Novel Macrocycles Incorporating Cyclic Urea Units

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The reaction of 1,3- and 1,4-bis(bromomethyl)benzenes with 5-*tert*-butyltetrahydro-1,3,5-triazin-2(1*H*)-one (**1**) and 2-imidazolidone (**2**) has been used to synthesize a series of 16- and 18-membered ring calixarene analogs which incorporate cyclic urea units. The structures and conformations of these novel macrocyclic ring systems have been investigated in the solid state by X-ray crystallography and in solution by various NMR methods. The results indicate important conformational equilibria dominated by species having *syn* and *anti* alignments of the urea carbonyl groups and that interconversion of these conformers likely occurs by carbonyl through the annulus rotation. AM1 semiempirical molecular orbital geometry optimizations are consistent with these findings.

Introduction

The synthesis and chemistry of macrocylic compounds has attracted considerable attention in recent years because of their unusual structures, conformational properties, and ability to act as hosts to both neutral molecules and ionic species.[1] The host–guest phenomenon warrants study as a mimic of enzyme–substrate interactions in biological systems. Despite the fact that carbonyl groups of amides and esters play dominating roles in biological systems, macrocycles incorporating these groups have received little attention compared to their polyoxo and polyaza congeners. Even fewer examples are known that involve cyclic urea units as binding sites either solely or in combination with other functional groups. The glycoluril unit has been used in the synthesis of a molecular clip,[2a] a spherical tennis ball complex,[2b] and cucurbituril,[2c] a macrocycle with cyclic urea units as the only functional groups. Cram and others[3] have synthesized a variety of macrocycles incorporating the tetrahydropyrimidinone unit, and a spherand assembled with this component is reported to be a strong complexer of sodium ions. More recently, Pratt, Sutherland, and Newton[4] have described the synthesis of a novel macrocycle also incorporating the tetrahydropyrimidinone unit. Additionally, it has been established that urea oxygen is less sterically hindered and a stronger complexing group than methoxy.[3b,d]

In this report we describe the reaction of 1,3- and 1,4-bis(bromomethyl)benzenes with 5-*tert*-butyltetrahydro-1,3,5-triazin-2(1*H*)-one (**1**) and 2-imidazolidone (**2**) to synthesize several novel macrocycles which incorporate the cyclic urea units.[5] The 16- and 18-membered macrocycles so produced contain alternating urea and benzyl components that profoundly influence the conformational properties of these ring systems. The X-ray structures of macrocycles **3a–c** derived from **1** have been published.[5] Investigation of the structural characteristics of these macrocycles by temperature-dependent NMR techniques and computational methods is detailed herein.

Results and Discussion

Synthesis. The triazone derivative **1** was synthesized from urea, *tert*-butylamine, and formaldehyde using the procedure developed by Coon et al.,[6] on the basis of the Peterson reaction.[7]

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1995.

(1) 1. For recent reviews, see: *Supramolecular Chemistry* Vogtle, F., Ed. John Wiley & Sons: New York, **1993.** *Molecular Inclusion and Molecular recognition. Clathrates I,* Weber, E., Ed.; Top. Curr. Chem. **1987**, 140; Rebek, J., Jr. *Science (Washington, D.C.)* **1987**, 235, 1478. Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039. Lehn, J. M. *Science (Washington, D.C.)* **1985**, *227*, 849. *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 2; Vogtle, F.; Muller W. M. *J. Inclusion Phenom.* **1984**, *1*, 369. Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161.

(2) (a) Sijbesma, R. P.; Wijmenga, S. S.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1992**, *114*, 9807. (b) Wyler, R.; de Mendoza, J.; Rebek, J. Jr. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1699. (c) Freeman, W. A.; Mock, W. L.; Shih, N-Y. J. Am. Chem. Soc. **1981**, *103*, 7367. Cintas, P. J. *Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *17*, 205.

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(4) Pratt, J. A. E.; Sutherland, I. O.; Newton, R. F. *J. Chem. Soc., Perkin Trans. I* **1988**, 13.

(5) Dave, P. R.; Doyle, G.; Axenrod, T.; Yazdekhasti, H.; Ammon, H. L. *Tetrahedron Lett.* **1992**, 33, 1021. Chemical Abstracts Service names for compounds: **3a** = 11,23-di-*tert*-butyl-1,9,11,13,21,23-hexaazapentacyclo[19.3.1.$1^{3,7}$.$1^{9,13}$.$1^{15,19}$]octacosa-3,5,7(28),15,17,19(26)-hexaene-25,27-dione; **4** = 5,16-di-*tert*-butyl-3,5,7,14,16,18-hexaazapentacyclo[18.2.2.2.$2^{9,12}$.$1^{3,7}$.$1^{14,18}$]octacosa-9,11,20,22,23,26-hexaene-25,28-dione. We thank Dr. K. L. Loening of Chemical Abstract Service for supplying the nomenclature. The atomic coordinates for X-ray structures of compounds **3a-c** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(6) Mitchell, A. R.; Pagoria, P. F.; Coon, C. L.; Jessop, E. S.; Poco, J. F.; Tarver, C.M.; Briethaupt, R. D.; Moody, G. L. *Prop. Expl. and Pyro.* **1994**, *19*, 232.

(7) Peterson, H. *Synthesis 1973*, 243.

