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Squaramido-based receptors: applicability of molecular interaction potential to molecular recognition of polyalkylammonium compounds

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Abstract. A computational study of the mechanism of host–guest complexation between quaternary ammonium compounds and squaramido-based tripodal receptors has been carried out. Semiempirical molecular orbital calculations, which are in qualitative agreement with experimental results have been performed using the PM3 Hamiltonian. Molecular interaction potential (MIP) maps were used to analyze the suitability of both host and guest binding units for a high-affinity recognition process. MIP calculations were computed from PM3 wavefunctions of the corresponding ammonium cations and dimethyl squaramide as a model compound for the hydrogen-bond-acceptor unit of the receptors. MIP analyses are helpful for understanding the host–guest process from the point of view of the double-complementarity principle.

Key words: Molecular recognition – Molecular interaction potential – Semiempirical calculations – Squaric acid amides – Alkylammonium compounds

1 Introduction

Molecules which interact with one another in organized assemblies to perform useful functions are termed supramolecules and are found in their most refined form in biological systems. Advances in supramolecular chemistry have given rise to the preparation of a great deal of molecular receptors which bear adequate functional groups to establish nonbonding interactions with molecular substrates [1]. The research of new methodologies for the design of such receptor molecules will have an impact in different fields, such as analytical and medicinal chemistry, and in the development of catalytic substances mimicking enzymes, etc.

Supramolecular species are characterized by the nature of the intermolecular bonds that hold these components together. Several types of interactions may be distinguished, that present different degrees of strength, directionality, dependence on distance and angles: metal ion coordination, electrostatic forces, hydrogen bonding, van der Waals interactions, etc. These strengths range from weak or moderate as in hydrogen bonds to strong or very strong for metal ion coordination. Intermolecular forces are in general weaker than in covalent bonds, so supramolecular species are thermodynamically less stable, kinetically more labile and dynamically more flexible than molecules.

Our group has been using several receptors for the recognition of a variety of compounds, including carboxylic acids [2], carboxylates [3], adenine derivatives [4] and ammonium salts [5]. Recently, some of us have reported [6] the synthesis and applications of squaramido-based tripodal receptors to the recognition of quaternary ammonium compounds.

In order to gain knowledge of the process of bringing together our tripodal receptors and the quaternary ammonium substrates in a predictable and useful fashion, a suitable theoretical study was warranted. Due to the size of our systems, for example, complexes of about 200 atoms, ab initio methods were clearly inappropriate and a semiempirical quantum mechanical treatment was chosen since, among other reasons (vide infra), adequate description of the C—H $\cdots$ O hydrogen bonds had been reported [7]. Classical molecular mechanics methods were not considered, because standard parameterization of commercial force fields resulted in a poor description of the squaramide structure due to the lack of suitable parameters for this highly functionalized small ring.

Molecular interaction potential (MIP) calculations have been shown to be a valuable method molecular reactivity [8] but also to rationalize and predict intermolecular interactions [9]. MIP calculations are only approachable from quantum mechanical methods since

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the MIP method is based upon the generalization of the rigorous quantum mechanical molecular electrostatic potential and further addition of classical repulsion and dispersion terms from suitable van der Waals parameters [8]. In our case, the detailed analysis of the topological characteristics of the MIP maps calculated at the semiempirical level was expected to provide a proper description of molecular recognition phenomena involving medium-sized to large-sized squaramido-based molecules.

This report deals with the host–guest chemistry between our tripodal receptors and some tetraalkylammonium cations [6]. Starting from semiempirical wavefunctions, MIP energy maps of the cations were calculated. PM3 free energies of complexation were calculated and compared with experimental data.

We first focused our attention on the previously mentioned complexes between our squaramido-based tripodal receptors (Scheme 1, 1a–c) and alkylammonium cations (Scheme 1, 2a–d, viz., benzyltrimethylammonium, acetylcholine, methylpyridinium and choline) [6]. The α-methyl or methylene hydrogen atoms in alkylammonium cations support a partial positive charge [10] and therefore can be engaged in nonbonding interactions, for example, hydrogen bonds. Multiple C—H $\cdots$ O=C interactions would be well suited for an effective complexation of alkylammonium cations. These interactions have been observed in crystals [11], and they have been reported to compete advantageously with cation π interactions in $(CH_3)_4N^+$-calixarene complexes [12].

2 Methods

Theoretical calculations were carried out at the restricted Hartree–Fock (HF) level using the PM3 [13] semiempirical self-consistent-field – molecular orbital method, as implemented in the MOPAC 93 package [14]. All structures were geometry-optimized and further refined by minimization of the gradient norm to less than 0.01 kcal/Å deg (keyword PRECISE) by means of the eigenvector-following routine (EF) [15]. No symmetry constraints were imposed unless otherwise noted. All stationary points on the potential-energy surfaces were characterized by calculating and diagonalizing the Hessian matrix and by checking the number of negative eigenvalues [16].

Thermodynamic properties (entropies, specific heats, Gibbs free energies of formation) were obtained from the calculated geometries and vibrational frequencies as previously described [17]. Coulson [18] atomic charges, shown later were obtained from the PM3 semiempirical method.

Several approximations were made in the theoretical study of the process of complexation. First, the proposed geometries of free hosts and guests correspond to the lowest energy minima found on the potential hypersurface. Due to the considerable flexibility of our hosts, a conformational analysis was performed. In any systematic examination of conformational space, one attempts to balance the inherent cost of a more accurate/exact model with an acceptable level of accuracy for the results. There are three main torsional degrees of freedom (ϕ, φ, ψ) as shown in Fig. 1. The starting geometries for each tripodal receptor correspond to the lowest energy minimum achieved from a PM3 conformational analysis obtained through the following procedure. The conformational search was carried out according to a 13×13 grid (169 points) having ϕ and φ dihedral angles as x- and y-axes, respectively (Fig. 1). Each point on the grid was optimized by minimization of the gradient norm to less than 1.0 kcal/Å deg by means of the EF routine. Only those low-energy conformations within a 1.0 kcal/mol range were selected and analyzed around the biaryl bond (ψ) by performing a torsional energy profile and varying the dihedral angle ψ every 15°. The minima obtained from the torsional energy profiles were reoptimized and refined by minimization of the gradient norm to less than 0.01 kcal/Å deg. The energies reported here correspond to the fully optimized geometries. Obviously, the "real" situation is a weighted mixture of several low-energy conformations, whereas the "calculated" (theoretical) situation consists of just one conformation.

Second, counterion and solvent effects were not taken into account. Experimentally, all association constants were

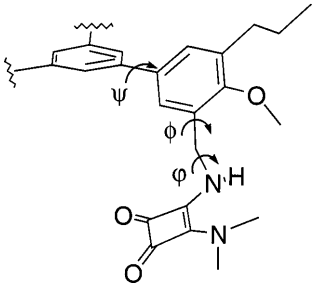
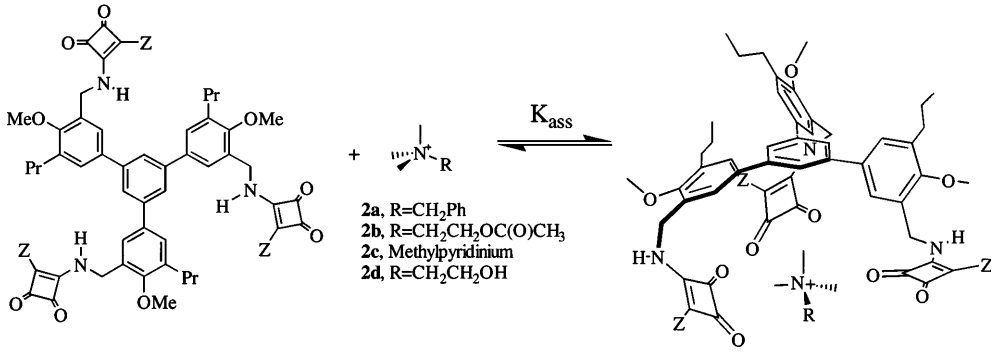


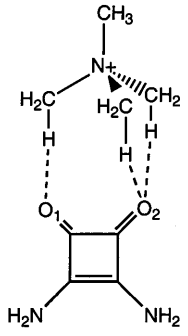
Fig. 1. Partial view of the tripodal hosts showing the three possible torsional degrees of freedom

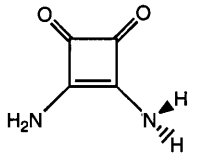


1a, Z=NEt_2
1b, Z=NH-CH_2Ph
1c, Z=NHp-$Me_2NC_6H_4$

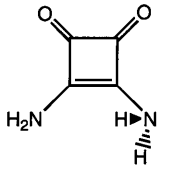
3a (1a+2a)
3b (1b+2a)
3c (1b+2b)
3d (1c+2b)
3e (1c+2d)
3f (1b+2c)

