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Conformational Preferences and Self-Template Macrocyclization of Squaramide-Based Foldable Modules

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Secondary squaramides have considerable potential as hydrogen bond donors and acceptors. In $CHCl_3$ both, *anti*- and *syn*-squaramide rotamers are observed by NMR. The energetic barrier for *anti*/*syn* mutual interconversion determined by complete band shape analysis is ~63 kJ mol^{-1}. As in proline derivatives, a low rotational barrier is crucial for the design of foldable modules. In this paper, folding based on the low rotational barrier of squaramides is driven by donor atoms (N or O) located in the γ position of an alkyl chain of a secondary squaramide. We demonstrate that the resulting minimal module exists as a folded conformer through the formation of a nine-membered ring stabilized by intramolecular hydrogen bonding. Molecular mechanics calculations and NMR studies support the existence of these folded conformers. The intramolecularly hydrogen bonded conformers are clearly visible even in $CHCl_3$−EtOH mixtures. Folding occurs even in pure ethanol. As an indirect test, we studied the effectiveness of macrocyclization reactions in pure ethanol that require an effective templating effect to take place. The high yields obtained support the dominant role of a folded conformer even in this solvent.

Introduction

Squaramides,[1] the amino derivatives of squaric acid, can be considered as vinilogous amides. Among others, they have in common with amides a considerable hydrogen bonding capability (Figure 1a). The donor−acceptor ability of squaramides is accentuated by the conjugation of a carbonyl group with its farthest substituents[2] by delocalization of a nitrogen lone pair through the partially aromatic cyclobutenedione system. The calculated gain in charge density for an oxygen carbonyl due to the influence of a nitrogen atom is appreciable (0.030*e*) but smaller in comparison to that observed with a typical amide, namely formamide (0.055*e*), at the same theoretical level.[3] From a structural point of view, the mutual influence of a squaramide NH and a carbonyl oxygen on the overall structure is reflected as a partial contribution of limiting zwitterionic structures (Figure 1b). Remarkably, the dipole represented by a zwitterionic squaramide form has been recognized to mimic the α-ammonium carboxylate motif in a number of α-amino acid bioisosters.[4] As a practical consequence, it can be anticipated

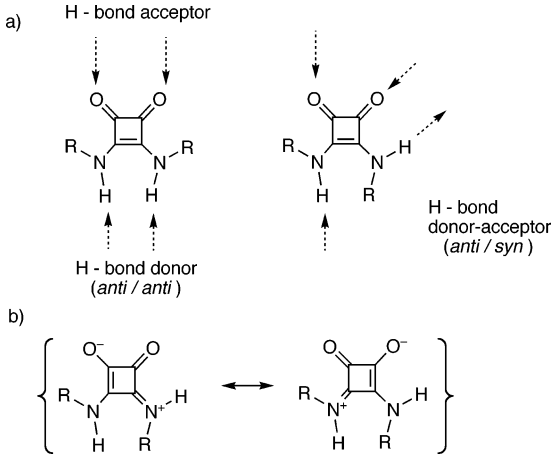

FIGURE 1. (a) Hydrogen bond options arising from *ant*,*anti* or *anti*,*syn* conformers of bis-secondary squaramides. (b) Zwitterionic forms.

that there will be restricted rotation about the C−N bonds of squaramides.

Although a number of similarities between squaramides and amides are evident, squaramides incorporate distinctive features. Among these, a rigid and planar structure of the cyclobutenedione system ($C_4N_2O_2$) seems crucial. In effect, a squaramide motif featuring two coplanar carbonyl and two squaramide NH that are almost coplanar is very well organized for the molecular recognition of complementary targets through hydrogen bonding. In addition, squaramides can form hydrogen bonds strengthened by favorable secondary interactions[5]

(1) Throughout this text, the word "squaramide" stands for both *N*- and *N*,*N*′-derivatives of 3,4-diamino-3-cyclobutene-1,2-dione.

