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The Use of Squaric Acid as a Scaffold for Cofacial Phenyl Rings

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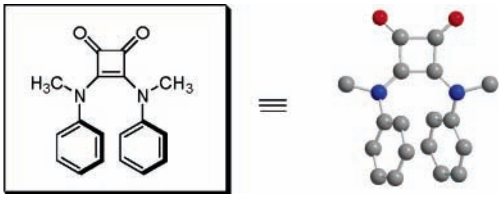
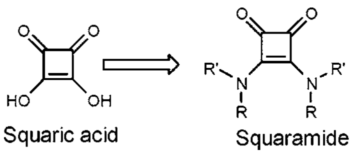
ABSTRACT



To examine the possibility of using squaric acid as a scaffold for organizing phenyl rings in a cofacial orientation, we undertook an investigation of the conformational preferences of secondary and tertiary *N*-phenylsquaramides. In secondary squaramides, the extended *ZZ* conformation is preferred, while in the *N*-methyl derivative, the folded *EE* conformation with cofacial phenyl rings is preferred. This conformational switch is likely driven by a combination of steric and electronic factors.

The design of conformationally flexible molecules with cofacial arene motifs has emerged as an area of intense contemporary interest. Design strategies for such systems include those that rely on donor−acceptor interactions,[1a−c] hydrogen bonding,[1d−e] solvophobic interactions,[1f] aromatic $\pi-\pi$ interactions,[1g] and the known propensity of *N*-methylarylureas and -guanidines to adopt a cisoid conformation.[1h] In connection with ongoing studies on bichromophoric molecules, we were interested in investigating whether squaric acid[2] could be used as a scaffold for organizing phenyl rings in a cofacial orientation. The *N*-phenylamides of squaric acid (henceforth referred to as squaramides) are of particular interest because of the unique four-atom tether connecting the phenyl rings in these compounds. Such a tether, which is integrated into a cyclobutene dione ring, has not yet been explored in model systems with stacked arenes.[3] We wish to report herein, for the first time, a comparison of the conformational preferences of squaramides. Structural evidence indicates that the secondary squaramide **1** exists in an extended conformation, while the *N*,*N*-dimethyl derivative **2** prefers a folded conformation with cofacial phenyl rings both in solution as well as in the solid state.



1. R = H, R' = Ph
2. R = CH_3, R' = Ph

Our design strategy (Figure 1) relied on exploiting steric and electronic factors which are known to induce confor-

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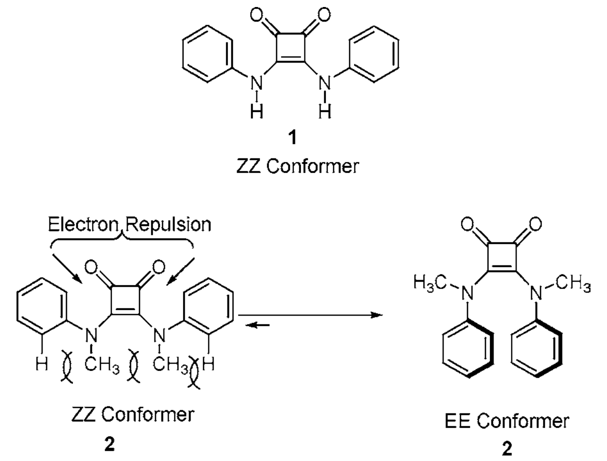

Figure 1. Conformational preferences of secondary and tertiary *N*-phenylsquaramides.

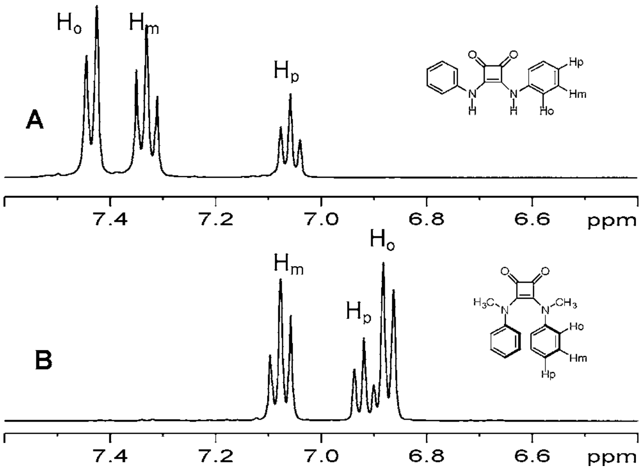

Figure 2. Comparison of the aromatic region of the 400 MHz ^{1}H NMR spectrum of **1** (A) and **2** (B) in DMSO-d_6.