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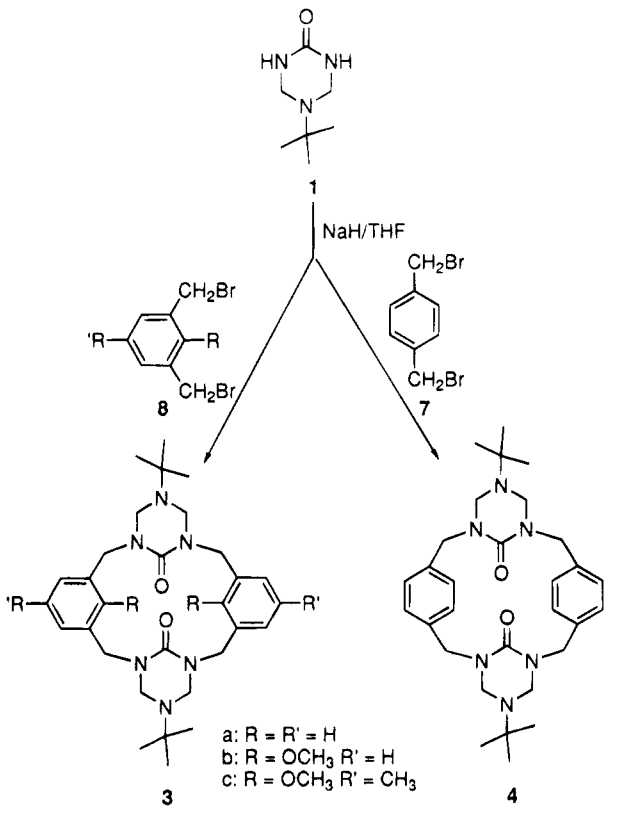
Scheme 1



As outlined in Scheme 1, the reaction of the disodium salt of **1** with 1,3-bis(bromomethyl)benzene or its derivatives 2,6-bis(bromomethyl)anisole[8] (**8b**) and 2,6-bis(bromomethyl)-4-methylanisole[9] (**8c**) in refluxing tetrahydrofuran gave the 16-membered macrocycles **3a–c** in yields of 54%, 11%, and 6%, respectively. Similarly, from the reaction of the disodium salt of **1** with 1,4-bis(bromomethyl)benzene (**7**) the 18-membered macrocycle **4** was obtained in 2% yield.

Additionally, treatment of the disodium salt of 2-imidazolidone (**2**) with 1,3-bis(bromomethyl)benzene (**8a**) or 1,4-bis(bromomethyl)benzene (**7**) afforded the 16- and 18-membered macrocycles **5** and **6** in 13% and 0.3% yields, respectively (Scheme 2). The yields reflect macrocycles isolated by chromatography from linear high molecular weight products and are unoptimized.

Conformational Analysis. These macrocycles may be considered as analogs of the calix[4]arenes which have been extensively studied by Gutsche and other researchers.[10] It was, therefore, of interest to investigate and compare the conformational features of these two types of ring systems. Four distinct conformations of the calix[4]arene system have been recognized, and the analogous conformations corresponding to the present urea-based macrocycles are represented schematically in Figure 1. Additional conformations can arise by flattening of one or more of the constituent rings to give a flattened cone (boat) or flattened partial cone (chair). Depending on structural considerations and other steric interactions, different degrees of conformational mobility are found in calix[4]arenes. These properties are manifested in the solid and liquid phases, but not necessarily to the same extent in the different states.

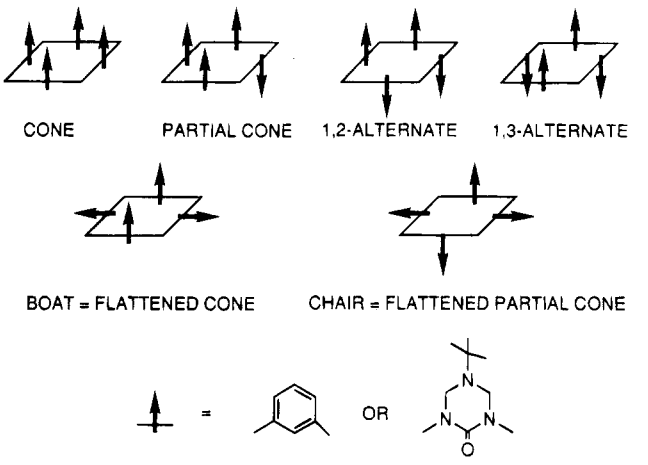
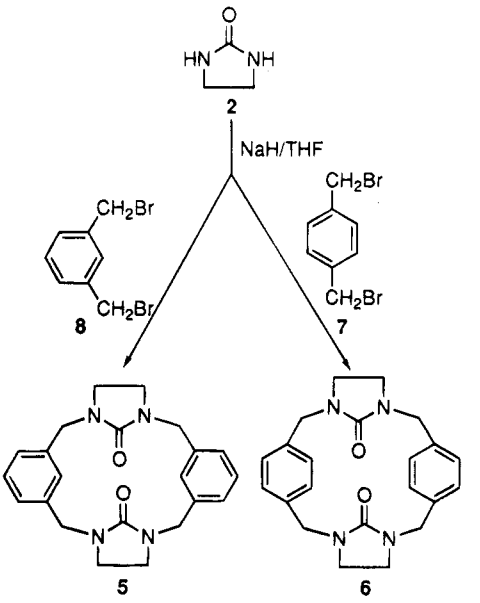


Figure 1. Iconographic representation of conformations.

Scheme 2



The structures of the urea-based macrocycles have been investigated by NMR studies in solution, by X-ray crystallographic studies in the solid state as well as by computational methods. The X-ray structures of macrocycles **3a–c** have been reported in a preliminary communication.[5]

In the solid state, the molecule **3a** adopts a flattened partial cone-like conformation with the two aromatic rings approximately perpendicular to the cone axis. The triazone units are essentially parallel to the cone axis with their respective carbonyl units pointing in opposite directions. The conformations adopted by both **3b** and **3c** are fundamentally the same, but quite different from that of **3a**. In all cases the triazone units are parallel to each other, but in contrast to **3a** the urea carbonyl groups in **3b** and **3c** point in the same direction. Compared with **3a**, one aromatic ring in **3b** and **3c** is partially rotated about the axis that passes through the *meta* carbon atoms joining the bridging benzyl CH_2 groups. This results in the two aryl groups in each molecule occupying perpendicular planes, with one of the methoxyl groups pointing into the cavity and the other pointing in the opposite direction from the triazone carbonyl groups. The cavity-directed methoxyl group appears to be close to the

(8) Browne, C. M.; Fergusion, G., McKervey, M. A.; Mulholland, D. L.; O'Connor, T.; Parvez, M. *J. Am. Chem. Soc.* **1985**, *107*, 2703.
(9) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553.
(10) Gutsche, C. D. *Calixarenes*, Monographs in Supramolecular Chemistry, Cambridge, 1989, and references therein.

