J|A|C|S
COMMUNICATIONS

Published on Web 08/28/2004

Simultaneous Freezing of Chirality and In−Out Conformation of a Macropentacyclic Cryptand by Protonation

Clément Bonnot, Jean-Claude Chambron,* and Enrique Espinosa

Laboratoire d'Ingénierie Moléculaire pour la Séparation et les Applications des Gaz (CNRS, UMR 5633), Université de Bourgogne, 6 boulevard Gabriel, 21100 Dijon, France

Received March 18, 2004; E-mail: Jean-Claude.Chambron@u-bourgogne.fr

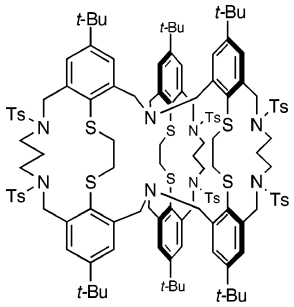
A great variety of molecules are chiral by virtue of a helical structure. Classical examples are helicenes, double-stranded DNA, and helicates.[1] Helicity results from twisting, an effect that is due to steric hindrance, strain, or stereoelectronic factors such as sequences of homochiral stereogenic units found in helical natural and synthetic polymers, or geometries of transition metal complexes. Currently explored issues are the control of the expression of helicity from a pre-existing achiral structure and the stabilization of the helical forms of a molecular structure that may encompass a variety of conformations while favoring one helix over the other and preventing helix racemization. These have been addressed by studies that have led to the development of the concepts of helicity programming, helicity amplification, supramolecular helicity induction, and chirality memory effects. Remarkable examples of systems that have been investigated in this context are zinc biliverdin[2a] and bis-porphyrin derivatives,[2b,c] oligo(pyridine−pyrimidine/dicarboxamide) strands,[3a,b] foldamers,[3c] saddle-shaped macrocycles,[4] self-assembled capsules,[5] columnar aggregates,[6] and polymers.[7]

An alternative would be to use flexible, covalent cage molecules that can adopt many conformations, including helical ones. In support of this proposition, a few such systems were shown to crystallize in helical forms[8] or, better, display helical shapes in solution.[9]

In this Communication, we show that protonation freezes the flexible molecule **1** (Chart 1) in a helically chiral in−out conformation both in solution and in the solid state. It is noteworthy that a significant diastereomeric excess (de) can be obtained when the optically active (*R*)-(−)-1,1′-binaphthyl-2,2′-diylphosphoric acid (BNPH) is used as proton source.

Compound **1** is a cryptand-derived macropentacycle.[10a] The 15-atom-membered N_2S_2 macrocyclic bridges are unsymmetrical, the shorter fragment being directed toward the inner part of the molecule, as suggested by a CPK model. The molecule looks like a ball-shaped bundle of atoms, with a crowded, S-rich core. Its room temperature (RT) ^{1}H NMR spectrum shows broad features that are diagnostic of slowly interconverting conformers. Easily identified are the signals of the tosyl (Ts) and *t*-Bu substituents, which suggest that the molecule has nevertheless a time-averaged D_{3h} symmetry. This ideally symmetrical molecule is fully realized at ∼110 °C ($C_2D_2Cl_4$), where relatively sharp signals are observed for all the groups of equivalent protons (Figure S1). At low temperature (−35 °C), numerous signals are observed which are indicative of a mixture of nonexchanging and/or unsymmetrical conformations. For example (Figure S2), the CH_3 signals of the Ts substituents are scattered in two groups (2.40 and 2.00 ppm). The coalescence temperature of these groups is +9 °C, which gives for the interconversion process between symmetrical and unsymmetrical conformations $\Delta G_c^{\ddagger} = 54.7$ kJ mol^{-1} ($T_c = 282$ K, $\Delta\nu = 200$ Hz).[10a−c] At lower temperature (−63 °C, CD_2Cl_2), characteristic patterns of diastereotopic protons indicate that chiral conformations have also been frozen (Figure S3a).

