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Preparation, Solid-State Characterization, and Computational Study of a Crown Ether Attached to a Squaramide

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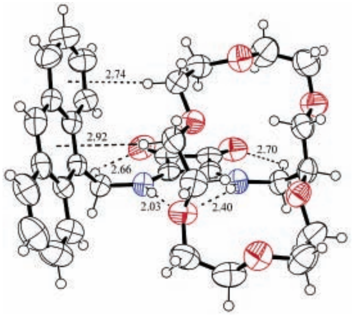
ABSTRACT



Crystals of a disecondary squaramide covalently linked to a crown ether presents a great variety of inter- and intramolecular nonbonded interactions including C–H/π contacts, C–H···O and N–H···O hydrogen bonds, and π–π stacking between squaramide rings. Latter interaction, the stacking between squaramide rings, can be considered as an experimental evidence for the proposed aromaticity of squaramide when it is forming hydrogen bonds, either as acceptor or donor.

Noncovalent interactions play a key role in many areas of modern chemistry, especially in the field of supramolecular chemistry and molecular recognition.[1] Ion-pair recognition, the simultaneous complexation of cationic and anionic guest species by heteroditopic receptors, is an emerging and topical field of coordination chemistry.[2]

In our pursuit of building heteroditopic ion-pair receptors, we have focused our efforts on attaching crown ethers to disecondary squaramides. Crown ethers have been widely used to recognize cations,[3] and Tomàs et al. have successfully used squaramide-based receptors for the molecular recognition of anions.[4] Additionally, we have demonstrated using geometrical and magnetic criteria that the remarkable hydrogen bond acceptor/donor character of squaramide is due to the gain in aromaticity of the four-membered ring upon formation of hydrogen bonds either with the carbonyl oxygen atoms, the N−H groups, or both.[5]

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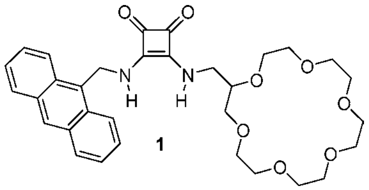
10.1021/ol0474608 CCC: $30.25

In this paper, we report the synthesis, X-ray structure, and some ab initio calculations of squaramide **1**. Crystal structures of squaramides are very scarcely found in the literature, and there is only one previous example in the Cambridge Structural Database[6] of an X-ray structure of a disecondary squaramide.[7] In the solid state, compound **1** presents three kinds of noncovalent intramolecular interactions and one intermolecular $\pi-\pi$ stacking interaction between two four-membered squaramide rings that provides experimental evidence of the previous theoretically proposed aromaticity of the ring. This is also corroborated by the observed covalent bond lengths of the ring compared with those of observed in other squaric acid derivatives.



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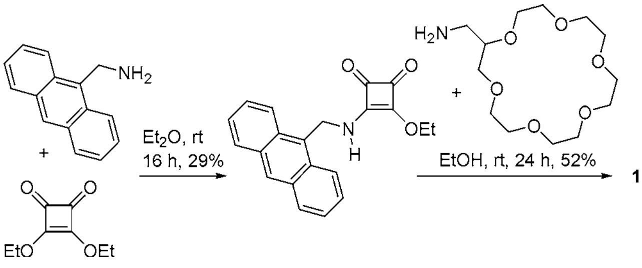
The two-step synthesis of **1** is outlined in Scheme 1. The condensation of diethyl squarate and 9-(aminomethyl)-anthracene gave the squaramide-ester intermediate. A subsequent condensation with 2-(aminomethyl)-18-crown-6 yielded the target compound **1**.

Scheme 1. Synthesis of Receptor **1**



The X-ray analysis of **1**, shown in Figure 1, revealed some very interesting features. First, two C−H/π intramolecular interactions are clearly established between two hydrogen atoms belonging to the crown ether and the aromatic rings of the anthracene. The hydrogen atoms are located at 2.74 and 2.92 Å from the corresponding center of the ring, and both C−H bonds are pointing to them. These observed distances are within the range of the typical ones of C−H/π interactions.[8] Second, two conventional N−H···O hydrogen bonds are present between both amidic hydrogen atoms of the squaramide and one oxygen atom of the crown ether.

