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Hydrogen Bonding Patterns of Calix[4]arenes with Thiourea Functionalities in Solution and in the Solid State

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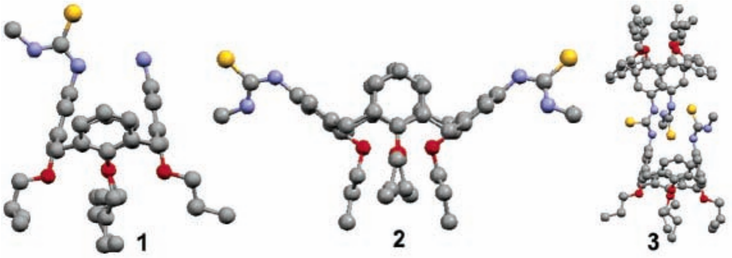
ABSTRACT



We have synthesized a number of calix[4]arene derivatives presenting thiourea functional groups at their upper rims by the condensation of a 1,3-di(*p*-amino)calix[4]arene with alkyl isothiocyanates. Mono- and dithiourea-substituted calix[4]arenes were prepared selectively in good yields, and homocoupling of the former led to calix[4]arene dimers with a thiourea linker. X-ray crystallography revealed interesting intra- and intermolecular hydrogen bonding patterns. ^{1}H NMR data and computational studies also provided some insight into the hydrogen bonding patterns.

Noncovalent interactions play a crucial role in the understanding of various disciplines such as molecular biology and material science.[1] Hydrogen bonds are known to be largely responsible for the inter- and intramolecular order in crystal engineering,[2] and there is little doubt that they are structurally important noncovalent interactions. Urea and thiourea functional groups, which have hydrogen bonding donors and acceptors, could provide interesting and contrasting examples of how small changes in molecular structures can have large influences upon crystal structure.[3] Investigating the basis for these effects can be of singular importance for understanding and designing crystal packing. These will eventually play an important role in crystal engineering.

Urea and thiourea functional groups containing calix[4]arene derivatives were synthesized for molecular capsules and reactors.[4] We designed and synthesized a number of repeating units by using 1,3-di(*p*-amino)calix[4]arene (Scheme

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(1) (a) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., Macnicol, D. D., Vogtle, F., Eds.; Pergamon Press: New York, 1996. (b) Gavezzotti, A. *Crystallogr. Rev.* **1998**, *7*, 5.

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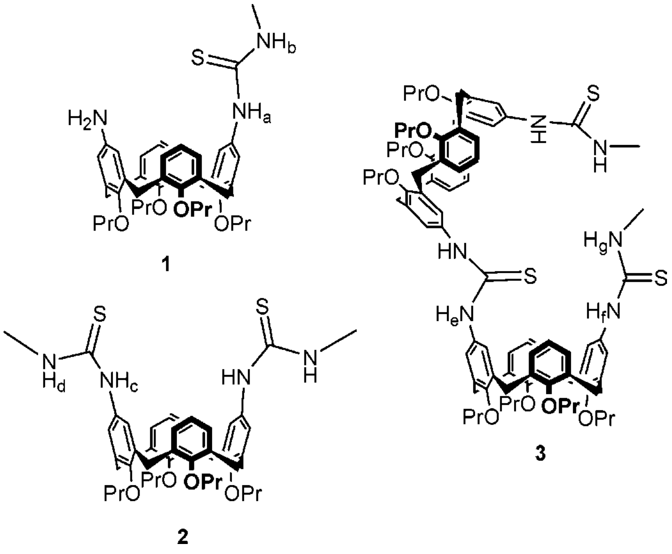
Scheme 1. Synthesis of Monothiourea- and Dithiourea-Substituted Calix[4]arenes and Calixarene Dimers



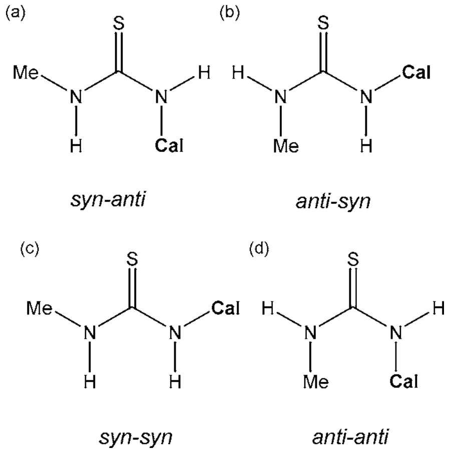


Figure 1. Four major conformations of an unsymmetrically substituted thiourea.

