Squaramido-Based Receptors: Design, Synthesis, and Application to the Recognition of Tetraalkylammonium Compounds

Salvador Tomàs, Rafel Prohens, Manuel Vega, M. Carmen Rotger, Pere M. Deyà, Pablo Ballester,* and Antoni Costa*

Departament de Química, Universitat de les Illes Balears, 07071 Palma de Mallorca, Spain

Received July 24, 1996[⊗]

A new series of tripodal receptors based on squaramido rings as unprecedented binding units has been devised. Among the different structural possibilities that this functionality offers, the ability of establishing multiple O to C−H interactions has been explored. On this basis, new receptors capable of recognizing choline, acetylcholine, and related ammonium salts have been synthesized. Association constants in the range 10^3−10^4 M^{-1} have been measured by a ^{1}H-NMR titration method using a 1:1 model. The formation of intracavity complexes is supported by the observation of characteristic changes in the NMR spectra of the complexes, of intermolecular cross peaks in 2D ROESY experiments, and by detection of signals corresponding to the molecular weight of the complexes by positive FAB mass spectrometry.

Introduction

The cation−π interaction observed in complexes between quaternary ammonium compounds and aromatic receptors has been recently exploited as a useful binding force for molecular recognition studies.[1,2−4,16] Recent work by Dougherty[1] has emphasized the importance of this attractive force in biological systems.[5] According to his argument,[6] the electrostatic interaction between a cationic ligand and the electron-rich surface of an aromatic ring would play a central role in binding interactions.

Fueled by these findings, several groups have studied the extent of the cation−π or CH−π[7] interaction for molecular recognition in nonpolar organic media. Studies on a number of suitable aromatic hosts have revealed that the association constants measured for these model systems are usually lower than 10^2 M^{-1} (∼2 kcal/mol),[8] reflecting the weak character of these forces in the absence of hydrophobic effects. Thus, the use of cation−π interactions as the sole binding force has led to very limited complexation of ammonium compounds with artificial receptors in nonpolar organic solvents.

An additional binding interaction arises from the charged character of the ammonium compounds. In fact, the α-methyl or methylene hydrogens in R_4N^+ cations bear a partial positive charge[9] and, therefore, can be engaged in hydrogen bonding. This interaction can have an important electrostatic component especially if the hydrogen acceptor is a basic oxygen atom located in a polar group.[10] This condition can be fulfilled by oxygen carbonyl atoms. On the basis of crystallographic data, it has been suggested that the C−H···O hydrogen bond is stronger for carbonyl oxygens than for other polar oxygen groups.[11] In an attempt to expand the repertory of forces suitable for binding a tetraalkylammonium compound in nonpolar organic media, we rationalized that multiple C−H···O (O═C) interactions would be well suited for an effective complexation of these charged compounds within neutral receptors.

Interestingly, C−H···O contacts involving quaternary ammonium compounds have been observed in crystals.[12] Additional support for the hydrogen-bonding ability of ammonium compounds comes from *ab initio* calculations on the tetramethylammonium cation performed by Kim *et al.*[13] These authors reported the existence of σ electronic transfer between the α-methyl hydrogens and the electron-donating lone pairs of oxygen, thus confirming previous theoretical work on this subject.[14]

Although the existence of C−H···O interactions is well established, their practical applications in molecular recognition are scarce.[15] It is worth mentioning here that recent work by Ungaro et al.[16] describes a preferential competitive complexation of Me_4N^+ to six amido carbonyl

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1996.

(1) (a) Shepodd, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1983−1985. (b) Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Org. Chem.* **1990**, *55*, 2762−2767. (c) Petti, M. A.; Shepodd, T. J.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825−6840. (d) Kearney, P. C.; Mizoue, L. S.; Kumpf, R. A.; Forman, J. A.; McCurdy, A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907−9919.

(2) (a) Collet, A.; Dutasta, J.-P.; Lozach, B. *Bull. Soc. Chim. Belg.* **1990**, *99*, 617−633. (b) Collet, A.; Dutasta, J. P.; Lozach, B. In *Advances in Supramolecular Chemistry*; Gokel, G. W., Ed.; JAI Press Inc.: Greenwich, CT, 1993; Vol. 3; pp 1−35.

(3) (a) Araki, K.; Shimizu, H.; Shinkai, S. *Chem. Lett.* **1993**, 205−208. (b) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933−8968. (b) Shinkai, S.; Araki, K.; Manabe, O. *J. Am. Chem. Soc.* **1988**, *110*, 7214−7218. (c) Arimura, T.; Kubota, M.; Araki, K.; Shinkai, S.; Matasuda, T. *Tetrahedron Lett.* **1989**, 2563−2566. (d) Shinkai, S.; Araki, K.; Matsuda, T.; Nishiyama, N.; Ikeda, H.; Takasu, I.; Iwamoto, M. *J. Am. Chem. Soc.* **1990**, *112*, 9053−9058. (e) Shinkai, S.; Araki, K.; Kubota, M.; Arimura, T.; Matsuda, T. *J. Org. Chem.* **1991**, *56*, 295−300.

(4) (a) De Iasi, G.; Masci, B. *Tetrahedron Lett.* **1993**, 6635−6638. (b) Masci, B. *Tetrahedron* **1995**, *51*, 5459−5464.

(5) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1558−1560.

(6) (a) Dougherty, D. A. *Science* **1996**, *271*, 163−168. (b) Mecozzi, S.; West, A. P., Jr.; Dougherty, D. A. *J. Am Chem. Soc.* **1996**, *118*, 2307−2308.

(7) (a) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665−8703. (b) Nishio, M.; Hirota, M. *Tetrahedron* **1989**, *45*, 7201−7245.

(8) (a) Stauffer, D. A.; Dougherty, D. A. *Tetrahedron Lett.* **1988**, *29*, 6039−6042. (b) Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032−4034. (c) Araki, K.; Shimizu, H.; Shinkai, S. *Chem. Lett.* **1993**, 205−208. (d) A.; Dalla Cort, A.; Mandolini, L. *J. Org. Chem.* **1995**, *60*, 8313−8314.

(9) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.,* **1988**, *27*, 994−998.

(10) (a) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290−296. (b) Aakeröy, C. B.; Seddon, K. R. *Acc. Chem. Res.* **1993**, 397−407.

(11) Steiner, T. *J. Chem. Soc., Chem. Commun.,* **1994**, 2341−2342.

(12) (a) Vazquez, C.; Calabrese, J. C.; Dixon, D. A.; Miller, J. S. *J. Org. Chem.* **1993**, *58*, 65−81. (b) Reetz, M. T.; Hütte, S.; Goddard, R. *J. Am. Chem. Soc.* **1993**, *115*, 9339−9340.

(13) Kim, K. S.; Lee, J. Y.; Lee, S. J.; Ha, T. K.; Kim, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 7399−7400.

(14) Meot-Ner, M.; Deakyne, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 469−474.

S0022-3263(96)01414-4 CCC: $12.00 © 1996 American Chemical Society

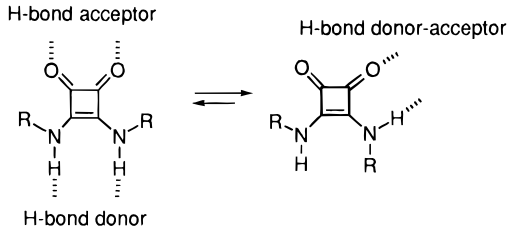


Figure 1. Three possible hydrogen bond patterns for squaramides.

groups conveniently located at the lower rim of a calixarene, rather to the aromatic π pool. In a previous communication we addressed briefly this subject,[17] and the present work assesses the ability of a series of tripodal squaramides as receptors for tetraalkylammonium salts.

Results and Discussion

Preliminary Studies. Crucial to the development of squaramido-based receptors is an understanding and characterization of their hydrogen-bonding patterns and capabilities. At first glance, the two eclipsed sp^2 hybridized carbonyl oxygens would allow hydrogen bonding to take place with additional contribution from the attractive secondary hydrogen bonding.[18] Secondly, in squaramides featuring two hydrogen bond donors (Z = NH), a behavior close to that observed for carboxylates and N,N′-disubstituted ureas could be anticipated.[19] Finally, depending upon the conformational preference of monoalkylamino-substituted squaramides, a hydrogen bond donor−acceptor pattern could also be expected (Figure 1). In order to test both, the validity of the proposed hydrogen bond patterns and the conformational preferences of squaramides, preliminary experiments using model squaramides were undertaken.

