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Published on Web 05/17/2002

Solvent Triggering between Conformational States in Amphiphilic Shape-Persistent Macrocycles

Sigurd Höger,* Donald L. Morrison,§ and Volker Enkelmann

Contribution from the Max Planck Institute for Polymer Research, Ackermannweg 10, 55128 Mainz, Germany

Received November 28, 2001

Abstract: The amphiphilic shape-persistent macrocycle **1** containing four phenol-OH groups as polar side groups and four hexyloxy groups as nonpolar side groups in an adaptable arrangement was recrystallized from solvents of different polarity. X-ray crystallography reveals that the conformation of the macrocycle is solvent dependent such that in the pyridine solvate only two of the nonpolar side groups point outward while in the THF solvate all four of them point outward. Moreover, in the latter case the three-dimensional packing leads to the formation of a supramolecular channel structure with a large pore size.

Introduction

The solvent influence on the conformational behavior of organic molecules is of great importance both in academia and in applied science. For example, hydrophobic interactions determine the conformation of biopolymers and their model systems.[1] The rational drug design by studying structure−activity relationships requires the analysis of the molecule conformation in solution that can change in different solvents.[2] Stimuli-responsive hybrid macromolecules based on branched structures alter the polarity of their shell in different surrounding media,[3] and defined linear oligomers can fold into helical superstructures by solvent effects.[4] In addition, conformational changes based on an external stimuli are the basis of molecular machines.[5]

However, so far most investigations on solvent-induced conformational changes in artificial minimal model systems have been performed in solution.[6] We have recently shown that amphiphilic shape-persistent macrocycles, like **1**, can adopt different conformations depending on the solvent and the presence of appropriate guest molecules in such a way that either the phenol-OH groups or the alkyloxy groups of the ring point inward (molecular reversible coats).[7] More specifically, when the propyloxy analogue of **1** is recrystallized from the polar solvent pyridine it adopts a conformation in which the polar phenol-OH groups point outward and the propyloxy groups form a rather nonpolar interior. On the other hand, NMR titration studies in $C_2D_2Cl_4$ have shown that **1** binds large rigid tetraamines in solution that can only be explained if the macrocycle adopts a conformation in which all four polar phenol-OH groups are pointing toward the interior of the ring. However, in both cases the interior of the ring is filled, either by the alkyloxy groups or by the guest molecule. Therefore, we are highly interested in the question of whether the conformation of these macrocycles can be influenced by solvent effects alone, leading to solid state structures in which the internal void is filled only by solvent molecules. Moreover, if the rings pack on top of each other this gives rise to the formation of channel structures.

Results and Discussion

To investigate if shape-persistent macrocycles with an adaptable arrangement of amphiphilc groups can adopt different conformations by solvent effects alone, macrocycles such as **1** with varied nonpolar side groups were prepared and recrystallized from solvents of different polarity.[8] After several attempts, we were able to obtain single crystals of **1** suitable for X-ray investigation from two solvents (Scheme 1).

From pyridine, **1** crystallizes with the inclusion of six solvent molecules per ring (**1**·6py). Four of them form hydrogen bonds (distances: 2.71 and 2.72 Å) with the four phenol-OH groups of the macrocycle (Figure 1). The remaining two pack within the crystal lattice without specific interactions, specifically no

* To whom correspondence should be addressed: Fax (+49) 6131 379 100. E-mail: hoeger@mpip-mainz.mpg.de. Present address: Universität Karlsruhe, Polymer-Institut, Hertzstrasse 16, 76187 Karlsruhe, Germany. E-mail: shoeger@polyibm2.chemie.uni-karlsruhe.de.

§ Present address: The Dow Chemical Company, P.O. Box 8361, 3200 Kanawha Turnpike, South Charleston, WV 25303-0361.

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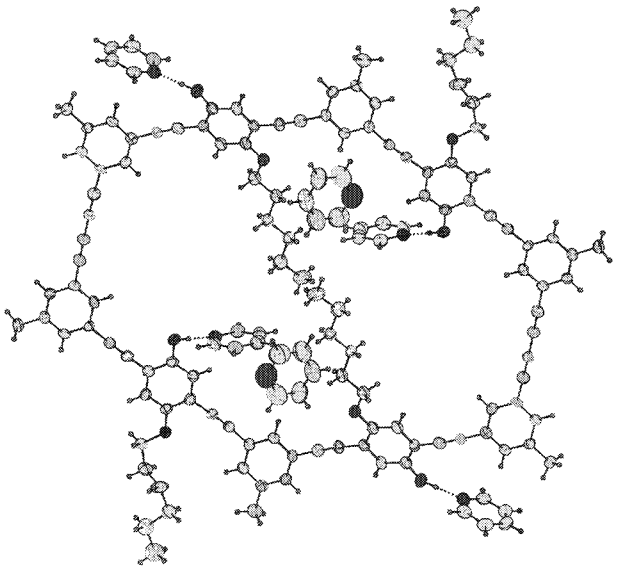


Figure 1. Crystal structure of **1**·6py. Only one of the disordered groups is shown for clarity.

