Synthesis and Conformational Analysis of Trioxatricornan-Based Macrocyclophanes

Michael Lofthagen† and Jay S. Siegel*

Department of Chemistry, University of California, San Diego, La Jolla, California 92093-0358

Received December 5, 1994®

The synthesis of macrocyclophanes **7** and **8** is described. The constructions are composed of one phloroglucinol and one 2,6,10-triaminotrioxatricornan subunit. The subunits are linked by tri- and hexamethylene (**7** and **8**, respectively) chains. Conformational analysis by empirical force field calculations and ^{1}H NMR techniques demonstrates that **7** has adopted a collapsed conformation, leaving no space between the two aromatic subunits. Macrocyclophane **1**, in which the phloroglucinol oxygens have been replaced by methylenes, has instead adopted an open conformation, leaving a void in the macrocyclophane interior. The conformational preference of the side chains is shown to be the dominant factor in determining the overall conformation of **7** and its α-methylene analog **1**. With the use of low-temperature ^{1}H NMR, the barrier for the process of equivalencing all exchangeable sites in **7** is estimated at 8.6 kcal/mol.

Control of the molecular structure of macrocyclophanes is essential in order to tailor these compounds for various applications in molecular recognition science.[1] Although it is fashionable to consider "π/π interactions" and "molecular voids" when predicting the conformations of these molecules, the effects coming from simple side-chain (linker arm) conformational preferences have been seriously neglected.[2,3] In order to emphasize this point we present a direct analysis of two cyclophanes, which demonstrates the primacy of side-chain conformational effects.[4]

Macrocyclophane **1** consists of the keystone triaminotrioxatricornan (**2**) to which a capping benzene ring is attached via alkyl chains (Figure 1).[5] In both the solution and solid state **1** assumes a structure with extended (open) alkyl chains and a void in the interior (Figure 2). A rationalization for the conformation of **1** comes from consideration of the conformational analysis of simple alkylbenzenes; the hydrocarbon chain prefers anti over gauche and the C–C bond α to the benzene prefers an out-of-plane orientation. Arene-π interactions and effects due to "molecular vacuums" are at best secondary. The natural prediction therefore, is that changing these alkyl-chain preferences can result in a macrocyclophane with a collapsed (closed) conformation. This prediction can be tested by replacing the methylene α to the capping benzene of **1** with oxygen. To this end, we present the synthesis of the oxa analogues of **1** (**6**–**8**) in which the Ar-CH_2 groupings are replaced by oxygens; conformational analysis of **7** reveals the structural consequences of the substitution.

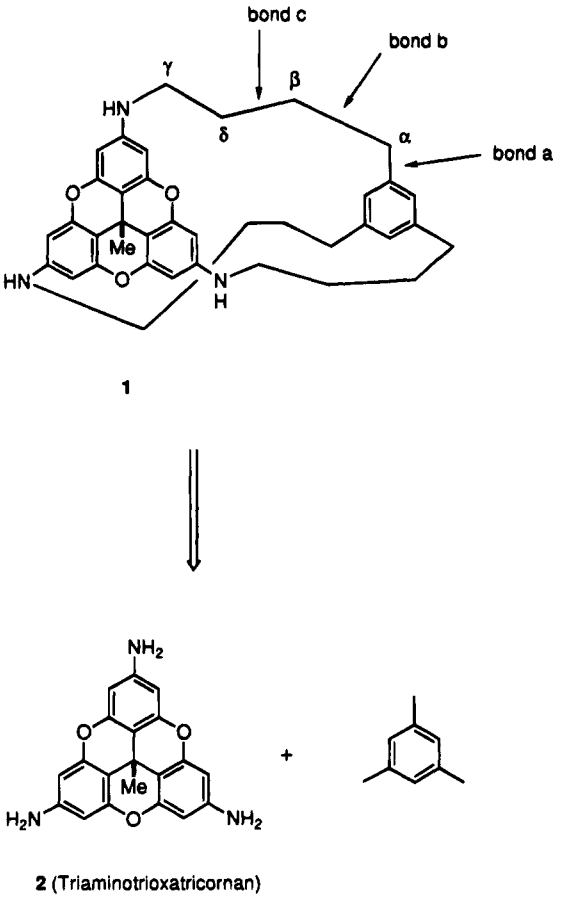


Figure 1. Macrocyclophane **1**, which consists of the keystone **2** to which a capping benzene ring is attached via alkyl chains.

† Present address: Astra Production Chemicals AB, Chemical Process Development Laboratory, S-15185 Södertälje, Sweden.

® Abstract published in *Advance ACS Abstracts,* March 1, 1995.

(1) (a) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112. (b) Cram, D. J.; Bauer, R. H. *J. Am. Chem. Soc.* **1959**, *81*, 5971–5977. (c) Diederich, F. In *Cylophanes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, 1991. (d) Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 744–3745. (e) Rebek, J. *Acc. Chem. Res.* **1990**, *23*, 399–404. (f) Breslow, R. *Science*, **1982**, *218*, 532–537. (g) Kellogg, R. M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 782–794. (h) Cram, D. J.; Tanner, H. J.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024–1027.

(2) For discussions on self-complexation in "flexible" cyclophanes see: (a) Grootenhuis, P. D. J.; v Eerden, J.; Sudhölter, E. J. R.; Reinhoudt, D. N.; Roos, A.; Harkema, S.; Feil, D. *J. Am. Chem. Soc.* **1987**, *109*, 4792–4797. (b) Loncharich, R. J.; Seward, E.; Ferguson, S. B.; Brown, F. K.; Diederich, F.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 3479–3491.