1).[5] We are aware of few reports describing the selective functionalization of only one of the amino groups of 1,3-diaminocalix[4]arene. Here we report our study on a crystal family that has been selectively engineered from thiosubstituted calix[4]arenes through the interplay of intramolecular and intermolecular hydrogen bondings and show different topologies of calix[4]arenes. The engineered crystals could be useful for anion recognition and gold nanoparticles. In this study, thiourea-substituted calix[4]arenes were synthesized to give crystals, and the interactions have been explained on the basis of experiments (X-ray crystallography and NMR spectroscopy) and ab initio calculations.

In general, thioureas can be synthesized by reacting an amino group with an isothiocyanate. Although 1,3-di(*p*-amino)calix[4]arene has two seemingly equally reactive amino groups, in practice, only one of the amino groups reacts when treated with 1 equiv of an isothiocyanate to give the monofunctionalized product selectively. We obtained four monoreacted products such as **1** in this way in excellent yields by using four different isothiocyanates. In the presence of over 2 equiv of isothiocyanate at elevated temperatures, we obtained disubstituted products such as **2** in good yields. The monoreacted products were converted into calix[4]arene dimers such as **3** upon treatment with 1,1′-thiocarbonyldiimidazole.

The unsymmetrical thiourea functional group can adopt several possible conformations. For **1**, there are four different conformational isomers, syn-anti (**1sa**), anti-syn (**1as**), syn-syn (**1ss**), and anti-anti (**1aa**), depending on the dihedral angles between N−Me and C═S and between N−**Cal** and C═S, where **Cal** represents calix[4]arene, in a thiourea group (Figure 1). Among these isomers, **1sa** is predicted to be the most stable conformer, which has lower energy than the others by about 4.4 kcal/mol, which is consistent with the crystal structures. The relative energies of **1sa**, **1ss**, **1aa**, and **1as** are 0, 4.42, 4.76, and 4.95 kcal/mol, respectively. Syn conformation between C═S and N−Me is favored by methyl hydrogen−sulfur interactions, and anti conformation between C═S and N−**Cal** is favored by additional amine hydrogen−aromatic interactions (see optimized structures in Supporting Information).

The X-ray crystal structure of **1** shows that the thiourea moiety adopts a syn-anti conformation, while the calix[4]arene moiety adopts a pinched-cone conformation (Figure 2). The distance between the carbon atoms located para to the PrO units of the two substituted benzene rings is 3.99 Å, while the corresponding distance for the unsubstituted benzene rings is 9.86 Å. The preference for the pinched-cone conformation arises because of the intramolecular hydrogen bond formed between the free amino (acceptor) and thiourea (donor) groups (N···N distance is 3.22 Å).

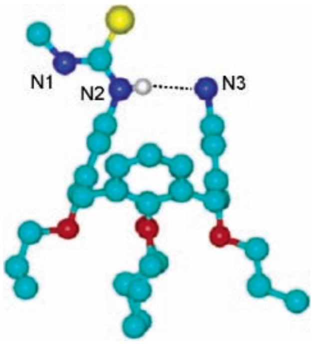


Figure 2. X-ray crystal structure of compound **1**.

The X-ray crystal structure of **2** indicates that it also adopts a pinched-cone conformation, but one that differs from that observed for **1** in the solid state; the thiourea conformations

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[5] Scheerder, J.; van Duynhoven, J. P. M.; Engbersen, J. F. L.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1090.