At this point, *N*,*N*′-diethylsquaramide **1** was selected to test the squaramide hydrogen bond acceptor mode. Titration of *N*,*N*′-diphenylurea (DPU) with **1** in chloroform resulted in large downfield shifts of the urea N−H resonances ($\Delta\delta$ = +1.6 ppm), consistent with the formation of a hydrogen-bonded complex. An association constant of 120 M^{-1} was determined from fitting the data to the corresponding 1:1 binding isotherm. Remarkably, upon addition of a 10-fold excess of **1**, the initially averaged spectrum of DPU spread, showing clearly three sets of first-order resonances for the aromatic protons of DPU. These data can be explained by formation of a mixed complex between **1** and a DPU molecule in the required trans, trans form. Consistent with the locked

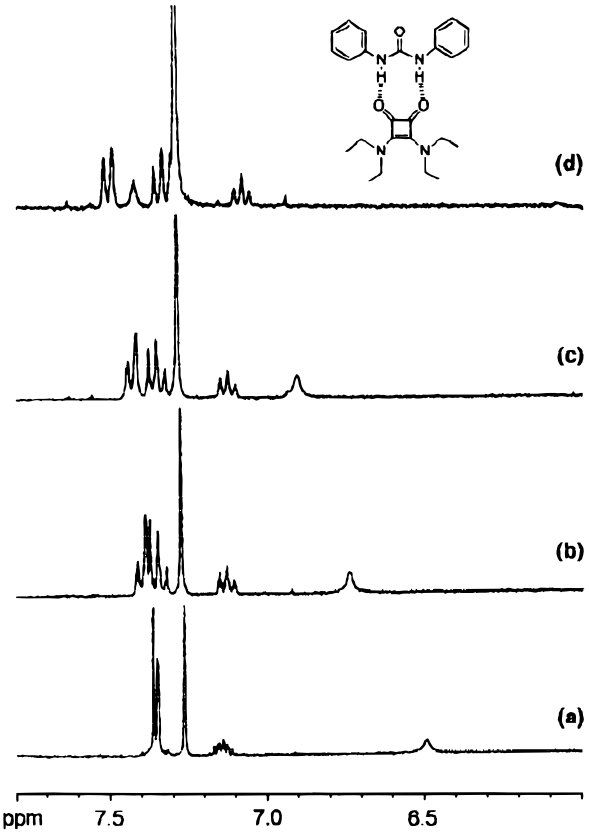
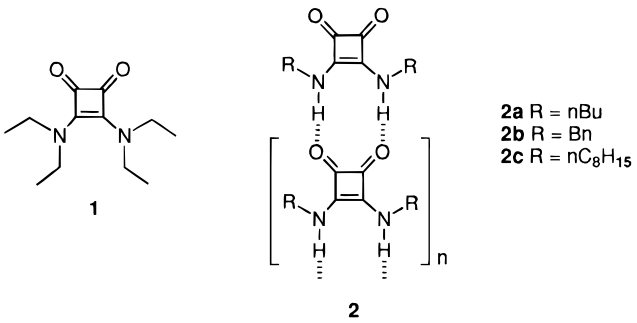


Figure 2. Partial ^{1}H-NMR ($CDCl_3$) spectra of uncomplexed DPU (a) and complexation-induced shifts produced after addition of 1 (b), 2 (c), and 10 equiv of **1** (d).

conformation of complexed DPU, the ortho aromatic hydrogens appear at lower field under the paramagnetic influence of the urea carbonyl group (Figure 2).

The next task was to test the hydrogen bond donor capabilities on 3,4-monoalkylamino-substituted-3-cyclobutene-1,2-dione **2**. Unfortunately, squaramides **2a**−**c** were insoluble in chloroform, precluding the determination of any association constant in this solvent.



An important issue for the development of squaramido-based receptors is the characterization of the conformational preferences of squaramides in solution.[20] The ^{1}H-NMR spectra of 10^{-3} M solutions of model squaramido esters **3a,b**[21] in $CDCl_3$ at room temperature showed broad signals consistent with the existence of exchange processes. On lowering the temperature, line broadening disappeared and two sets of resonances were clearly

(15) Intramolecular CH···O interactions have been used to restrict conformational freedom in urea-based receptors for carboxylates, see: Smith, P. J.; Reddington, M. V.; Wilcox, C. S. *Tetrahedron Lett.* **1992**, *33*, 6085−6088.

(16) Casnati, A.; Jacopozzi, P.; Pochini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, *51*, 591−598.

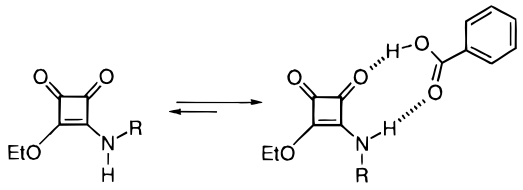
(17) Tomàs, S.; Rotger, M. C.; González, J. F.; Deyà, P. M.; Ballester, P.; Costa, A. *Tetrahedron Lett.* **1995**, *36*, 2523−2526.

(18) (a) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamp, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201−209. (b) Jorgensen, W. L.; Pranata, J. *J. Am. Chem. Soc.* **1990**, *112*, 2008−2010. (c) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 209−216.

(19) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369−370. (b) Galan, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511−1512. (c) Albert, J. S.; Hamilton A. D. *Tetrahedron Lett.* **1993**, *34*, 7363−7366. (d) Flack, S. S.; Chaumette, J.-L.; Kilburn, J. D.; Langley, G. J.; Webster, M. *J. Chem. Soc., Chem. Commun.* **1993**, 399−401. (e) Jairam, R.; Potvin, P. G. *J. Org. Chem.* **1992**, *57*, 4136−4141.

(20) MM calculations are of little assistance in this case as the carbon atom types present in squaramides are not parametrized.

(21) For solubility reasons, the study was limited to squaramido esters **3**. Full details concerning the conformational behavior of squaramides will be published elsewhere.



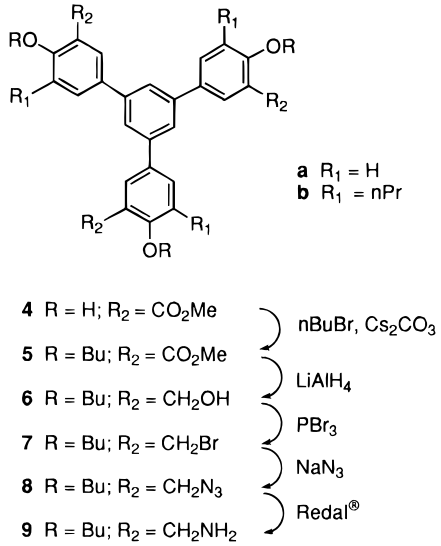
3a R = tBu
3b R = Bn

observed for both the NH and ethoxy groups. At 273 K **3b** exists as an apparent mixture of two isomers in a 74:26 ratio. Coalescence occurred at ~285−290 K, while at 300 K the spectrum showed only one set of sharp signals corresponding to the fast exchange limit. These observations can be accounted for by rotation around the C−N bond giving rise to a mixture of two conformers in equilibrium. The assignment of the ^{1}H-NMR signals for each conformer was derived from their response toward the presence of benzoic acid. The addition of increasing amounts of benzoic acid to a 10^{-3} M solution of **3a,b** shifted the equilibrium toward the major conformer and, at the same time, produced a strong downfield shift of the NH signal of this conformer. In contrast, an almost constant chemical shift was observed for the NH of the minor isomer in the presence of benzoic acid. These results clearly indicate that the signals of the major component in the equilibrium can be assigned to the cis conformer.