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owing to the position of the carbonyl oxygen and squaramide nitrogen atoms. Furthermore, recent theoretical calculations show that the partial aromatic character of squaramides increases upon complexation both, with anions and cations.[6] This chameleon-like response is in good agreement with the demonstrated complexing ability of squaramides in squaramide-based receptors for choline phospholipids[7] and other tetraalkylammonium cations,[8] as well as for carboxylate[9] or sulfate anions.[10]

Assuming the existence of amide-like restricted rotation about the C−N bond of a squaramide, a double secondary squaramide having two C−N bonds might exist, in principle, as mixtures of *anti*/*syn* conformers. Previous work confirms this. For example, the simultaneous participation of the two NH groups in a carboxylate−squaramide complex force the squaramide to adopt an extended *anti*/*anti* conformation.[8] The *syn*/*anti* state is also observed in a mixed *N*-carbamoyl squaramide dimer[11] Finally, a *syn*/*syn* conformer is not significantly populated because the Gibbs free energy of this form must be higher than any other conformer due to the mutual steric hindrance of substituents in the 3,4 position of disubstituted 3-cyclobutene-1,2-dione systems.

An early study of the conformational preferences of squaramides showed that tertiary squaramides can exist as a mixture of conformers with rotational barriers ranging from 16 to 18 kcal mol^{-1}.[12] However, little or nothing is known about the conformational preferences of secondary squaramides, although small differences in population and low barriers to rotation about the C−N bond can be anticipated.[8]

In this work, we studied the conformation and rotational barriers of secondary squaramide models because these parameters are important for the future development of squaramides as switchable molecular modules.[13] These modules would be useful not only for mechanistic and structural peptidomimetics studies,[14] but also for the design of responsive molecules capable of controlled changes between conformers[15] as well as for the development of predictable foldable systems for biomedical applications.[16]

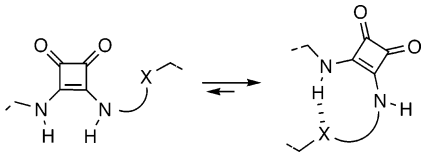
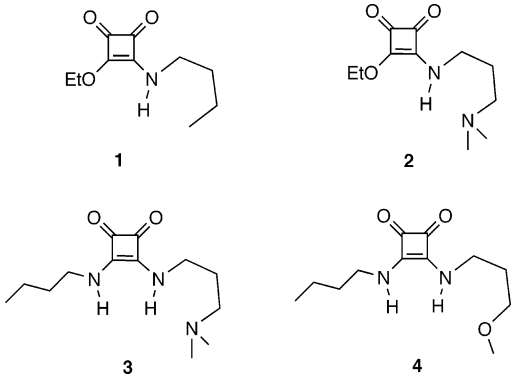


FIGURE 2. Representation of a squaramide-based turn-forming structural fragment stabilized by intramolecular hydrogen bonding.

Knowledge of the conformational preferences of a potentially foldable unit is crucial for practical applications.[17] For example, the well-known preference[18] for the anti form of acyclic secondary amides and related carbamates,[19] combined with a notable hydrogen bonding ability, dictates the extensive use of these groups for the construction of supramolecular architectures with defined geometries.[20] However, the high barrier to rotation of simple amides[21] prevents their use as switches or foldable elements in molecular devices. In the second part of this paper, we study the possible stabilization of *syn*/*anti* conformers by intramolecular hydrogen bonding to give a turn-forming fragment. Starting from secondary squaramides this approach would be possible provided that the C−N rotational barrier was low enough to enable the conformational exchange to take place. Also, a low rotational barrier would suffice in order to generate a turn-forming structural motif based on squaramides. In this particular case, the conformational equilibrium could be driven by intramolecular noncovalent interactions[22] (Figure 2). Here, the rigid cyclobutenedione ring is expected to decrease the entropy penalty associated with folding by restricting the conformational freedom of a part of the chain in the unfolded state.[23]

Results and Discussion

Stepwise characterization is of prime importance for interpreting the conformational events in nonrigid hydrogen bonded systems. Therefore, we carried out the conformational analysis of model squaramides **1**−**4** that feature incremental possibilities of interaction. The effect on the NMR chemical shifts produced by variations in temperature, concentration, and addition of DMSO as a competitive solvent were investigated and interpreted in line with the above discussion.



The ^{1}H NMR spectrum of **1** in $CDCl_3$ (4.0 mM) is temperature-dependent. At 315 K, rotation about the