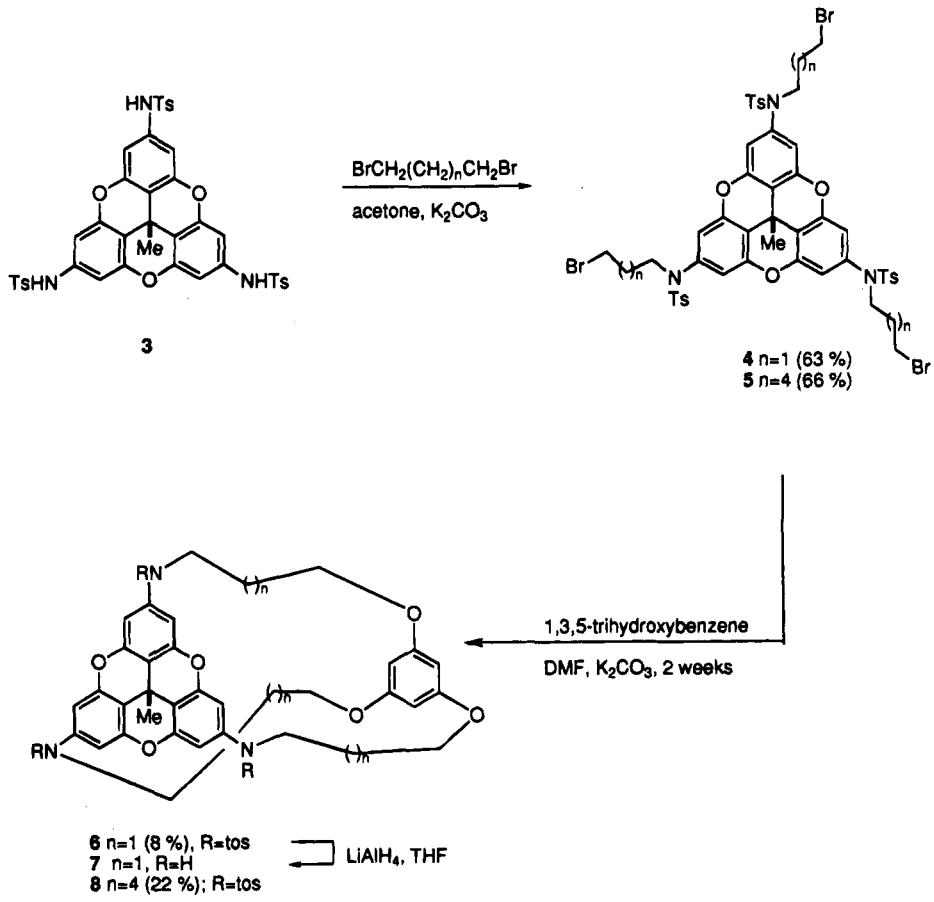
(3) (a) For a discussion on solvent perturbation (compression) of conformational equilibria, see: Schaefer, T.; Penner, G. H.; Sebastian, R. *Can. J. Chem.* **1987**, *65*, 873–877 and references cited therein. (b) For a discussion on molecular vacuums and cyclophanes, see: Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 7717–7727.

(4) For a discussion on conformational design of flexible molecules, see: Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124–1134. (b) And for an example thereof, see: Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 4128–4137.

(5) (a) Lofthagen, M.; Chadha, R.; Siegel, J. *J. Am. Chem. Soc.* **1991**, *113*, 8785–8790. (b) Lofthagen, M.; VernonClark, R.; Baldridge, K. K.; Siegel, J. S. *J. Org. Chem.* **1992**, *57*, 61.

0022-3263/95/1960-2885$09.00/0

Scheme 1



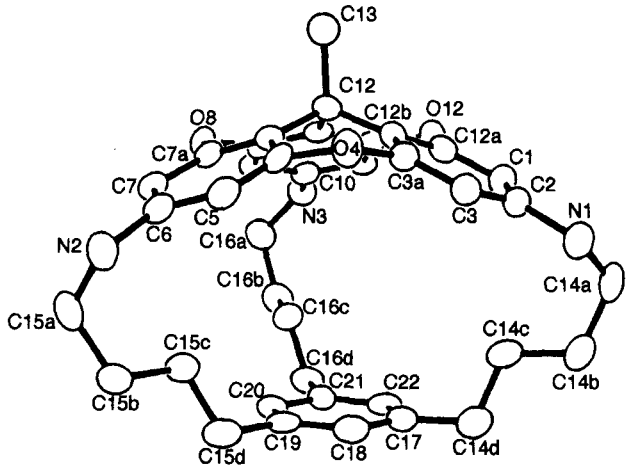


Figure 2. X-ray structure of cyclophane **1**, two views.