Scheme 1





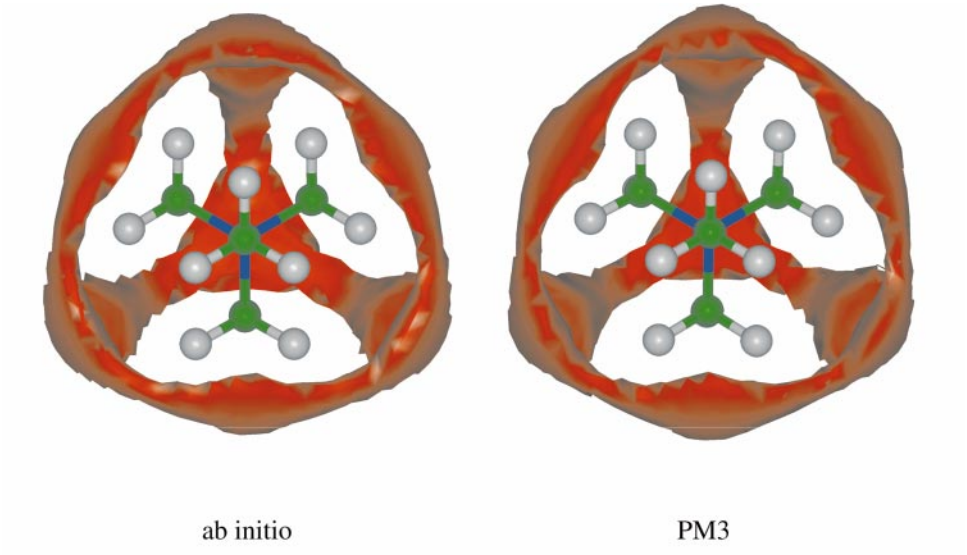
TS_{syn}



TS_{anti}

Fig. 2. *PM3 and HF/6-31+G* N-O distances* (Å) of optimized tetramethylammonium cation-squaramide complex. *Rotational barriers* (kcal/mol) of the NH_2 group in squaramide are also indicated

	PM3	HF/6-31+G*			
$d_{O1\text{-}N}$ (Å)	4.80	4.54	PM3:	3.56	6.48
$d_{O2\text{-}N}$ (Å)	3.73	3.80	HF/6-31+G*:	3.64	7.92



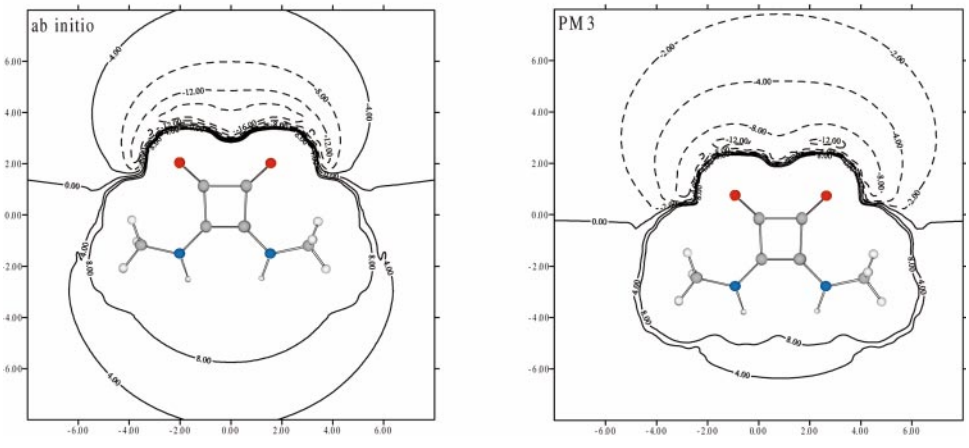


Fig. 3. (*Top*) 3D molecular interaction potential (*MIP*) cube of the tetramethylammonium cation versus the negative particle ½ O^- using ab initio and PM3 wavefunctions. The global minima are −45.59 and −45.82 kcal/mol, respectively. *Interaction energy contours* ranging 4.0 kcal/mol from global minima are shown for both calculation methods. (*Bottom*) Ab initio and PM3 MIP (½ H^+) energy maps for dimethylsquaramide. The global minima are −18.73 and −12.40 kcal/mol, respectively. The axes of the Cartesian coordinates are in angstroms

determined in the same solvent (chloroform); hence, solvent and solvent reorganization effects, though being fairly important, can be considered approximately equal in all complexation processes. In all the cases studied, the counterion was a halide atom (bromide or iodide); consequently the counterion effect was considered to be similar in the complex formation process.

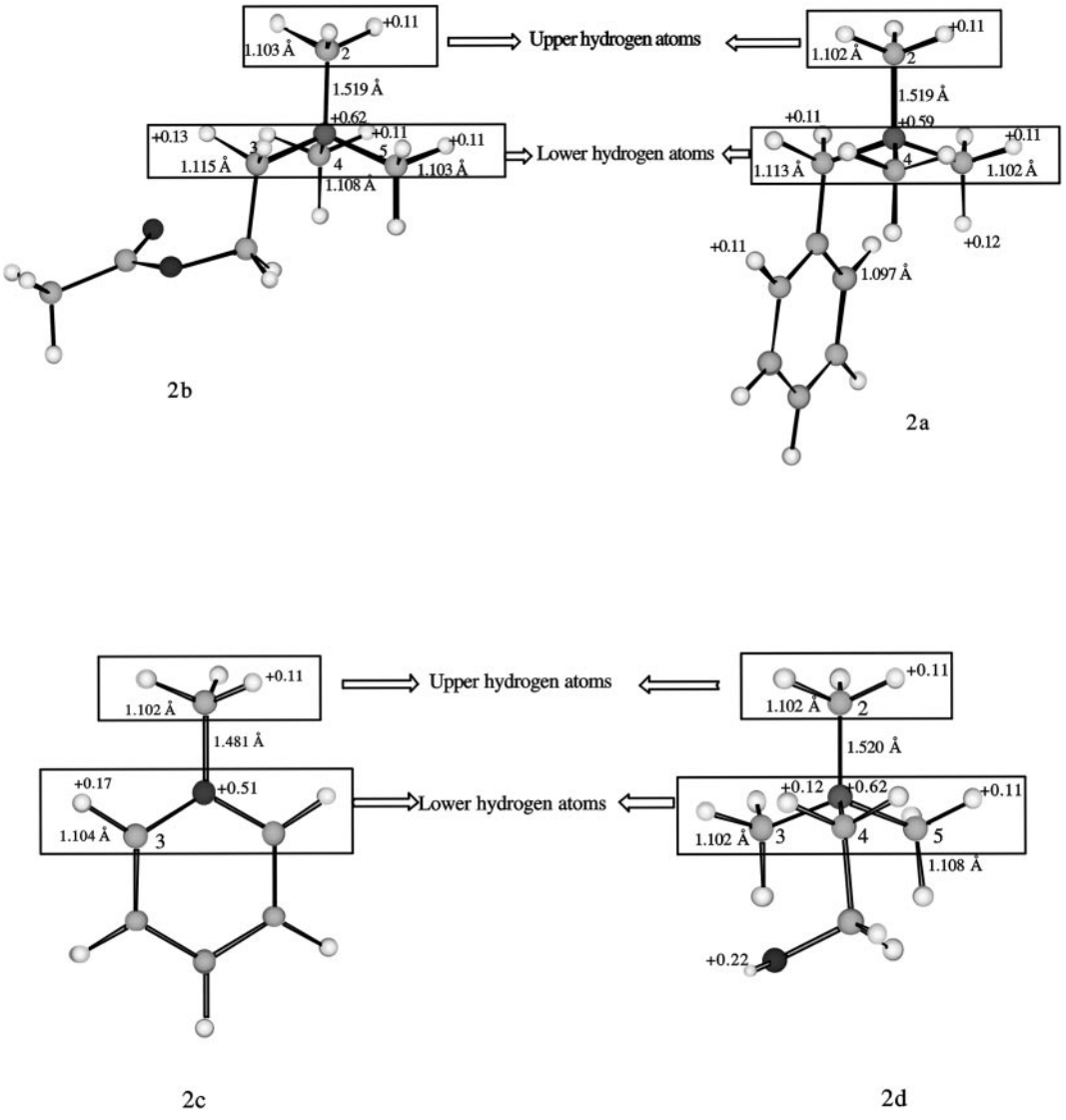


Fig. 4. PM3-optimized geometries of cations benzyltrimethylammonium (**2a**), acetylcholine (**2b**), methylpyridinium (**2c**) and choline (**2d**). Relevant *Coulson atomic charges* (*italic*) and *distances* are directly indicated on the structures (atom numbers in *bold*)

[1] Therefore, these effects should not play a major role in the divergences in K_{ass} between the different complexes. Moreover, the polarity is similar in all complexes studied and the polarity of the solvent used is low, making possible the comparison between our gas-phase calculations and the experimental results.

Patterns of interaction with potential nucleophilic groups or hydrogen-bond acceptors were determined using the MIP. Standard optimized van der Waals parameters were used to describe the steric interactions of the classical particle (½ O^-). In all cases, the semiempirical PM3 wavefunctions determined from calculations at the self-consistent-field level were used in the evaluation of the MIP. The MIP was computed using the MOPETE-97 computer program [19].