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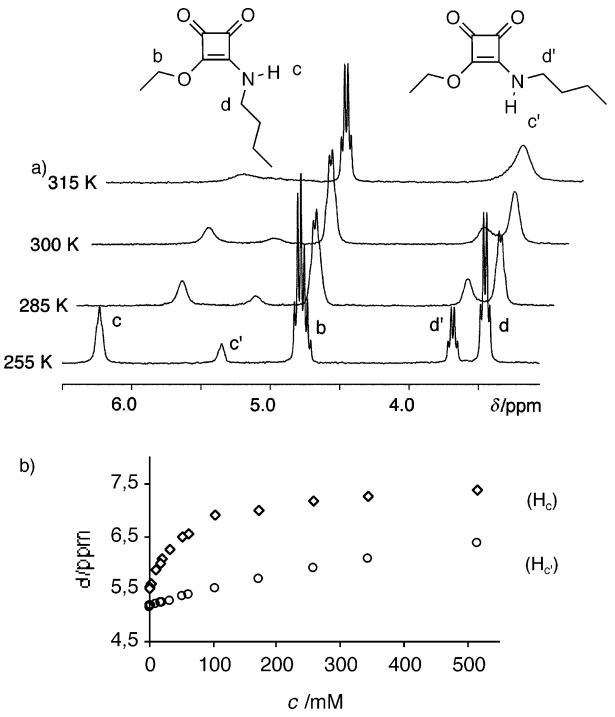
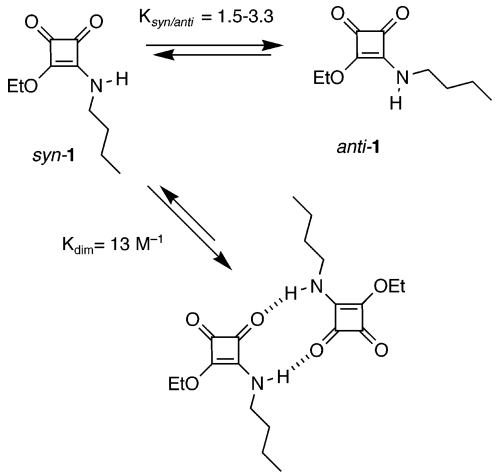


FIGURE 3. (a) Temperature-dependent ^{1}H NMR spectrum of squaramide **1** (4.0 mM) in $CDCl_3$. (b) Concentration-dependent ^{1}H NMR shifts of NH signals at 294 K.

C−N bond is fast on the NMR time scale, and a simple time-averaged spectrum is observed. As the temperature is lowered, both *O*- and *N*-alkyl signals broaden and split into two unequally populated signals due to hindered rotation about the squaramide bond (Figure 3a). At 255 K, two distinct species are clearly observed. Assignment of stereochemistry is based on the expectation that signals of *syn* N-substituents are shifted downfield relative to those of N-substituents *anti* due to the paramagnetic influence of the squaramide carbonyl group. On this basis, the major conformer is assigned to the *syn* form. In a series of related squaramides, the *syn* rotamer is always favored over the *anti*. The observed chemical shifts are temperature-dependent. The magnitude of the rate of change ($\Delta\partial_{NH}/\Delta T$) for the NH signal in *syn*-**1** and *anti*-**1** is −18.8 and −3.8 ppb/K,[24] respectively. This result indicates that the hydrogen bonding state of *syn*-**1**, but not that of *anti*-**1**, is changing probably due to a process of intermolecular association. For **1**, the *syn*/*anti* ratio is also concentration-dependent. A plot of chemical shift versus concentration for the NH groups is shown (Figure 3b). Equilibrium constants for the interconversion between *syn*-**1** and *anti*-**1** ranging from 3.3 to 1.5 at 294 K were obtained by integration of the two sets of signals at each concentration. In the range 3−500 mM, the *syn* NH and *anti* NH move downfield 1.4 and 0.13 ppm, respectively. The large shift observed for the *syn* NH in *syn*-**1** is an indication of substantial hydrogen bonding for this conformer. Taken together, these results are consistent with a conformational equilibrium between *syn*-**1** and *anti*-**1** partially affected by homodimerization[25] of *syn*-**1** to give a $R_2^2(10)$ hydrogen-bonded motif.[26] In accordance, the observed chemical shifts for the syn NH fits well to a 1:1 dimerization model allowing an estimation of the dimerization constant (K_{dim} of 13 ± 1.5 M^{-1}) at 294 K (Scheme 1).