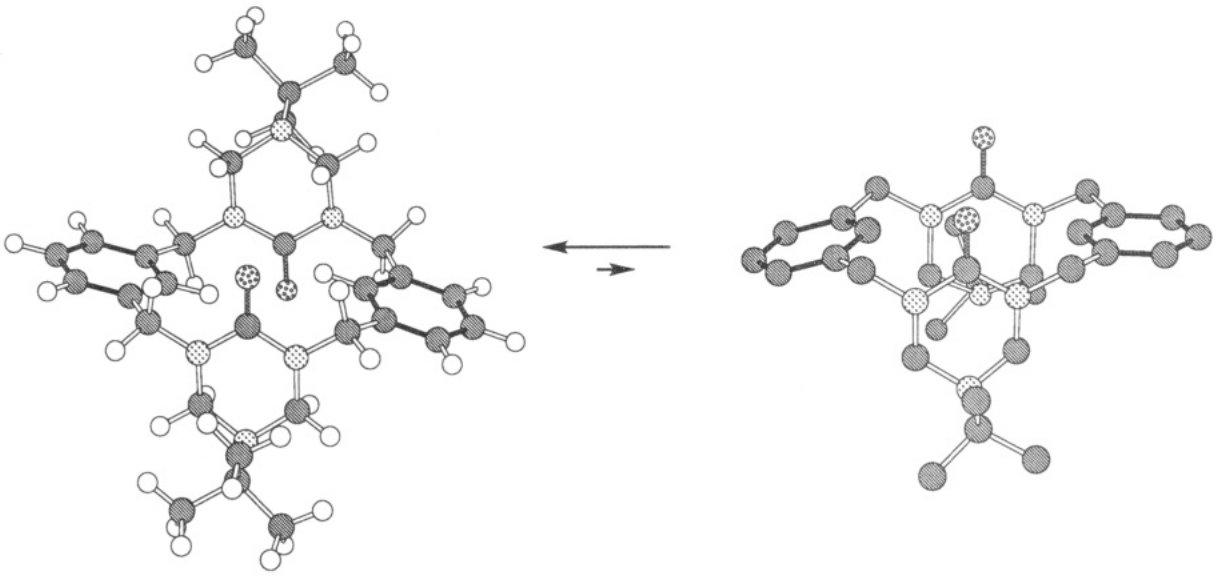


Figure 2. Conformational equilibrium in **3a**. Hydrogen atoms in the *syn* conformer were omitted for clarity.

orthogonal π-cloud of the facing aromatic ring. This resembles a partially flattened 1,3-alternate conformation.

In the room-temperature ^{1}H NMR spectrum of **3a** in $CDCl_3$, the 16 methylene protons are seen as broad signals at δ 5.8, 4.2, and 3.7 with an intensity ratio of 1:2:1. On the basis of 2D correlation experiments, the signals at δ 5.8 and 3.7 are assigned to benzylic protons and the others at δ 4.2 to the heterocyclic ring methylene groups. The ^{13}C NMR spectrum exhibits the requisite number of signals for the benzylic carbons at δ 48.8 and 62.4 for the N$-CH_2-$N groups. The broad appearance of the signals observed in both the room-temperature ^{1}H and ^{13}C spectra suggests the presence of two or more conformations slowly interconverting on the NMR time scale.

The temperature-dependent behavior observed in the NMR spectra confirms the existence of a conformational equilibrium. In both the ^{1}H and ^{13}C spectra at low temperatures there is clear evidence for the presence of two approximately equally-populated conformations. From COSY and HETCORR 2D correlation experiments, recorded at 250 K, the broad signals in **3a** assigned to the benzylic protons in the regions δ 5.8 and 3.7 appear as two sets of equal intensity AB systems. These signals coalesce at room temperature, and finally at 375 K the individual A and B proton signals coalesce. Temperature-dependent behavior is also noted for the N$-CH_2-$N protons in the triazone portion of the molecule at δ 4.2. At low temperature, the latter signal appears as a pair of doublets of doublets. In addition, two sets of equally intense *tert*-butyl resonance signals appear at δ 1.14 and 1.27 in place of the one signal at δ 1.10 in the room-temperature spectrum. Similarly, in the low-temperature ^{13}C spectrum (250 K) all signals are doubled, further indicating the slow interconversion of two conformers on the NMR time scale. For example, the signals assigned to the benzylic carbons at δ 48.8 and to the N$-CH_2-$N groups at δ 62.4 in the room-temperature spectrum, now appear as clearly individual signals at δ 48.3, 48.6, 61.8, and 62.3, respectively.

Thus, each conformer is highly symmetric as evidenced by the presence of a single AB pattern for the benzylic hydrogens. This is consistent with the cone, 1,3-alternate, boat, and chair conformations. However, on the basis of the X-ray structure we propose that at low temperature **3a** exists as a slowly interconverting mixture of boat (*syn*-**3a**) and chair (*anti*-**3a**) conformers, as shown in Figure 2. A similar conformation has recently been reported by McMurry and Phelan.[11]

The coalescence of signals is observed at higher temperatures. In $CDCl_3$ solution at 338 K, the two broad signals at δ 5.8 and 3.7 have flattened into the base line, and a new broad signal begins to emerge at δ 4.6. The other broad shoulder at δ 4.8 has sharpened considerably. This coalescence process continues in DMSO as the temperature is raised to 405 K yielding a sharp signal due to the N$-CH_2-$N groups at δ 4.2 and a much sharpened benzylic proton singlet at δ 4.5. This is qualitatively consistent with the energetics of the two processes that lead to equivalence of the heterocyclic methylene protons and the benzylic protons.

