Pergamon

Tetrahedron Letters, Vol. 36, No. 14, pp. 2523-2526, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00297-9

Squaramide-Based Receptors: Synthesis and Application to the Recognition of Polyalkyl Ammonium Salts.

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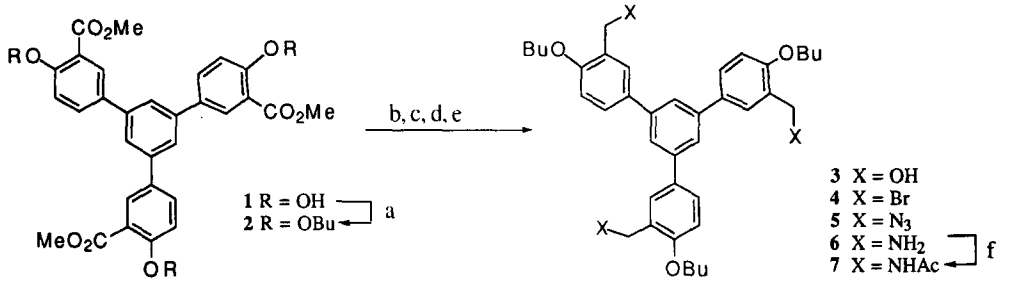
Abstract: The design and synthesis of a novel series of receptors based on mixed squaric acid diamides subunits are reported. The use of the new tripodands as receptors for several tetraalkyl ammonium salts in chloroform was studied and the resulting complexes were characterized by NMR and FAB mass analysis.

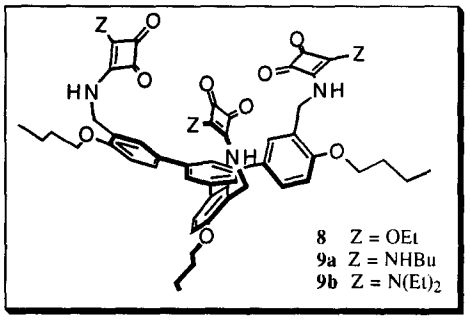
Squaramides[1] are remarkable compounds in many aspects. For example, they are known antihistaminic compounds[2] and Kinney et al. have recently reported that squaramides are aminoacid bioisosteres.[3] Structurally, squaramides have two coplanar accepting groups[4] (C=O) which are geometrically well disposed for a simultaneous interaction with positively charged groups. These interesting pharmacological and structural properties prompted us to study their potential use as binding subunits for molecular recognition. We reasoned that three squaramide subunits could be held together by means of a triaryl benzene spacer similar to that we have recently described[5] yielding a tripodand receptor. This new family of positive charge-accepting tripodands is expected to be useful for the recognition of neurological active "onium" compounds[6] and as catalysts in reactions proceeding through a positively charged transition state.[7]



[a] BuBr, Cs_2CO_3, DMF-acetone, Δ, 24h. (89%). [b] LAH, THF, 5°C, 4h. (88%). [c] PBr_3, r.t., 2h then Δ, 3h. (90%). [d] NaN_3, DMF-benzene, Δ, 3h. (90%). [e] REDAL, toluene, r.t. 15 min. (88%). [f] AcCl, CH_2Cl_2, Et_3N, (65%).

The synthesis of the required spacer **6** involved reduction of the phenolic butyl ether derivative **2** obtained from available triester **1**.[8] Reaction of **3** with PBr_3, followed by nucleophilic displacement of the benzyl halide with sodium azide allowed the preparation of the azide derivative **5** which upon reduction

afforded the aromatic fragment **6** containing three benzylamine groups. The tris acetamide **7** was also prepared to be used in control experiments. Reaction of **6** with excess (3 eq.) of diethyl squarate in ethanol at room temperature gave the mixed squaramide ester[9] **8** in 64% yield. Subsequent condensation of **8** with n-butylamine or diethyl amine in ethanol produced the expected squaramides **9a** (m.p. 287°C) and **9b** (m.p. 173°C) in 88% and 83% yield, respectively, after purification. Compound **9a** is insoluble while **7**, **8** and **9b** are almost freely soluble in chloroform.



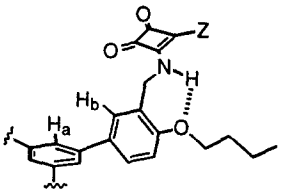


Figure 1. Convergent conformation of the receptors and schematic representation of the intramolecular hydrogen-bond.