[1] H-NMR studies carried out by us (see Ref. [6]) revealed that tetraalkylammonium salts in chloroform solution exist mainly in the form of interpenetrated ion pairs

3 Preliminary calculations

In order to test that the PM3 semiempirical method is indeed a useful tool to study the complexation of squaramido-based receptors and tetraalkylammonium cations where multiple C—H···O=C interactions are present, we carried out some calculations on model systems using both PM3 and ab initio (HF/6-31 + G*) methods. Results are shown in Fig. 2. First, a complex between a single unit of squaramide and the tetramethylammonium cation was calculated and compared using the previously mentioned methods. The results shown in Fig. 2 correspond to the lower-energy conformation of the complex found on the potential-energy surface using the PM3 semiempirical method; this conformer was used to initiate the ab initio optimization. Geometrical parameters such as the N—O distances compare well. Second, the rotational barrier around the C—N bond in squaramide was also calculated using both methods. Energy barriers for anti and syn transition states are quite coincident, with the syn transition state having the lowest rotational energy in both methods. Finally, we calculated a 3D MIP energy cube of the

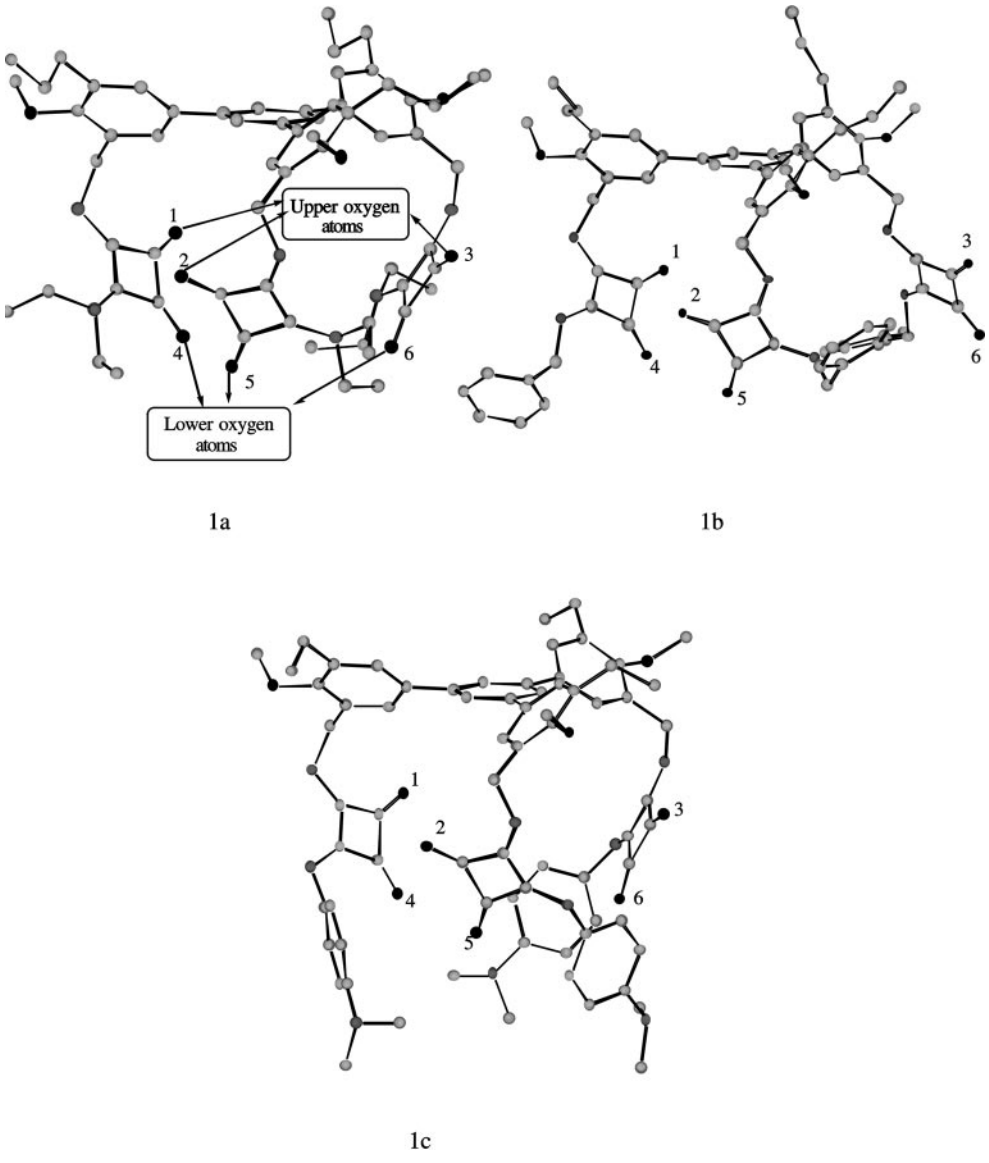


Fig. 5. PM3-optimized geometries of hosts **1a**, **1b** and **1c** indicating, for host **1a**, which oxygen atoms (*black*) are called upper and lower oxygen atoms (see text). Hydrogen atoms have been omitted for clarity (atom numbers in *bold*)

tetramethylammonium cation and a 2D MIP energy map of dimethylsquaramide using both semiempirical and ab initio wavefunctions versus a negative particle (½ O^-) for the tetramethylammonium cation and a positive particle (½ H^+) for dimethylsquaramide. As shown in Fig. 3, both representations (PM3 and ab initio) of the 3D MIP of the tetramethylammonium cation give similar shapes for the interaction potential with comparable global minima (−45.82 and −45.59 kcal/mol for semiempirical and ab initio calculations, respectively). Moreover, the common topology of both representations of the 2D MIP of dimethylsquaramide (PM3 and ab initio) is clear in Fig. 3.[2] As a consequence of these results, PM3 was deemed suitable to carry out a theoretical study involving squaramido-based receptors and tetraalkylammonium cation complexes.

4 Results

The process of complexation of tripodal receptors **1** with cations **2** to form complexes **3** was studied by means of PM3-calculated geometries and their thermodynamic values (see Scheme 1).[3] The PM3-optimized geometries for cations and receptors are shown in Figs. 4 and 5, respectively. As can be seen, the α-methyl and methylene hydrogen atoms bear enough positive charge to participate in nonbonding interactions. As expected, the largest positive atomic charge belongs to the nitrogen atom; however, it is not accessible by the "negative sites" of the receptor due to steric effects of the alkyl chains, except for methylpyridinium (**2c**).

[2] Ab initio provides larger MIP minimum values (in absolute values) than PM3 ones, reflecting the well-known systematic underestimation of electrostatic interaction energy in regions far from the molecule in semiempirical calculations (see Ref. [8])

[3] Coordinates and energies for the PM3-optimized structures are available upon request by contacting tonif@soller.uib.es

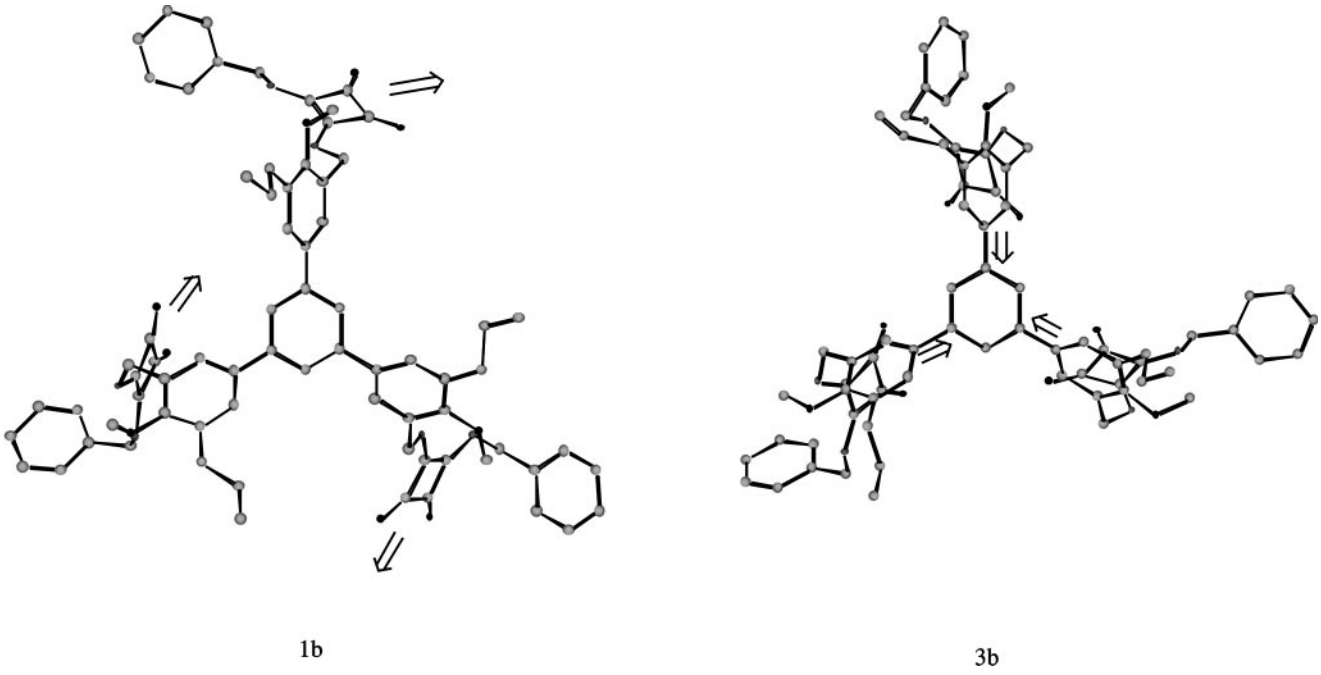
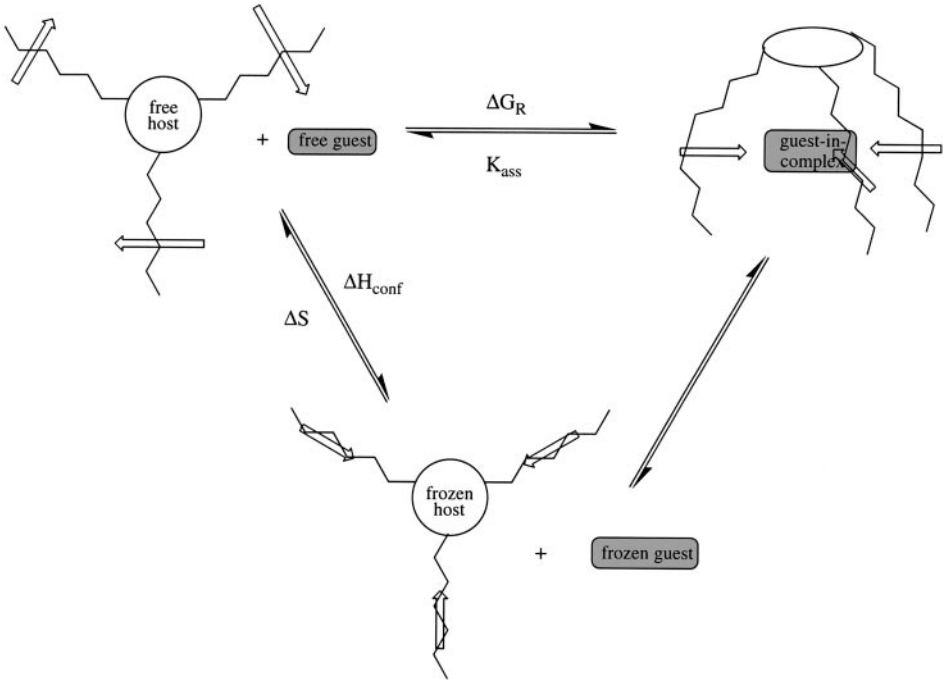


Fig. 6. PM3-optimized geometries of host **1b** and complex **3b** (cation omitted) where the conformational change of the squaramide units is observed. Hydrogen atoms have been omitted for clarity

As indicated in Fig. 4, the hydrogen atoms directly bonded to carbon atom 2 are referred to as upper hydrogen atoms and those directly bonded to carbon atoms 3, 4 and 5 (3 and 4 for **2c**) are referred to as lower hydrogen atoms. The oxygen atoms, numbered 1, 2 and 3, on the receptors are referred to as upper oxygen atoms and those numbered 4, 5 and 6 are referred to as lower oxygen atoms (Fig. 5).