SCHEME 1. Conformational Equilibrium and Homodimerization of 1



Introduction of a dialkylamino group in the alkyl chain of the squaramide has a clear effect on the chemical shifts of the NH hydrogen atoms. The ^{1}H NMR spectrum of **2** (5.5 mM) is both temperature- and concentration-dependent and, as above, displays two separate sets of signals (Figure 4a). At 255 K in $CDCl_3$, the chemical shifts of the two NH hydrogens are at 8.1 and 8.3 ppm, respectively, and roughly 2.5−3.0 ppm deshielded compared to **1**. In addition, the temperature dependence of the NH chemical shifts for *syn*-**2** (−14.6) and *anti*-**2** (−13.3 ppb/K) is similar, indicating a substantial and comparable hydrogen bonding state for the two conformers. Also in contrast with **1**, the NH resonance of *syn*-**2** and *anti*-**2** is only slightly concentration-dependent, since the NH chemical shifts move only −0.14 and −0.10 ppm in the range 0.5−100 mM (Figure 4b). In the same interval, the apparent isomerization constant $K_{syn/anti}$ remains almost invariable, changing from 1 to 1.5 (±0.2) M^{-1}. These data clearly indicate the existence of intramolecular hydrogen bonding in *syn*-**2** and *anti*-**2**. In this case, the observations can be accounted for by assuming that both conformers are mainly monomeric species and that the dimethylamino group is involved in a six-membered ring intramolecular hydrogen bond. As a result, model compound **2** does not show any appreciable intermolecular association.

This structure was confirmed with the help of 2D NOESY and COSY experiments. A 2D NOESY experi-

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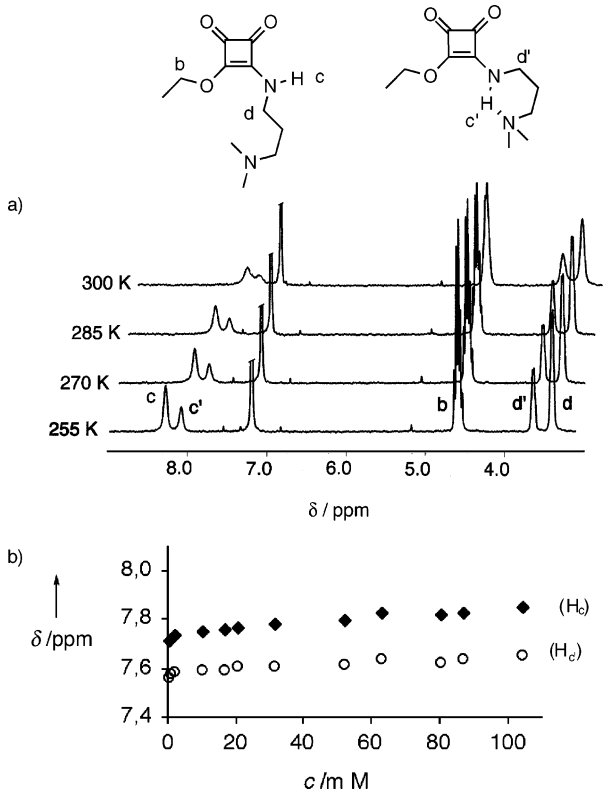
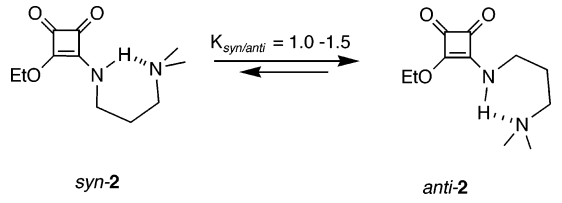


FIGURE 4. (a) Temperature-dependent ^{1}H NMR spectrum of squaramide **2** (5.5 mM) in $CDCl_3$. Solvent peak is truncated for clarity. (b) Concentration-dependent ^{1}H NMR shifts of NH signals at 294 K.

SCHEME 2



ment (10 mM) recorded at 255 K, besides the standard peaks connecting neighboring hydrogen atoms, shows cross-peaks between the squaramide NH(c) and NH(c′) protons and those of the dimethylamino group, demonstrating their spatial proximity. Overall, these observations are in agreement with the equilibrium outlined below (Scheme 2).

These data also exclude the formation of dimers or higher order aggregates that would cause concentration-dependent shifts for the squaramide NH protons of **2**. However, the results of an X-ray analysis on **2** showed an alternative hydrogen bond pattern.[27] The crystal structure (Figure 5a) consists of alternate stacked squaramides forming columns in the a-direction that are held together by intercolumnar NH↔N hydrogen bonding. If one considers an isolated dimeric pair (Figure 5b), two dialkylaminopropyl residues are mutually joined through two almost linear hydrogen bonds (NH↔N angle 170°),