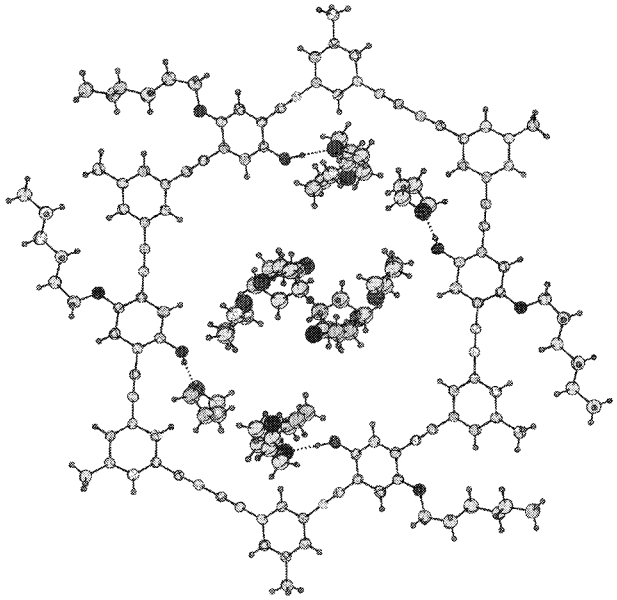
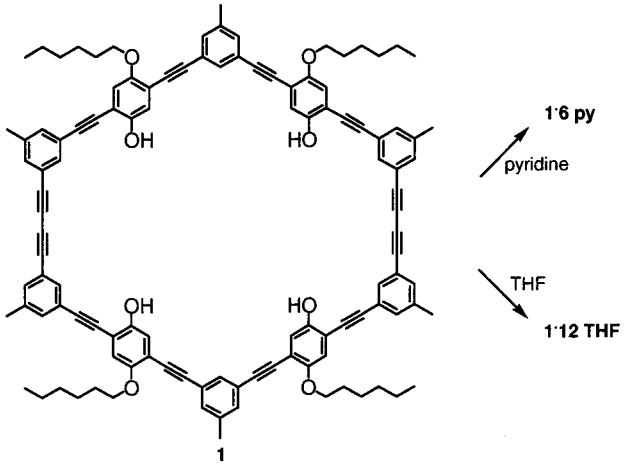


Figure 2. Crystal structure of **1**·12THF. Only one of the disordered groups is shown for clarity.

Scheme 1



apparent $\pi-\pi$ interactions between the pyridine molecules and the aromatic parts of the macrocycles were observed.

The macrocycle adopts a conformation in which two of the four phenol groups point inward as well as two of the hexyloxy groups. The terminal two carbon atoms of the internal hexyloxy groups are in close contact, thus crossing the whole lumen. The remaining two hexyloxy groups of the ring point outward and fill the space between neighbored rings. The external groups are disordered, i.e., the terminal three C-atoms occupy two sites which are occupied by 31% and 69%, respectively. This is different from the results obtained for the propyloxy analogue of **1**, where the pyridine solvate adopts a conformation such that all four alkoxy side groups point inward.[7a] The fact that in **1**·6py only two of the alkoxy groups point inward might be attributed to steric reasons.

A different result was obtained by crystallizing **1** from the less polar solvent THF affording **1**·12THF (Figure 2). Like crystals of **1**·6py, these crystals also decompose, even more rapidly, when removed from the mother liquor due to the loss of solvent. Nevertheless, as with **1**·6py, embedding in inertoil allowed the low-temperature data collection. Four of the included twelve solvent molecules form hydrogen bonds to the phenol-OH groups of the macrocycle (distances: 2.76 and 2.85 Å). The conformation of the macrocycle in **1**·12THF differs from the ring conformation in **1**·6py such that now all nonpolar hexyloxy groups point to the outside. Two of them as well as all solvent molecules are disordered. The results of the crystal structure analysis are in accordance with the Hildebrand solubility parameter δ.[9]