It is well-known that substances dissolved in aromatic solvents generally give signals at higher fields than when dissolved in aliphatic solvents because of the anisotropic fields associated with aromatic rings. In an attempt to use solvent-induced shifts to simplify overlapping resonance signals, a profound change was observed when the ^{1}H and ^{13}C NMR spectra of **3a** were measured in either $CDCl_3-C_6D_6$ (3:1) or toluene-d_8 at 253 K. In contrast to the situation in $CDCl_3$ solution where there are approximately equal amounts of two conformations present, the spectra in the two aromatic solvent systems indicated a change in the ratios of the two conformers of 2:1 and 5:1, respectively.

In the case of **3b** and **3c** the NMR spectra are consistent with the presence of a major conformation along with additional signals due to a minor conformation. The ^{1}H NMR spectra of **3b** and **3c** suggest the presence of similar conformations. The major conformation exhibits a single resonance due to the *tert*-butyl hydrogens and two singlets at δ 2.8 and 3.8 for the methoxyl groups, indicating that the triazone units are

(11) McMurry, J. E.; Phelan, J. C. *Tetrahedron Letters* **1991**, *32*, 5655.

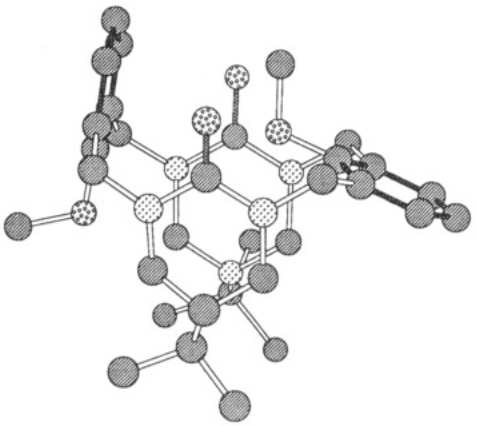


Figure 3. AM1-optimized model for the major conformation of **3b** (and **3c**). H atoms have been omitted for clarity. The conformation of **3d** is identical with H atoms relacing the CH_3O substituents.

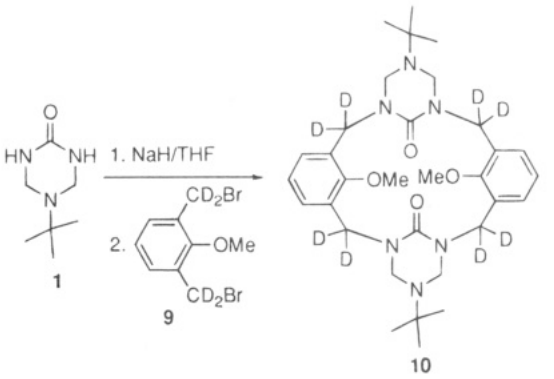
equivalent but that the two aromatic rings are not. The benzylic hydrogens exhibit two AB systems centered at δ 3.3 and 5.6 (total of 8 H's) and at δ 3.7 and 4.7. There are also two AB patterns associated with the heterocyclic ring methylene hydrogens. This is consistent with the partially flattened 1,3-alternate conformation observed in the X-ray structures. The benzylic hydrogens, ideally, are expected to exhibit two AB patterns, but flattening of the aromatic ring could lead to a decrease in $\Delta\delta$, as shown by Gutsche,[11] that could lead to the AB system collapsing to a doublet of double the intensity. The chemical shift difference between the two methoxyl signals of ~1 ppm can be accounted for by the interaction of the methoxyl group of the flattened aromatic unit with the π-cloud of the facing aromatic ring. This interaction then results in an upfield shift. This interpretation is further supported by an examination of the ^{1}H NMR spectrum of **3b** in C_6D_6. In this case the two methoxyl groups appear at δ 3.0 and 3.2, indicating anisotropic associations of both methoxyl units with the aromatic solvent. The ^{1}H NMR of **3c** also shows the same effects. The methoxyl signals appear at δ 2.9 and 3.8, respectively, in $CDCl_3$ and at δ 3.0 and 3.1 in C_6D_6. The $CDCl_3$ spectrum also shows two singlets at δ 2.20 and 2.25 for the two nonequivalent toluene-like methyl groups. An AM1-optimized model for the major conformation of **3b** (and **3c**) is shown in Figure 3.

An examination of the spectrum of the octadeuterio analog **10** was undertaken to further verify the signal assignments in the ^{1}H NMR spectrum of **3b**. The deuterated compound **10** was prepared by the procedure shown in Scheme 3. The original assignments of the benzylic and triazone-ring methylene protons in **3b** were confirmed by the absence of signals at δ 5.6 and 3.3 and at δ 3.7 and 4.7 in the ^{1}H NMR spectrum of **10**.

The room-temperature ^{1}H NMR spectrum of the 18-membered ring macrocycle **4** measured in $CDCl_3$ solution similarly indicates two dominant conformations present in the ratio of 3:1. From COSY and HETCORR 2D correlation experiments, the major conformer exhibits a *tert*-butyl resonance at δ 1.21, an AB pattern at δ 3.2 and 5.4 (J = 14.0 Hz) assigned to the benzylic protons, an AB system at δ 3.7 and 4.0 (J = 10.8 Hz) arising from the N−CH_2−N protons, and a singlet for the aromatic protons at δ 7.09.

The minor conformer shows a *tert*-butyl resonance at δ 1.25, an AB pattern at δ 3.5 and 5.0 (J = 14.9 Hz) for

Scheme 3



the benzyl protons, an AB system at δ 4.2 and 4.3 (J = 10.6 Hz) arising from the N−CH_2−N protons, and an aromatic singlet at δ 7.30. The ^{13}C NMR spectrum is consistent with these observations. Resonances in the ^{13}C NMR due to the major conformer occur at δ 28.7 (C(CH_3)$_3$), 49.1 ($PhCH_2$), 54.1 ($C(CH_3)_3$), 61.8 (NCH_2N), 127.8 ($C_{Ar}H$), and 157.0 (C=O), while the minor conformer exhibits signals at δ 28.5 (C(CH_3)$_3$), 49.5 ($PhCH_2$), 53.9 ($C(CH_3)_3$), 63.4 (NCH_2N), 128.8 ($C_{Ar}H$), and 156.6 (C=O). These observations are compatible with the conformational equilibrium involving species *syn*-**4** and *anti*-**4** which interconvert, presumably by passage of the carbonyl group through the annulus of the macrocycle. In contrast to the situation with **3a**, the ratio of these conformers remains unchanged in going from chloroform to aromatic solvents. Although the NMR spectra do not allow an unequivocal assignment of the major conformation, AM1 calculations suggest that the dominant conformation is *syn*-**4** (Figure 4).