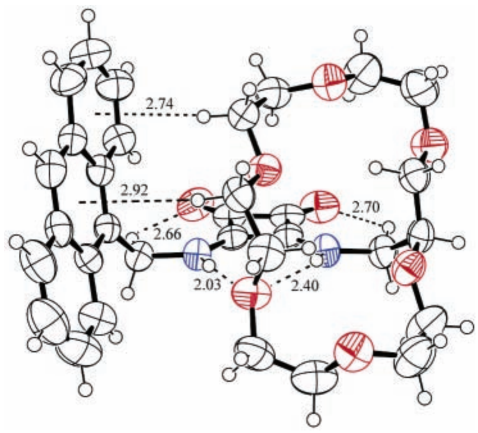


Figure 1. Thermal ellipsoid plot of **1** (50% probability). Some relevant distances (Å) are shown. Noncovalent interactions are represented by broken lines.

Distances and angles (2.03 Å, 173.4° and 2.40 Å, 162.1°) are a clear confirmation of the formation of both noncovalent interactions (see Figure 1). Third, an unconventional C−H···O hydrogen bond is formed between one of the carbonyl oxygen atoms of the squaramide and a hydrogen atom attached to the crown ether (2.70 Å, 138.9°), and another one is formed between the other carbonyl oxygen atom and a methylene hydrogen atom in the α position to the anthracenyl group (2.66 Å, 143.0°).

We have demonstrated theoretically that the aromaticity of the squaramide ring is especially enhanced when it is forming hydrogen bonds as acceptor and donor simultaneously.[5] A first indication of this behavior comes from the distance of the C−C bond that connects the two carbonyl carbon atoms, which is 1.49 Å, significantly shorter than the predicted theoretically for squaramide[5a] (1.55 Å at MP2/6-311+G** level of theory) and experimentally for other *cis*-diketones[9] (1.54 Å, average of 43 X-ray structures retrieved from the Cambridge Structural Database[10]). It is known that *cis*-diketones have negative hyperconjugative interaction between lone pairs of the oxygen atoms and the adjacent C−C σ^* orbital being this the main reason for the long C−C bond.[11] A second and more significant indication of the aromatic character of the ring is the arrangement of the squaramide units in the crystal packing along the crystallographic *b*-axis, the compound forms dimeric structures stabilized by a π-stacking interaction between both squaramides. The representation of the dimeric arrangment of **1** in the solid state is shown in Figure 2.

The distance between the ring centroids of the two stacked squaramides in the dimer is 3.40 Å, close to that observed in crystals of aromatic molecules,[12] which form stacks with

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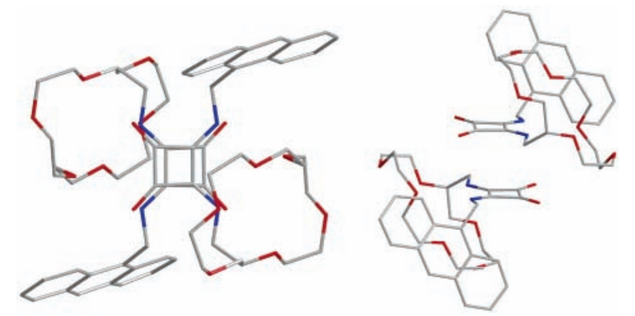

Figure 2. Representation of the dimeric arrangement of **1** in the X-ray crystal packing. A zenithal view is shown on the left and a side view on the right. The hydrogen atoms have been omitted for clarity.

approximately parallel molecular planes separated by 3.3−3.6 Å. It also correlates well with the computed distance of the sandwich dimer of benzene using state of the art calculations (MP2/aug-cc-VTZ),[13] which is 3.7 Å.