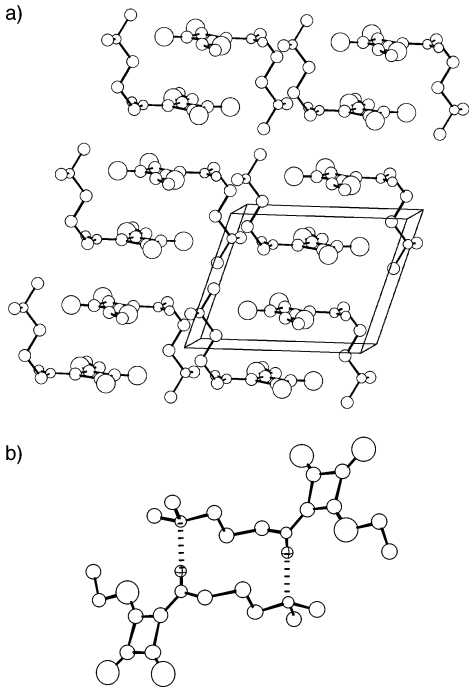


FIGURE 5. Crystal structure of **2**. (a) View parallel to the *bc*-plane. (b) Detail of an squaramide pair in the anti conformation showing NH↔N intermolecular contacts. In this view only the NH hydrogens are shown.

while the distance NH to N (2.023 Å) is within the standard interval (1.75−2.32 Å) for NH↔N hydrogen bonds.[28] Although not detected for **2** in solution, the structure found in the solid state suggests a dimerization pattern that probably occurs in chloroform solutions of certain squaramides (see below).

To study the *anti* to *syn* isomerization of secondary squaramides, the energetics of the rotation about the C−N bond was also investigated. Exchange-broadened spectra of **1** (4.0 mM) and **2** (5.5 mM) were obtained in $CDCl_3$ at temperatures between 250 and 300 K. Complete band shape analysis[29] of the NMR spectra provided rates of rotation that were used to construct the Eyring plots. Linear regression analysis and calculation give significant but energetically accessible barriers to rotation for **1** ($\Delta G^{\ddagger} = 63.7 \pm 1.2$ kJ mol^{-1}) and **2,** ($\Delta G^{\ddagger} = 63.3 \pm 1.5$ kJ mol^{-1}) at 298 K.[30] Remarkably, despite the existence of intramolecular hydrogen bonding in **2**, both squaramides give similar results.[31] The reported values are slightly lower than the barrier to rotation reported for tertiary squaramides (ca. ∼71 kJ mol^1)[12] and are comparable to what is found for carbamates (∼65 kJ mol^1).[32] Indeed, the C−N bond of a secondary squaramide also compares well with the C−N bond of proline derivatives.[33] As in prolines, the *syn* conformer is slightly

(27) Cambridge Crystallographic Data Centre, ref CCDC-206868, contains the supplementary crystallographic data for this compound. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.

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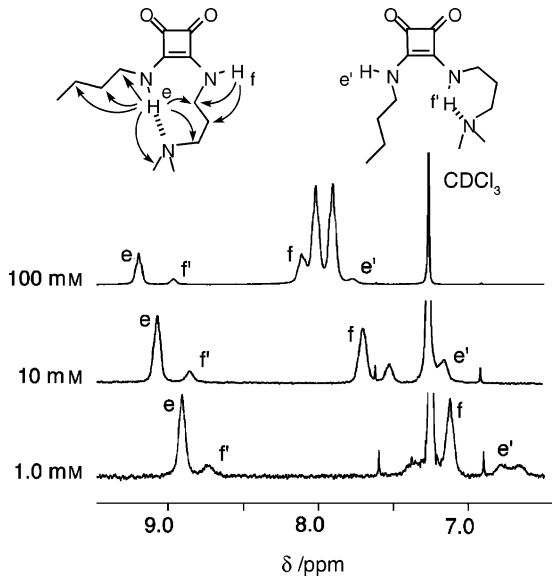


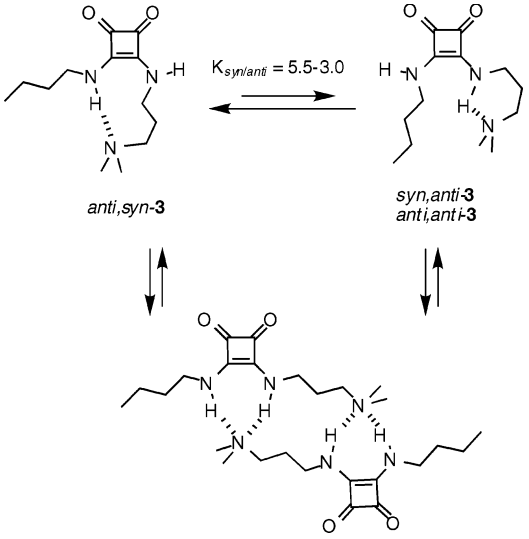
FIGURE 6. Proposed monomeric structures detected for **3** with indication of significative ROESY contacts (top). Partial concentration-dependent spectra of **3** in $CDCl_3$ (bottom). The residual signal of the solvent is truncated for clarity.

