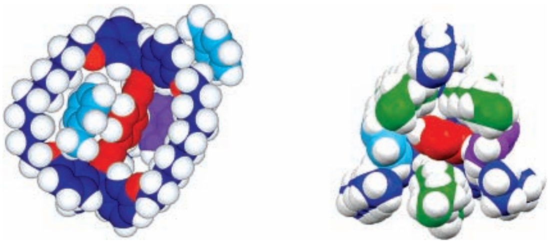


Figure 2. (Left) Space-filling model from the X-ray structure of **2** with the dialkynyl phenylene and oxygens shown in red, alkyl bridges in blue, and solvent molecules in magenta (toluene) and purple (benzene). (Right) Representation of the environment of the central phenylene viewed along its 1,4-axis illustrating the cage formed by its own alkyl chains, those of neighboring molecules (in green), and solvent molecules. The disorder in the structure is not shown (see text).

Acknowledgment. This work was supported by the National Science Foundation through Grant Nos. DMR0307028, DMR0605688, and DGE-0114443 [NSF IGERT: Materials Creation Training Program (MCTP)].

Supporting Information Available: Syntheses and characterization of **2** and **5a−c**. Crystallographic information for **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL071379Y

---

(9) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(10) Shultz, D. A.; Kumar, R. K. *J. Am. Chem. Soc*. **2001**, *123*, 6431.

(11) Ockey, D. A.; Lewis, M. A.; Schore, N. E. *Tetrahedron* **2003**, *59*, 5377.

(12) Takeda, T.; Ozaki, M.; Kuroi, S.; Tsubouchi, A. *J. Org. Chem*. **2005**, *70*, 4233.