Synthesis

Slow (syringe pump) addition of **3**[5b] to a dilute refluxing acetone solution containing an excess of α,ω-dibromopropane or α,ω-dibromohexane and potassium carbonate affords the ω-bromoalkane-substituted keystones **4** and **5** in 63% and 66% yield, respectively (Scheme 1).[6] Macrocylophanes **6** and **8** are formed by reacting **4** and **5**, respectively, with phloroglucinol in dimethylformamide for 14 days at room temperature, followed by chromatographic isolation of the nonpolymeric products (only one in each case).[7] The isolated yields of **6** and **8** are 8% and 22%, respectively.[8] The tosyl groups in **6** are removed by refluxing the cyclophane in dry tetrahydrofuran with excess lithium aluminum hydride for 24 h.[9]

Macrocage formation is proven by key spectral features: Mass spectroscopy (FAB technique) of the isolated macrocages **6**, **7** and **8** display the expected parent (MH^+) *m/z* of 1054, 592, and 1180, respectively. The NMR spectra of the "capping" phloroglucinol nucleus of **7** shows a proton signal at 5.2 ppm and carbon resonances at 151 and 91 ppm; the phloroglucinol region of **6** shows a proton resonance at 5.0 ppm and carbon resonances at 159 and 91 ppm; the phloroglucinol region of the larger macrocage **8** shows a proton signal at 5.8 ppm and carbon resonances at 161 and 93 ppm. All of these signals are shifted upfield due to aromatic anisotropic shift effects from the trioxacornan keystone.

Computational Studies

Empirical force field (EFF)[10,11] calculations estimate the difference between the open and closed conformations of **1** to be ca. 6 kcal/mol (Figure 3). On the other hand, EFF computations comparing the different conformations of the α-oxa analog **7** predict a conformational preference for the closed structure **7-II** over its open counterpart **7-I**

(6) The surprisingly high yield is explained by the fact that **3** does not react with **4** or **5** under the reaction conditions. On the other hand, alkylation of tris(*p*-tosylamino)triphenylethane with α,ω-bromoalkanes has been reported to proceed in 17% yield, see: Franke, J.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 219–221.

(7) Curtis, W. D.; Stoddart, J. F.; Jones, G. H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 785–788.

(8) Compare with the intramolecular technique used in the formation of **1** which proceeded in 41% yield see ref 5.

(9) Fujita, T.; Lehn, J.-M. *Tetrahedron Lett.* **1988**, *29*, 1709–1712.

(10) EFF calculations were done on PC-MODEL from Serena Software. PCMODEL uses the MMX force field, an extension of MM2.

(11) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982.

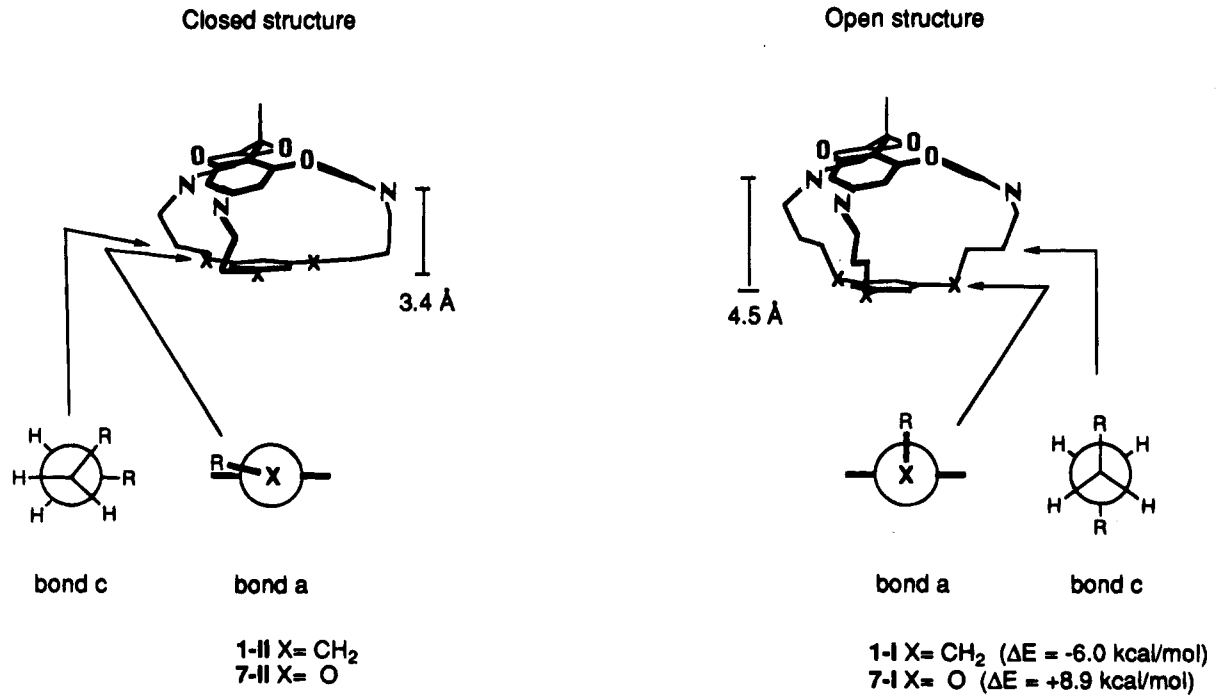


Figure 3. Sideviews of the open and closed conformations of cyclophanes **1** and **7** with Newman projections of the differing dihedral angles.