mational bias in amides.[4,5] We anticipated that in the secondary squaramide **1** the preferred conformation would be *ZZ*[5] with the two phenyl groups syn to the carbonyl oxygens. We reasoned that upon conversion to a tertiary derivative **2**, the unfavorable interactions between the two *N*-methyl groups and between the phenyl ring and the oxygen lone pairs in the *ZZ* conformer would drive the molecule to preferentially adopt the *EE* conformation. The phenyl groups in this conformation would be anti to the carbonyl oxygen and consequently cofacial to one another.

A literature survey shows that, to date, studies on the conformations of squaric acid derivatives rely on either intra- or intermolecular[2d,e,6] hydrogen bonding as a conformational control element. Experimentally, it has been demonstrated that tertiary squaramides such as *N*,*N*-dialkyl derivatives show little preference for any particular conformation and are known to exist as a mixture of conformers.[7] The significance of the present study stems from the fact that it demonstrates that conformational preferences could be engendered in squaric acid derivatives that are apparently devoid of any hydrogen-bonding elements.

Squaramides **1** and **2** were synthesized as described earlier[8] and their conformations examined by NMR spectroscopy. From solution ^{1}H NMR data of **1** (Figure 2a), the signal due to the ortho hydrogen is the most deshielded presumably due to its proximity to the carbonyl oxygen. The next upfield peak is that of the meta hydrogen, while the para proton is the least deshielded. This peak pattern together with the observation of only one set of signals for all hydrogens leads us to assign the symmetrical *ZZ* conformation for **1**.

Upon conversion to the *N*,*N*-dimethyl derivative **2**, the ^{1}H NMR spectrum shows a distinct change in the aromatic region (Figure 2b).[9] The peaks for the methylated derivative **2** are all shifted upfield relative to compound **1** with the signals due to the ortho and meta hydrogens experiencing more shielding ($\Delta\delta$ for H_o and H_m is 0.62 and 0.25, respectively) than the para hydrogen ($\Delta\delta = 0.14$). This observed general upfield shift of the peaks in **2** is likely caused by the two aromatic rings stacked one above another in a cofacial orientation. Thus, the switch from an extended *ZZ* to a folded *EE* conformation did indeed occur, as anticipated, in going from **1** to **2**. Furthermore, the fact that the ortho and the meta protons experience a greater ring-current effect than the para hydrogens suggests that the two phenyl rings are offset relative to one another.[10] The NMR spectrum of compound **2** showed no temperature dependence (between -85 and $+60$ °C) and showed only minor variations in chemical shift with changes in solvent polarity.[11]

The conformation of **2** was also examined in the solid state (Figure 3). To our knowledge, this is the first reported crystal structure of a diaryl squaramide. The cofacial orientation of the phenyl rings in **2** is somewhat different from a similar stacked geometry in tertiary diaryl ureas and guanidines.[1h,12] For example, the angle between the planes of the two phenyl rings in **2** is 15.24°. In comparison, in tertiary aryl guanidines[1h] the dihedral angle between the phenyl groups is between 31

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(9) Although the NMR of **2** was reported (ref 8b) in trifluoroacetic acid and the signals are upfield as we observed in DMSO, the authors, apparently, did not deem it necessary to consider the possibility of a stacked conformation. We thank Ms. Rolande Hodel for translating the manuscripts.

(10) The folded EE conformation is also predicted to be the most stable for **2** according to semiempirical calculations (AM1). The *EZ* and the *ZZ* conformations are less stable by 2 and 6 kcal, respectively. The same calculations also show that an edge to face orientation of the phenyl rings in the EE conformation of **2** is 60 kcal higher in energy relative to the cofacial geometry.

(11) The solvents used were toluene, methylene chloride, chloroform, acetontrile, pyridine, methanol, dimethyl sulfoxide, and trifluoroethanol.