The analogous 16- and 18-membered ring macrocycles **5** and **6** have also been investigated. The room-temperature ^{1}H NMR spectrum of macrocycle **5** in $CDCl_3$ exhibits partially coalesced broad signals at δ 5.2, 3.8, and 3.3 which are present in a relative intensity ratio of 1:1:2. By analogy with **3a** the former are assigned to the benzylic protons and the latter to imidazolidone protons. The ^{13}C spectrum displays the requisite number of signals for the benzylic carbons at δ 47.2 and at δ 41.8 for the imidazolidine carbon atoms. Both the ^{1}H and ^{13}C spectra are doubled at low temperature (250 K). The resonances assigned to the benzyl carbons now appear as equal intensity signals at δ 46.9 and 46.7, while the imidazolidine carbon atoms resonate at δ 41.7 and 41.0. Similar observations are made in the ^{1}H spectrum. These findings reinforce the conclusion that macrocycle **5** behaves in a manner similar to **3a** with two equally-populated *syn* and *anti* conformers in equilibrium (Figure 5).

The situation in the imidazolidone-derived 18-membered ring macrocycle **6** is somewhat different. The room-temperature ^{1}H spectrum of macrocycle **6** in $CDCl_3$ exhibits a well-defined AB pattern centered at δ 3.37 and 5.05 (J = 14.1 Hz) and an easily identified A_2B_2 pattern for the imidazolidone protons centered at δ 2.56 and 3.22. The spectrum remains unchanged as the temperature is lowered to 250 K. This behavior can be interpreted in terms of (1) a single predominant conformation in solution or (2) a rapid exchange between two conformations (e.g. *syn*- and *anti*-**6**) that is essentially unaltered at 250 K (Figure 6).

Calculations of Conformer Stability. The relative stabilites of the *syn* and *anti* conformations of **3a** and a

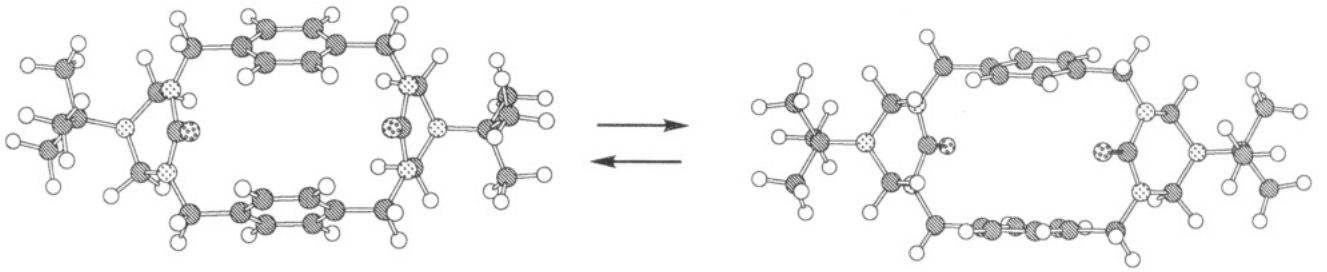


Figure 4. Conformational equilibrium in **4**. The view is down the cylinder axis.

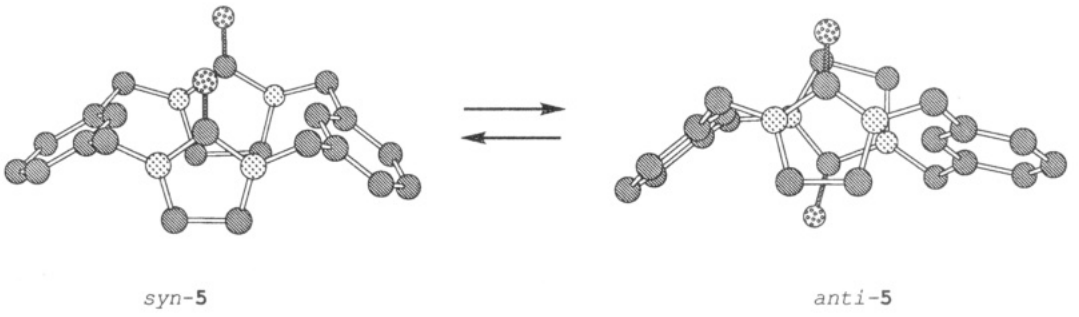


Figure 5. Conformational equilibrium in **5**. Hydrogen atoms have been omitted for clarity.

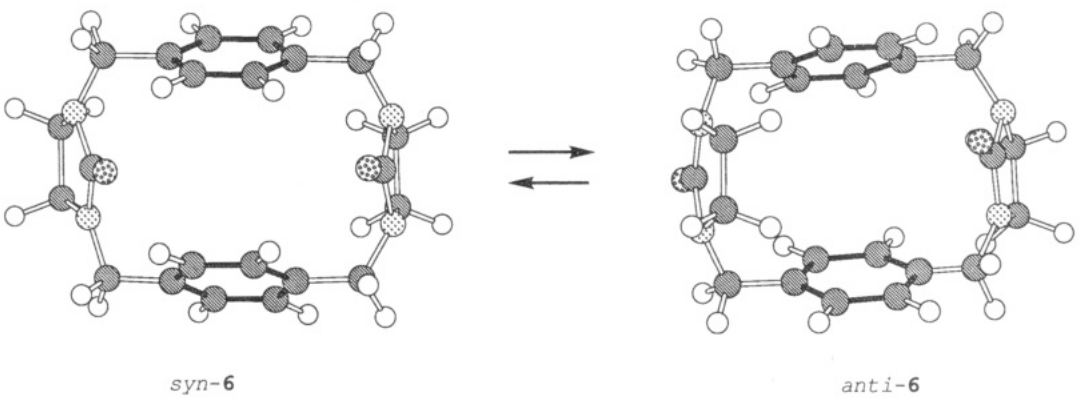


Figure 6. Conformational equilibrium in **6**. The view is down the cylinder axis.