Further information was obtained from the temperature dependence chemical shift coefficients[22] ($\Delta\delta/\Delta T$), determined from variable-temperature ^{1}H-NMR measurements. In agreement with the previous assignments, values of −5.9 and −21.9 ppb/K were calculated for the minor and the major conformers of **3a**, respectively, indicating clearly an enhanced self-association tendency for the major rotamer. The rates of interconversion of both isomers were also calculated at different temperatures by line shape analysis,[23] and from the data, an apparent[24] free energy of activation of the rotational barrier ($\Delta G^{\ddagger}$) was derived giving a value of 61.4 kJ/mol calculated at 298 K, which is in accordance with previous data on this subject.[25] The lack of a clear conformational preference in *N*-monoalkyl-substituted squaramides together with the low barrier of rotation about their C−N bond are distinctive factors when compared to N-monosubstituted amides whose strong preference for the *E* form as well as a higher activation energy of the internal rotation is well established.[26]

Encouraged by these results, the considerable potential of squaramides warranted their incorporation into model receptors for the recognition of biologically relevant tetraalkylammonium compounds. Our receptor design would consist of three squaramido units tethered by a tripodal aromatic spacer, taking advantage of the low barrier of interconversion observed for squaramides to produce, initially, a nonpreorganized array of up to six hydrogen-bonding acceptors. According to our hypothesis, such a structure should be able of recognizing quaternary ammonium compounds by "grasping" them through multiple O to CH hydrogen-bonding interactions. Our prototype would require a spacer that is large enough to accommodate the bulky ammonium guests. On the basis of modeling studies,[27] a tripodal spacer was synthesized, based on semirigid triarylbenzene framework **9** which seemed well suited for the above purposes.

Synthesis. The preparation of squaramido-based tripodal receptors **10**−**16** would rely on the availability of the pivotal triamines **9a,b** as outlined in Scheme 1. The starting ester **4a** was obtained in multigram scale,



a R_1 = H
b R_1 = nPr

4 R = H; R_2 = CO_2Me
5 R = Bu; R_2 = CO_2Me (nBuBr, Cs_2CO_3)
6 R = Bu; R_2 = CH_2OH ($LiAlH_4$)
7 R = Bu; R_2 = CH_2Br (PBr_3)
8 R = Bu; R_2 = CH_2N_3 (NaN_3)
9 R = Bu; R_2 = CH_2NH_2 (Redal®)

using the highly efficient trimerization of salicylic acid esters promoted by $SiCl_4$.[28] In order to improve the solubility of the receptors, a propylated triester **4b** was also prepared.

Triamines **9a,b** were synthesized uneventfully in five steps starting from **4a,b**. Upon treatment of triamines **9a,b** with a 3-fold excess of diethyl squarate in ether at room temperature, the key squaramido esters **10a,b** were obtained in good yields (Scheme 1). The existence of the squaramido rings as a mixture of conformers was deduced from the ^{1}H-NMR spectra. In DMSO-d_6, the spectra of **10a,b** showed two NH signals at 9.09 and 9.31 ppm as well as two methylene resonances at 4.92 and 4.74 ppm in a 1:1 ratio (estimated by integration).

Condensation of **10a,b** with several representative primary and secondary aliphatic amines in ethanol at room temperature produced squaramides **11**−**14** in high yields. Aryl squaramide **15** was prepared by condensation of an excess of 3-[[4-(dimethylamino)phenyl]amino]-4-ethoxy-3-cyclobutene-1,2-dione[29] with **9b**. Finally, 4-[4-(dimethylamino)phenyl]-3-ethoxy-3-cyclobutene-1,2-dione (**16**), featuring a direct aryl to cyclobutenedione ring bond, was synthesized by condensation of *N*,*N*-dimethylaniline with diethyl squarate using $TiCl_4$ as catalyst[30]

(22) (a) Winningham, M. J.; Sogah, D. Y. *J. Am. Chem. Soc.* **1994**, *116*, 11173−11174. (b) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 1054. (c) Gellman, S. H.; Dado, G. P.; Liang, G. B. ; Adams, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 1164.

(23) DNMR5. *Iterative Nuclear Magnetic Resonance Program for Unsaturated Exchange-Broadened Bandshapes* (IBM-PC version); Program QCMP059, Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN, 1988.

(24) The value is apparent as it is affected for the dimerization of the *Z* form, and it reflects not only the rotation around the C−N squaramido bond but also the process of forming and breaking hydrogen bonds.

(25) Thorpe, J. E. *J. Chem. Soc. B* **1968**, 435−436.

(26) Kessler, H.; Anders, U.; Schudok, M. *J. Am. Chem. Soc.* **1990**, *112*, 5908−5916.

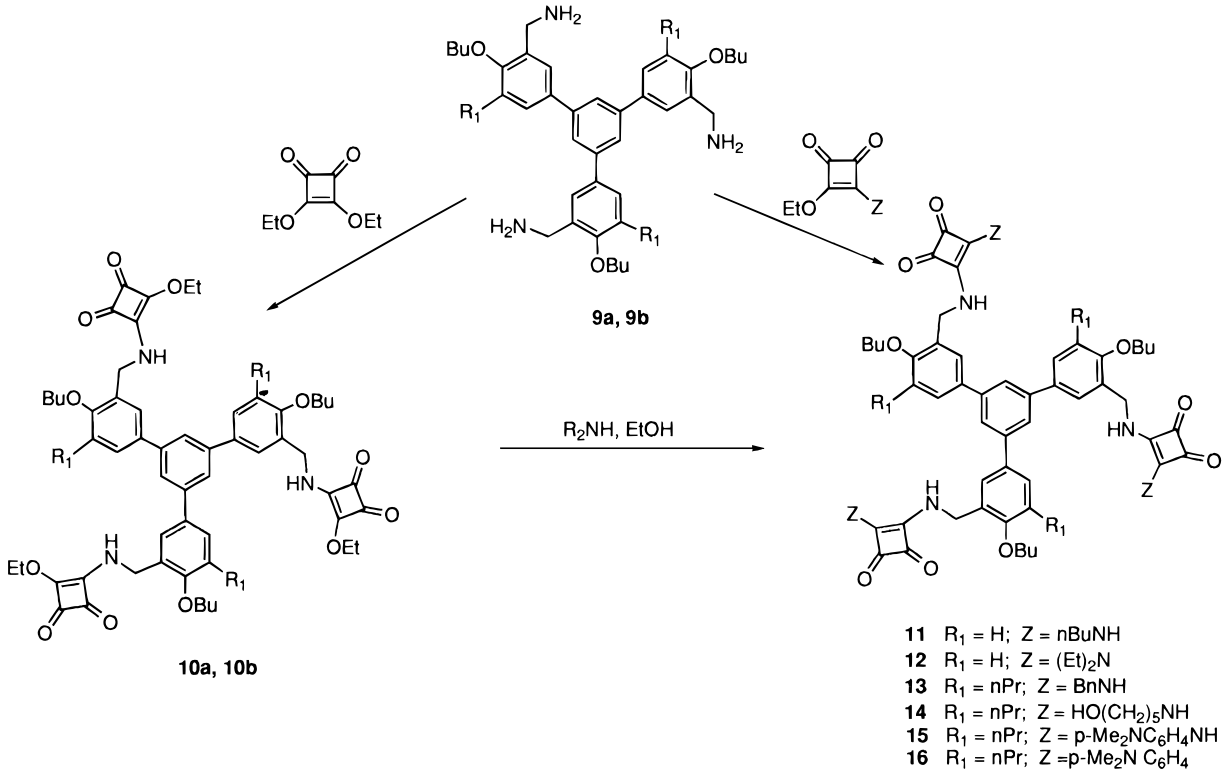
(27) W. C. Still, Macromodel 3.5X, Columbia University, New York, 1990.

(28) Elmorsy, S. S.; Pelter, A.; Smith, K. *Tetrahedron Lett.* **1994**, *32*, 4175−4176.

(29) Schmidt, A. H. *Synthesis* **1980**, 961−993.

(30) (a) Ohno, M.; Yamamoto, Y.; Shirakasi, Y.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 263−271. (b) Law, K.-Y.; Court, F. *J. Org. Chem.* **1992**, *57*, 3278−3286.

Scheme 1



and condensed with **9b**. The resulting tripodal squaramides **11**−**16** were well characterized spectroscopically and furnished correct elemental analyses. The diagnostic IR bands[31] at 1790−1800 cm^{-1} and ^{13}C-NMR signals at 184−186 ppm, present in **11**−**16** confirmed the presence and integrity of the squaramido moiety. **11** was insoluble, while **12**−**16**, were soluble enough in $CDCl_3$ (~10^{-2} M) to be studied by NMR.

The existence of at least two different conformers in solution was evident from the splitting and broadening of several resonances in the ^1H- and ^{13}C-NMR spectra of **12**−**16** at room temperature. In all cases, raising the temperature to the fast exchange limit (~340 K) reduced the spectra to their first-order appearance, simplifying the interpretation of the signals.