Chart 1



1

After standing for several days, a $CHCl_3$ solution of **1** shows two spots by TLC, which correspond to the neutral starting material and to a new, polar product, respectively. Protonation is immediate when a dry $CDCl_3$ solution of **1** is stirred in the presence of an equimolar amount of CF_3CO_2H (TFAA, p$K_a = 0$). When 1 equiv of CF_3SO_3H (TfOH, p$K_a = -16$) is used, the protonation is slow ($t_{1/2} = 2.5$ h) and proceeds through intermediates (Figure S4). The protonated species shows an intense peak in the MALDI-TOF spectrum at $m/z = 2401$ that corresponds indeed to the singly charged species $[M + H]^+$. The RT ^{1}H NMR spectrum of the monoadduct [**1**-H](OTf) in $CDCl_3$ is perfectly resolved (Figure S5) and is consistent with that of a molecule with C_3 symmetry, lower than that of neutral **1** at high temperature. It is noteworthy that several features of the spectrum of the protonated species are reminiscent of those observed for the neutral form at low temperature (Figure S3). In addition, all the methylene protons form pairs of diastereotopic atoms. Therefore, at least on the NMR time scale, the monoprotonated species is rigidly chiral in solution and has the in−out conformation. The proton is presumably encapsulated in the cavity, where it can form hydrogen bonds with the inner sulfur atoms, as suggested by its low-field NMR resonance (9.40 ppm).[10b] $[\mathbf{1}\text{-H}]^+$ would thus have the (i^+,o) form, while monoprotonated cryptands usually take up the (i^+,i) form in solution.[10d,e] The encapsulated proton does exchange with D_2O and is removed by reaction of [**1**-H](OTf) with sodium methoxide (20 equiv in CH_3-OH) within several hours. Unlike cryptand [1.1.1], which cannot be deprotonated in 5 M KOH,[10d] but as noted earlier for cryptand [2.2.2],[10e] macropentacycle **1** behaves as an ordinary tertiary amine, its basicity being intermediate between that of DABCO (p$K_{BH^+} =$ 18.29) and that of [2.2.2] (p$K_{BH^+} = 18.60$) in CD_3CN (Supporting Information).

Additional information was provided by single-crystal X-ray diffraction analysis. The ORTEP representation of Figure 1a clearly shows that the monoprotonated species has the in−out conformation. It is noteworthy that the proton was unambiguously located

10.1021/ja048441w CCC: $27.50

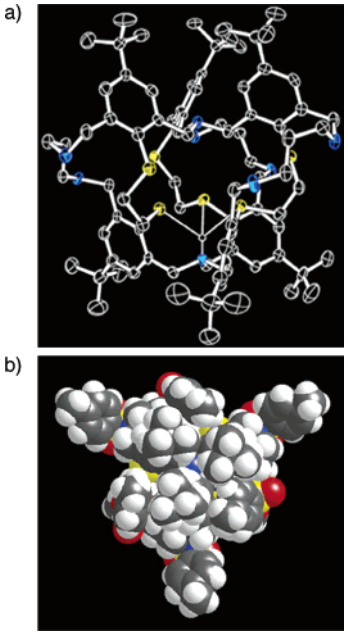


Figure 1. X-ray crystal structure of [**1**-H](OTf). (a) ORTEP representation (Ts groups and H atoms removed for clarity). Selected H-bonding distances (Å) and angles (°): (N1)H···S = 2.64(5), 2.54(5), 2.60(5); N1—H···S = 120(3), 133(4), 123(4). (b) CPK representation down the C_3 axis (exo side).

using a Fourier difference map and its positional parameters were refined leading to a fast convergence. As expected, it was found to reside on the endo bridgehead nitrogen atom. It is hydrogen-bonded to the three closest sulfur atoms (average distance, 2.59 Å). The exo nitrogen is involved in weak hydrogen-bonding interactions (Table S1) with three aryl hydrogen atoms (average distance, 2.43 Å) and is buried in a hydrophobic pocket that is efficiently locked by the *t*-Bu groups, as shown by a CPK view down the C_3 axis (Figure 1b).

