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Synthesis and Structures of a New Class of Calixarene Analogs Derived from 5-*t*-Butyltetrahydro-1,3,5-triazine-2(1H)one.

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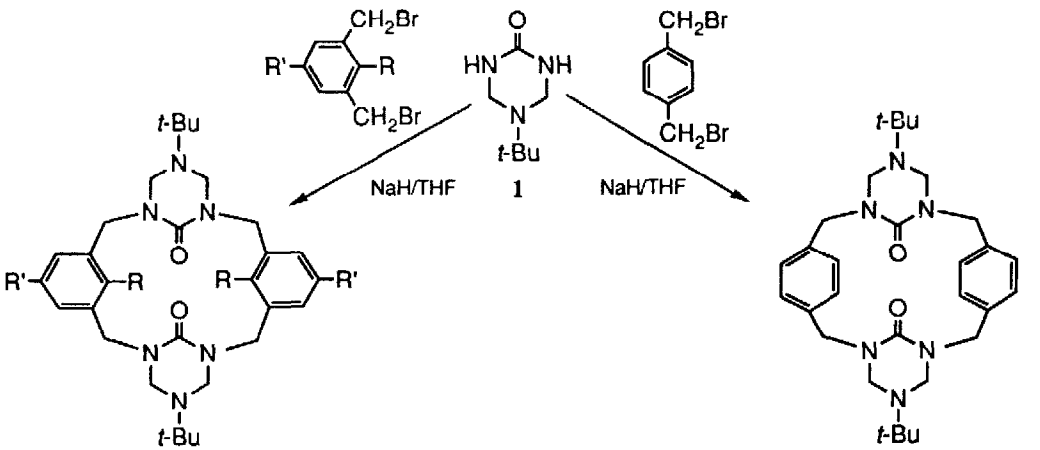
Summary. Representative members of a novel class of calixarene analogs derived from 5-*t*-butyltetrahydro-1,3,5-triazine-2(1H)one **1** have been synthesized and their structures and conformations investigated by X-ray crystallography and NMR spectroscopy.

An important goal of supramolecular chemistry is to understand the association of molecules and ions organized through non-covalent interactions. Calixarenes are cyclic phenol-formaldehyde oligomers capable of admitting small molecules or ions into their cavities. Since the host properties are strongly influenced by the molecular conformation as well as the spatial disposition of binding sites, considerable effort in recent years has centered on the synthesis of modified calixarenes with improved complexation characteristics.[1] As a means of elucidating the conformational considerations important in such molecular assemblies, several members of a new class of macrocyclic calixarene analogs, incorporating the biologically ubiquitous urea unit, have been synthesized and their structural properties investigated.

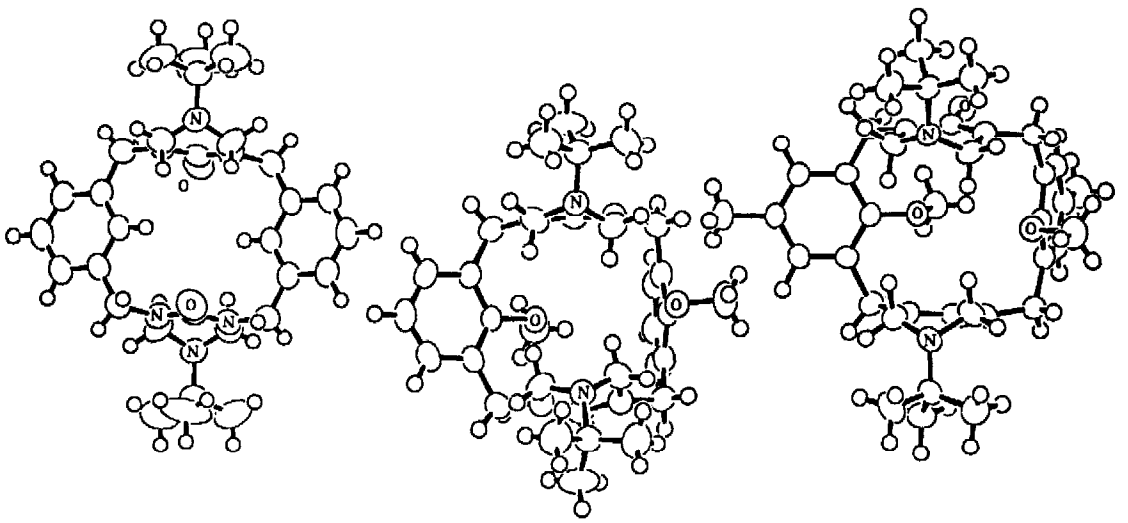
This preliminary report describes the synthesis and investigation of the structures in solution and in the solid-state of representative members of a novel class of macrocycles derived from the 5-*t*-butyltetrahydro-1,3,5-triazine-2(1H)one unit **1**.[2] Triazinone **1** was synthesized in 70% yield via the procedure of Coon *et al.*,[3] based on the Peterson reaction,[4] from urea, *t*-butylamine and formaldehyde. Reaction of **1** with NaH and 1,3-bis(bromomethyl)benzene, 1,3-bis(bromomethyl)anisole[5] or 1,3-bis(bromomethyl)-4-methylanisole[6] in refluxing THF, gave the 16-membered macrocycles **2a** (54% yield, mp 215-216 °C, M^+, m/e, 518), **2b** (11% yield, mp 247-249 °C, M^+, m/e, 578) and **2c** (6% yield, mp 261-263 °C, M^+, m/e, 606), respectively. Similarly, reaction of **1** with NaH and 1,4-bis(bromomethyl)benzene gave the 18-

membered macrocycle **3** (2% yield, mp 220-222 °C, M^+, m/e, 518).