Table 1. EFF-Calculated Structures of Cyclophanes 1 and 7[a]

	EFF calculated structures				
	7-I	**7-IIa**	**7-IIb**	**1-I**	**1-IIa**
A	4.3	2.8	3.2	4.5	3.4
ΔE^b	+8.9	0.0	+2.5	0.0	+6.0

[a] Key: *A*, distance (Å) from the center of the capping aromatic (benzene-1,3,5) to the best plane formed by radial carbons on the trioxatricornan (C_{Ar}–N)$_3$. [b] Calculated relative energies in kcal/mol.

by ca. 9 kcal/mol (Table 1). This switch in macrocage conformation can be understood by examining the individual contribution of steric effects about bond-a and bond-c to the overall steric energy of the molecule. The open structure is characterized by an out-of-plane conformation about bond-a and an antiperiplanar conformation about bond-c. In contrast, the closed structure requires an in-plane conformation about bond-a and a gauche (synclinal) conformation about bond-c.[12] The conformational energy about bond-a can be estimated using anisole and ethylbenzene as models. In anisole the in-plane conformation around the C_{ar}–O bond is favored by ca 2.7 kcal/mol,[13] whereas in ethylbenzene the out-of-plane conformation is favored by ca. 1.0 kcal/mol (Figure 4a).[14] The anti to gauche preference about bond-c can be modeled by methyl propyl ether[15] and butane.[16] The gauche structure of methyl propyl ether is energetically less expensive than gauche butane, 0.2 vs 0.8 kcal/mol, respectively (Figure 4b). Assuming a simple additivity of effects and ad hoc application of the quantitative data from methyl propyl ether and anisole to the conformational analysis of **7**, the closed structure is predicted to be favored by ca. 7.5 kcal/mol (EFF predicts 8.9 kcal/mol). A parallel analysis for **1** predicts the open structure to be favored by 5.4 kcal/mol. The good agreement of these numbers supports our claim that the side-chain effects are dominant in determining the molecular conformation of **1** and **7**.

Several possible conformations of the closed structure result from differences in the symmetry of the connecting sites on the two aromatic systems (C_1 vs C_3) as well as the orientation of the alkyl chains (S- vs U-like geometry). EFF calculations reveal that the strain energy of these closed conformations are within 2.5 kcal/mol of each other. The C_1 on C_1 with S oriented alkyl chains **7-IIb** has the highest energy, and C_3 on C_3 with U oriented alkyl chains **7-IIa** has the lowest energy (Figure 5).

NMR Studies

Two probes were used to distinguish between open and closed conformations in solution: (1) the vicinal ^{1}H NMR coupling constants ($^3J_{HH}$) between the C_β and C_γ methylenes; and (2) the relative upfield shift ($\Delta\delta$) of the β-methylene protons and the capping phloroglucinol protons relative to model compounds.

The β-methylene of **7** appears at 3.6 ppm as a triplet with a coupling constant of 5.2 Hz ($CH_{2\beta}$–$CH_{2\gamma}$) (Table 2). In cyclophane **1** the corresponding coupling constant

(12) The dihedral angle about bond-b is anti in both the open (**1-I/7-I**) and closed (**1-II/7-II**) conformation.

(13) The gas phase conformation of anisole has been experimentally determined as planar; see: Seip, H. M.; Seip, R. *Acta Chem. Scand.* **1973**, *27*, 4024–4027. Ab initio calculations estimate the barrier to rotation at ca. 2 kcal/mol, with the planar geometry as the favored structure; see: Spellmeyer, D. C.; Grootenhuis, P. D. J.; Miller, M. D.; Kuyper, L. F.; Kollman, P. A. *J. Phys. Chem*, **1990**, *94*, 4483–4491 and references cited therein.

(14) The solution barrier for ethylbenzene has been determined as ca. 1.3 kcal/mol (assuming a 2-fold barrier) and ab initio calculations demonstrate that the perpendicular conformation is lowest in energy; see ref 3a.

(15) Ab initio calculations suggest that the gauche conformation in methyl propyl ether (O-C-C-C fragment) is favored by 0.4 kcal/mol; see: Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4821–4828. Experimental data (^{13}C NMR) indicate that both gauche and trans conformers are present in solution; see: Hayashi, M.: Adachi, M. *J. Mol. Struct.* **1982**, *78*, 53.

(16) The trans conformation in *n*-butane has been calculated as 0.9 kcal/mol lower in energy than the gauche structure, and experimental data support this; see: Jorgensen, W. L. *J. Phys. Chem.* **1983**, *87*, 5304–5314 and references cited therein.