Binding Properties of Squaramido Receptors. The new structures possess attendant rotational possibilities owing to the presence of several unrestricted single bonds and low barriers of rotation of the squaramido C−NH bonds. Nevertheless, the rigid triaryl spacer, common to all the compounds, prevents the collapse of these structures and reduces the self-association due to steric factors. Thus, these compounds can accommodate tetraalkylammonium cations of different alkyl sizes. The length and shape of the alkyl chains modulate the aperture of the squaramidic arms of the receptors until an effective grasping of the ammonium guests is achieved.

Initially, complexation of ammonium compounds was studied by ^1H-NMR spectroscopy. In general, the addition of increasing amounts of different ammonium salts to **12**−**16** in chloroform caused a considerable simplification of the spectra. Upon saturation, the resulting signals appeared sharp and well defined allowing first-order interpretation. Moreover, the spectra of the complexes were essentially temperature independent. In contrast, the spectra of the receptors alone showed considerable changes in both chemical shifts and signal broadening, upon lowering the temperature. This behavior provides indirect evidence for the formation of the intracavity complexes since binding the ammonium salt would effectively restrict the conformational mobility of the receptor in these complexes.

Table 1. Association Constants (K_{asn})[a] and Limiting Complexation-Induced Shifts ($\Delta\delta$)

receptor	NR_4^+ (anion)	K_{asn} (M^{-1})	$\Delta\delta$ (ppm)
10b	TMA (AcO^-)	594 ± 31	−0.29
16	BTA[c] (Br^-)	90 ± 5	−0.41
12	TBA[b] (Br^-)	117 ± 4	−0.41
12	BTA[c] (Br^-)	272 ± 7	−0.53
12	BTA (AcO^-)	324 ± 4	−0.56
12	TMA (AcO^-)	487 ± 24	−0.55
13	BTA (Br^-)	4624 ± 256	−0.47
13	BTA (Br^-)	271 ± 41[d]	−0.25
13	methylpyridinium (I^-)	4050 ± 1091	−0.43
13	acetylcholine (I^-)	1473 ± 59	−0.42
14	acetylcholine (I^-)	5669 ± 931	−0.34
14	acetylcholine (I^-)	205 ± 13[d]	−0.22
15	acetylcholine (I^-)	8559 ± 175	−0.66
15	choline (I^-)	14509 ± 1403	−0.52

[a] At 21 °C in $CDCl_3$. Calculated errors at a confidence level of 95%. [b] Tetrabutyl ammonium. [c] Benzyltrimethylammonium. [d] In 10% MeOD-d_4−$CDCl_3$.

Analogously, the reverse addition of the receptor to a solution of the ammonium guests produced consistent and reproducible upfield shifts of the α-methyl and/or α-methylene protons, supporting the contribution of diamagnetic effects due to the close proximity of the aryl and carbonyl shielding groups (see Table 1). Altogether, these observations provide ample support for the formation of pseudosymmetric C_3 complexes as depicted in Figure 3.

The proposed C_3 geometry (Figure 3) is in agreement with the NOE intermolecular contacts[32] detected on several complexes. 2D ROESY experiments performed

(31) West, R., Ed. In *Oxocarbons*; Academic Press: New York, 1980.

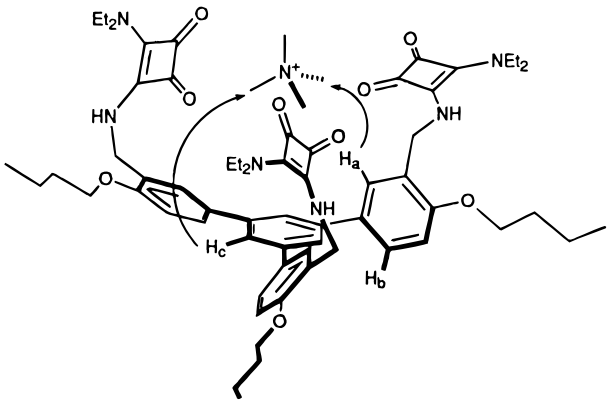


Figure 3. Computer-generated view of a complex between **12** and the TMA cation.

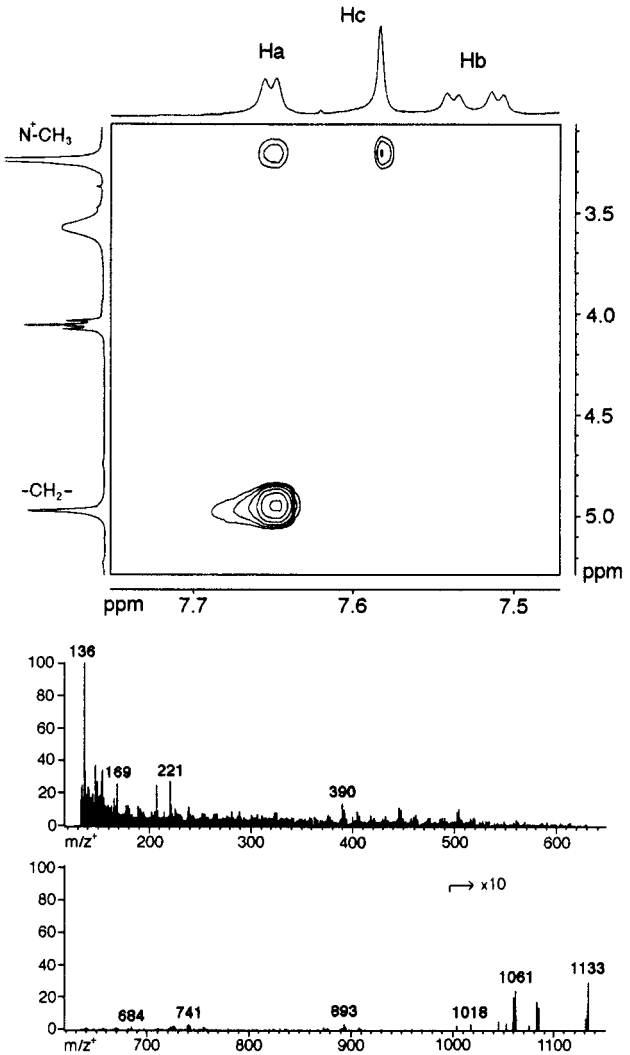


Figure 4. Partial ROESY spectrum showing intermolecular contacts between H_a, H_c of **12** and TMA. Only positive peaks are shown (above). Positive FAB^+ mass spectrum showing the presence of peaks at the *m*/*z* of the complex (below).

on complexes of receptor **14** and acetylcholine (ACh) iodide (see Supporting Information) as well as with receptor **12** and tetramethylammonium (TMA) acetate showed (Figure 4), in both cases, cross peaks correlating protons H_a and H_c of the receptor, but not H_b, with the α-methyl hydrogens of the guests. The observation of *inter*molecular NOE contacts implies a close proximity between the receptor and the ammonium group and, basically, demonstrates the formation of intracavity complexes where the ammonium is deeply buried within the receptors. The evidence already presented suggests that the receptors bind in a "three-finger grip" to ammonium compounds.

Next, we shifted our attention to determine whether the relative position of the ammonium counterion could be affected by the complexation. ^{1}H-NMR studies carried out by Pochapsky *et al.*[34] revealed that tetraalkylammonium salts in chloroform solution exist mainly in the form of interpenetrated ion pairs whose van der Waals volumes are smaller than the sum of the volumes of the single ion pairs.[33] In our studies, precise information on the relative position of the counterion in one of our receptor−ammonium complexes was deduced from the observation of specific ^{1}H,^{1}H NOE interionic effects using tetra-*n*-butylammonium borohydride as guest.[34] ROESY experiments performed on $Bu_4N^+BH_4^-$ showed that the BH_4^- anion and the quaternary ammonium nitrogen were in the form of interpenetrated ion pairs, due to the observation of NOE contacts between the protons of BH_4^- anion and mainly the α- and *β*-methylene hydrogens of the alkyl chains. When the ROESY experiment was repeated on a complex of receptor **14** with $Bu_4N^+BH_4^-$, in addition to the above-described signals, diagnostic ion to receptor cross peaks between protons H_a and H_c of the receptor and the α-methylene protons of the ammonium alkyl chain, as well as between the H_a and BH_4^- protons, were detected. Since both interionic and molecule to ion contacts were observed, it was evident that complexation of $Bu_4N^+BH_4^-$ did not disturb significantly the interpenetrated structure of the ion pair. This is also in agreement with a mode of complexation that maintains the counterion close to the ammonium ion in the open part of the receptor.