favored by ca. 1 kJ mol^{-1} over the *anti*, which, in practical terms, results in the observation of a 20−40% of the *anti* conformer at room temperature. Also, the activation energy barrier for *syn*/*anti* interconversion in proline-type residues (ca. 55 kJ mol^{-1}) is comparable but lower than the value obtained for squaramides. From these data, it is clear that secondary squaramides can fold without paying a high energetic penalty.

Assuming the existence of *anti*/*syn* mixtures of secondary squaramides in solution, doubly substituted squaramides **3** and **4** were studied in order to investigate the folding abilities of these compounds. As above, proton NMR spectra of **3** in $CDCl_3$ showed several NH resonances revealing the existence of at least three species in solution. At 255 K, the spectra show two unequally populated (85:15) NH signals. The observation of a peak at ca. 9 ppm indicates the existence of a strongly hydrogen bonded species. Concentration-dependent measurements reveal substantial changes in both chemical shifts and intensity in the NH portion of the spectra. Figure 6 illustrates these changes when the concentration of **3** is raised from 1.0 to 100 mM. At elevated concentrations, besides the above peaks, the spectra display several concentration-dependent signals around 8 ppm. Therefore, apparently at low concentrations **3** is present as two monomeric forms, whereas at higher concentration the aggregated forms predominate.

The structural assignment of the two suspected monomers is based on 2D NMR experiments (COSY, TOCSY, ROESY) performed at 255 K. As a whole, the NMR experiments support the existence of **3** as 2-folded conformers. The major conformer *anti*/*syn*-**3** would have a folded structure stabilized through the formation of a rather unusual nine-membered hydrogen bonded ring

SCHEME 3. Conformational Equilibrium and Homodimerization of 3



between the *N*-butyl squaramide hydrogen and the nitrogen of the aminoalkyl residue.[34] The *anti*/*syn* disposition of the squaramide segment in this conformer is clearly established by ^{1}H NMR spectroscopy since both squaramide NH protons appear as separate signals. On its turn, the spectral data for the minor conformer *anti*/*anti*-**3** and/or *syn*/*anti*-**3** were only partially solved. These data are consistent with a standard six member hydrogen bonded conformer stabilized by hydrogen bonding between the tertiary nitrogen and the NH on the same sidearm of the squaramide. The structure of the main conformer *anti*/*syn*-**3** is also supported by ROESY experiments performed at 255 K. The spectrum of this conformer exhibits diagnostic cross-peaks that reveal spatial proximity between the squaramide butyl-NH and the *N*-methyl and CH_2-NMe protons (Figure 6). In addition, *anti*/*syn*-**3** resists competition from externally added protic solvents such as EtOH. The ^{1}H NMR of **3** (2.8 mM) in $CDCl_3$−EtOH mixtures containing up to 30% EtOH display a persistent deshielded NH signal characteristic of this conformer. However, unfolding to the *anti*/*anti* conformation is induced by stepwise addition of DMSO-d_6 to a solution of **3** in $CDCl_3$.[35] In this case, DMSO may bind to *anti*/*syn* and *syn*/*anti*-**3** to give a complex with the NH hydrogens in *anti*/*anti* conformation that typically results in upfield but similar chemical shifts for both squaramide NH protons (Scheme 3).

The prevalence of *anti*/*syn*-**3** over *syn*/*anti*- or *anti*/*anti*-**3** is only slighty concentration-dependent. In the range 1.0−100 mM, *anti*/*syn*-**3** is always favored over $\mathbf{3}_6$ (K_{ap} = 3.3−5.5). From a thermodynamic standpoint, this value implies that the folded rotamer *anti*/*syn*-**3** is 2.5−3.6 kJ mol^{-1} lower in energy than others at 255 K. At this stage, it is interesting to note that the poor confor-

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mational constraints and the low rotational barriers of a squaramide segment provide an excellent opportunity for extending the usual six-member intramolecular hydrogen bonding to the much less common nine-member ring, in the present case, even with a gain in energy.