The main structural change produced as a consequence of the complexation process is the 3D reorientation of the carbonyl groups of the squaramide units (Scheme 1). Within the geometry of the complex, the carbonyl groups of the receptors point toward the center of the cavity, whereas in free hosts they are tangent to the cavity, as shown in Fig. 6. Furthermore, conformational changes were also observed on going from the free cations to the complexed cations.

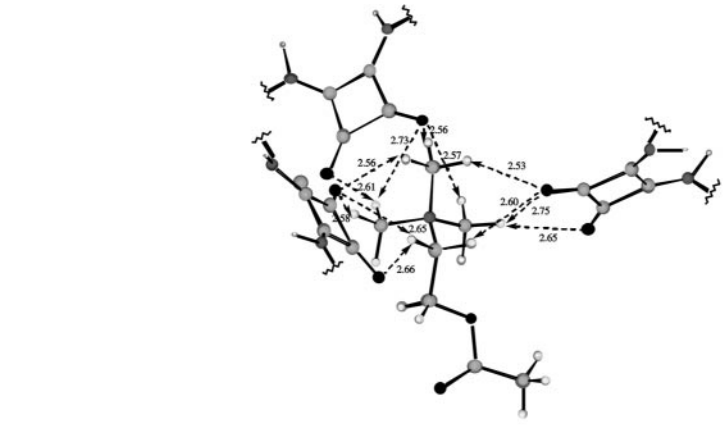
It is evident that the structures of the hosts and guests have a high degree of complementarity. The ''acidic'' hydrogen atoms of the ammonium cations may be envisaged as being divided in two topographical types, i.e.



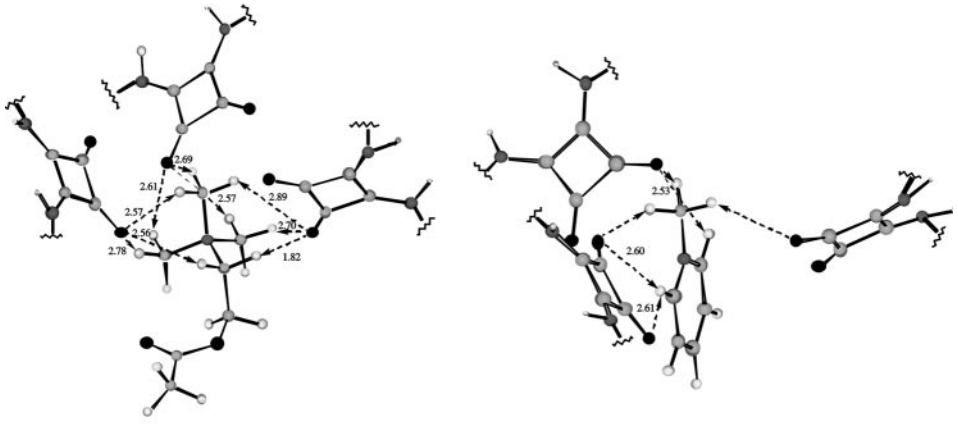
Scheme 2

Table 1. PM3 calculated free energies (kcal/mol) of complexation (ΔG_R) and conformational energies (ΔH_{conf}, see text) and experimental association constants at 21°C in $CDCl_3$ from Ref. [6] (K_{ass}). ΔG_R was calculated by taking the difference between the free energy of the complex and the free energy of the isolated members of the complex

Entry	Complex	ΔH_{conf}			ΔG_R	K_{ass}
		Host	Guest	Total		(M^{-1})
Benzyltrimethylammonium complexes						
1	**3a** (**1a** + **2a**)	4.06	3.56	7.62	−8.12	272 ± 7
2	**3b** (**1b** + **2a**)	0.11	0.07	0.18	−9.39	4624 ± 256
Acetylcholine complexes						
3	**3c** (**1b** + **2b**)	0.80	1.91	2.71	−8.72	1473 ± 59
4	**3d** (**1c** + **2b**)	0.94	0.73	1.67	−9.95	8559 ± 175
Host **1b** complexes						
5	**3b** (**1b** + **2a**)	0.11	0.07	0.18	−9.39	4624 ± 256
6	**3c** (**1b** + **2b**)	0.80	1.91	2.71	−8.72	1473 ± 59
7	**3f** (**1b** + **2c**)	0.50	0.02	0.52	−10.22	4050 ± 1091
Host **1c** complexes						
8	**3d** (**1c** + **2b**)	0.94	0.73	1.67	−9.95	8559 ± 175
9	**3e** (**1c** + **2d**)	2.22	0.32	2.54	−10.15	14509 ± 1403



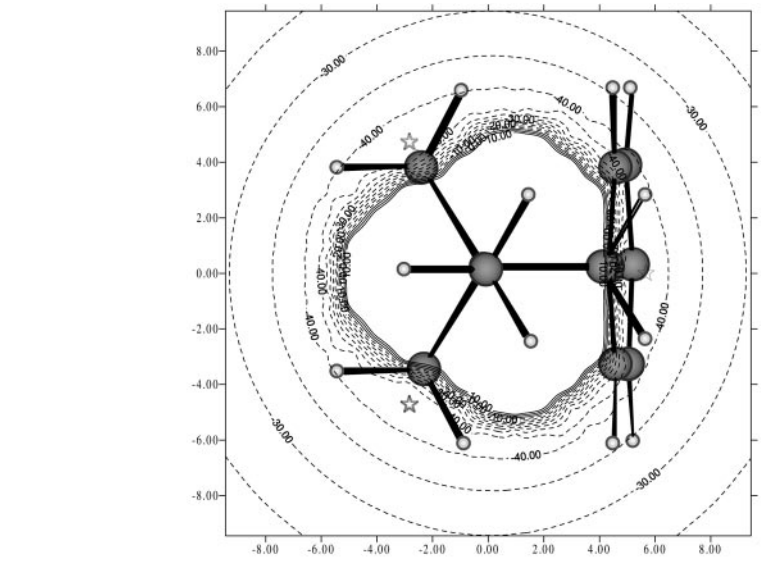
3c



3d 3f

Fig. 7. PM3-optimized geometries (partial view) of complexes **3c**, where 12 nonbonding interactions are found, **3d**, where nine interactions are found, and **3f**, where just six interactions are found

upper and lower hydrogen atoms (Fig. 4) that may respectively complement "basic" upper and lower carbonyl oxygen atoms of the squaramide units in the hosts (Fig. 5). As a matter of fact, this complementarity determines the structural recognition, but the power of the binding is probably determined by the preorganization [20]. In our case, preorganization was used in the following sense: the better the geometries of free hosts and guests adjust to the complexed host and guest geometries, the larger is the preorganization of the system and the more stable will be their complexes. Therefore, the degree of preorganization could be