Complex formation was also studied by FAB-MS.[35] Stirring of an equimolar mixture of **11** or **12** with tetramethylammonium acetate or **15** with acetylcholine iodide during 1 h in $CDCl_3$ followed by evaporation of the solvent gave the corresponding 1:1 complexes. FAB^+ mass spectra (*m*-nitrobenzyl alcohol as matrix) exhibited peaks at *m*/*z* 1134 [**11** + TMA]$^+$, 1134 [**12** + TMA]$^+$, and 1524 [**15** + ACh]$^+$ in addition to the peaks of free **11**, **12**, and **15**.

It is well established that in squaramides the substituents of the cyclobutenedione ring are conjugated with the *nonadjacent* carbonyl group by resonance delocalization through the double bond of the ring.[36] According to this, the binding abilities of the squaramido carbonyls can be expected to be modulated by placing adequate substituents on the squaramidic nitrogens. We ad-

(32) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989.

(33) (a) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 731−732. (b) Abbott, A. P.; Schiffrin, J. *J. Chem. Soc., Faraday Trans. 2* **1990**, *86*, 1453−1459.

(34) (a) Pochapsky, T. C.; Stone, P. M. *J. Am. Chem. Soc.* **1991**, *113*, 1460−1462. (b) Pochapsky, T. C.; Stone, P. M. *J. Am. Chem. Soc.* **1990**, *112*, 6714−6715.

(35) (a) Rudkevich, D. M.; Brzozka, Z.; Palys, M.; Visser, H. C.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Eng.* **1994**, *33*, 467−468. (b) Rudkevich, D. M.; Stauthamer, W. P. R. V.; Verboom, W.; Engbersen, J. F. J.; Harkema, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 9671−9673. (c) Flack, S. S.; Chaumette, J.-L.; Kilburn, J. D.; Langley, G. J.; Webster, M. *J. Chem. Soc., Chem. Commun.* **1993**, 399−401.

(36) (a) Sun, L.; Liebeskind, L. S. *J. Org. Chem.* **1995**, *60*, 8194−8203. (b) Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345.

dressed this point by preparing several receptors featuring different squaramido substituents. The effect of these changes can be followed through ^{1}H-NMR titrations. The formation of 1:1 complexes was deduced from the corresponding Job plots as well as by the fit of the data to the 1:1 isotherm model. From the data in Table 1, it follows that receptors featuring a primary amino substituent in positions 3 of the cyclobutenedione ring are more effective than the others, as their respective association constants are clearly higher.

Replacement of the ethoxy or aryl groups as in **10b** and **16** with an alkylamino group drastically increased the binding ability of the receptors. This is probably due to the enhanced basicity of the carbonyl oxygen that is under the influence of the outer amino substituents. Receptor **12** exhibited low association constants toward several ammonium salts, suggesting that the diethylamino substituent is not able to enhance the basicity of the carbonyl. Molecular modeling suggested that 3,4-monoalkylamino-disubstituted squaramides can form almost coplanar structures where both nitrogens can remain conjugated with the cyclobutenedione ring. In contrast, 3,4-dialkylamino-disubstituted squaramides produced unavoidable steric repulsions between the nitrogen substituents. In fact, literature X-ray data of a 4-dialkylamino cyclobutenedione has shown that the coplanar arrangement of both substituents in positions 3 and 4 of the cyclobutenedione ring is impossible.[37] If this were the case for receptor **12**, the simultaneous participation of both nitrogen lone pairs would be impossible. In accordance to this, larger K_{asn} were obtained with squaramides **13**−**15**. The largest value of 14 509 ± 1403 M^{-1} obtained with **15** can be rationalized by considering the participation of the 4-(dimethylamino)phenyl ring via extended delocalization.

Complexation studies carried out in 10% MeOD-d_4/$CDCl_3$ mixtures gave association constants that were roughly 20−25 times weaker than in $CDCl_3$ alone. In such cases, the formation of the corresponding complexes were still evident. These results can be explained by competitive interaction of methanol with the ammonium salt combined with the increased polarity of the solution.

The relevant issue in these examples is that K_{asn} in the range 10^3−10^4 M^{-1} have been routinely obtained, thereby demonstrating the significant role that multiple O to C−H interactions can play in molecular recognition.

Conclusion

The most relevant result of the present work is the introduction of squaramides as binding units for abiotic receptor designs. The binding features of this functionality and the easy incorporation within a molecular framework allows the preparation of efficient receptors for tetraalkylammonium compounds. In addition, the strength of the host−guest complexes can be conveniently modulated by modifying the external substituents of the cyclobutenedione ring. The results outline the role of the squaramido moiety and confirm binding of tetraalkylammonium ion pairs. On that basis, the synthesis of more selective receptors to be used as molecular sensors or catalysts can be envisaged.

(37) LePage, T.; Kazuhiro, N.; Breslow, R. *Tetrahedron Lett.* **1985**, *26*, 5919−5922.

Experimental Section

General Information. All reagents were obtained from commercial sources and used without further purification. Solvents were purified as follows: dichloromethane and ethanol were distilled from CaH_2; diethyl ether, toluene, and benzene were distilled from sodium/benzophenone; DMF was treated with molecular sieves (3 Å). Organic solutions were dried over Na_2SO_4 before being concentrated. $CDCl_3$ (99.8% D) was stored on molecular sieves (3 Å). Flash chromatography was performed on E. Merck silica gel 60 (230−400 mesh). Thin-layer chromatography was performed on E. Merck 60F-254 precoated silica plates (0.25 mm layer thickness). Melting points were taken on a capillary melting point apparatus. Ions for positive FAB mass spectra were produced from a matrix of 4-nitrobenzyl alcohol. The ^{1}H- and ^{13}C-NMR spectra were recorded at 300 and 75 MHz, respectively, at 23 °C. Chemical shifts are reported as parts per million (δ) and were referenced to the deuterium lock solvents (δ 7.26 for ^{1}H and 77.0 for ^{13}C). Microanalyses were conducted by Servei de Microanàlisi CID (CSIC), Barcelona, Spain.

Titrations. NMR titrations were peformed in a 5 mm o.d. NMR tube at ambient temperature. The required ^{1}H-NMR spectra were taken at 300 MHz using a reverse broad-band probe to improve proton sensitivity. In a typical titration, 500 μL of a solution ranging from 10^{-2} to 5×10^{-5} M ammonium salt in $CDCl_3$ was treated with aliquots of a solution containing receptor and alkylammonium guest. Changes in the chemical shifts of methyl and/or methylenic ammonium salt protons were monitored. In the experimental conditions described above, dimerization or other agreggation phenomena were negligible. The HOSTEST5 package[38] was used to estimate association constants, along with the limiting chemical shifts of each of the monitored protons. The concentrations of both components were adjusted to achieve Weber's p values ranging from 20 to 80. The reported values for K_{asn} are the average of the association constants obtained in three independent titrations.

1,3,5-Tris[4-butoxy-3-(methoxycarbonyl)-5-propylphenyl]benzene (5b). To a solution of triester **4b**[39] (5.2 g, 7.9 mmol) in 80 mL of acetone and 35 mL of DMF was added Cs_2CO_3 (11.2 g, 33 mmol) in several portions. After stirring for 15 min, butyl bromide (5.45g, 39.8 mmol) was added dropwise over 20 min and the mixture was heated at reflux for 18 h. The mixture was cooled to room temperature and filtered through a pad of Celite; solvents were evaporated under reduced pressure. The residue was redissolved in ether (∼100 mL), washed with water (2 × 50 mL) and brine (1 × 40 mL), dried, and evaporated to give a yellow oil pure by NMR (6.3 g, 97%). An analytical sample was obtained by column chromatography (silica, hexanes AcOEt, 9:1 v/v). The purified material solidified slowly on standing to give the tributyl ether **5b** as a pale yellow solid; mp 93−94 °C. The product was recrystallized in EtOH−benzene affording white prisms: mp 102−103 °C; ^{1}H-NMR δ 7.91 (d, J = 2.4 Hz, 3H), 7.66 (s, 3H), 7.62 (d, J = 2.6 Hz, 3H), 3.94 (s, 9H), 3.92 (t, J = 6.5 Hz, 6H), 2.71 (m, 6H), 1.83 (m, 6H), 1.66 (m, 6H), 1.55 (m, 6H), 1.01 (t, J = 7.4 Hz, 9H), 1.00 (t, J =7.3 Hz, 9H); ^{13}C-NMR δ 166.0, 155.8, 140.2, 136.7, 134.9, 131.8, 126.8, 123.9, 123.7, 74.0, 51.1, 31.2, 31.0, 22.8, 18.1, 13.0, 12.8; FAB-MS (m/z) 822 (M^+,73), 791 (98), 735 (100); IR (KBr) 1730, 1260−1210, 1150, cm^{-1}. Anal. Calcd for $C_{51}H_{66}O_9$: C, 74.41; H, 8.08. Found: C, 74.32; H, 8.16.