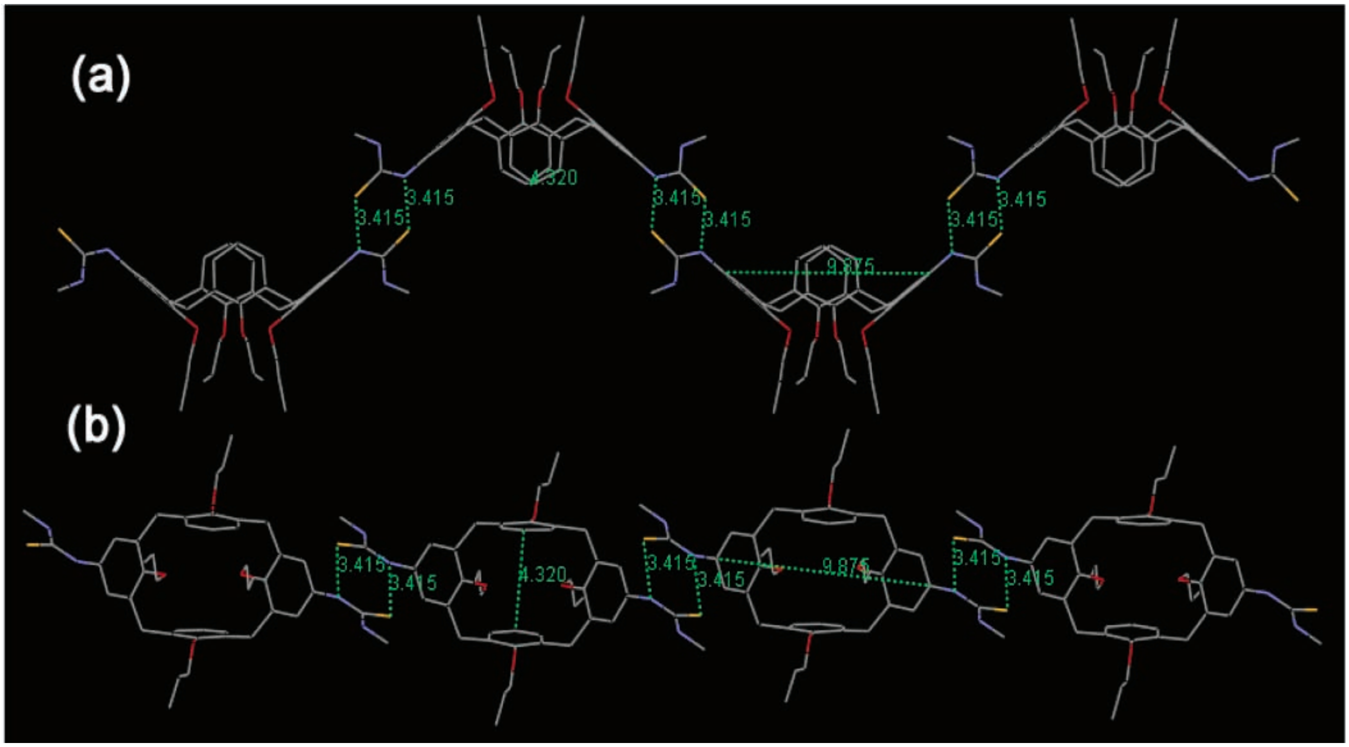

Figure 3. Two-dimensional hydrogen-bonded network found in the X-ray crystal structure of compound **2**. (a) Side view; (b) plane view.

are the same, however (Figure 3). The distance between the carbon atoms situated para to the PrO groups of the substituted benzene rings is 9.88 Å, while that of the unsubstituted benzene rings is 4.32 Å. The thiourea units of adjacent calix[4]arene derivatives are involved in hydrogen bonding: the S···N distance is 3.42 Å. Presumably, this pinched-cone conformation is preferred in the solid state over that observed for **1** by the stabilization brought about by this intermolecular hydrogen bonding. In an earlier study, Reinhoudt et al. reported[6] structural studies of a different group of di(thio)urea-substituted calixarenes and found that intramolecular hydrogen bonding between the (thio)urea groups (which adopt syn-syn conformations) can stabilize the resulting pinched-cone conformations in solution and, computationally, in the gas phase. In the case of our molecule **2**, however, intermolecular hydrogen bonding between thiourea groups (each of which adopts the syn-anti conformation) in the solid state seems to be more favorable than intramolecular bonding; thus, the opposite pinched-cone conformation is adopted as a result of the steric requirements of the hydrogen bonding.

The X-ray crystal structure of **3** shows an interesting mode of intramolecular hydrogen bonding (Figure 4). The two terminal thiourea groups exist in syn-anti conformations, and the central thiourea group, which links the two calix[4]arenes together, exists in a syn-syn conformation. These three thiourea units form a network of four hydrogen bonds that combine to stabilize the pinched-cone conformations of both calix[4]arene moieties of **3**.

Figure 5 depicts the ^{1}H NMR spectra of compounds **1**−**3** in $CDCl_3$, a solvent in which intramolecular hydrogen bonding of these molecules is expected to take place. The chemical shifts of proton H_a of **1** (Figure 5a) and of protons H_e and H_f of **3** (Figure 5c) at ambient temperature appear relatively downfield of the signal of protons H_c of **2** (Figure 5b) under the same conditions. A similar trend appears for