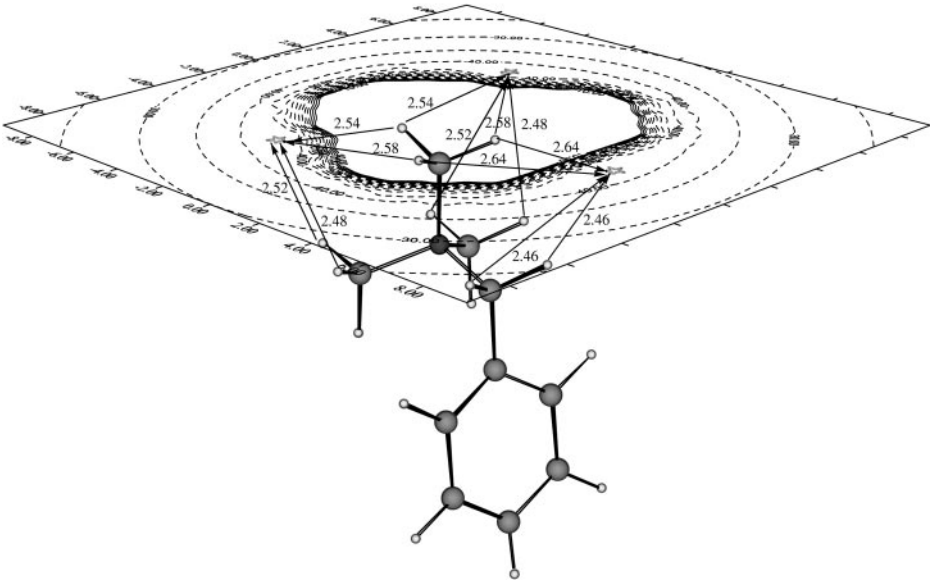


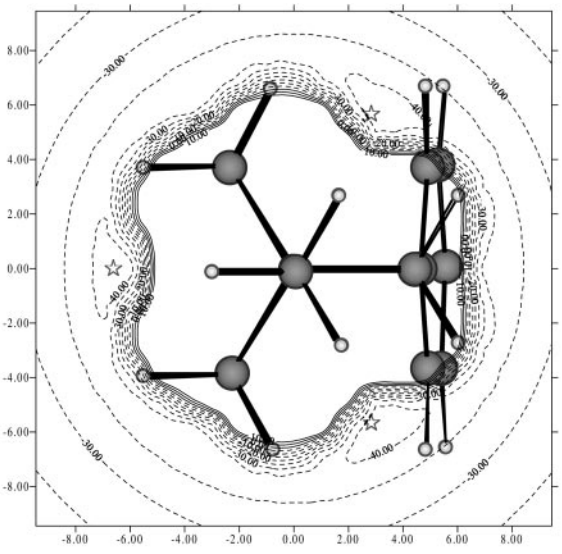
Fig. 8. *Upper* and *perspective view* of MIP (½ O^-) energy maps for cation **2a**, at an *x*-coordinate value of 2.0 Å. *Isocontour lines* are shown every 5 kcal/mol. The axes of the Cartesian coordinates are in atomic units (1 Å = 1.89 au). *Distances* between minima, represented by *stars*, and hydrogen atoms are given in angstroms

roughly estimated by calculating the conformational energy (ΔH_{conf}) difference between free and complexed hosts (Scheme 2). [4] Using this procedure, the enthalpic effect of preorganization was evaluated and should provide an acceptable idea of the degree of preorganization of our hosts and guests prior to complexation.

First, conformational changes of the hosts on going to complexation are only significant for **1a** in complex **3a** (Table 1, entry 1). Second, guest conformational changes due to complexation (ΔH_{conf} values) are important particularly for **3a** and **3c** complexes (Table 1, entries 1, 3). Thus, if we take into account the sum of the ΔH_{conf} values corresponding to the host and guest on going to complexation, one can observe a qualitative agreement between the total ΔH_{conf} values and the experimental association constant (K_{ass}) [6] shown in Table 1. The complex **3e**, where additional interactions take place, is an exception to this behavior and will be discussed later.

The geometry of the cations is quite similar in all complexes; the $N{-}C_2$ bond is directed perpendicular to the central aromatic ring of the receptors, such that the upper hydrogen atoms of the guest interact mainly with upper oxygen atoms of the host. The lower squaramide

[4] The energies of complexed host and guest were calculated by performing a single-point calculation of the conformation presented by host or guest in the complex (frozen host and guest); thereby, they were not stationary points



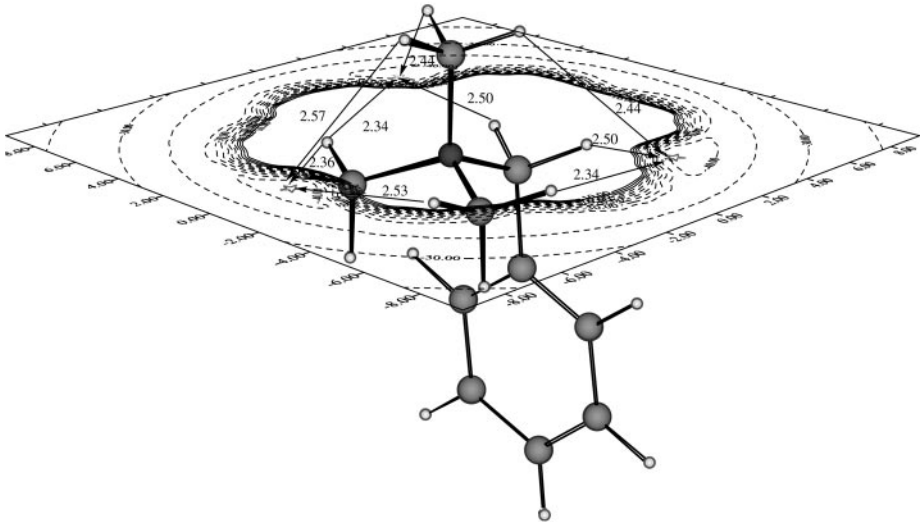


Fig. 9. *Upper* and *perspective view* of MIP (½ O^-) energy maps for cation **2a**, at an *x*-coordinate value of 1.0 Å. *Isocontour lines* are shown every 5 kcal/mol. The axes of the Cartesian coordinates are in atomic units. *Distances* between minima, represented by *stars*, and hydrogen atoms are given in angstroms

oxygen atoms of the host interact with both upper and lower hydrogen atoms of the guest. As a result, 12 short C—H · · · O interactions are found (less than 2.90 Å) for all complexes studied, except for two cases. First, complex **3d** formed by acetylcholine and the host **1c**, where upper and lower hydrogen atoms interact exclusively with lower oxygen atoms giving rise to nine interactions (Fig. 7). Second, for methylpyridinium (**2c**) in complex **3f**, fewer interactions were found as a consequence of the two hydrogen atoms in the ortho position which participate in the complexation process (Fig. 7). In all optimized geometries, hydrogen bonds in the complexes show an average C · · · O distance of 3.5 Å and an average C—H · · · O angle of 150°, both in agreement with Desiraju's findings for this type of hydrogen bond [21]: distances between 3.0 and 4.0 Å and angles in the range 150–160°.

As can be seen in Table 1, gas-phase calculated free energies of complexation are able to reproduce the experimental results (K_{ass}) in a qualitative manner. Benzyltrimethylammonium cation (**2a**) is better recognized (larger value of K_{ass}) by host **1b** than **1a** in agreement with computed free energies of complexation and ΔH_{conf} (Table 1, entries 1, 2). In fact, host **1a** has a high ΔH_{conf} (4.06 kcal/mol) and the lowest association constant, probably due to an unfavorable conformation adopted by the bulky *N*,*N*-diethyl squaramide in complex **3a**, that also hinders the interaction with the cation as deduced by the ΔH_{conf} value of the guest (3.56 kcal/mol). Acetylcholine (**2b**) is better recognized by host **1c** than **1b**, in agreement with PM3-computed ΔG_R and ΔH_{conf} for complexes **3d** and **3c** (entries 4 and 3, respectively). Host **1b** recognizes benzyltrimethylammonium and methylpyridinium more effectively compared to acetylcholine (entries 5, 6 and 7), in qualitative agreement with computed ΔG_R and ΔH_{conf}. ΔH_{conf} in complex **3e** is appreciable for host **1c**

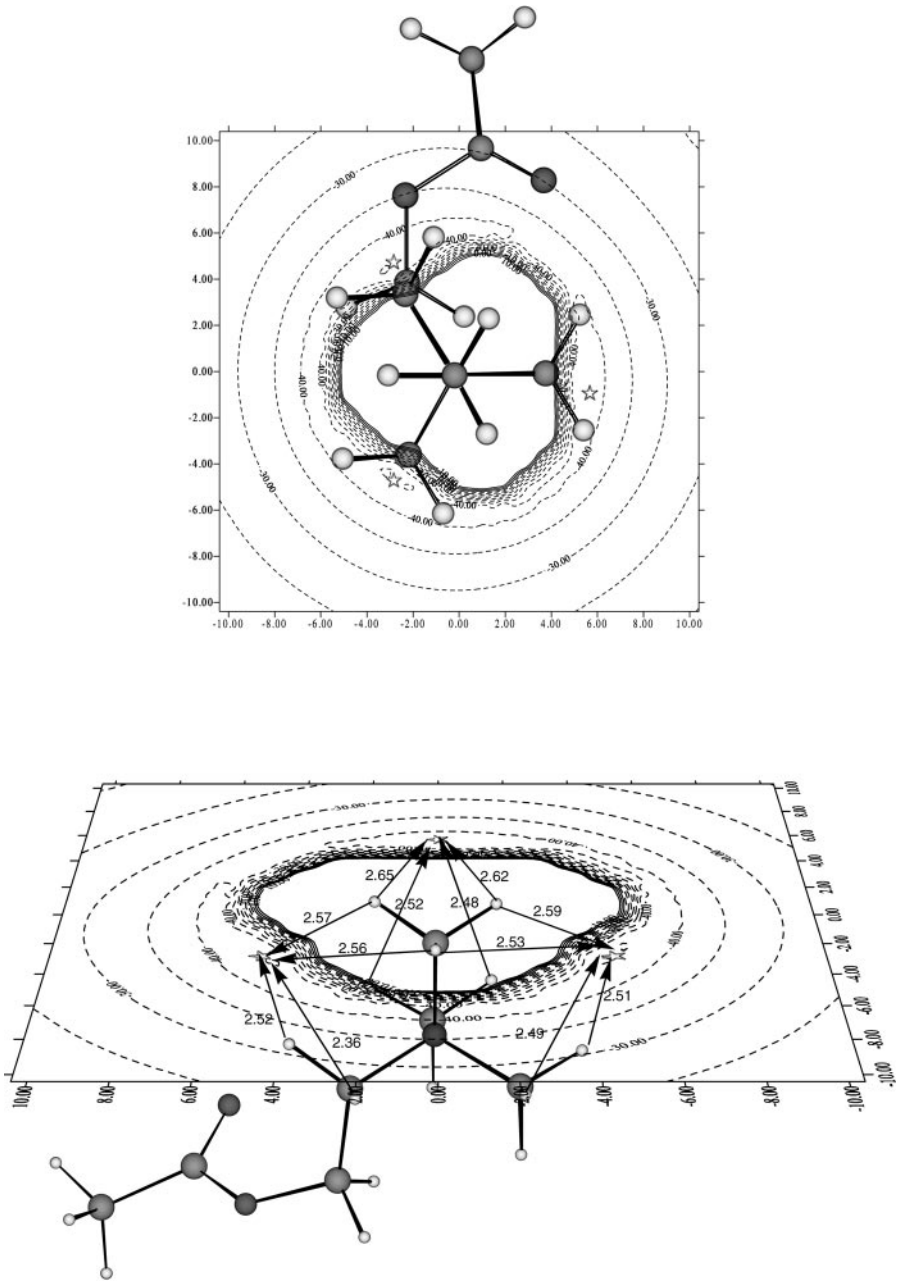


Fig. 10. *Upper* and *perspective view* of MIP (½ O^-) energy maps for cation **2b**, at an *x*-coordinate value of 2.0 Å. *Isocontour lines* are shown every 5 kcal/mol. The axes of the Cartesian coordinates are in atomic units. *Distances* between minima, represented by *stars*, and hydrogen atoms are given in angstroms