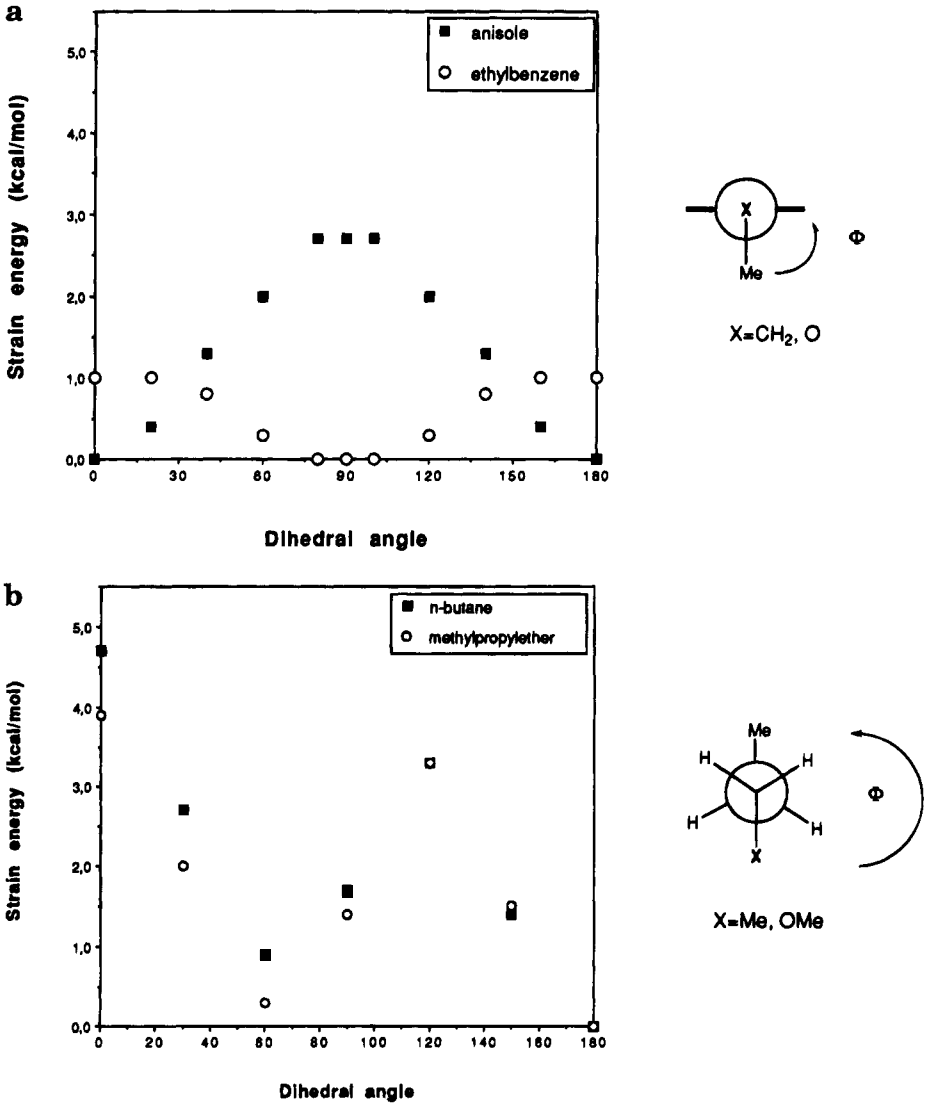
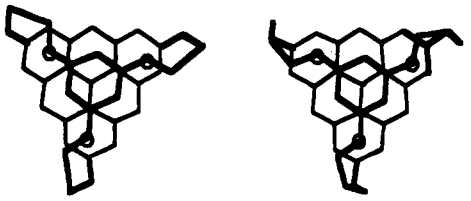


Figure 4. EFF-calculated torsional barriers for internal sp^2-sp^3 rotations in ethylbenzene and anisole.



7-IIa (ΔE=0.0) **7-IIb** (ΔE=+2.5 kcal/mol)

Figure 5. Two EFF-calculated closed conformations, **7-IIa** and **7-IIb**, of cyclophane **7**.

is 8.5 Hz. Using a Karplus-type relation,[17,18] one can determine qualitatively that the dihedral angle in the alkyl chain segment $C\gamma-C_\delta-C_\beta-O$ of **7** is synclinal. In cyclophane **1**, on the other hand, the same portion of the alkyl chain ($C\gamma-C_\delta-C_\beta-C_\alpha$) has adopted an antiperiplanar arrangement.

The differential anisotropic NMR shifts ($\Delta\delta$) of the protons in the alkyl chains and the capping aromatic are caused by the magnetic field generated by the keystone aromatic rings. The magnitude of the anisotropic shift varies depending on the location of the hydrogen atom in the magnetic field. Using a nomogram developed by Johnson and Bovey one can calculate the chemical shift alteration on a proton induced by the ring current of a proximal benzene ring.[19,20] With this technique one can estimate the anisotropic shifts for the various protons in the two conformations (open and closed). By comparing these values with the experimentally obtained anisotropic shifts ($\Delta\delta$) it is possible to determine the solution conformation of cyclophanes **1** and **7**.[21]

In cyclophane **1**, the β-methylene protons experience the largest upfield shift (Table 3). This is consistent with

(17) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870–2871.
(18) Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, C. *Tetrahedron*, **1980**, *36*, 2783–2792.

(19) Johnson, C. E.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012–1014.
(20) Emsley, J. W.; Feehy, J.; Sutcliffe, L. H. *High resolution Nuclear Magnetic Resonance Spectroscopy;* Pergamon Press: Oxford, 1965; Vol. 1, pp 595–604.
(21) The calculated $\Delta\delta$ was obtained as follows: From the EFF minimized structures **1-I/7-I** and **1-II/7-II** the positions of the methylene hydrogens and the benzene (1, 3, 5) hydrogens relative to the benzene rings of the keystone were expressed in p and z coordinates (according to Johnson et. al[19]). From the tabulated calculations for benzene, the upfield shifts could then be obtained.[20] The experimental $\Delta\delta$ was obtained by using appropriate model compounds, and then subtracting the chemical shift of the relevant proton on the model compound from the chemical shift of the anisotropically shifted proton in the cyclophane. 1,3,5-tris(4-bromobutyl)phloroglucinol was used as model compound for **7**.[7] Hexa-(*n*-propylbenzene, *n*-propylbenzene[a] and 1,3,5-tris-*n*-propylbenzene[b] were used as model compounds for **1**. (a) Radcliffe, M. D.; Mislow, K. *J. Org. Chem.* **1984**, *49*, 2058–2059. (b)