1,3,5-Tris[4-butoxy-3-(methoxycarbonyl)phenyl]benzene (5a). 5a was prepared in a manner analogous to that described above starting from triester **4a**.[39] The product was obtained as a viscous oil in 89% yield: ^{1}H-NMR δ 8.09 (d, J = 2.3 Hz, 3H), 7.70 (dd, J = 8.6, 2.3 Hz, 3H), 7.66 (s, 3H), 7.07 (d, J = 8.7 Hz, 3H), 4.10 (t, J = 6.4 Hz, 6H), 3.92 (s, 9H), 1.85 (m, 6H), 1.56 (m, 6H), 1.00 (t, J = 7.3 Hz, 9H); ^{13}C-NMR δ

(38) (a) Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6204−6210. (b) Wilcox, C. S. HOSTEST (v5.0), University of Pittsburgh, Pittsburgh, PA, 1994.

(39) Rotger, M. C.; Costa, A.; Saá, J. M. *J. Org. Chem.*, **1993**, *58*, 4083−4087. Full details of an improved procedure for multigram synthesis of **5a,b** will be published shortly.

166.8, 158.2, 141.0, 132.7, 131.9, 130.2, 120.6, 113.5, 68.7, 52.0, 31.1, 19.1, 13.8; FAB-MS *m/z* (%) 718 ($M^+ + Na^+$, 18), 696 (70), 695 (M^+, 100), 664 (86.6), 608 (88.0); IR (neat) 1720, 1310−1210, 1170, 1080 cm^{-1}. Anal. Calcd for $C_{42}H_{48}O_9$: C, 72.39; H, 6.94. Found: C, 72.45; H, 7.06.

1,3,5-Tris[4-butoxy-3-(hydroxymethyl)-5-propylphenyl]-benzene (6b). Lithium aluminum hydride (LAH; 2.6 g, 69 mmol) was slowly added to a cooled (0 °C) solution of **5b** (7.1 g, 8.6 mmol) in dry THF (140 mL), under argon. After stirring on ice for 4 h, the reaction mixture was partitioned between 100 mL of saturated Na_2SO_4 solution and 100 mL of ether. The organic layer was separated, washed with water (2 × 50 mL) and brine (1 × 50 mL), dried, and evaporated under reduced pressure. The crude concentrate was purified by column chromatography (silica, hexanes−AcOEt, 8:2 v/v) to give the title alcohol as a white solid (5.6 g, 88%). The product was crystallized using MeOH−water to give white needles: mp 147−148 °C; ^{1}H-NMR δ 7.66 (s, 3H), 7.49 (d, J = 2.3 Hz, 3H), 7.44 (d, J = 2.3 Hz, 3H), 4.79 (d, J = 6.2 Hz, 6H), 3.89 (t, J = 6.5 Hz, 6H), 2.68 (m, 6H), 2.26 (t, J = 6.2 Hz, 3H), 1.85 (m, 6H), 1.85 (m, 6H), 1.67 (m, 6H), 1.60 (m, 6H), 1.02 (t, J = 7.3 Hz, 9H), 0.99 (t, J = 7.4 Hz, 9H); ^{13}C-NMR δ 154.0, 140.7, 135.9, 133.2, 127.6, 124.5, 123.5, 73.1, 60.7, 31.4, 30.8, 28.5, 22.8, 18.16, 13.1, 12.8; FAB-MS *m/z* (%) 737 (M^+, 75), 664 (53); IR (KBr) 3650−3100, 1170, cm^{-1}. Anal. Calcd for $C_{48}H_{66}O_6$: C, 78.01; H, 9.01. Found: C, 78.08 H, 9.09.

1,3,5-Tris[4-butoxy-3-(hydroxymethyl)phenyl]-benzene (6a). Similar reduction gave this product as an amorphous yellow solid in 93% yield, which was used directly in the next reaction. An analytical sample was obtained by crystallization in toluene−pentane (1:1 v/v): mp 124−125 °C, ^{1}H-NMR δ 7.65 (s, 3H), 7.61 (d, J = 2.1 Hz, 3H), 7.57 (dd, J = 8.3, 2.3 Hz, 3H), 6.98 (d, J = 8.3 Hz, 3H), 4.78 (d, J = 6.6 Hz, 6H), 4.09 (t, J = 6.4 Hz, 6H), 2.44 (t, J = 6.6 Hz, 3H), 1.84 (m, 6H), 1.54 (m, 6H), 1.00 (t, J = 7.3 Hz, 9H); ^{13}C-NMR δ 157.3, 142.4, 134.2, 130.2, 128.3, 128.2, 124.5, 112.1, 68.6, 63.0, 32.0, 20.0, 14.5; FAB-MS *m/z* (%) 612 (M^+, 100), 595 (33), 539 (41); IR (KBr) 3650−3100, 1250, cm^{-1}. Anal. Calcd for $C_{39}H_{48}O_6$: C, 76.44; H, 7.89. Found: C, 76.28; H, 7.92.

1,3,5-Tris[3-(bromomethyl)-4-butoxy-5-propylphenyl]-benzene (7b). To a solution of alcohol **6b** (4.8 g, 6.5 mmol) in toluene (200 mL) was added dropwise PBr_3 (7.1 g, 26 mmol) in toluene (40 mL). After stirring at room temperature for 2 h, and 3 h at reflux, the mixture was allowed to cool to room temperature and 5% aqueous $NaHCO_3$ was added slowly. The organic layer was separated, washed with water and brine, and evaporated at reduced pressure. The residue was triturated twice with pentane to afford the crude tribromide (5.9 g, 97%) pure enough to be used in the next step. An analytical sample was obtained by flash chromatography (silica, hexanes−AcOEt, 97:3 v/v) and crystallization to yield pure tribromide as small white needles: mp 146−7 °C; ^{1}H-NMR δ 7.62 (s, 3H), 7.53 (d, J = 2.2 Hz, 3H), 7.43 (d, J = 2.1 Hz, 3H), 4.66 (s, 6H), 3.99 (t, J = 6.5 Hz, 6H), 2.68 (t, J = 7.6 Hz, 6H), 1.88 (m, 6H),1.66 (m, 6H), 1.58 (m, 6H), 1.04 (t, J = 7.3 Hz, 9H), 1.00 (t, J = 7.4 Hz, 9H); ^{13}C-NMR δ 156.1, 142.3, 1337.8, 137.5, 132.3, 130.5, 128.7, 125.5, 74.8, 33.1, 32.7, 29.3, 24.5, 19.9, 14.9, 14.6. Anal. Calcd for $C_{48}H_{63}O_3Br_3$: C, 62.14; H, 6.84; Br, 25.85. Found: C, 62.22; H, 7.04; Br, 25.30.

1,3,5-Tris[3-(bromomethyl)-4-butoxyphenyl]benzene (7a). The same procedure was used as above. The crude tribromide was recrystallized from pentane−toluene (1:1 v/v) to give the title compound as white needless in 98% yield: mp 115−116 °C; ^{1}H-NMR (300 MHz, CDCl3) δ 7.64 (d, J = 2.2 Hz, 3H), 7.61 (s, 3H), 7.58 (dd, J = 8.5, 2.3 Hz, 3H), 6.97 (d, J = 8.5 Hz, 3H), 4.65 (s, 6H), 4.11 (t, J = 6.3 Hz, 6H), 1.87 (m, 6H), 1.57 (m, 6H), 1.02 (t, J = 7.1 Hz, 9H); ^{13}C-NMR δ 157.4, 142.1, 134.1, 130.4, 129.5, 127.2, 124.6, 112.7, 68.8,.32.0, 29.8, 20.0, 14.5; FAB-MS *m/z* (%) 801 (M^+, 15), 800 (15), 721 (22). Anal. Calcd for $C_{39}H_{45}O_3Br_3$: C, 58.44; H, 5.66. Found: C, 58.40 H, 5.66.