(2.22 kcal/mol, Table 1, entry 9). The apparent contradiction between the value of ΔH_{conf} and the ΔG_{R} value showed by complex **3e** is explained by means of the additional interactions that take place in that complex. The hydrogen atom of the hydroxyl group of choline (**2d**) interacts with the two carbonyl oxygen atoms of a squaramide. These latter interactions result in the conformational energy cost of the host being compensated by the additional binding forces.

Experimental association constants can be qualitatively explained through PM3-calculated total ΔH_{conf}; thereby, the preorganization degree of host and guest seems to play an important role in complex formation. Hence, the calculation of the MIP of cations to establish their complexation requirements with hosts must be important in our theoretical study. The MIP is a useful tool to study reactivity because it can represent electrostatic interactions with high accuracy but it can also represent steric effects in a suitable way [8]. Moreover, the MIP is able to provide a suitable description of the geometric and energetic features of nonbonding interactions, in particular hydrogen bonds; therefore, it can also be a valuable tool for understanding the preorganization phenomenon in host–guest chemistry (where nonbonding interactions are present) by means of comparing the complementarity of the MIP of the guest with the host and vice versa.

The MIP corresponding to the interaction between our cations and the classical particle ½ O^- was calculated by means of the MOPETE-97 program. We used the previously mentioned classical particle as a model of the carbonyl oxygen atom to analyze the

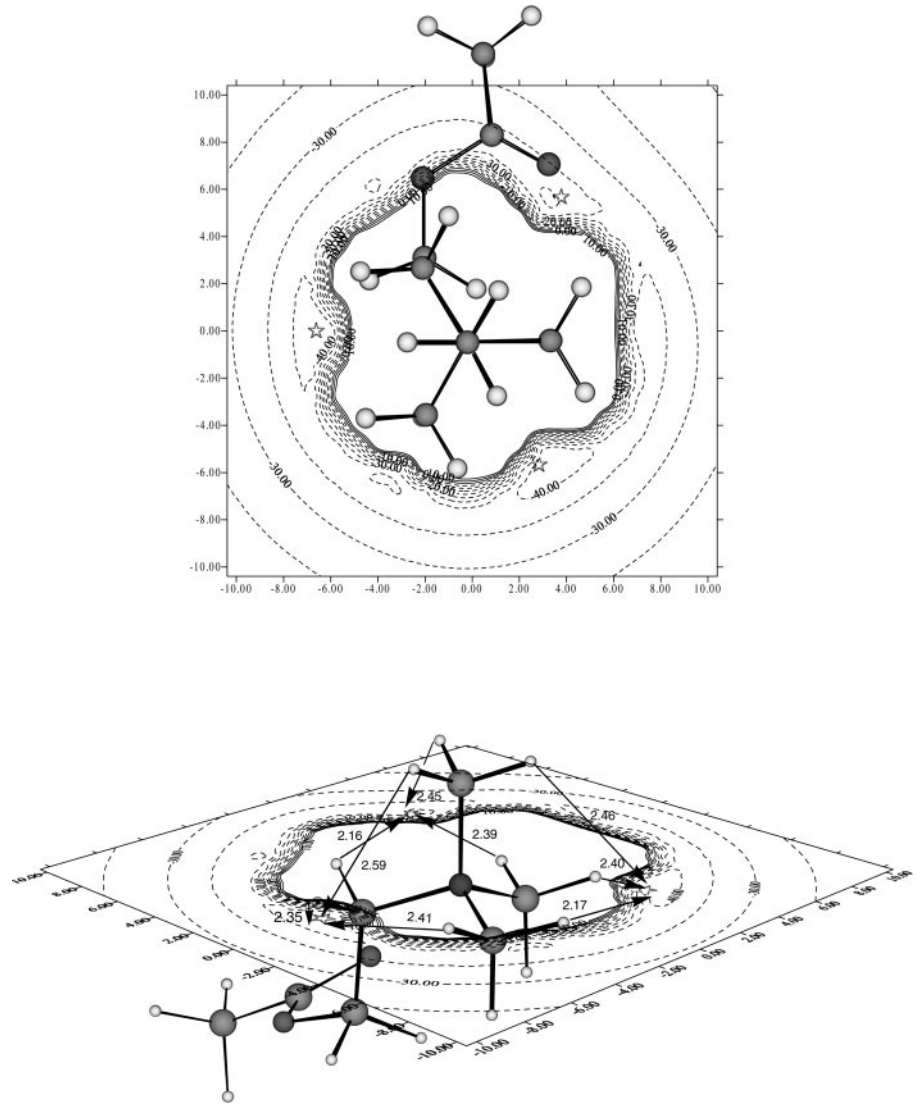


Fig. 11. *Upper* and *perspective view* of MIP (½ O^-) energy maps for cation **2b**, at an *x*-coordinate value of 1.0 Å. *Isocontour lines* are shown every 5 kcal/mol. The axes of the Cartesian coordinates are in atomic units. *Distances* between minima, represented by *stars*, and hydrogen atoms are given in angstroms

$N^+C{-}H\cdots O{=}C$ interactions between ammonium cations and the squaramido-based receptor.

First of all, MIPs (½ O^-) of the cations were evaluated in a 3D grid around the molecule. The 3D rectangular grid is generated by the program adding a given distance (3.0 Å in our case) to the maximum and minimum values of the Cartesian coordinates of atoms in the axes *x*, *y* and *z* determined previously. The other parameter required is the step along the axis that modulates the density of points in the grid, and 0.5 Å was the value selected for this study. MIP maps obtained in this way provide a rough but complete picture of ideal positions in space for the different carbonyl oxygen atoms of the squaramide units to bind ideally to the corresponding cation.

Second, as a result of the grid calculation, several minimum energy points were found, mainly located in both YZ_1, and YZ_2 parallel planes. YZ_1 was located slightly above the plane defined by the upper hydrogen atoms of the cations (2.0 Å over the nitrogen atom), whereas the other plane (YZ_2) was located between the planes defined by both upper and lower hydrogen atoms (1.0 Å above the nitrogen atom).

At this point, in order to obtain precisely the positions of the YZ_1 and YZ_2 energy minima, several 2D grid calculations were carried out, thus increasing the density of points, and 0.3 Å was set as the new step value. Furthermore, calculations were focused on the YZ_1 plane and on two more parallel planes situated 0.2 Å above and below the first one to ensure the location of the minima. The same operation was done for the YZ_2 plane. As a result, three minima were found for each bidimensional grid calculation, where the more significant potential-energy minima were again located on the YZ_1 and YZ_2 planes. The resulting MIP maps for these planes are shown in Figs. 8 and 9 for the benzyltrimethylammonium cation (**2a**), in Figs. 10 and 11 for acetylcholine (**2b**), in Figs. 12 and 13 for the methylpyridinium cation (**2c**) and in Figs. 14 and 15 for choline (**2d**). For the sake of clarity, a perspective and upper views of the maps are shown, in which the minima are denoted by stars.

For the MIP (½ O^-) maps corresponding to **2a** (Figs. 8, 9), three global minima are situated on the YZ_1 plane. Each minimum is a consequence of four interactions, two of these with upper hydrogen atoms and the others