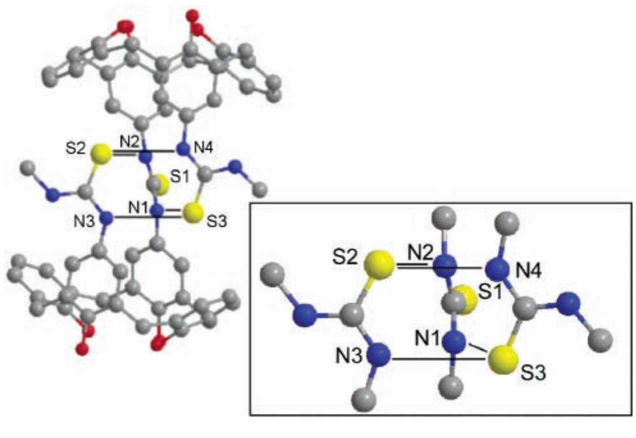

Figure 4. X-ray crystal structure of compound **3** (Chem3D rendering). The S···N distances are: S2···N2, 3.39 Å; S2···N4, 3.39 Å; S3···N1, 3.65 Å; S3···N3, 3.57 Å. Propyl ethers were omitted for clarity.

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[6] Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. L.; Verboom, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476.

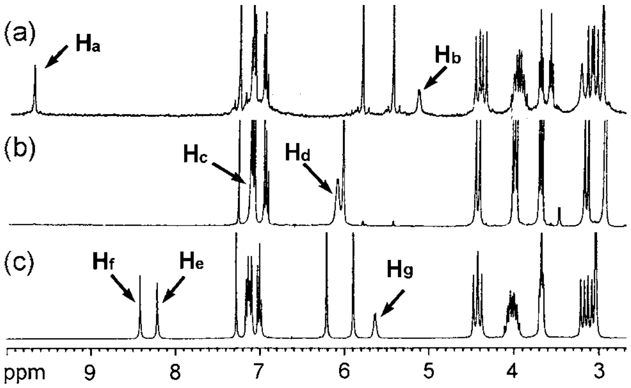

Figure 5. Partial ^{1}H NMR spectra (300 MHz, $CDCl_3$, 25 °C) of (a) **1**, (b) **2**, and (c) **3**. Protons are labeled as in Scheme 1.

the chemical shifts of protons H_b of **1** and H_g of **3**, which are relatively upfield of the signal of proton H_d of **2**. These trends are consistent with the crystal structures, which show that compounds **1** and **3** form intramolecular hydrogen bonds in the solid state, but **2** does not. In addition, **1** is expected to possess the strongest hydrogen bond among the three because of its relatively stronger hydrogen-bond-accepting amino group, which is manifested by the most downfield signal appearing for H_a of **1**. Thus, the strengths of the intramolecular hydrogen bonding interactions increase in the order **1** > **3** > **2**. One more reasonable explanation for the downfield shift of proton H_a of **1** is the anisotropic effect by the aromatic π-electron currents of the calix[4]arene.

The NMR spectra suggest that all of the monosubstituted compounds are stabilized in nonpolar solvents by a hydrogen bond between H_a of the thiourea group and the amino nitrogen atom. This phenomenon explains why the monofunctionalization of the diaminocalix[4]arene is so selective: the stabilizing hydrogen bonding interaction reduces the reactivity of the second amino group at room temperature. At elevated temperature, however, this hydrogen bond is weaker and the free amino group reacts.

To understand the reason different calix[4]arene topologies are taken in compounds **1**−**3**, a detailed investigation on the molecular interactions was conducted from quantum chemical calculations. The calculated structures regarding the intramolecular hydrogen bonds in **3** are in agreement with the X-ray crystallographic data except that the calculations overestimate the hydrogen bond distances by about 0.25 Å. This overestimation may be due in part to the lack of electron correlation effect in Hartree−Fock calculations; however, the main discrepancy probably arises from the packing effect in the solid states. All calculations for the complete molecular systems were carried out at the Hartree−Fock (HF) level of theory with 6-31G* basis sets using the Gaussian 98 suite of programs (see Supporting Information).

In summary, the monothiourea-substituted calixarenes are chemically stable compounds at room temperature in $CHCl_3$ as a result of intramolecular hydrogen bonding between the amino and thiourea moieties. These compounds are converted easily to bisthiourea-substituted derivatives and calix[4]arene dimers containing three thiourea functional groups. The solid-state structures of a monothiourea derivative and a calix[4]arene dimer show that their calix[4]arene moieties possess pinched-cone conformations as a result of intramolecular hydrogen bonding, but the solid-state structure of a bisthiourea derivative exhibits the opposite pinched-cone conformation because of intermolecular hydrogen bonding.

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Supporting Information Available: Synthetic details and characterization data, CIF files, and comparison of calculated conformations in the gas phase for compounds **1**−**3** with those obtained from the solid state. This material is available free of charge via the Internet at http://pubs.acs.org.

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