Analysis of squaramide **4** provides confirmation of the competition between the two hydrogen bonded conformers. As above, the ^{1}H NMR spectrum of **4** (9.8×10^{-3} M) in $CDCl_3$ at 255 K reveals the presence of several species in solution. Concentration-dependent experiments on **4** demonstrate that this squaramide is more aggregated in comparison to **3**; however, two monomers are still detected albeit in low proportion. Their structures were tentatively assigned on the basis of 2D-NMR experiments. The spectra show that the two monomeric conformers *anti*/*syn*-**4** and *syn*/*anti*-**4** are predominant only at the lower limit of concentration reached in this study (0.1−1.0 mM), while oligomeric forms predominate at higher concentrations.

To gain insight about the preferential folding of monomeric squaramides **3** and **4**, we calculated the energy difference between the nine- and six-membered ring conformers. Molecular mechanics calculations were performed using the BOSS force field modified by inclusion of atomic parameters for squaramides.[36] The results show a more linear hydrogen bond angle for *anti*/*syn*-**3** (172°, NH···N) and for *c*-**4** (159°, NH···O) than for the corresponding six-membered conformers *syn*/*anti*-**3** (135°) and *syn*/*anti*-**4** (131°), respectively. These values are relevant because the intramolecular hydrogen bond in the folded squaramides *anti*/*syn* does not experience strong conformational constraints. On the contrary, they exhibit geometrical angles that are close to those formed by intermolecular hydrogen bonded systems.[37] In terms of calculated relative energies these nine-membered quasi-intermolecular bonds are more stable than the six-membered intramolecular ones. In $CHCl_3$, the energy of *anti*/*syn*-**3** is 7.5 kJ mol^{-1} lower than that calculated for *syn*/*anti*-**3**, while *anti*/*syn*-**4** is 12.9 kJ mol^{-1} lower in comparison with *syn*/*anti*-**4**. Remarkably, the calculated (7.5 kJ mol^{-1}) and experimental values (2.5−3.6 kJ mol^{-1}) for the difference in energy of the conformers in **3** are in reasonable agreement giving further support for this new type of molecular scaffolds. The stoichiometry and structural features of the oligomers observed in solution are partially deduced from experimental observations. Thus, the similar chemical shifts of the two NH protons at 7−8 ppm in the aggregated form are consistent with an *anti*/*anti* conformation of the squaramide moiety. The change in conformation from a *anti*/*syn* or *syn*/*anti* found in monomeric squaramides, to *anti*/*anti* in the oligomers is probably due to the very low energetic barrier to rotation of secondary squaramides. Initially we assumed the formation of only dimers. However, the chemical shift data for the aggregates arising from **3** or **4** in $CDCl_3$ could not be well fitted to a pure dimeric model. These results suggest that higher order aggregation occurs to some extent. More information on this issue was obtained by electrospray mass spectrometry (ESI-MS). The ESI mass spectra of solutions of **3** and **4** in $CHCl_3$−EtOH (9:1 v/v) exhibit characteristic trends. In squaramide **3**, the maximum intensity is observed for the $[\mathbf{3}_2 + Na]^+$ and $[\mathbf{3}_2 + H]^+$ ions but the other peaks can be assigned to the $[\mathbf{3}_n + H]^+$ and $[\mathbf{3}_n + Na]^+$ series ($n = 3-6$). In **4**, the signal of the dimer $[\mathbf{4}_2 + H]^+$ is predominant together with other ions of the series $[\mathbf{4}_n + H]^+$. In EtOH the spectra simplified and the intensity of the dimeric ions at *m*/*z* 507.3 and 529.3 for $\mathbf{3}_2$ and *m*/*z* 503 for $\mathbf{4}_2$, respectively, appear much more intense than the other oligomeric species. These are consistent with the information available from ^{1}H NMR, in particular with the tendency to give oligomers observed for **3** and **4** at relatively high concentrations and with the observation of cross-peaks between the MeO- or M_2N- residues of the oligomer signals and the squaramido hydrogens and *n*-butyl substituents in ROESY experiments.

In our opinion, the above observations illustrate two competitive pathways of aggregation. One more specific takes place by mutual interaction of donor and acceptor groups of **3** or **4** to give a dimer stabilized by four hydrogen bonds. A second nonspecific head-to-tail aggregation of squaramides would explain the presence of oligomeric species in $CDCl_3$. Unfortunately; it was not possible to study the dimerization by NMR in EtOH due to the disappearance of the NH signals due to fast exchange and the poor sensitivity of the chemical shifts of any other signals.