The supramolecular organization of the macrocycles is shown in Figure 3 in comparison. In both cases the packing of the rings is quite similar, forming a honeycomb-like ribbon in which the long sides of the cycles are stacked on top of each other. This gives rise to channel structures in which the channels extend along the line of view in Figure 3.[10] However, the accessible pore diameter in **1**·6py is quite limited (ca. 4−5 Å)

(9) A good solvent for a certain nonelectrolyte should have a δ value close to that of the solute. The δ value of hexane (14.1 $MPa^{1/2}$), which was chosen as a substitute for the nonpolar side group, is closer to THF (19.4 $MPa^{1/2}$), while the δ value of methanol (29.7 $MPa^{1/2}$), which was chosen as a substitute for the polar side group, is closer to pyridine (21.9 $MPa^{1/2}$). Brandrup, J.; Immergut, E. H.; Grulke, E. A., Eds. *Polymer Handbook*, 4th ed.; Wiley: New York, 1999; Vol. VII, p 688. It was expected that with crystallization from solvents with a higher polarity than pyridine all four side groups of **1** would pack inside the macrocycle. However, crystals obtained from DMSO (δ = 29.7 $MPa^{1/2}$), DMF (δ = 24.8 $MPa^{1/2}$), or dimethylacetamide (DMA) (δ = 22.1 $MPa^{1/2}$) turned out to be extremely sensitive and degraded within minutes at ambient conditions so that all attempts to obtain satisfactory X-ray data failed. Crystals formed by slow evaporation of DMA solutions which were immersed into inert oil developed striations within seconds and exhibited an increased mosaic spread and finally turned opaque even if kept at low temperatures. With these crystals data were collected rapidly (t < 2 h) at 120 K on a Nonius KCCD diffractometer [triclinic, $P\bar{1}$, a = 9.374(1) Å, b = 18.419(1) Å, c = 23.233(2) Å, α = 77.134(2)°, β = 85.923(2)°, γ = 87.434(2) °, V = 3899.1 $Å^3$]. Of 13742 unique reflections only 1911 were considered observed ($I > 3\sigma(I)$). All attempts to solve the crystal structure with these data failed. Assuming a density of about 1.1 g cm^{-3} the solvent content can be assessed as 12 molecules of DMA per macrocycle. However, the direction of the side groups could not be determined.

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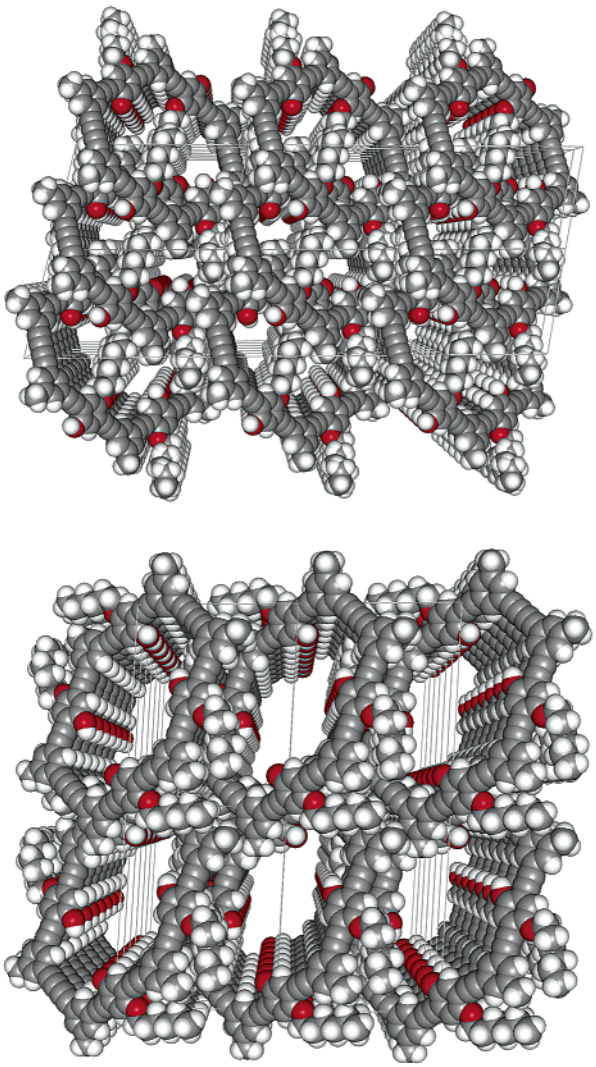

Figure 3. Top: A view down the crystalographic *a*-axis of **1**·6py showing small channels within the crystal lattice. Bottom: A view down the crystalographic *b*-axis of **1**·12THF showing large channels within the crystal lattice (solvent molecules are removed in both cases).

because two of the hexyloxy groups point inside the channel.[11] As has been pointed out before, this is not the case in **1**·12THF. Here, all hexyloxy side groups of the rings point outward so that large cavities inside the rings are formed.