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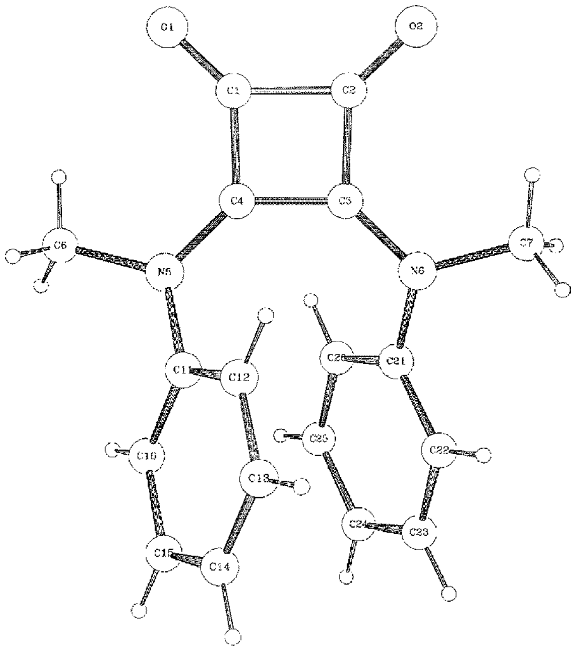

Figure 3. Ball-and-stick representation of the crystal structure of **2**. The atom labels are indicated and selected structural information is provided. Bond distances (Å): C1−O1 (and C2−O2) = 1.216; C1−C2 = 1.505; C2−C3 = 1.472; C3−C4 = 1.411; C1−C4 = 1.465; C4−N5 =1.339; C3−N6 = 1.336. Bond angles (deg): C4−N5−C11 = 119.96; C4−N5−C6 = 119.6; C11−N5−C6 = 118.74; C3−N6−C21 = 121.29; C3−N6−C7 = 119.32; C21−N6−C7 = 117.13.

and 38°. The distance between the centers of the two phenyl rings in **2** is 3.61 Å while the closest contact distance is 3.15 Å (between C11 and C21). In *N*,*N*-dimethyldiarylguanidine the centroid−centroid distance between the two phenyl rings is 3.85 Å.[1h] Presumably, the increased separation brought about by the presence of the cyclobutene dione ring leads to a more parallel orientation of the two phenyl rings in squaramides compared to the splayed orientation in ureas and guanidines. It is interesting to note that the centroid to centroid distance of 3.61 Å in **2** is close to that calculated[13] and experimentally observed[14] for the interaction of two phenyl rings in a parallel offset orientation.[15] The C4−N5 and the C3−N6 bonds in **2** are shorter (both 1.34 Å) than a typical C−N single bond (1.38−1.42 Å) in enamines[16] indicating significant double-bond character in the exocyclic C−N bonds.[17] However, examination of the improper dihedral angles[18] around N5 and N6 showed some nonplanarity with average values of 15.1° and 17.2°, respectively.[19]

In summary, we have disclosed in this paper the use of squaric acid as a novel template (with a four-atom tether) for organizing phenyl rings in a cofacial orientation. While secondary squaramide **1** exists in the extended *ZZ* conformation, the tertiary squaramide **2** exists in a folded *EE* conformation both in solution and in the solid state. The ready accessibility to the squaramides augurs well for the incorporation of this motif in longer oligomers (foldamers).[20] For our purposes, with the conformations of *N*-arylsquaramides now clearly characterized, work is currently underway to examine their excited-state properties. Results will be reported in due course.

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Supporting Information Available: X-ray data for **2** in CIF file format. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] Consider the atoms C6, C4, N5, and C11 in compound **2**. The improper dihedral angle C6−C4−N5−C11 is defined as the angle between the planes C6−C4−N5 and C4−N5−C11. Ideally, for a nitrogen atom with sp^2-hybridized orbitals, the improper dihedral angle should be zero.

[19] The specific improper dihedral angles measured were C6−C4−N5−C11 = 15.2°; C4−C11−N5−C6 = 15.1°; C11−C6−N5−C4 = 15.0°; C7−C3−N6−C21 = 17.6°; C3−C21−N6−C7 = 17.2°; C21−C7−N6−C3 = 16.9°.

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