To confirm the diversity of noncovalent intramolecular interactions present in **1**, we have performed some ab initio calculations at the HF/6-31G** using the X-ray geometry by means of the Gaussian-98 program.[14] Topological analysis of the charge density $\rho(r)$ distribution and properties of critical points (CP) were determined by using the "atoms-in-molecules" (AIM) method which is widely used to characterize nonbonded interactions.[15] For instance, it has been successfully used to understand conventional[16] and unconventional[17] hydrogen bonds, cation-π[18] and anion-π[19] interactions; and it provides an unambiguous definition of chemical bonding.[20] The AIM analysis was carried out by means of the suit of programs AIMPAC[21] using the HF/6-31G** wave function. For compound **1** exploration of CPs revealed the presence of two bond CPs which connect two methylene hydrogen atoms of the crown ether with the aromatic rings of the anthracene (see Figure 3, left) confirming the existence of two noncovalent C−H/π interactions. It also revealed the existence of one bond CP for each conventional N−H···O hydrogen bond and one bond CP for each unconventional C−H···O hydrogen bond present in **1**, connecting the oxygen atoms with the hydrogen atoms; see Figure 3. The Laplacian of the bond CPs is positive, as is common in closed-shell interactions. The values of the density (ρ) at the CPs are shown in Figure 3, and as expected, they are higher for the conventional (N−H···O) than for the unconventional (C−H···O and C−H/π) hydrogen bonds. We have also performed the AIM analysis of the dimeric arrangement of compound **1** in order to verify the stacking interaction between the squaramide rings. We have found in the dimeric arrangement retrieved from the X-ray structure a bond CP connecting the center both squaramide rings and, additionally, four ring CPs connecting approximately the middle of the C═O bond of one squaramide with the middle of the C−N bond of the other, see Figure 3, where only a partial view of the whole dimer is shown.

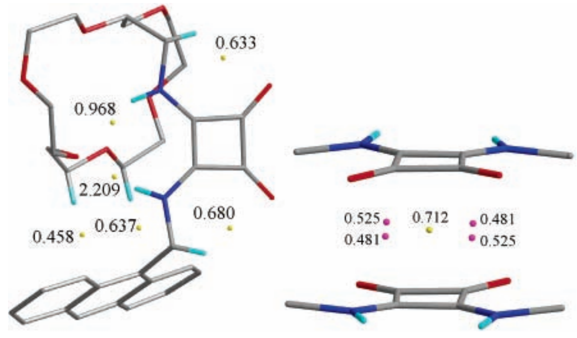

Figure 3. Representation of the CPs obtained for the crystal structure of **1**. The intramolecular CPs are shown on the left side and the intermolecular CPs on the right (partial views). The value of the charge density ($10^2\rho$) at the CPs is also shown in au. Bond CPs are represented in yellow and ring CPs in pink.

The aromatic character of the squaramide rings in the dimer has been analyzed using the nucleus independent chemical shift (NICS) method,[22] which is an effective criterion for studying aromaticity. NICS agrees well with the energetic (ASE), geometric, and magnetic criteria and does not require increment systems for other references.[23] Negative NICS values denote aromaticity and positive values denote anti-aromaticity. NICS values were calculated using the GIAO method[24] at HF/6-31G** at 0.6 Å above the ring center in order to reduce the local shielding of nearby σ-bonds which complicates the analysis in small rings.[25] The

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NICS criterion has successfully used before for the study of oxocarbon derivatives.[26] The NICS(0.6) value obtained for **1** is −9.5 ppm, which indicates aromaticity of the four-membered ring and it is in agreement with previous calculations on squaramide derivatives.[26c]

In summary, we have synthesized and characterized receptor **1** in the solid state, which forms four kinds of noncovalent interactions, i.e., conventional and unconventional hydrogen bonds, C−H/π and stacking $\pi-\pi$ interaction. The latter is confirmed by the presence of several critical points that connect two parallel squaramide rings, which indicates that both rings are interacting. Furthermore, we have found that the NICS value in the squaramide rings is negative indicating aromaticity. The $\pi-\pi$ stacking interaction of the squaramide rings present in the X-ray structure of **1** is in accord with the theoretically proposed aromaticity of the squaramide ring when it is forming hydrogen bonds.