This, together with the three-dimensional packing leads to the formation of a supramolecular tube in which the crystal lattice contains now large channels with pore sizes (ca. 8 × 12 Å) which are larger than those found in cyclodextrines. In addition, the channels carry polar functional groups which offer the possibility of specific interactions (e.g. hydrogen bonding) with suitable guest molecules. In the future it may also give rise to the construction of organic materials as functional analogues of zeolites if cross-linking can overcome the mechanical instability of the crystals.[12]

(11) In addition, the tilt angle of the macrocycles within the stacks is in **1**·6py slightly larger that in **1**·12THF.

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Table 1. Crystallographic Data

	1·6py	1·12THF
a (Å)	10.1282(7)	17.6104(10)
b (Å)	14.4441(8)	9.2651(5)
c (Å)	21.890(1)	22.0135(10)
α (deg)	75.375(1)	88.493(2)
β (deg)	81.124(1)	92.791(2)
γ (deg)	69.916(1)	82.962(2)
Z	2	2
V (Å^3)	2909.0	3558.6
D_x (g cm^{-1})	1.186	1.116
space group	$P\bar{1}$	$P\bar{1}$
no. of reflcns	10488	7060
no. of obsd reflcns	3917	3292
R	0.0618	0.0631
R_w	0.0715	0.0653
GOF	1.046	0.872

Conclusion

In summary, we deal here with the interesting case of a rigid, noncollapsible macrocycle where the substituents can change between different conformational states (in or out) which can be triggered by an external stimuli (solvent). This leads in the case of THF to the formation of large channels whereas the rotation of two of the adaptable units in pyridine effectively blocks most of the accessible pore size.

Experimental Section

Synthesis. Macrocycle **1** was prepared by the acid-catalyzed deprotection of the corresponding THP−ether in methanol/$CHCl_3$ overnight and subsequent precipitation by the addition of methanol as described detailed elsewhere.[8,13] ^{1}H NMR (300 MHz, THF-d_8): δ 8.36 (s, 4 H), 7.59−7.57 (m, 4 H), 7.48−7.46 (m, 2 H), 7.43−7.41 (m, 4 H), 7.36−7.33 (m, 4 H), 7.32−7.29 (m, 4 H), 7.01 (s, 4 H), 6.93 (s, 4 H), 4.00 (t, J = 6.3 Hz, 8 H), 2.36 (s, 18 H), 1.95−1.35 (m, 32 H), 0.91 (t, J = 7.1 Hz, 12 H); ^{13}C NMR (75 MHz, THF-d_8): δ 153.9, 153.1, 139.7, 138.8, 133.7, 133.2, 133.0, 132.5, 132.3, 125.0, 124.8, 122.7, 120.2, 117.1, 115.7, 112.0, 94.3, 94.2, 87.5, 87.0, 81.5, 74.4, 70.2, 32.5, 30.2, 26.7, 23.5, 20.9, 14.3. MALDI-TOF: 1599 (M^+), 1825 (M^+ + dithranol), 3197 ($2M^+$). Anal. Calcd for $C_{114}H_{100}O_8$ (1598.14): C 85.67, H 6.31. Found: C 85.42, H 6.54.

Structure Determination. X-ray structure data collections were carried out on a Nonius CAD4 diffractometer with graphite monochromated Cu Kα radiation at 165 K. Lattice parameters were obtained from a least-squares fit of the setting angles of 25 reflections with θ > 20°. An empirical absorption correction was applied to the data. The structures were solved by direct methods (Shelxs97). Refinement was done with anisotropic temperature factors for all non-hydrogen atoms. The hydrogen atoms were refined with fixed isotropic temperature factors in the riding mode. For **1**·12THF the disordered solvent molecules were refined with a common isotropic temperature factor applied to each individual THF molecule. Pertinent crystallographic data are summarized in Table 1.

Supporting Information Available: X-ray crystallographic details for **1**·6py and **1**·12THF (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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