

## Squaramido-Based Receptors: Molecular Recognition of Carboxylate Anions in Highly Competitive Media.

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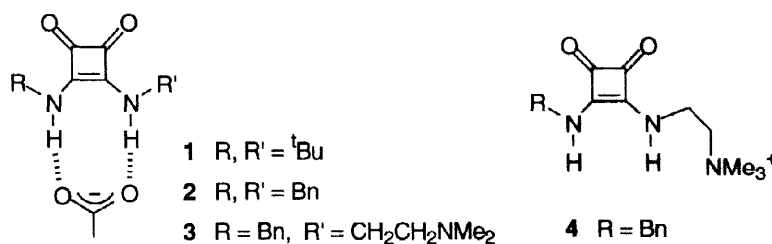
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**Abstract:** A new series of artificial receptors for binding carboxylates has been developed. The receptors are based on the hydrogen bonding abilities of secondary squaramides as binding subunits. The data reveal the formation of 1:1 complexes in highly competitive media. Using convenient spacers, receptors for di- and tri-carboxylates that incorporate two and three squaramide subunits have been prepared. The complexes are characterized by nmr and, when possible, by FAB spectral analysis.

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The ubiquitous presence of carboxylate groups in biologically relevant molecules have prompted a considerable interest in developing artificial receptors based on the recognition of the carboxylate group.<sup>1,2,3-5</sup> Since water is the solvent in which the majority of carboxylates are present in natural systems, our contribution will focus on developing receptors possessing strong binding abilities and good selectivity for carboxylates in water or water-mixture solvents.

In this report we use the hydrogen bonding ability of secondary squaramides,<sup>6</sup> alone or combined with electrostatic forces, to prepare a new series of receptors for carboxylates in highly competitive aqueous media. Although the use of squaramides as binding subunits for carboxylate anions is totally unprecedented its hydrogen bonding pattern, featuring two hydrogen donor atoms, parallels those in ureas,<sup>3</sup> thioureas,<sup>4</sup> and guanidium cations.<sup>5</sup>



In previous work with squaramides we have demonstrated the relationship existing between the two adjacent carbonyls and the squaramidic hydrogens.<sup>7</sup> On this basis we assumed that secondary squaramides could be effective hydrogen bond donors, capable of forming supramolecular complexes stabilized by secondary interactions.<sup>8</sup>

In order to evaluate the hydrogen bonding donor capability of squaramides, model compounds **1** to

**3** were prepared following standard procedures.<sup>9</sup> Charged squaramide **4** was obtained from **3** by exhaustive methylation with methyl iodide in refluxing acetone-DMF (2:1 v/v).

Initial binding experiments performed in different media confirmed our expectations. Addition of a solution of TMA acetate to model compounds **1** to **4** produced characteristic shifts of both squaramidic and methylenic protons. These shifts were analyzed using a 1:1 stoichiometry model (Table 1)<sup>10</sup>

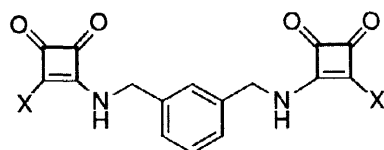
Table 1. Association constants ( $K_a$ )<sup>a</sup> obtained in several media with TMA acetate

Host	Solvent	$K_a$ ( $M^{-1}$ )	$p$ (range) <sup>b</sup>	$\Delta\delta$ (ppm)	H (type) <sup>c</sup>
<b>1</b>	DMSO- $d_6$	217 $\pm$ 8	0.08 - 0.65	+ 2.11	NH
<b>2</b>	DMSO- $d_6$	1980 $\pm$ 40	0.36 - 0.94	+ 3.35	NH
<b>2</b>	10% $D_2O$ / DMSO- $d_6$	48 $\pm$ 7	0.29 - 0.88	- 0.06	CH <sub>2</sub>
<b>3</b>	DMSO- $d_6$	1120 $\pm$ 86	0.23 - 0.91	+ 3.15	NH
<b>4</b>	DMSO- $d_6$	14200 $\pm$ 3700	0.49 - 0.94	+ 3.35	NH
<b>4</b>	10% $D_2O$ / DMSO- $d_6$	311 $\pm$ 48	0.11 - 0.75	+ 0.04	CH <sub>2</sub>
<b>4</b>	50% MeOD- $d_4$ / $CDCl_3$	965 $\pm$ 290	0.49 - 0.98	- 0.03	CH <sub>2</sub>
<b>4</b>	10% $D_2O$ / $CD_3CN$	396 $\pm$ 108	0.19 - 0.83	+ 0.06	CH <sub>2</sub>