Finally, some preliminary theoretical and experimental work to explore the binding properties of **1** has been performed. To carry out the theoretical investigation, we have used the resolution of the identity DFT methodology (BP86), implemented in the program TURBOMOLE,[27] using for the optimization the SVP basis set[28] (double-ζ with polarization). This level of theory, taking into account the size of the system, is adequate to perform this preliminary study. We have optimized and analyzed complexes of receptor **1** with sodium acetate and potassium acetate. The optimized structures are shown in Figure 4. The acetate anion interacts with both NH of the squaramide unit and the cation interacts with the crown ether unit and with one oxygen atom of the acetate. The binding energies are very similar for both complexes (−56.3 kcal/mol for AcONa and −56.6 kcal/mol for AcOK). Experimentally, a solution of **1** in chloroform is able to dissolve, otherwise insoluble, carboxylate salts (i.e., sodium benzoate and sodium acetate). In Figure 5, we show the ^{1}H NMR spectra of **1** and **1** + AcOK in $CDCl_3$. The complexation-induced chemical shift of the NH signals ($\Delta\delta$) are 2.69 ppm for NH_a and 3.29 ppm for NH_b. The results for AcONa are very similar and are included in the Supporting Information. The determination of association constants of receptor **1** with soluble carboxylate salts, as tetrabutylammonium benzoate, is currently under research in our laboratory and will be published elsewhere. For instance, the association constant of **1** with tetrabutylammonium *p*-nitrobenzoate salt is 23.7 M^{-1} in the competitive DMSO medium and 120.0 M^{-1} in $CHCl_3$.

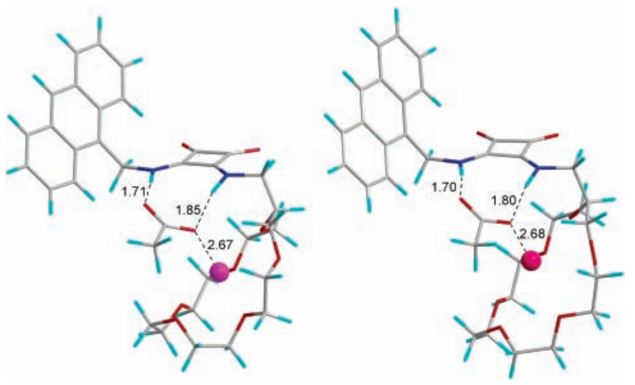

Figure 4. PB86/SVP optimized structures if **1** interacting with AcONa (left) and AcOK (right) salts, distances in Å.

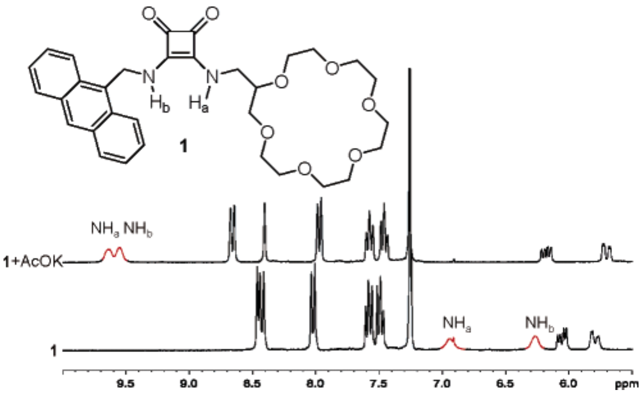

Figure 5. ^{1}H NMR spectra of **1** and **1** + AcOK at 298 K in $CDCl_3$.

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Supporting Information Available: Crystallographic information file (CIF) and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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