Table 2. Dihedral Angles in the Aliphatic Chain of 1 and 7, from EFF-Calculated and X-ray Structures, Compared to the Dihedral Angles Estimated Using Measured Solution $^3J_{HH}$ Coupling Constants[a]

	experimental dihedral angles			calculated dihedral angles			
	X-ray:	^{1}H NMR $^3J_{HH}$		EFF			
	1	1	7	1-I	1-IIa	7-I	7-IIa
C_{Ar}–C_{Ar}-X-C_β	82			79	22	70	15
C_{Ar}-X-C_β-C_γ	177	ap (8.2 Hz)		177	171	168	179
X-C_β-C_γ-C_δ	178	ap (8.5 Hz)	sc (5.2 Hz)	176	80	175	80
C_β-C_γ-C_δ-N	62	sc (5.2 Hz)	sc (5.5 Hz)	61	66	68	64
C_{Ar}-C_{Ar}-N-C_δ	35			35	58	34	20

[a] Key: ap, antiperiplanar; sc, synclinal. **1**: X = CH_2. **7**: X = O.

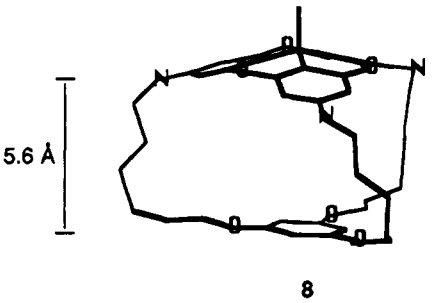
Table 3. Calculated Anisotropic Upfield ^{1}H NMR Shifts in the EFF-Minimized Structures 1-I/7-I and 1-II/7-II and Observed Upfield ^{1}H NMR Shifts in 1, 1-tos, 6, 7, and 8[a]

	$\Delta\delta^b$ (ppm)						
	calculated[c]		observed				
	1-I/7-I	1-II/7-II	1-tos	1	6[f]	7[f]	8[f]
C_{Ar}-*H*	0.60	0.89	0.56[d]	0.38[d]	1.02	0.81	0.24
C_{Ar}-X-*CH_2*	1.11	0.58	0.73–0.83[e]	0.52–0.62[e]	0.18	0.31	0.17

[a] Key: **1** and **1-tos** X = CH_2; **6**, **7** and **8** X = O. [b] Anisotropic upfield ^{1}H NMR shifts. [c] Calculated values, based on distance and angle between affected proton and trioxatricornan aromatics. [d] Relative to 1,3,5-tripropylbenzene (δ = 6.69 ppm, $CDCl_3$).[21b] [e] Relative to hexa-*n*-propylbenzene (lower limit) or *n*-propylbenzene (higher limit).[21a] [f] Relative to 1,3,5-tris(4-bromobutyl)phloroglucinol (δ_{ar} = 6.03 ppm, δ_{alk} = 3.94 ppm $CDCl_3$).[7]

the trend seen in the calculated values ($\Delta\delta$) for an open structure **1-I/7-I**, where the β-protons are situated over the keystone aromatic rings. In the cyclophanes **6** and **7**, on the other hand, the phloroglucinol protons are experiencing a larger upfield shift than the β-protons. This trend in $\Delta\delta$ is as expected for a closed conformation **1-II/7-II**, where the proximity between the phloroglucinol protons and the keystone aromatic rings causes a large upfield shift. The results of both the coupling constant and the chemical shift analyses point to a closed conformation for **7** in solution, in accord with the EFF prediction.

CPK models of the larger cyclophane **8** can be constructed with the position of the *cent*-methyl group on the trioxatricornan "out" or "in" relative to the internal cavity.[22] The position of the methyl group is revealed by its ^{1}H NMR chemical shift; an internal methyl group should be shifted upfield by several ppm due to the ring current of the phloroglucinol. The *cent*-methyl group of **8** resonates at 1.6 ppm, which is virtually identical to the corresponding signals in the *out*-cyclophanes **1** and **7**, and supports an *out* geometry for **8**. EFF calculations indicate that the six-carbon chain is too short for a strain-free *in* structure. On the basis of the minimal ^{1}H NMR upfield shift of the phloroglucinol protons (relative to tris-(4-bromobutyl)phloroglucinol) in **8** the spacing between the π-systems can be estimated to exceed 5 Å. This expanded conformation is supported by an EFF minimized structure of **8**, arranged in a sigmoidal C_3 arrangement, which shows a separation of 5.6 Å between the two π-systems (Figure 6). Thus, even with the flexibility of longer alkyl chains, the *out* isomer of **8** forms preferentially and the π-systems remain distant from one another.



8

Figure 6. Sideview of an EFF-minimized structure of cyclophane **8**.

Variable-Temperature NMR

In **1** and **7** the aromatic protons of the trioxatricornan keystone appear as singlets, due to fast chemical exchange on the NMR time scale. By cooling the NMR samples the exchange process is slowed down, and a decoalesence of the ^{1}H NMR keystone signal (Ar–H) is seen for **1** at −105 °C (180 Hz) and for **7** at −95 °C (50 Hz). By using the Gutowski–Holm approximation[23,24] the barriers for the process of equivalencing all exchangeable sites in **1** and **7** are estimated at 7.6 and 8.6 kcal/mol, respectively.