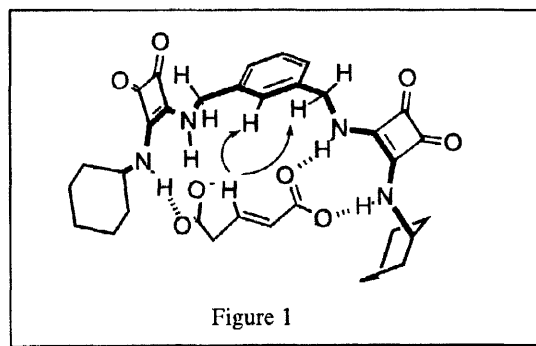
<sup>a</sup> At 22 °C. <sup>b</sup> Weber's  $p$  value. See ref. 10. <sup>c</sup> Proton responsible for the  $K_a$

Neutral compounds **1** to **3** showed moderate to good association constants. Taken together the  $K_a$ 's in Table 1 underline the important role of hydrogen bonding in the presence of water or in strongly polar solvents. As expected, the presence of a positively charged group near to the binding center, as in **4**, produce a eight to ten fold increase in binding.

Selective binding of di- and tri-carboxylates can be achieved using convenient spacers to **8**. place two or three squaramide binding units adequately in space. Thus, reaction of 1,3-bis(aminomethyl)benzene with diethyl squarate produced the mixed bis squaramide ester **5**. Further condensation of **5** with, cyclohexylamine, benzylamine or N,N-dimethylethylenediamine lead to bis squaramides **6** to **8**.<sup>11</sup> Compound **8** can be converted into the bis tetraalkylammonium diiodide salt **9** by exhaustive methylation.



- 5** X = OEt
- 6** X =  $NHC_6H_{11}$
- 7** X = NHBn
- 8** X =  $NHCH_2CH_2NMe_2$
- 9** X =  $NHCH_2CH_2NMe_3^+$



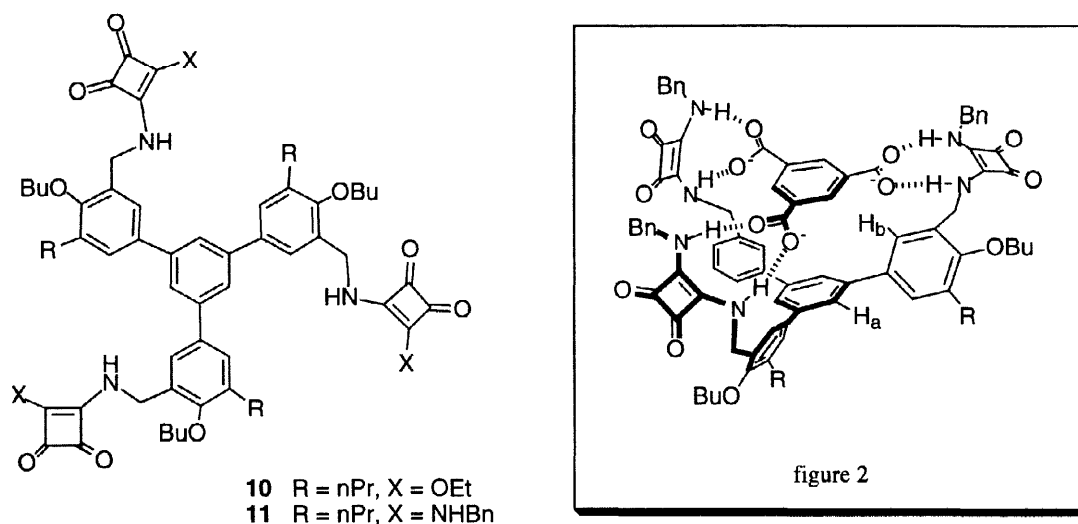
Molecular modeling showed that compounds **6** to **9** are appropriated for binding dicarboxylates derived from glutaric or glutaconic diacids. In pure DMSO the association constants of the complexes formed between the bis-tetrabutylammonium (TBA) glutarate and compounds **6** to **9** are too large ( $>10^4 M^{-1}$ ) to be measured by nmr. The addition of water lowered the association constants into a measurable range. Thus the

stability of the TBA-glutarate **7** complex in 10% D<sub>2</sub>O/DMSO ( $K_a = 1.4 \pm 0.2 \times 10^3 \text{ M}^{-1}$ ), and in 15% D<sub>2</sub>O/DMSO ( $K_a = 1.5 \pm 0.4 \times 10^2 \text{ M}^{-1}$ ) was readily determined.

The structure proposed in figure 1 can be assumed to be general for the complexes formed with receptors **6** to **9** and dicarboxylates. It is supported by the observation of large downfield shifts on both squaramidic protons and by nOe studies.<sup>12</sup> In pure DMSO, the ROESY spectrum of the TBA-glutaconate **6** complex produced intermolecular cross peaks between the olefinic proton and both, the isolated aromatic proton and benzylic protons of **6**.