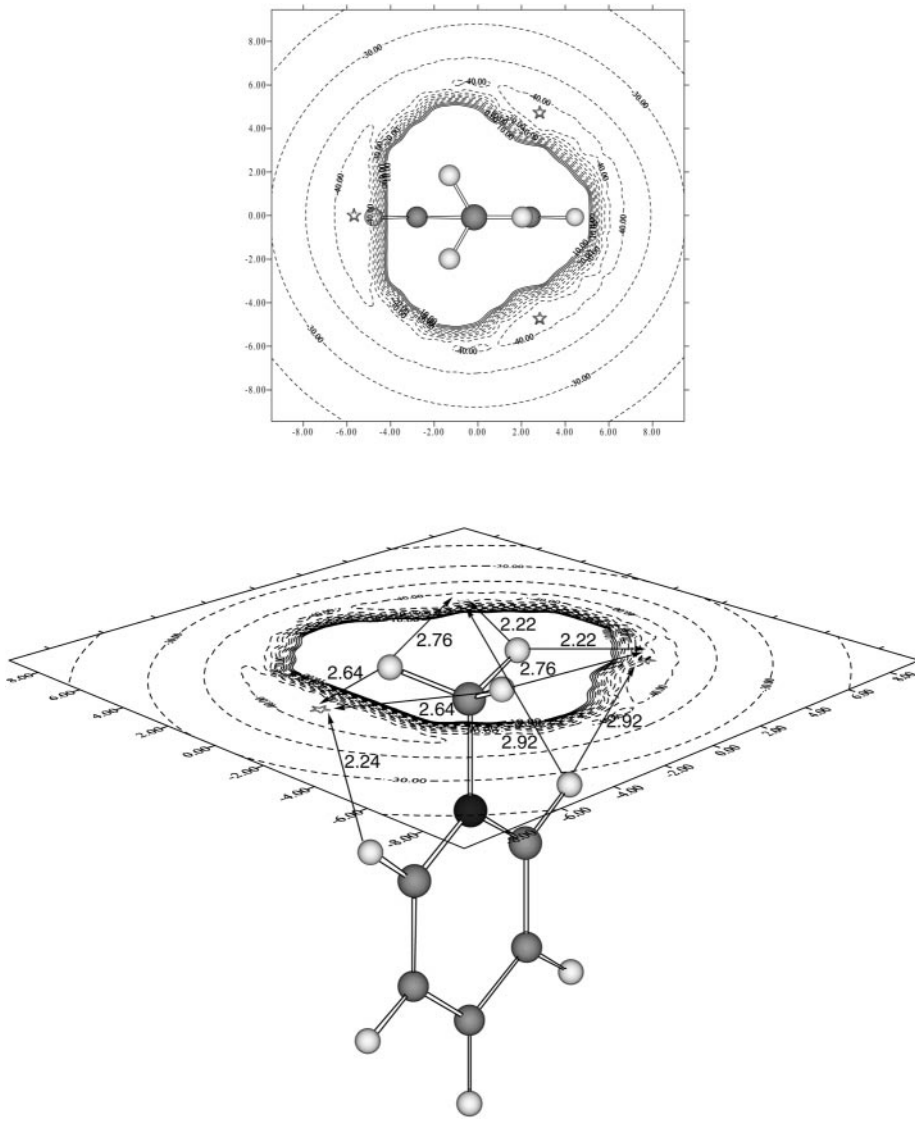
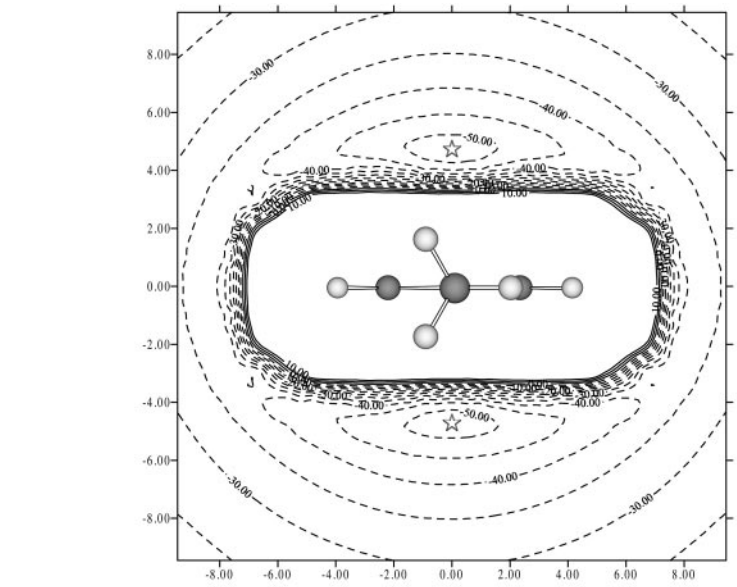


Fig. 12. *Upper* and *perspective view* of MIP (½ O^-) energy maps for cation **2c**, at an *x*-coordinate value of 2.0 Å. *Isocontour lines* are shown every 5 kcal/mol. The axes of the Cartesian coordinates are in atomic units. *Distances* between minima, represented by *stars*, and hydrogen atoms are given in angstroms

with two lower hydrogen atoms, as indicated by the solid arrows. The minima are approximately 2.5 Å from both upper and lower hydrogen atoms, with a corresponding average interaction potential of −43.2 kcal/mol. Three other minima are found on the YZ_2 plane (Fig. 9), each one generated by three interactions, two with two lower hydrogen atoms and the other with the upper hydrogen atoms, giving rise to nine significant nonbonding interactions between hydrogen atoms and the ½ O^- classical particle. The minima are found in a range of 2.3–2.5 Å from the upper and lower hydrogen atoms, with an average depth (−43.5 kcal/mol) similar to that corresponding to the YZ_1 plane.

The same patterns are found for **2b** (Figs. 10, 11) and **2d** (Figs. 14, 15). For acetylcholine, the average interaction potentials are −44.0 and −44.7 kcal/mol for the upper (YZ_1 plane) and lower (YZ_2 plane) minima, respectively, and for choline these are −45.49 and −45.06 kcal/mol for the upper (YZ_1 plane) and lower (YZ_2 plane) minima, respectively. One small difference of the latter cation is the presence of a more acidic hydrogen atom in the hydroxyl group which is capable of strongly interacting with our probe particle.

As expected, different behavior is observed for the methylpyridinium cation. MIP (½ O^-) maps (Figs. 12, 13) show three global minima situated on the YZ_1 plane. In this case, each minimum has principally the contribution of three interactions, two with upper hydrogen atoms and the other with one aromatic hydrogen atom, as indicated by the solid arrows. The minima are located 2.9–2.2 Å from both upper and aromatic hydrogen atoms, with a corresponding average interaction potential of −42.4 kcal/mol. Two other minima are found on the YZ_2 plane (Fig. 13), each one being generated by two interactions, one with the nitrogen atom and the other with an upper hydrogen atom, giving rise to four significant nonbonding interactions. The minima are found 2.6 Å from the upper hydrogen atom and 2.5 Å from the nitrogen atom, with an average depth (−51.9 kcal/mol) larger than that corresponding to the YZ_1 plane.



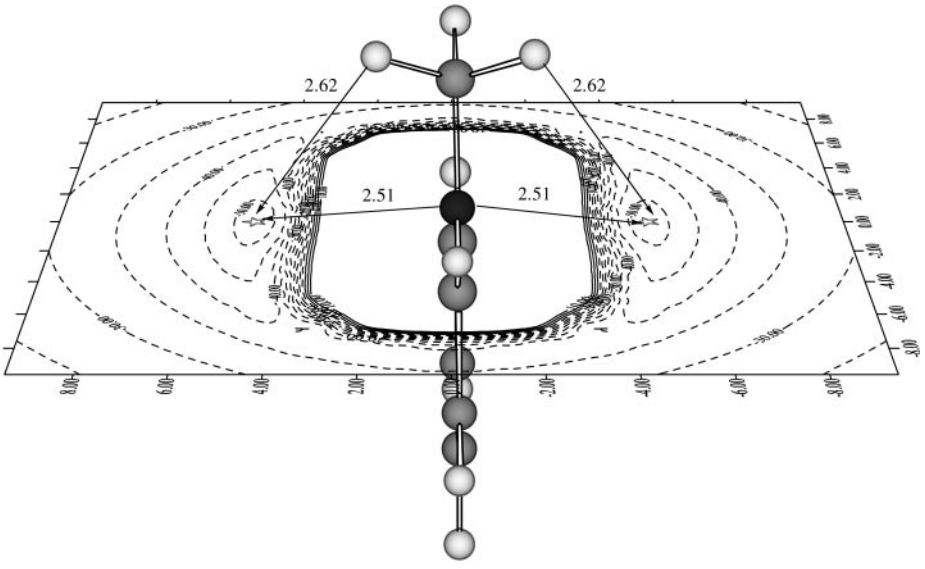
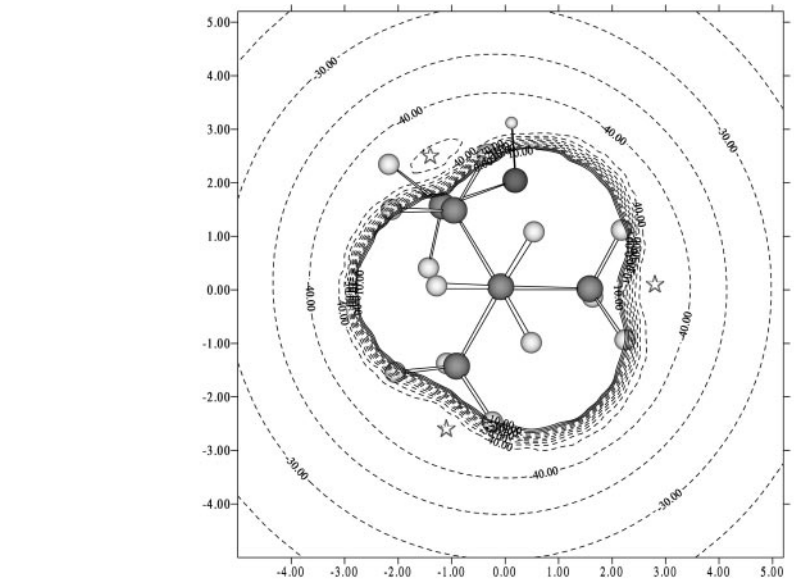


Fig. 13. *Upper* and *perspective view* of MIP (½ O^-) energy maps for cation **2c**, at an *x*-coordinate value of −0.2 Å. *Isocontour lines* are shown every 5 kcal/mol. The axes of the Cartesian coordinates are in atomic units. *Distances* between minima, represented by *stars*, and hydrogen atoms are given in angstroms

5 Discussion

From the analysis of the results, the following interesting fact arises: for the tetraalkylammonium cations **2a**, **2b** and **2d**, six energy minima are found, distributed in two parallel planes. The plane-to-plane distance is 1.0 Å and the upper minima alternate in relation to the lower minima by 60°. The squaramido-based receptors studied in this work to recognize tetraalkylammonium cations were compared and a remarkable complementarity was found initially: six squaramide oxygen atoms are present in the receptors distributed in three upper oxygen atoms which define a plane and three lower oxygen atoms which define a second plane. In the free hosts, the distance between the two planes defined by upper and lower oxygen atoms is 2.6 Å, whereas in the complexes the distance is 1.8 Å, closer to the distance between the planes (YZ_1 and YZ_2) provided by MIP energy calculations, as evident in Scheme 3. The upper oxygen atoms alternate in relation to the lower oxygen atoms by approximately 27° in the complexes and by 18° in the free receptors. The spatial disposition of the squaramide oxygen atoms of the receptor changes in the process of complexation, at they attempt to attain an ideal conformation for recognizing the cations in a most effective way, as predicted by the MIP study. In fact, the ideal host conformation in the complexes is probably not achieved due to the structural characteristics of the tripodal receptors. Preliminary studies have been made on increasing the flexibility of the tripodal hosts in order to allow them to reach a more ideal conformation.