Stiffness of the molecule in the monoprotonated state most likely results from the $[NH\cdots S]^+$ hydrogen bonds. To relieve the strain that is enforced by the in−out orientation of the bridgehead nitrogens, the protonated molecule takes up the shape of a three-blade propeller, each blade consisting of a macrocyclic subunit, with a 49° global twist. Therefore, the molecule is also helically chiral in the solid state.

Once it was established that the chirality of [**1**-H](OTf) resulted from the regioselective protonation of **1**, the experiments were conducted using an acid derived from an optically active anion. It was hoped that, by analogy with the Pfeiffer effect in coordination chemistry,[11] asymmetric induction on the helicity of $[\mathbf{1}\text{-H}]^+$ would take place. (*R*)-(−)-BNPH was selected as chiral proton source.[12] [**1**-H]((*R*)-(−)-BNP) was prepared by reaction of equimolar amounts of **1** and (*R*)-(−)-BNPH in CH_2Cl_2/CH_3OH 5%. The solvents were removed and the residue was examined by ^{1}H NMR. Several signals of the product were split by comparison with [**1**-H](TFA). In $CDCl_3$ the integration ratio of the split signals was 62:38 (Figure 2), which corresponds to a 24% de. In more polar acetone-d_6, the dr was lowered to 55:45 (Figure S6). This ratio was left unchanged after heating the mixture at 50 °C overnight, indicating that the diastereoselectivity induced by the optically active (*R*)-(−)-BNP^- anion is of thermodynamic origin.

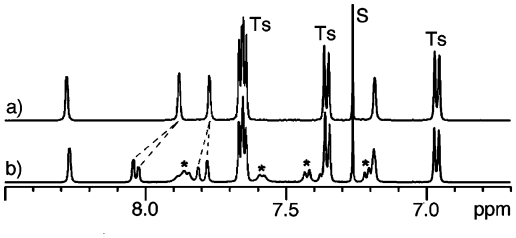


Figure 2. 500 MHz ^{1}H NMR spectra ($CDCl_3$) of (a) [**1**-H](TFA) and (b) **1** after reaction with (*R*)-(−)-BNPH (∗).

Acknowledgment. This paper is dedicated to Professor Jean-Pierre Sauvage on the occasion of his 60th birthday. We thank the reviewers for helpful comments and Dr. Michel Meyer for fruitful discussions.