Despite the existence of several flexible bonds, **9b** showed a well resolved ^{1}H-NMR spectrum[10] that was almost temperature independent[11] The NH resonance at 6.07 ppm, appeared downfield shifted when compared with model compounds lacking the phenolic ether group.[12] This evidence gives support to a rapid interconversion of the different rotamers in solution and to the existence of an intramolecular hydrogen bond between the NH and the oxygen of the ether function. In fact, molecular modeling studies[13] performed on **9b** suggested that the conformational freedom of the benzylamine squaramide portion of the receptor would be constrained by such intramolecular hydrogen-bonding interactions,[14] giving rise to a minimized folded and helical twisted structure. This intramolecular hydrogen-bond was thought to be useful as a preorganizing element of the receptor.

The modelling studies also showed that the receptor could very easily accommodate polyalkylamonium cations in the cavity formed between the six oxygen carbonyls in the convergent conformation illustrated in Fig1, consequently some experiments were undertaken to examine their binding abilities.

Table 1. Association Constants (K)[a] and Limiting Complexation Induced Shifts (Δδ)

Host	Guest	K (M^{-1})	Δδ(CH_2)	Δδ(CH_3)
7	TMA (AcO^-)	43 ± 10	--	-0.43
8	TMA (AcO^-)	594 ± 31	--	-0.29
9b	TBA[b] (Br^-)	117 ± 4	-0.41	--
9b	BTA (Br^-)	272 ± 7	-0.65	-0.53
9b	BTA (AcO^-)	324 ± 4	-0.70	-0.56
9b	TMA (AcO^-)	487 ± 24	--	-0.55

[a] At 21 °C in $CHCl_3$. Calculated errors at a confidence level of 95%. [b] Tetrabutyl ammonium.

We found that, upon addition of a solution of **9b** to different "onium" salts such as benzyl trimethyl

ammonium bromide (BTA) or tetramethyl ammonium acetate (TMA) in chloroform, the methyl and methylene protons of TMA and BTA experienced characteristic upfield shifts. Inverse addition of TMA to a diluted solution of **9b** also produced detectable changes mainly in the phenol ether ring hydrogens.

The association constants for the complexes obtained between hosts **7**, **8** and **9b** and a series of "onium" salts were obtained by a ^{1}H-NMR titration method. The binding isotherms were very well fitted in all cases using a 1:1 theoretical model[15], while the corresponding Job plots confirmed this stoichiometry. The values obtained for the association constants and limiting complexation induced shifts are summarized in Table 1. Remarkably complexation of TMA with hosts **8** and **9b** is roughly ten times more effective than with triacetamide **7**. Since the entropic cost of binding should be similar in these receptors, the approximate ten-fold increase of the association constant is significant and illustrates the utility of the squaramide subunit in the molecular recognition of "onium" salts.[16] At the same time, the weak binding observed with **7** rules out any relevant contribution to the stabilization of the complex due to cation-π interaction from the triaryl benzene spacer.[17]

The evidence obtained so far allow us to account for the formation of the host-guest complexes on the basis of electrostatic cation-dipole interactions between the negative end of the squaramide carbonyls and the positive methyl or methylene attached to the quaternary ammonium nitrogen.[18]. This kind of interaction can be well modeled using force field calculations, thus a theoretical structure of the complex has been obtained with MacroModel 3.5X[12] using the OPLS*[19] force field and GB/SA-$CHCl_3$ solvation model[20]. This minimized geometry reveals the existence of up to twelve NC-OC close contacts[21].