conformation for **3a** similar to that observed in the solid state of **3b**[12] (called **3d**) have been investigated with the AM1 semiempirical molecular orbital procedure.[13] The X-ray structure of **3a** formed the starting point for AM1-geometry optimization of the *anti* conformer; all other preliminary models were constructed with MacroModel 4.5[14] and optimized with the MM2 force field of MacroModel prior to AM1 optimization. The similarity of the X-ray and AM1-optimized structures of *anti*-**3a** can be found in the 0.157 Å rms deviation from a least-squares fit of the 38 C, N, and O common atoms in both structures. Chem3D[15] drawings of the optimized models are shown in Figures 2–6, and the AM1 heats of formation are listed in Table 1.

Table 1. AM1 Heats of Formation (kcal mol^{-1})

model	ΔH_f	model	ΔH_f
anti-**3a**	37.4	*anti*-**5**	34.7
syn-**3a**	37.3	*syn*-**5**	32.9
3d	39.7	anti-**6**	34.7
anti-**4**	42.3	*syn*-**6**	34.9
syn-**4**	41.0		

The calculated heats of formation of the *syn* and *anti* conformations of **3a** are essentially identical, suggesting that the *anti* conformation found in the crystal structure of **3a** is favored by crystal packing energies. These heats are in accord with the NMR data for two conformations of approximately equal population. In *anti*-**3a**, the two benzene rings are almost perpendicular to the cylinder axis and the cross-cyclinder H···H separation is 2.9–3.0 Å (2.90 Å in the AM1-optimized model; 2.97 Å in the X-ray structure with C–H = 1.084 Å). The H···H van der Waals separation of two touching hydrogens is about 2.4 Å (2 × 1.2 Å). A similar conformation for the dimethoxy derivative **3b** is precluded because it would require both methoxy groups to point into the center of the cylinder. In **3d** (see Figure 3), the shortest distance from the inward pointing benzene hydrogen to the

(12) The **2d** model has a structure very similar to that of the dimethoxy analog **2b**, with one benzene ring parallel and the other approximately perpendicular to the axis of the macrocycle cylinder.

(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. Stewart, J. J. P. MOPAC Manual, v. 7.0, QCPE program 455, 1994. All calculations were performed on an IBM RS/6000 model 390 workstation.

(14) Still, C. MacroModel, Columbia University Chemistry Molecular Modeling System, v. 4.5, Columbia University, New York, NY, 1994.

(15) Chem3D, Molecular Modeling and Analysis, v. 3.1, Cambridge Scientific Computing, Inc., Cambridge, MA, 1993.

benzene on the opposite side of the cylinder of 4.01 Å is substantially larger than the van der Waals H···C distance of about 2.9 Å (1.2 + 1.7 Å).

Syn and *anti* models of **4**, viewed down the cylinder axes, are shown in Figure 4. The benzene rings are almost perfectly parallel to the cylinder axis in *anti*-**4**, while in *syn*-**4** the benzene rings are slightly canted inward. The cross-cylinder benzene···benzene separations are substantially larger than van der Waals separations ($2 \times 1.7 = 3.4$ Å). If one assumes that the difference in the AM1 calculated heats of formation of 1.3 kcal mol^{-1} is the same as the difference in free energies, an equilibrium constant of approximately 9 in favor of *syn*-**4** is calculated at 298 K. This is in reasonable agreement with the 3:1 conformer ratio from NMR data. The discrepency between the calculated and NMR conformer ratios probably is due to the assumption that the ΔH_f and ΔF values are parallel by virtue of identical or very similar ΔS values for the conformations. Any differences in the conformer ΔS's will be reflected by differences in the calculated and experimental conformer ratios. The observed 3:1 conformer ratio corresponds to a $\Delta\Delta F$ of 0.6 kcal/mol.

In conclusion, a number of novel macrocycles incorporating cyclic urea units have been synthesized and their structures studied by X-ray crystallography, dynamic NMR, and computational methods. The results indicate that these systems in solution are dominated by conformational equilibria involving readily interconvertible species with *syn* and *anti* alignments of the urea carbonyl groups. Interconversion of these conformers likely occurs by carbonyl through the annulus rotation. In the solid state, depending on the steric interactions in the different compounds investigated, the molecule exists in either the *syn* or *anti* conformation. AM1 semiempirical molecular orbital geometry optimizations are consistent with these findings.

Experimental Section

General. Melting points are uncorrected. All solvents and available precursors were obtained from commercial sources and used without further purification unless otherwise noted. 2-Imidazolidone, 1,3-bis(bromomethyl)benzene, and 1,4-bis-(bromomethyl)benzene were purchased from Aldrich. 2,6-Bis-(Bromomethyl)anisole[8] and 2,6-bis(bromomethyl)-4-methylanisole[9] were prepared according to literature precedents. Tetrahydrofuran (THF) was distilled from Na/benzophenone prior to use.

Cyclization of 1,3-Bis(bromomethyl)benzene to Macrocycle (3a). To a suspension of NaH (460 mg, 19.2 mmol) in THF (180 mL) was added triazone **1** (1.00 g, 6.4 mmol). The reaction mixture was heated under reflux for 1 h and then allowed to cool to room temperature, at which time a solution of 1,3-bis(bromomethyl)benzene (1.69 g, 6.4 mmol) in THF (50 mL) was injected all at once. The reaction mixture was heated under reflux for an additional 18 h and allowed to cool to room temperature, and the remaining NaH was destroyed with H_2O (Caution!). After evaporation of the solvent the residue was taken up in $CHCl_3$ (50 mL) and the $CHCl_3$ layer was washed with brine (25 mL), dried ($MgSO_4$), and evaporated to yield a colorless solid which was recrystallized from ethyl acetate to yield **3a** (700 mg, 54%) as a colorless solid: mp 214–218 °C; ^{1}H NMR ($CDCl_3$, −23 °C) δ 1.11 (s, 9H), 1.14 (s, 9H), 4.15–4.35 (m, 8H), 3.65 (m, 4H), 5.68 (m, 4H), 7.20-7.50 (m, 6H); ^{13}C NMR ($CDCl_3$, −23° C) δ 28.25, 28.49, 53.73, 54.09, 61.72, 62.24, 48.55, 48.20, 123.18, 124.93, 125.62, 126.41, 128.05, 128.07, 138.45, 138.74, 155.25; HRMS (FAB) calcd for $C_{30}H_{43}N_6O_2$ (MH)$^+$ 519.3447, found m/z 519.3451.