Supporting Information Available: ^{1}H NMR spectra of **1** (VT), $[\mathbf{1}\text{-H}]^+$ as TFA^-, OTf^-, and (*R*)-(−)-BNP^- salts, determination of the relative basicity of **1**, crystallographic data for [**1**-H](OTf) (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Meurer, K. P.; Vögtle, F. In *Topics in Current Chemistry, Vol. 127, Organic Chemistry*; Boschke, F. L., Ed.; Springer-Verlag: New York, 1985; pp 1−76. (b) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995; Chapter 9.
(2) (a) Mizutani, T.; Yagi, S.; Honmaru, A.; Ogoshi, H. *J. Am. Chem. Soc.* **1996**, *118*, 5318. (b) Huang, X.; Borhan, B.; Rickman, B. H.; Nakanishi, K.; Berova, N. *Chem.-Eur. J.* **2000**, *6*, 216. (c) Kubo, Y.; Ohno, T.; Yamanaka, J.-i.; Tokita, S.; Iida, T.; Ishimaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 12700.
(3) (a) Ohkita, M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem.-Eur. J.* **1999**, *5*, 3471. (b) Berl, V.; Huc, I.; Khoury, R. G.; Lehn, J.-M. *Chem.-Eur. J.* **2001**, *7*, 2798. (c) Prince, R. B.; Barnes, S. A.; Moore, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 2758.
(4) Mizuno, Y.; Aida, T. *Chem. Commun*. **2003**, 20.
(5) (a) Ishi-i, T.; Crego-Calama, M.; Timmerman, P.; Reinhoudt, D. N.; Shinkai, S. *J. Am. Chem. Soc.* **2002**, *124*, 14631. (b) Ikeda, A.; Udzu, H.; Zhong, Z.; Shinkai, S.; Sakamoto, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **2001**, *123*, 3872. (c) Hiraoka, S.; Harano, K.; Tanaka, T.; Shiro, M.; Shionoya, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5182. (d) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469.
(6) (a) Engelkamp, H.; Middelbeek, S.; Nolte, R. J. M. *Science* **1999**, *284*, 785. (b) Brunsveld, L.; Lohmeijer, B. G. G.; Vekemans, J. A. J. M.; Meijer, E. W. *Chem. Commun.* **2000**, 2305. (c) Fenniri, H.; Deng, B.-L.; Ribbe, A. E. *J. Am. Chem. Soc.* **2002**, *124*, 11064.
(7) (a) Green, M. M.; Garetz, B. A.; Munoz, B.; Chang, H.-P.; Hoke, S.; Cooks, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 4181. (b) Yashima, E.; Matsushima, T.; Okamoto, Y. *J. Am. Chem. Soc.* **1995**, *117*, 11596. (c) Schlitzer, D. S.; Novak, B. M. *J. Am. Chem. Soc.* **1998**, *120*, 2196. (d) Sanji, T.; Yoshiwara, A.; Sakurai, H.; Tanaka, M. *Chem. Commun*. **2003**, 1506.
(8) (a) Vögtle, F.; Wallon, A.; Müller, W. M.; Werner, U.; Nieger, M. *J. Chem. Soc., Chem. Commun.* **1990**, 158. (b) MacGillivray, L. R.; Atwood, J. L. *J. Org. Chem*. **1995**, *60*, 4972. (c) Perkins, D. F.; Lindoy, L. F.; Meehan, G. V.; Turner, P. *Chem. Commun*. **2004**, 152.
(9) (a) Vögtle, F.; Hohner, G. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 497. (b) Nakazaki, M.; Yamamoto, K.; Toya, T. *J. Org. Chem*. **1981**, *46*, 1611. (c) Bolm, C.; Sharpless, K. B. *Tetrahedron Lett.* **1988**, *29*, 5101. (d) L'Esperance, R. P.; West, A. P., Jr.; Van Engen, D.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 2672. (e) Alajarín, M.; López-Leonardo, C.; Vidal, A.; Berná, J.; Steed, J. W. *Angew. Chem., Int. Ed*. **2002**, *41*, 1205.
(10) (a) Dietrich, B.; Lehn, J. M.; Sauvage, J. P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629. (b) Cheney, J.; Kintzinger, J. P.; Lehn, J. M. *Nouv. J. Chim.* **1978**, *2*, 411. (c) Adam, K. R.; Atkinson, I. M.; Kim, J.; Lindoy, L. F.; Matthews, O. A.; Meehan, G. V.; Raciti, F.; Skelton, B. W.; Svenstrup, N.; White, A. H. *J. Chem. Soc., Dalton Trans*. **2001**, 2388. (d) Smith, P. B.; Dye, J. L.; Cheney, J.; Lehn, J. M. *J. Am. Chem. Soc.* **1981**, *103*, 6044. (e) Cox, B. G.; Schneider, H. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1293.
(11) (a) Pfeiffer, P.; Quehl, K. *Chem. Ber*. **1931**, *64*, 2667. (b) Lacour, J.; Jodry, J. J.; Monchaud, D. *Chem. Commun*. **2001**, 2302.
(12) Jacques, J.; Fouquey, C.; Viterbo, R. *Tetrahedron Lett.* **1971**, 4617.

JA048441W