In general, the above data demonstrate the tendency of bis-secondary squaramides containing acceptor atoms toward the formation of nine-membered ring structures. In an effort to discover if these folded structures were still present in ethanol, we planned a macrocyclization as a test reaction to demonstrate that intramolecular hydrogen bonding was operating in this protic solvent.

It is known that intramolecular hydrogen bonding can direct the course of certain macrocyclization reactions in solvents of low polarity.[38] However, to our knowledge, hydrogen bonding self-templated synthesis of macrocycles has never been reported in protic solvents, although it is conceivable that this should work because intramolecular hydrogen bonds can survive in protic solvents.[39] Indeed, squaramides are particularly well suited to investigate the existence of a template effect because the condensation of mixed squaramide esters with amines is routinely carried out in ethanol at room temperature without any other added reagent. In this way, squaramides **5**−**7**, differring only in the central atom were reacted with the corresponding diamines under identical experimental conditions (Scheme 4). All reactions were performed under identical conditions. In two series of experiments the concentrations of squaramide and diamine in the reaction mixture were 7.1 and 71.0 mM, respectively, where the highest common concentration attainable were limited by the relatively low solubility of squaramides **5**−**7**.

In both series, reaction of squaramides **5** and **6** gave very high and comparable yields of macrocycles **8** (80−

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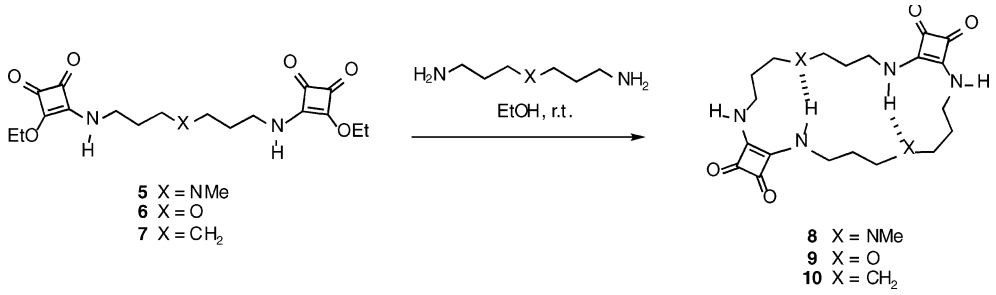
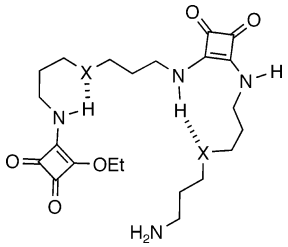
SCHEME 4. Synthesis of Macrocycles 8−10



85%) and **9** (70−80%), respectively, based on the starting squaramides. In addition, ESI-MS studies revealed that oligomerization was practically eliminated. In contrast, reaction of squaramide **7** (X = CH_2) with 1,7-diaminoheptane afforded a highly insoluble material. After partial dissolution in warm DMSO and subsequent ESI-MS analysis, macrocycle **10** was detected only as a trace.



It is clear that macrocycles **8** and **9** are obtained due to a highly efficient templating effect. Facile macrocyclization in non-high-dilution conditions can be explained by formation of the hydrogen bonded noncyclic intermediate shown below. After an initial condensation, the resulting bis-squaramide could give a nine-membered cyclic hydrogen bonded conformer, which is thermodynamically favored over the six-membered ring conformer. In the resulting folded conformation, the terminal amino group can reach easily the remaining squaramide ester group to cycle. Note that competitive folding is necessary to promote the desired macrocyclization and that the observed template effect cannot be rationalized on the basis of a more common intramolecular six-membered ring hydrogen bonding motif. If this were the case, oligomerization would result owing to the easy anti to syn isomerization of the three C−N squaramide bonds available in the proposed intermediate shown above.

Conclusions

Our studies show that squaramides have unique conformational properties that allow the design of a new foldable motif by combining squaramide segments with a donor atom. These are completely new and unnatural systems that resemble proline amino acids in their ability to promote folding and turns. In fact the potential applications of folding of these new modules are under investigation. As a first demonstration of this feature, we carried out an effective macrocyclization in ethanol. The effectiveness of the macrocyclization in ethanol is a novelty that opens the door to the formation of many other squaramide-based hydrogen bonded supramolecular structures in protic solvents.

Experimental Section

See the Supporting Information.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**−**9**. Details on molecular mechanic calculations. ESI-MS spectra of **3** and **4**. ROESY spectra of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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