The barrier heights in **1** and **7** approximately equal that of an internal rotation around the C_{ar}–N bond in *N*-methylaniline, which has been measured at 6.9 kcal/mol.[25] This indicates that a change of pitch of the three connecting arms in **1** and **7**, which interconverts C_3 conformers, occurs through a stepwise rather than a concerted mechanism.[26]

Conclusion

NMR solution studies and computational analysis show that replacement of a methylene group by an oxygen atom in the linkers of macrocyclophane **1** drastically changes the solution conformation, from an ex-

Van Meurs, N. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 111–114. (c) For another example of the use of this technique in conformational analysis, see: Fukazawa, Y.; Usui, S.; Tanimoto, K.; Hirai, Y. *J. Am. Chem. Soc.* **1994**, *116*, 8169.

(22) For a discussion on *in-out* isomerism, see: Simmons, H. E.; Park, C. H. *J. Am. Chem. Soc.* **1968**, *90*, 2428–2432.

(23) Gutowski, H., S.; Holm, C., H. *J. Chem. Phys.* **1956**, *25*, 1228–1234.

(24) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982.

(25) Anet, F. A. L.; Ghiaci, M. *J. Am. Chem. Soc.* **1979**, *101*, 6857–6860.

(26) Similar dynamic behavior has been observed in other bicyclic cyclophanes; see: Olsson, T.; Tanner, D.; Thulin, B.; Wennerström, O. *Tetrahedron* **1981**, *37*, 3485–3490.

tended structure with a vacant interior to a collapsed structure, **7**. Lengthening the alkyl chains connecting the trioxatricornan to the phloroglucinol from three carbons, in **7**, to six carbons, in **8**, increases the distance between the two π-systems, as shown by EFF calculations and solution studies by NMR.

Experimental Section

General Data. Proton NMR spectra were recorded on a ^{1}H NMR spectrometer equipped with a Nicolet 1180E computer interfaced with an Oxford magnet operating at 360 MHz or on a Varian 500 MHz Unity spectrometer. Carbon NMR were recorded on a Varian 500 or on a Nicolet NT200, operating at 125 and 50 MHz, respectively. Infrared spectra were recorded on a Perkin-Elmer 1420 IR spectrometer. Unless otherwise stated, commercial chemicals were used as supplied.

2,6,10-Tris[*N*-(3-bromopropyl)tosylamino]-12c-methyl-4,8,12-trioxatricornan (4). **3** (1.15 g, 1.42 mmol) was dissolved in 50 mL of acetone and then added, over 6 h, to 1000 mL of refluxing acetone containing 1,6-dibromopropane (8.62 g, 42.7 mmol) and potassium carbonate (10.0 g). Reflux was continued for an additional 8 h after the addition, followed by removal of the solvent under reduced pressure. The solid residue was thoroughly washed with diethyl ether and the resulting solution was extracted first with 10% aqueous HCl and then with water. The organic phase was collected, dried with magnesium sulfate, and evaporated under reduced pressure to yield crude **4.** The crude material was purified by flash chromatography on silica gel (230–450 mesh) eluting with 30% ethyl acetate/hexanes (r_f = 0.18) yielding 0.95 g (63%) of solid **4**, which can be recrystallized from absolute ethanol: mp 149–156 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (6 H, d, J = 8.2 Hz), 7.31 (6 H, d, J = 8.2 Hz), 6.70 (6 H, s), 3.65 (6 H, t, J = 6.6 Hz), 3.43 (6 H, t, J = 6.5 Hz), 2.47 (9 H, s), 2.04 (6 H, tt, J= 6.5 Hz; J = 6.6 Hz), 1.57 (3 H, s); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 151.8, 144.0, 139.6, 134.7, 129.7, 127.7, 113.8, 112.4, 49.28, 31.85, 31.44, 29.75, 24.13, 21.61; IR (KBr) 1610, 1345, 1160, 660 cm^{-1}; FABMS (high resolution) found 1172.0083 (calcd for $C_{50}H_{49}Br_3N_3O_9S_3$ (MH^+) 1172.0140).

2,6,10-Tris[*N*-(6-bromohexyl)tosylamino]-12c-methyl-4,8,12-trioxatricornan (5). **3** (0.50 g, 0.62 mmol) was dissolved in 20 mL of acetone and then added, over 6 h, to 500 mL of refluxing acetone containing 1,6-dibromohexane (4.53 g, 18.6 mmol) and potassium carbonate (3.0 g). Reflux was continued for an additional 8 h after the addition, followed by removal of the solvent under reduced pressure. The solid residue was thoroughly washed with diethyl ether and the resulting solution was extracted first with 10% aqueous HCl and then with water. The organic phase was collected, dried with magnesium sulfate, and evaporated under reduced pressure to yield crude **5.** The crude material was purified by flash chromatography on silica gel (230–450 mesh) eluting with 30% ethyl acetate/hexanes (r_f = 0.2) yielding 0.50 g (62%) of solid **5:** mp 166–168 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (6 H, d, J = 8.2 Hz), 7.30 (6 H, d, J = 8.2 Hz), 6.69 (6 H, s), 3.49 (6 H, t, J = 6.8 Hz), 3.36 (6 H, t, J = 6.7 Hz), 2.46 (9 H, s), 1.81 (6 H, m), 1.57 (3 H, s), 1.50–1.30 (18 H, m); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 151.8, 143.8, 139.6, 135.1, 129.6, 127.6, 113.7, 112.4, 50.40, 33.68, 32.51, 31.90, 27.89, 27.55, 25.48, 24.13, 21.60; IR (KBr) 1610, 1340, 1160 cm^{-1}; FABMS found 1300 (calcd for $C_{59}H_{66}N_3O_9S_3$ (MH^+) 1300).