The structures of these calixarene analogs have been investigated by mass spectrometry, 1D and 2D temperature and solvent-dependent NMR spectroscopy and by X-ray crystallography. The X-ray crystallographic results and the NMR spectra provide complementary insights helpful in identifying the dominant conformations



adopted by these macrocycles in solution and in the solid state. The X-ray structures of macrocycles **2a-c** are illustrated in Fig. 1.



2a **2b** **2c**

Fig. 1. X-ray crystal structures of compounds **2a, 2b** and **2c**.[7,8]

In the solid state, **2a** adopts a flattened partial cone-like conformation in which the two aromatic rings and the attached methylene carbons are planar. The triazinone units are essentially parallel to each other with their respective carbonyl units pointing in opposite directions (*anti*-**2a**). The conformations adopted by **2b** and **2c** are similar to each other, but quite different from that of **2a**. In contrast to **2a,** the urea carbonyl groups in the parallel triazinone units of **2b** and **2c** are pointing in the same direction. One aromatic ring in **2b** and **2c** is partially rotated about the axis that passes through the meta carbon atoms joining the bridging benzyl CH_2 groups. This results, as shown in Fig. 1, in the two aryl groups in each molecule occupying perpendicular planes with one of the methoxy groups pointing into the cavity and the other pointing in the opposite direction from the triazinone carbonyl groups. The cavity-directed methoxy group appears to be close to the orthogonal π cloud of the facing aromatic ring.

Different degrees of conformational mobility are apparent in the NMR spectra of these macrocycles. In the room temperature ^1H NMR spectrum of **2a** in $CDCl_3$ the 16 aliphatic methylene protons are seen as broad signals at δ5.8, 4.2, and 3.7 with an intensity ratio of 1:2:1. From 2D correlation experiments, the signals at δ5.8 and 3.7 were assigned to benzylic protons, and the others at δ4.2 to the heterocyclic ring methylene groups. The ^{13}C NMR spectrum exhibits the requisite number of signals for the benzylic carbons at δ48.8 and at 62.4 for the N-CH_2-N groups.

There is clear evidence for the presence of two approximately equally-populated conformations in both the ^1H and ^{13}C spectra at low temperatures. At 250 °K, the broad signals in **2a** assigned to the benzyl protons in the regions, δ5.8 and 3.7, appear as two sets of equal intensity AB systems (distorted apparent triplets or doublet of doublets, J_{AB} =16.2 Hz). 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 triazinone portion of the molecule at δ4.2. At low temperature, the latter signal appears as a pair of doublet of doublets. In addition, two sets of equally intense peaks appear at δ1.14 and 1.27 replacing the one *t*-butyl signal at δ1.10 observed at room temperature. Similarly, in the low temperature ^{13}C spectrum all signals are doubled: benzylic carbons at δ48.3 and 48.6 and N-CH_2-N signals at δ61.8 and 62.3 appear. This observed temperature-dependence confirms the existence of an equilibrium involving two conformers slowly interconverting on the NMR time scale.

These observations are provisionally interpreted in terms of a conformational equilibrium involving *syn* and *anti*-forms of **2a** (both triazinone rings in the *syn*-conformer are oriented with the carbonyls in the same direction, similar to the triazinones found in **2b** and **2c**) which interconvert by carbonyl-through-the-annulus rotation. It is interesting to note that the ratio of these two approximately equally-populated conformations in $CDCl_3$ solution is profoundly changed by increasing

amounts of aromatic solvents. The ratios of the two conformers were 1:2 and 1:5, respectively, at 253 °K in $CDCl_3$-C_6D_6 (3:1) or toluene-d_8. This behavior can arise from the preferential stabilization of the conformer with higher dipole moment (*i.e. syn*) in $CDCl_3$ while non-polar aromatic solvents favor the *anti*-form prevalent in the solid state.[9]

The room temperature NMR spectrum of the 18-membered macrocycle **3** in chloroform solution similarly indicates two conformations present in the ratio of 3:1. Although at elevated temperature the AB patterns due to the benzyl and N-CH_2-N signals can be caused to coalesce, the ratio of conformers is unaffected by the solvent. In the case of **2b** and **2c**, the NMR spectra are consistent with the presence of a major conformation along with additional signals due to a minor conformation. For the major conformation of either **2b** or **2c**, the chemical shift difference between the two methoxy signals of *ca.* 1 ppm can be accounted for by the interaction of the intercavity methoxy group with the π-cloud of the facing aromatic ring. This is further verified by the examination of the ^1H NMR of **2b** in C_6D_6 in which the two methoxy groups appear at δ3.0 and 3.2, indicating anisotropic association of both methoxy units. The ^1H NMR of **2c** shows the same effects.

In conclusion, representative compounds of a new class of conformationally mobile calixarene analogs derived from 5-*t*-butyltetrahydro-1,3,5-triazine-2(1H)one have been synthesized and their structures studied by X-ray crystallography and dynamic NMR. Inclusion complexation studies as well as Molecular Mechanics and AM1 calculations are in progress.

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