Anal. Calcd for $C_{30}H_{42}N_6O_2$: C, 69.46; H, 8.16; N, 16.20. Found: C, 69.30; H, 8.15; N, 16.27.

Cyclization of 2,6-Bis(bromomethyl)anisole to Macrocycle 3b. A suspension of NaH (460 mg, 19.2 mmol) and triazone **1** (1.00 g, 6.4 mmol) in THF (250 mL) was heated under reflux for 1 h. After the reaction mixture was cooled to room temperature, a solution of 2,6-bis(bromomethyl)anisole (**7**, 1.88g, 6.4 mmol) in THF (100 mL) was added dropwise over a 40 min period. The resulting mixture was heated under reflux for 21 h, after which time the remaining NaH was destroyed with ice-cold H_2O (Caution!). Evaporation of the solvent resulted in a syrupy residue which was taken up in CH_2Cl_2 (50 mL). The organic layer was washed with brine (25 mL), dried ($MgSO_4$), and evaporated to yield a yellow amorphous solid. Silica gel chromatography (acetone/hexane 1:4) of this residue afforded **3b** (110 mg, 11%): mp 247–249 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.21 (s, 9H), 2.77 (s, 3H), 3.73 (s, 3H), 3.60 (d, J = 11.97 Hz, 4H), 4.90 (d, J = 11.97 Hz), 3.70 (d, J = 12 Hz, 4H), 4.20, (m, 4H), 3.30, (d, J = 14.7 Hz, 4H, major), 5.63 (d, J = 14.6 Hz, 4H), 3.42, (d, J = 13.9 Hz, 4H, minor), 5.87 (d, J = 13.9 Hz, 4H, minor), 3.76 (m, 4H), 4.72 (d, J = 14.2 Hz, 4H), 6.89–7.46 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 29.00, 29.67, 53.98, 60.35, 60.77, 61.39, 65.66, 47.78, 45.70, 133.66, 130.94, 123.22, 122.51, 132.35, 131.13, 157.66, 159.32; HRMS (FAB) calcd for $C_{32}H_{51}N_6O_4$ (MH)$^+$ 579.3659, found m/z 579.3662.

Cyclization of 2,6-Bis(bromomethyl)-4-methylanisole to Macrocycle 3c. A suspension of triazone **1** (1.00 g, 6.4 mmol) and NaH (460 mg, 19.2 mmol) in THF (300 mL) was heated under reflux for 1 h and then allowed to cool to room temperature. A solution of 2,6-bis(bromomethyl)-4-methylanisole **7**, (1.88 g, 6.4 mmol) in THF (150 mL) was added dropwise over a 60 min period. The resulting mixture was heated under reflux for 18 h, and allowed to cool to room temperature, and ice-cold water was carefully added to destroy excess NaH. After evaporation of the solvent the mixture was taken up in $CHCl_3$ (50 mL) and the solution was washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography (acetone/hexane 1:4) of this residue afforded pure **3c** (125 mg, 5.9%): mp 261–263 °C; ^{1}H NMR ($CDCl_3$) δ 1.12, (s, 9H), 1.20 (s, 9H), 2.86 (s, 3H), 3.77 (s, 3H), 2.24, (s, 3H), 2.28 (s, 3H), 3.60, (d J = 12.6 Hz, 4H), 4.90 (d, J = 11.90 Hz, 4H), 3.75 (m, 4H), 4.30 (d, J = 15.3 Hz, 4H), 3.75 (m, 4H), 4.65 (d, J = 14.1 Hz, 4H), 3.27 (d, J = 14.62 Hz, 4H, major), 5.60 (d, J = 14.60 Hz, 4H, major), 3.40 (d, J = 13.9 Hz, 4H, minor), 5.83 (d, J = 13.7 Hz, 4H, minor), 4.47 (d, J = 14.1 Hz, 4H), 3.80 (m, 4H), 6.80 (s, 4H), 7.30 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 29.00, 29.67, 53.92, 60.35, 60.77, 62.0, 65.0, 47.71, 45.73, 134.14, 131.39, 132.35, 131.13, 131.78, 130.69, 155.34, 156; HRMS (FAB) calcd for $C_{34}H_{47}N_6O_4$ (MH)$^+$ 607.3972, found m/z 607.3971.

Cyclization of 1,4-Bis(bromomethyl)benzene to Macrocycle 4. A suspension of triazone **1** (1.00 g, 6.4 mmol) and NaH (460 mg, 19.2 mmol) in THF (300 mL) was heated under reflux for 1 h and then allowed to cool to room temperature. A solution of 1,4-bis(bromomethyl)benzene (1.68 g, 6.4mmol) in THF (50 mL) was added dropwise over a 20 min period to the ice-cold reaction mixture. After the addition was completed, the resulting mixture was heated under reflux for 18 h. Then ice-cold water was added to destroy excess NaH (Caution!). After removal of the solvent, the residue was taken up in $CHCl_3$ (60 mL) and the solution washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give an amorphous solid. Silica gel chromatography (ethyl acetate/hexane 4:1) of this amorphous solid afforded **4** (119 mg, 2.3%): mp 220–222 °C; ^{1}H NMR ($CDCl_3$) δ 1.22, (s, 9H) 1.25 (s, 9H), 3.72, (d, J = 10.7 Hz, 4H, major), 4.05 (d, J = 10.8 Hz, 4H, major), 4.20 (d, J = 10.8 Hz, 4H, minor), 4.36 (d, J = 10.6 Hz, 4H, minor), 3.26 (d, J = 14.0 Hz, 4H, major), 5.41 (d, J = 14.0 Hz, 4H, major), 3.50 (d, J = 14.9 Hz, 4H, minor), 5.04 (d, J = 14.9 Hz, 4H, minor), 7.11 (s, 4H), 7.28 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 28.72, 28.54, 53.94, 54.07, 63.45, 61.81, 49.50, 49.08, 137.24, 128.86, 127.78, 157.07; HRMS (FAB) calcd for $C_{30}H_{43}N_6O_2$ (MH)$^+$ 519.3447, found m/z 519.3461.