1,3,5-Tris[3-(azidomethyl)-4-butoxy-5-propylphenyl]-benzene (8b). A mixture of tribromide **7b** (2.4 g, 2.6 mmol) and sodium azide (1.0 g, 15.3 mmol) in 20 mL of benzene and 20 mL of DMF was heated at reflux for 3 h. After cooling at room temperature, the organic salts were removed by filtration. Benzene (80 mL) was added, and the mixture was washed with water (5 × 75 mL) and brine. After drying, solvents were evaporated at reduced pressure, affording 1.9 g (93.7%) of **8b**. An analytical sample was recrystallized from ethanol affording transparent prisms: mp 96−98 °C; ^{1}H-NMR δ 7.65 (s, 3H), 7.48 (d, J = 2.2 Hz, 3H), 7.46 (d, J = 2.2 Hz, 3H), 4.47 (s, 6H), 3.87 (t, J = 6.5 Hz, 6H), 2.69 (m, 6H), 1.84 (m, 6H), 1.72 (m, 6H), 1.58 (m, 6H), 1.02 (t, J = 7.3 Hz, 9H), 1.00 (t, J = 7.4 Hz, 9H); ^{13}C-NMR δ 156.2, 142.4, 137.7, 137.4, 130.2, 129.8, 127.4, 125.5 75.2, 50.7, 33.1, 32.8, 24.5, 19.9, 14.8, 14.6; FAB-MS *m/z* (%) 813 (M^+, 17); IR (KBr) 2100 cm^{-1}. Anal. Calcd for $C_{48}H_{63}N_9O_3$: C, 70.82; H, 7.80; N, 15.48. Found: C, 70.87; H, 7.85; N, 15.25.

1,3,5-Tris[3-(azidomethyl)-4-butoxyphenyl]benzene (8a). Prepared using the above procedure in 93% yield. The solid was recrystallized from toluene: pentane (1:1 v/v) to give white prisms of the triazide; mp 69−70 °C. ^{1}H-NMR δ 7.64 (s, 3H), 7.62 (dd, J = 8.5, 2.2 Hz, 3H), 7.57 (d, J = 2.2 Hz, 3H), 6.97 (d, J = 8.5 Hz, 3H), 4.65 (s, 6H), 4.11 (t, J = 6.3 Hz, 6H), 1.87 (m, 6H), 1.57 (m, 6H), 1.02 (t, J = 7.1 Hz, 9H); ^{13}C-NMR δ 157.5, 142.3, 134.1, 129.6, 129.1, 127.2, 125.1, 124.6, 112.3, 68.7, 51.0,.31.9, 20.0, 14.5; FAB-MS *m/z* (%) 687 (M^+, 50), 660 (16), 645 (30); IR (KBr) 2100 cm^{-1}. Anal. Calcd for $_{39}H_{45}N_9O_3$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.24; H, 6.68; N, 18.25.

1,3,5-Tris[4-butoxy-5-propyl-3-[[(4-ethoxy-1,2-dioxo-3-cyclobutenyl)amino]methyl]phenyl]benzene. Squaramide Ester 10b. A solution of tripropylated triazide **8b** (1.3 g, 1.6 mmol) in toluene (60 mL) was treated with Red-Al (1.5 mL of a 65 wt % solution in toluene, ∼7.7 mmol). After stirring over a 15 min period, the reaction was quenched with water. The organic layer was separated and washed with water (1 × 40 mL) and brine (1 × 25 mL). Solvent was removed by rotary evaporation, and the crude solid was triturated twice with pentane (20 mL) to yield triamine **9b** (0.97 g, 82%) as a yellownish amorphous solid which was used directly in the next step: ^{1}H-NMR δ 7.66 (s, 3H), 7.42 (d, J = 2.2 Hz, 3H), 7.40 (d, J = 2.2 Hz, 3H), 3.93 (s, 6H), 3.85 (t, J = 6.5 Hz, 6H), 2.68 (m, 6H), 1.84 (m, 6H), 1.69 (m, 6H), 1.58 (m, 6H), 1.02 (t, J = 7.3 Hz, 9H), 1.00 (t, J = 7.4 Hz, 9H). Triamine **9b** (0.97 g, 1.3 mmol) and diethyl squarate (2.0 g, 11.9 mmol) were dissolved in ether (100 mL). The solution was stirred under argon at room temperature overnight (20 h). Solvent was removed under reduced pressure, and the product was purified by column chromatography (silica, CH_2Cl_2−MeOH, 99:1 v/v) to afford pure **10b** (0.92 g, 52% from the azide) as an off-white, amorphous solid: mp 92−94 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.31 and 9.08 (t, 3H), 7.77 (s, 3H), 7.64 (m, 6H), 4.93 and 4.74 (m, 6H), 4.73 (q, J = 7.02 Hz, 6H), 3.89 (m, 6H), 2.75 (t, J = 6.9 Hz, 6H), 1.83 (m, 6H), 1.71 (m, 6H), 1.63 (m, 6H), 1.41 (m, 9H), 1.07 (m, 9H), 1.05 (m, 9H); FAB-MS *m/z* (%) 1109 (M^+, 91), 967 (17), 685 (23), 629 (100); IR (KBr) 3350−3100, 1805, 1710, 1610 cm^{-1}. Anal. Calcd for $C_{66}H_{81}N_3O_{12}$: C, 71.52; H, 7.37, N, 3.79. Found: C, 71.55; H, 7.40; N, 3.78.

1,3,5-Tris[4-butoxy-3-[[(4-ethoxy-1,2-dioxo-3-cyclobutenyl)amino]methyl]phenyl]benzene. Squaramide Ester 10a. The corresponding triazide **8a** was reduced as above to yield triamine **9a** as a yellow solid in 90% yield: ^{1}H-NMR δ 7.65 (s, 3H), 7.52 (m, 6H), 6.96 (d, J = 8.9 Hz, 3H), 4.06 (t, J = 6.5 Hz, 6H), 3.90 (s, 6H), 2.68 (m, 6H), 1.84 (m, 6H), 1.56 (m, 12H), 1.00 (t, J = 7.4 Hz, 9H). Triamine **9a** and diethyl squarate were condensed by using the same procedure as for **10b**. Product **10a** was obtained as an off-white amorphous solid in 65% yield. This compound could not be crystallized and was used without further purification: mp 104−105 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.20 and 9.00 (br, 3H), 7.80 (m, 9H), 7.23 (d, J = 8.1 Hz, 3H), 4.92 (s, 3H), 4.7 (m, 9H), 4.15 (m, 6H), 1.79 (m, 6H), 1.53 (m, 6H), 1.44 (t, J = 7.0 Hz, 9H), 1.03 (t, J = 7.0 Hz, 9H); FAB-MS *m/z* (%) 981 (M^+, 3.0), 841 (5), 647 (100), 441 (95); IR (KBr) 3350−3100, 1800, 1710, 1605 cm^{-1}. Anal. Calcd for $C_{57}H_{63}N_3O_{12}$: C, 69.71; H, 6.47, N, 4.28. Found: C, 69.74; H, 6.61, N, 4.13.

1,3,5-Tris[4-butoxy-5-propyl-3-[[[4-(benzylamino)-1,2-dioxo-3-cyclobutenyl]amino]methyl]phenyl]benzene. Squaramide 13. Squaramide ester **10b** (0.57 g, 0.5 mmol) and benzylamine (0.5 g, 4.6 mmol) in EtOH (80 mL) were

stirred at room temperature for 24 h. The solid was collected by filtration, washed with cold ethanol, and digested in hot methanol for 1 h. After filtration, the residue was recrystallized in $CHCl_3$−MeOH to give 0.59 g (89%) of a white powder: mp 253−258 °C; ^{1}H-NMR (DMSO-d_6) δ 7.80 (br s, 3H), 7.77 (s, 3H), 7.67 (s, 6H), 7.36 (br s, 15H), 7.33 (br s, 3H), 4.91 (m, 6H), 4.78 (m, 6H), 3.91 (t, J = 6.3 Hz, 6H), 2.72 (m, 6H), 1.84 (m, 6H), 1.74 (m, 6H), 1.59 (m, 6H), 1.04 (t, J = 7.3 Hz, (18H); FAB-MS m/z (%) 1313 (M^++ Na); IR (KBr) 3400−3100, 1800, 1670, 1580 cm^{-1}. Anal. Calcd for $C_{81}H_{90}N_6O_9$: C, 75.32; H, 7.02; N, 6.50. Found: C, 75.08; H, 7.01, N, 6.42.