The association constant of the TBA-glutarate, **9** complex in 10% D<sub>2</sub>O/DMSO was too high to be measured accurately ( $K_a$  c.a.  $3.6 \times 10^5 \text{ M}^{-1}$ ). In 30% H<sub>2</sub>O/CD<sub>3</sub>CN,  $K_a = 5.6 \pm 0.5 \times 10^2 \text{ M}^{-1}$  and, in this hydrophilic medium, a downfield shift of the squaramidic signals (c.a. + 0.7 ppm) was still clearly observable. This observation is an evidence of the role of hydrogen bonding as a non-negligible, binding interaction even in highly aqueous media.<sup>6a</sup>

A receptor suitable for tricarboxylate anions of pseudo-C<sub>3</sub> symmetry was also synthesized by a two-step strategy similar to that described above. 1,3,5-Tris-(3-aminomethyl-5-butoxy-6-propylphenyl)benzene was reacted first with diethylsquarate and the resulting tris squaramide-ester **10** condensed with benzylamine to afford the tris squaramide **11** in high yield.



The association constants of the tris-tetrabutylammonium (TBA) trimesoate, **11** and TBA cis-cyclohexentricarboxylate, **11** in 10% D<sub>2</sub>O/DMSO are  $K_a = 3.9 \pm 0.4 \times 10^3 \text{ M}^{-1}$  and  $7.7 \pm 1.3 \times 10^3 \text{ M}^{-1}$  respectively. The increase in binding constant is due to the presence of an extra squaramide unit, and the NMR shifts are similar to those to that already observed for the ditopic receptors **6** to **9**.

The binding geometry proposed in figure 2, was supported by 2D ROESY experiments. The spectra obtained from 1:1 mixtures of **11** and the TBA salt of trimesic acid in pure DMSO, showed cross peaks correlating the aromatic hydrogens of the trimesoate anion with H<sub>a</sub>, H<sub>b</sub> and both squaramidic hydrogens in **11**, demonstrating the inclusion of the tricarboxylate anion within the cavity as shown.

Complex formation was also confirmed by mass spectrometry. The FAB<sup>+</sup> spectra (*m*-nitrobenzyl alcohol as matrix) of a 1:1 mixture of TMA acetate with **4** (I<sup>-</sup>) in DMSO, showed a signal at *m/z* 474 assigned to [**4**(I<sup>-</sup>) + H<sup>+</sup> + Me<sub>4</sub>N<sup>+</sup>]<sup>+</sup>, while the corresponding FAB<sup>-</sup> spectrum gave a peak at *m/z* 346

assigned to  $[4 + \text{AcO}^-]$ . The FAB<sup>+</sup> spectrum of a 1:1 mixture of TBA glutarate and **7** showed a signal at  $m/z$  1363 assigned to  $[7 + \text{glutarate-TBA} + \text{TBA}^+]$  while the mixture of TBA trimesoate + **11** produced a signal at  $m/z$  2226 assigned to  $[11 + \text{trimesoate-TBA} + \text{H}^+]^+$ .

In summary we have proved that secondary squaramides can be used as binding subunits for carboxylates, in polar hydrophilic media. Tailored receptors for the recognition of specific carboxylates and their use as part of sensing devices are the subject of our current work and will be reported in due course.

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- Compound **5**: 1,3-bis(aminomethyl)benzene (0.5 g, 3.67 mmol) in ether (100 ml) were added dropwise at room temperature to a solution of diethyl squarate (1.9 g, 11.2 mmol) in ether (2 ml). After stirring overnight the mixture was evaporated to dryness. The residue was purified by column chromatography (silica/dichloromethane-MeOH 3%) to afford squaramide ester **5** (1.24 g, 88 %) as a white solid. Analysis of the NMR spectra of **5** showed the existence of at least two conformers in solution, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 7.71, 7.46, 6.83 (3 x br s, 2H), 7.35-7.19 (m, 4H), 4.78-4.60 (m, 8H), 1.41 (br t, 6H) ppm; IR (KBr) 3240, 1810, 1710, 1605 cm<sup>-1</sup>  
Compound **8**: N,N-Dimethylethyldiamine (140 mg, 1.56 mmol) were added dropwise to a solution of **5** (213 mg, 0.52 mmol) in ethanol (10 ml). After stirring overnight, solid bis-squaramide **8** (167 mg, 64%) was obtained by decantation. The solid was purified by washing with several portions of ethanol and dichloromethane, respectively. An analytical sample of **8** was obtained by recrystallization in dichloromethane/methanol, NMR(DMSO-d<sub>6</sub>) δ 7.98 (br s, 2H), 7.40 (br s, 2H), 7.51-7.35 (m, 4H), 4.81 (m, 4H), 3.70 (m, 4H), 2.49 (t, J = 5.7 Hz, 4H), 2.26 (s, 12H) ppm; IR (KBr) 3170, 1800, 1645, 1580 cm<sup>-1</sup>  
Consistent spectral data and correct elemental analysis were obtained for all new compounds.
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