Cyclophane 6. **4** (700 mg, 0.60 mmol) was dissolved in 350 mL of dimethylformamide (freshly distilled from calcium hydride). To this solution were added phloroglucinol hydrate (97 mg, 0.60 mmol), potassium carbonate (4.0 g), and 6.0 g of Amberlite 4B (CO_3^{2-} form). The mixture was stirred at room temperature under a static blanket of argon for 14 days, after which the solvent was removed under reduced pressure. The solid residue was triturated with tetrahydrofuran and the resulting solution was filtered. The tetrahydrofuran solution was diluted with 100 mL of diethyl ether and extracted with 10% HCl, 1 M sodium bicarbonate, and finally water. The organic phase was collected, dried with magnesium sulfate, and evaporated to dryness under reduced pressure. The crude product was flash chromatographed on silica gel (230–450 mesh) eluting with 40% ethyl acetate/hexanes yielding 50 mg (8%) of **6**. **6** crystallizes from the ethyl acetate/hexanes eluent, forming thin clear plates: mp > 290 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.65 (6 H, d, J = 8.2 Hz), 7.35 (6 H, d, J = 8.2 Hz), 6.77 (6 H, s), 5.01 (3 H, s), 3.76 (6 H, t), 3.51 (6 H, t, J = 5.3 Hz), 2.48 (9 H, s), 2.02 (6 H, m), 1.53 (3 H, s); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 159.2, 152.0, 143.8, 142.0, 135.7, 129.7, 127.5, 114.8, 113.1, 90.86, 62.20, 47.15, 31.63, 29.67, 25.23, 21.59; IR (KBr) 1610, 1160, 660 cm^{-1}; FABMS found 1054.2651 (calcd for $C_{56}H_{52}N_3O_{12}S_3$ (MH^+)1054.2713).

Cyclophane 8. **5** (200 mg, 0.154 mmol) was dissolved in 130 mL of dimethylformamide (freshly distilled from calcium hydride). To this solution were added phloroglucinol hydrate (40 mg, 0.25 mmol), potassium carbonate (700 mg), and 1.0 g of Amberlite 4B (CO_3^{2-} form). The mixture was stirred at room temperature under a static blanket of argon for 14 days, after which the solvent was removed under reduced pressure. The solid residue was triturated with tetrahydrofuran and the resulting solution was filtered. The tetrahydrofuran solution was diluted with 100 mL of diethyl ether and extracted with 10% HCl, 1 M sodium bicarbonate, and finally water. The organic phase was collected, dried with magnesium sulfate, and evaporated to dryness to yield 190 mg of solid material. The crude product was flash chromatographed on silica gel (230–450 mesh) eluting with 30% ethyl acetate/hexanes yielding 45 mg (22%) of **8**, which can be recrystallized from acetone: mp > 300 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.58 (6 H, d, J = 8.5 Hz), 7.33 (6 H, d, J = 8.5 Hz), 6.57 (6 H, s), 5.79 (3 H, s), 3.77 (6 H, t, J = 5.7 Hz), 3.36 (6 H, t, J = 7.5 Hz), 2.47 (9 H, s), 1.60 (3 H, s), 1.55 (6 H, m), 1.36 (6 H, m), 1.25 (6 H, m), 1.10 (6 H, m); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 160.5, 152.0, 143.7, 139.7, 135.3, 129.6, 127.6, 114.0, 112.6, 92.81, 66.31, 51.59, 32.16, 28.64, 28.13, 25.82, 25.14, 24.34, 21.58; IR (KBr) 1610, 1155, 660 cm^{-1}; FABMS found 1180.4167 (calcd for $C_{65}H_{70}N_3O_{12}S_3$ (MH^+)1180.4122).

Cyclophane 7. **6** (50 mg, 47 μmol) was dissolved in 10 mL of dry tetrahydrofuran. A large excess of lithium aluminum hydride (200 mg) was added, and the solution was refluxed under argon for 72 h. The solution was then cooled with ice, and excess lithium aluminum hydride was quenched by slow addition of 1 mL of water. A 3 mL portion of 1 M sodium hydroxide was added, and the layers were separated. The organic layer was collected, dried with sodium sulfate and the solvent was removed under reduced pressure to yield **7** as a colorless powder: mp > 300 C dec; ^{1}H NMR ($CDCl_3$) δ 6.35 (6 H, s), 5.22 (3 H, s), 3.63 (6 H, t, J = 5.2 Hz), 3.48 (6 H, t, J = 5.5 Hz), 1.91 (6 H, tt), 1.56 (3 H, s); ^{13}C{^{1}H} NMR (DMSO-d_6) δ 159.0, 153.1, 152.3, 107.1, 99.54, 91.02, 63.29, 43.05, 32.36, 30.01, 24.16; FABMS (high resolution) found 592.2463 (calcd for $C_{35}H_{34}N_3O_6$ (MH^+) 592.2448).

Computational Geometries. Empirical force field calculations were performed using PC-MODEL (Serena software) on a Macintosh IIci (PC-MODEL version 2.0) or on a Silicon Graphics (PC-MODEL, version 4.0). Atom coordinates from calculated structures were analyzed using MacMoMo, a crystallographic program provided by Max Dobler, ETH, Zürich.

Acknowledgment. This work was supported by the National Science Foundation (CHE-9307582) and the Alfred P. Sloan Foundation (J.S.S.).

Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR of **6–8** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

JO9420477