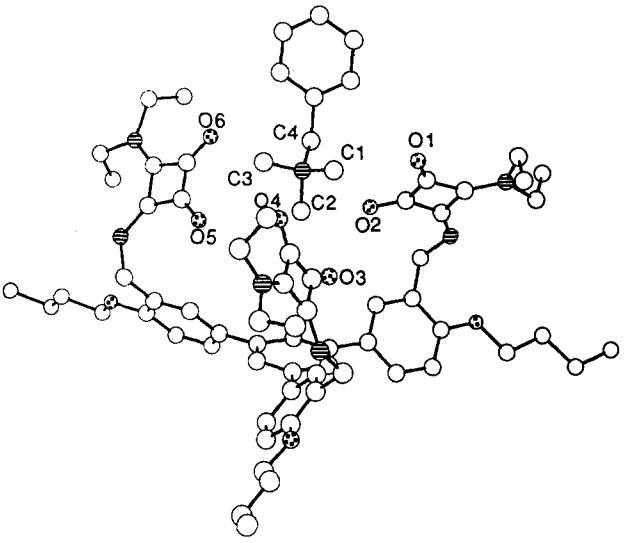


Figure 2. Chem3D minimum energy structure of the complex between **9a** and BTA. Hydrogen atoms are omitted for clarity. Some important distances (Å): O1-C1, 3.7; O2-C1, 4.6; O3-C1, 3.7;.O4-C1, 3.8; O1-C2, 4.3; O2-C2, 3.5; O3-C2, 3.6. Arbitrary numbering.

The proposed binding geometry was supported by 2D ROESY experiments.[22] The spectra obtained from 1:1 mixtures of **9b** and TMA or BTA in $CDCl_3$ solutions, showed cross peaks between H_a and H_b hydrogens of the receptor and the methyl hydrogens of the salt, demonstrating the inclusion of the polyalkyl ammonium cation within the cavity as shown in Figure 2. The complexation of polyalkyl ammonium salts by **9a** and **9b** was further confirmed by mass spectrometry. The FAB^+ spectra (matrix: m-nitrobenzyl alcohol) of a 1:1 mixture of TMA with **9a** or **9b** showed the diagnostic $[M + TMA^+]^+$ peaks that clearly prove the formation of these complexes. In conclusion the

combination of three squaramide subunits in a host which has a preorganized structure locked by hydrogen bonding, provides a new environment for the effective binding of "onium" salts in apolar non-protic solvents. Further research on these squaramide based receptors is under progress and will be reported.

Acknowledgments. We thank the DGICYT (Project PB92-0251) for financial support. M.C.R. wishes to thank the Spanish Ministry of Education for a pre-doctoral fellowship.

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10. ^{1}H-NMR (300 MHz, $CDCl_3$, δ_{ppm}): **9b**, 7.67 (d, J = 2.1 Hz, 3H); 7.58 (s, 3H); 7.57 (dd, J = 8.5, 2.1 Hz, 3H); 6.95 (d, J =8.6 Hz, 3H); 6.07 (t, J = 6.3 Hz, 3H); 4.97 (d, J = 6.2 Hz, 6H); 4.05 (t, J = 6.5 Hz, 6H); 3.51(bs, 12H); 1.79 (m, 6H); 1.51(m, 6H); 1.20 (t, J =7.2 Hz, 18H); 0.99 (t, J =7.2 Hz, 9H).
11. Upon decreasing the temperature until 240 K, a small upfield shift (less than 0.4 ppm) was observed for the squaramide NH proton. The only broad signals in the spectrum correspond to those of the diethyl portion of the squaramide. At c.a. 260K these signals split, thus proving their dynamic behavior. See: J. Chem. Soc. (B), **1968**, 435-436.
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13. Macromodel 3.5X, W. C. Still. Columbia University. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440-467.
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16. Evidence for complex formation between **9a** and "onium" salts were also obtained. Addition of a $CDCl_3$ solution containing excess TMA or BTA to solid **9a** led to its complete dissolution. The ^{1}H-NMR spectrum of this mixture displayed large shifts for the test protons indicating a tight binding. Unfortunately all attempts to evaluate the binding by dilution methods have been unsuccessful due to problems of self aggregation and poor fit to the models simulated until present.
17. For examples of cation-π interactions between "onium" salts and electron-rich aromatic rings, see: Dougherty, D. A.; Stauffer, D.A. *Science*, **1990**, *250*, 1558-1560. See also ref. 17.
18. It is well established that tetraalkyl ammonium ions have a tetrahedral distribution of charge located on the nitrogen α carbons. See: Reetz, M.T. *Ang. Chem. Int. Ed. Engl.* **1988**, *27*, 994-998.
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21. By visual inspection, taking an intermolecular distance of < 3.8 Å as arbitrary discriminating criteria.
22. 2D ROESY obtained with a reverse probe at 300 MHz. Mixing time = 0.4-0.5 s., spinlock = 2 Khz.

(*Received in UK* 30 *November* 1994; *accepted* 10 *February* 1995)