Cyclization of 1,3-Bis(bromomethyl)benzene to Macrocycle 5. A suspension of 2-imidazolidone (550 mg, 6.4 mmol) and NaH (460 mg, 19.2 mmol) in THF (300 mL) was

heated under reflux for 1 h. The mixture was cooled to room temperature; then a solution of 1,3-bis(bromomethyl)benzene (1.68 g, 6.4 mmol) in THF (100 mL) was added dropwise over a 40 min period. This mixture was heated under reflux for an additional 18 h after which time it was allowed to cool to room temperature and ice-cold water was added to destroy excess NaH (Caution!). After evaporation of the solvent, the mixture was taken up in $CHCl_3$ (50 mL) and the solution was washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. Silica gel chromatography (ethyl acetate/acetone 9:1) of this residue afforded **5** (311 mg, 13%): mp 272–274 °C; ^1H NMR ($CDCl_3$) δ 3.00–3.40 (m, 4H, m, 4H), 3.63–3.85 (m, 4H), 5.08–5.23 (m, 4H), 6.98–7.25 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 41.02, 41.72, 46.69, 46.86, 120.87, 123.94, 125.58, 126.90, 128.38, 128.60, 137.62, 137.71, 160.70, 160.90; HRMS (FAB) calcd for $C_{22}H_{25}N_4O_2$ $(MH)^+$ 377.1978, found m/z 377.1986.

Cyclization of 1,4-Bis(bromomethyl)benzene to Macrocycle 6. A suspension of 2-imidazolidone **2** (550 mg, 6.4 mmol) and NaH (460 mg, 19.2 mmol) in THF (350 mL) was heated under reflux for 1 h. The resulting mixture was cooled to room temperature, and a solution of 1,4-bis(bromomethyl)-benzene (1.68 g, 6.4 mmol) in THF (50 mL) was added dropwise over a 30 min period. The mixture was heated under reflux for an additional 18 h allowed to cool to room temperature and ice-cold water was added to destroy excess NaH (Caution!). After evaporation of the solvent the mixture was taken up in $CHCl_3$ (50 mL) and the resulting solution was washed with brine (25 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Silica gel (ethyl acetate/hexane, 7:3) of this residue afforded pure **6** (7.0 mg, 0.32%): mp 277–310 ° C; ^1H NMR ($CDCl_3$) δ 2.56 (m, 4H), 3.22 (m, 4H), 3.37 (d, J = 14.1 Hz, 4H), 5.05 (d, J = 14.1, 4H), 7.27 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 40.35, 47.98, 137.52, 129.37, 161.92, 161.90; HRMS (FAB) calcd for $C_{22}H_{25}N_4O_2$ $(MH)^+$ 377.1978, found m/z 377.1974.

2,6-Bis(bromomethyl-d_2)anisole 9. This compound was prepared by the $LiAlD_4$ reduction of the diethyl ester of 2-methoxy-1,3-benzenedicarboxylic acid followed by treatment of the diol with $SOBr_2$ according to the method used for the protium isotopomer. Compound **9** was obtained as a crystalline solid, mp 80–82 °C; ^1H NMR ($CDCl_3$) δ 4.03 (s, 3H), 7.11 (m, 1H), 7.37 (m, 2H); ^{13}C NMR ($CDCl_3$): δ27.11, 62.22, 125.10, 131.78, 132.18, 156.55; LRMS (CI, NH_3) calcd for $C_9H_{10}OD_4NBr_2$ 314, 316, 318, found m/z 314, 316, 318.

Cyclization of 2,6-Bis(bromomethyl-d_2)anisole to Macrocycle 10. A suspension of triazone **1** (380 mg, 2.4 mmol) and NaH (647 mg, 2.7 mmol) in THF (200 mL) was heated under reflux for 2 h and then allowed to cool to room temperature. A solution of 2,6-bis(bromomethyl-d_2)anisole (**9**, 0.722 g, 2.42 mmol) in THF (10 mL) was added dropwise over a 60 min period to the ice cold reaction mixture. After the addition was completed, the reaction mixture was heated under reflux for 18 h. Ice-cold water was added to destroy excess NaH (Caution!). After removal of the solvent, the residue was chromatographed on silica gel. Elution (methanol/ethyl acetate, 7:93) gave a colorless viscous oil. This was further purified by preparative thin layer chromatography (2000 μm). Elution (methanol/ethyl acetate, 7:93) afforded 44 mg of **10** as a colorless viscous oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H), 2.87 (s, 3H), 3.80 (s, 3H), 3.60, (d, J = 12 Hz, 4H), 3.75 (m, 4H), 4.30 (d, J = 15.3 Hz, 4H), 4.90 (d, J = 12.2 Hz, 4H), 6.87–7.47 (m, 6H); ^{13}C NMR ($CDCl_3$): δ29.65, 54.04, 60.40, 60.78, 61.91, 65.56, 122.51, 123.26, 130.94, 131.21, 132.17, 133.60, 155.40; LRMS (CI, NH_3) calcd for $C_{32}H_{42}O_4N_7D_8$ $(M+18)^+$ 606, found m/z 606.

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Supporting Information Available: ^1H NMR spectra of **3a**, **3b**, **3c**, **4**, **6**, and **10** and ^{13}C NMR spectrum of **5** (7 pages). This material is contained in libraries on micrifiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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