1,3,5-Tris[4-butoxy-5-propyl-3-[[[4-[(5-hydroxypentyl)-amino]-1,2-dioxo-3-cyclobutenyl]amino]methyl]phenyl]-benzene. Squaramide 14. Squaramide ester **10b** and 5-amino-1-pentanol were condensed using the same procedure as for **13** except that the residue was washed with ethanol and recrystallized with CH_2Cl_2−ethanol to give a white solid in 71% yield: mp 150−153 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.78 (s, 3H), 7.70 (br, 3H), 7.69 (s, 6H), 7.44 (br, 3H), 4.92 (br s, 3H), 4.44 (t, J = 5.0 Hz, 3H), 3.93 (t, J = 6.1 Hz, 6H), 3.56 (m, 6H), 3.44 (obscured by residual water), 2.77 (t, J = 7.1 Hz, 6H), 1.83 (m, 6H), 1.75 (m, 6H), 1.60 (m, 12H), 1.46 (m, 6H), 1.37 (m, 6H), 1.07 (t, J = 7.2 Hz, 18H); FAB-MS m/z (%) 1279 (M^+, 72), 1081 (14), 664 (73); IR (KBr) 3600−3100, 1800, 1670, 1590 cm^{-1}. Anal. Calcd for $C_{75}H_{102}N_6O_{12}$: C, 70.39; H, 8.03; N, 6.57. Found: C, 70.02; H, 8.03, N, 6.51.

1,3,5-Tris[4-butoxy-3-[[[4-(butylamino)-1,2-dioxo-3-cyclobutenyl]amino]methyl]phenyl]benzene. Squaramide 11. Squaramide ester **10a** and butylamine were condensed as described to give a white solid in 80% yield: mp 282−287 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.82 (m, 9H), 7.65 (br s, 3H), 7.40 (br, s, 3H), 7.24 (d, J = 8.4 Hz, 3H), 4.90 (m , 6H), 4.17 (br t, 6H), 3.58 (m, 6H), 1.82 (m, 6H), 1.54 (m, 12H), 1.35 (m, 6H), 1.03 (t, J = 7.3 Hz, 9H), 0.92 (br t, 9H); FAB-MS m/z (%) 1083 (M^++ Na, 1.5); 1062 (M^+, 1.8). Anal. Calcd for $C_{63}H_{78}N_6O_9$: C, 71.14; H, 7.39; N, 7.90. Found: C, 71.04; H, 7.35; N, 7.78.

1,3,5-Tris[4-butoxy-3-[[[(4-*N*,*N*′-(diethylamino)-1,2-dioxo-3-cyclobutenyl]amino]methyl]phenyl]benzene. Squaramide 12. Squaramide ester **10a** and *N*,*N*-diethylamine were condensed following the standard procedure. The crude product was purified by column chromatography (silica, CH_2Cl_2−MeOH, 96:4 v/v) to afford **12** in 93% yield. An analytical sample was obtained by crystallization in ethanol: mp 173−174 °C; ^{1}H-NMR δ 7.67 (d, J = 2.2 Hz, 3H), 7.60 (s, 3H), 7.56 (d, J = 2.2 Hz, 3H), 6.95 (d, J = 8.5 Hz, 3H), 6.07 (t, J = 6.1 Hz, 3H), 4.97 (d, J = 6.1 Hz, 6H), 4.06 (t, J = 6.4 Hz, 6H), 3.51 (br s, 12H), 1.78 (m, 6H), 1.51 (m, 6H), 1.20 (t, J = 7.14 Hz, 18H), 0.99 (t, J = 7.3 Hz, 9H); ^{13}C-NMR δ 182.1, 181.0, 166.0, 165.9, 155.4, 140.1, 132.1, 127.5, 126.5, 125.6, 122.5, 110.3, 66.8, 443.6, 43.0, 30.2, 18.2, 14.0, 12.7; FAB-MS m/z (%) 1085 (M^+ + Na^+, 9.3), 1063 (M^+ + H^+, 6.5), 1062 (M^+, 7.1), 895 (7); IR (KBr) 1790, 1670, 1570 cm^{-1}. Anal. Calcd for $C_{63}H_{78}N_6O_9$: C, 71.14; H, 7.39; N, 7.90. Found: C, 69.17; H, 7.42; N, 7.23.

1,3,5-Tris[4-butoxy-5-propyl-3-[[[[[(4-(*N*,*N*′-dimethylamino)phenyl]amino]-1,2-dioxo-3-cyclobutenyl]amino]-methyl]phenyl]benzene. Squaramide 15. Triamine **9b** (0.14 g, 0.2 mmol) and 4-[[4-(dimethylamino)phenyl]amino]-3-ethoxy-3-cyclobutene-1,2-dione (0.21 g, 0.8 mmol) in 25 mL of ethanol were condensed stirring at room temperature for 1 h. The mixture was filtered and washed with ethanol, and the crude precipitatepurified by column chromatography (silica, CH_2Cl_2−MeOH, 98:2 v/v) to afford **15** (0.125 g) in 48% yield: mp 238−242 °C dec; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.67 (d, J = 2.2 Hz, 3H), 7.60 (s, 3H), 7.56 (d, J = 2.2 Hz, 3H), 6.95 (d, J = 8.5 Hz, 3H), 6.07 (t, J = 6.1 Hz, 3H), 4.97 (d, J = 6.1 Hz, 6H), 4.06 (t, J = 6.4 Hz, 6H), 3.51 (br s, 12H), 1.78 (m, 6H), 1.51 (m, 6H), 1.20 (t, J = 7.14 Hz, 18H), 0.99 (t, J = 7.3 Hz, 9H); FAB-MS m/z (%) 1392 (M^+ + Na^+, 9), 1379 (M^+, 100), 895 (7), 1305 (14), 1148 (34); IR (KBr) 1790, 1675, 1590 cm^{-1}. Anal. Calcd for $C_{84}H_{99}N_9O_9$: C, 73.18; H, 7.24; N, 9.14. Found: C, 72.52; H, 7.29; N, 8.94.

1,3,5-Tris[4-butoxy-5-propyl-3-[[[[4-(*N*,*N*′-dimethylamino)phenyl]-1,2-dioxo-3-cyclobutenyl]amino]methyl]phenyl]benzene. Squaramide 16. Triamine **9b** (0.18 g, 0.24 mmol) and 4-[4-(dimethylamino)phenyl]-3-ethoxy-3-cyclobutene-1,2-dione (0.24 g, 0.97 mmol) in 15 mL of absolute ethanol were condensed as above. Ethanol was removed at vacuo, and the mixture was purified by column chromatography (silica, CH_2Cl_2−MeOH, 98:2 v/v) to afford **16** (0.17 g) in 53% yield: mp 157−161 °C; ^{1}H-NMR δ 7.72 (d, J = 9.0 Hz, 6H), 7.56 (s, 3H), 7.49 (br s, 3H), 7.43 (d, J = 2.1 Hz, 3H), 6.93 (br t, 3H), 6.65 (d, J = 9.0 Hz, 3H), 5.09 (d, J = 5.4 Hz, 6H), 3.92 (t, J = 6.5 Hz, 6H), 3.00 (s, 18H), 2.67 (t, J = 7.6 Hz, 6H), 1.86 (m, 6H), 1.69 (m, 6H), 1.56 (m, 6H), 1.02 (t, J = 7.4 Hz, 9H), 0.99 (t, J = 7.4 Hz, 9H); FAB-MS m/z (%) 1334 (M^+, 100), 1320 (18); 1118 (43); IR (KBr) 1770, 1710, 1605 cm^{-1}. Anal. Calcd for $C_{84}H_{96}N_6O_9$: C, 75.65; H, 7.26; N, 6.30. Found: C, 75.40; H, 7.41; N, 6.23.

Acknowledgment. We thank the Dirección General de Investigación Científica y Técnica (DGICYT, Project PB92-0251) for financial support. S.T. thanks the Fundació Muntaner, M.C.R. thanks the Ministerio de Educación y Ciencia of Spain for fellowship support. FAB mass spectra were obtained at the facilities of the University of New Brunswick (Canada) and University of Sheffield (U.K.). We express our gratitude to Prof. Craig S. Wilcox for generously providing a copy of HOSTEST (v5.0).

Supporting Information Available: ROESY spectra of complexes and ^{1}H-NMR spectra of tripodands **10**−**16** (11 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9614147