From the double-complementarity principle, in addition to the geometrical features, the so-called interactional complementarity [22] must be borne in mind for a high-affinity recognition process. A study of the electronic and nuclear distribution (electrostatic, hydrogen-bonding and van der Waals) maps of both guests and



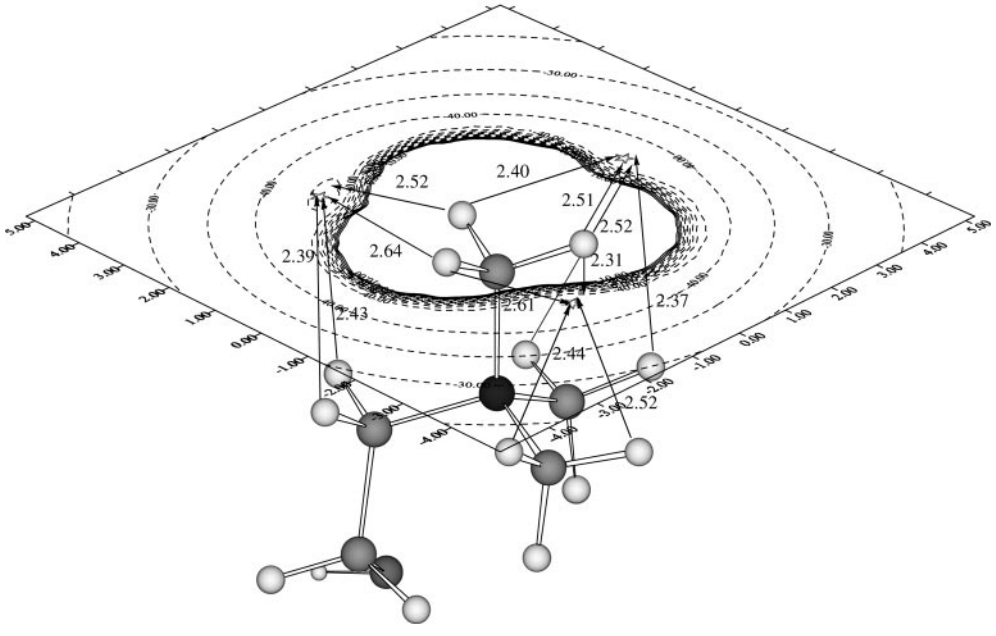
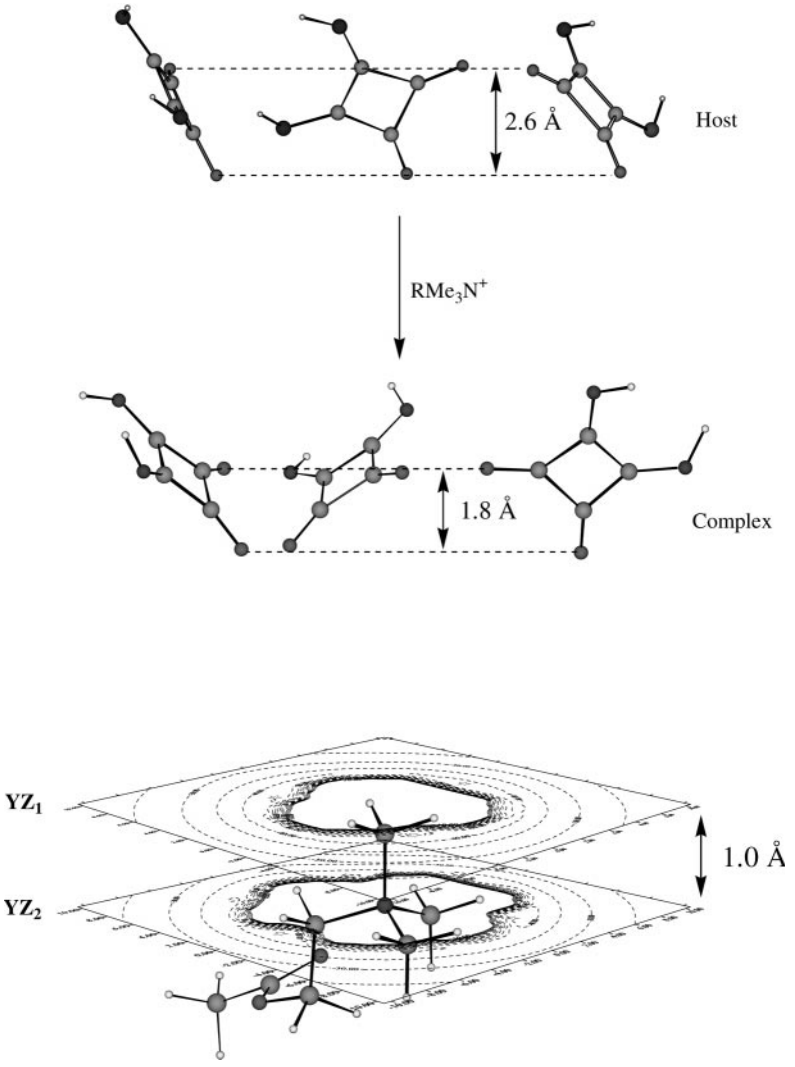


Fig. 14. *Upper* and *perspective view* of MIP (½ O^-) energy maps for cation **2d**, at an *x*-coordinate value of 2.0 Å. *Isocontour lines* are shown every 5 kcal/mol. The axes of the Cartesian coordinates are in atomic units. *Distances* between minima, represented by *stars*, and hydrogen atoms are given in angstroms

receptors must be carried out to evaluate the interactional complementarity factor between the ammonium cations and the squaramido-based receptors. In fact, this information can be supplied by the MIP maps. Thus, for an optimum recognition process, the position of the oxygen atoms of the squaramide units in the complex must coincide with the respective positions of the minima in the MIP (½ O^-) of the corresponding ammonium cations and vice versa, i.e., for the positive hydrogen atoms of the guests and the MIP (½ H^+) for the binding units of the receptors.

The analysis of the topography of the MIP (½ H^+) map of the squaramide unit (Fig. 3, PM3 map) shows the presence of two global minima (−12.22 kcal/mol) separated by 4.66 Å. At first sight, this does not appear to be the best pattern for the ammonium cations, where the upper hydrogen atoms are separated by approximately 2.53 Å from the lower hydrogen atoms (Fig. 4); however, two reasons can explain the fact that our tripodal receptors notably recognize the ammonium cations. First, the MIP (½ H^+) map shows a large region of significant negative potential (less than −8.0 kcal/mol), involving the two carbonyl groups, offering a reasonable explanation for the binding ability of squaramide. Second, the high complementarity between the MIP (½ O^-) maps of the cations (minima separated by 3.35 Å, Scheme 3, where minima are represented by stars) and the spatial position of the oxygen atoms of squaramide (3.32 Å).

Methylpyridinium shows different behavior. First, it has an association constant with host **1b** similar to that of benzyltrimethylammonium, even though it has fewer hydrogen atoms suitable for interacting with the host. This fact can be explained by the higher positive charge



Scheme 3

(0.17*e*) borne by the ortho hydrogen atoms (Fig. 4). Second, its complexation pattern is different compared to the tetraalkylammonium cations. Accordingly, a tweezer-type receptor could be more pertinent as deduced by the presence of two deep energy minima on both sides of the aromatic ring (2.51 Å from the nitrogen atom) derived from MIP maps (Fig. 13).

An easy way of determining the relative thermodynamic stabilities of complexes was introduced (ΔH_{conf}), taking into account that the recognition patterns of the complexes to be compared must be strictly the same (**3a–d**). If other interactions take place, the recognition pattern would not be the same and, consequently, the ΔH_{conf} values would not be useful for prediction purposes. Benzyltrimethylammonium complexes accomplish the proposed correlation between ΔH_{conf} and K_{ass} (Table 1). The same behavior is observed for acetylcholine complexes, except for complex **3e**, where the recognition pattern is not the same due to additional interactions. Host **1b** complexes also follow that correlation, apart from the complex with methylpyridinium (**3f**), which is not a tetraalkylammonium cation. All groups of complexes shown in Table 1 have an acceptable agreement between PM3-calculated ΔG_R values and the experimentally derived association constants.

6 Conclusion

The most relevant aspect of the present work is the applicability of the MIP to explain the capabilities of squaramido-based receptors to recognize tetraalkylammonium compounds. The spatial positions of the upper and lower squaramide oxygen atoms in the complexes are close to the 3D localization of the energy minima in MIP calculations. Nevertheless, because of the structural characteristics of the receptors, mainly determined by the spacer, an optimum fitting is not completely reached. Therefore, MIP calculations may be used to design and predict potential guests susceptible to being recognized by the host and vice versa. On this basis, the synthesis of more selective receptors to be used as molecular sensors or catalysts can be envisaged. In addition, the association constants of host–guest complexes have been qualitatively explained by means of PM3 semiempirical calculations.

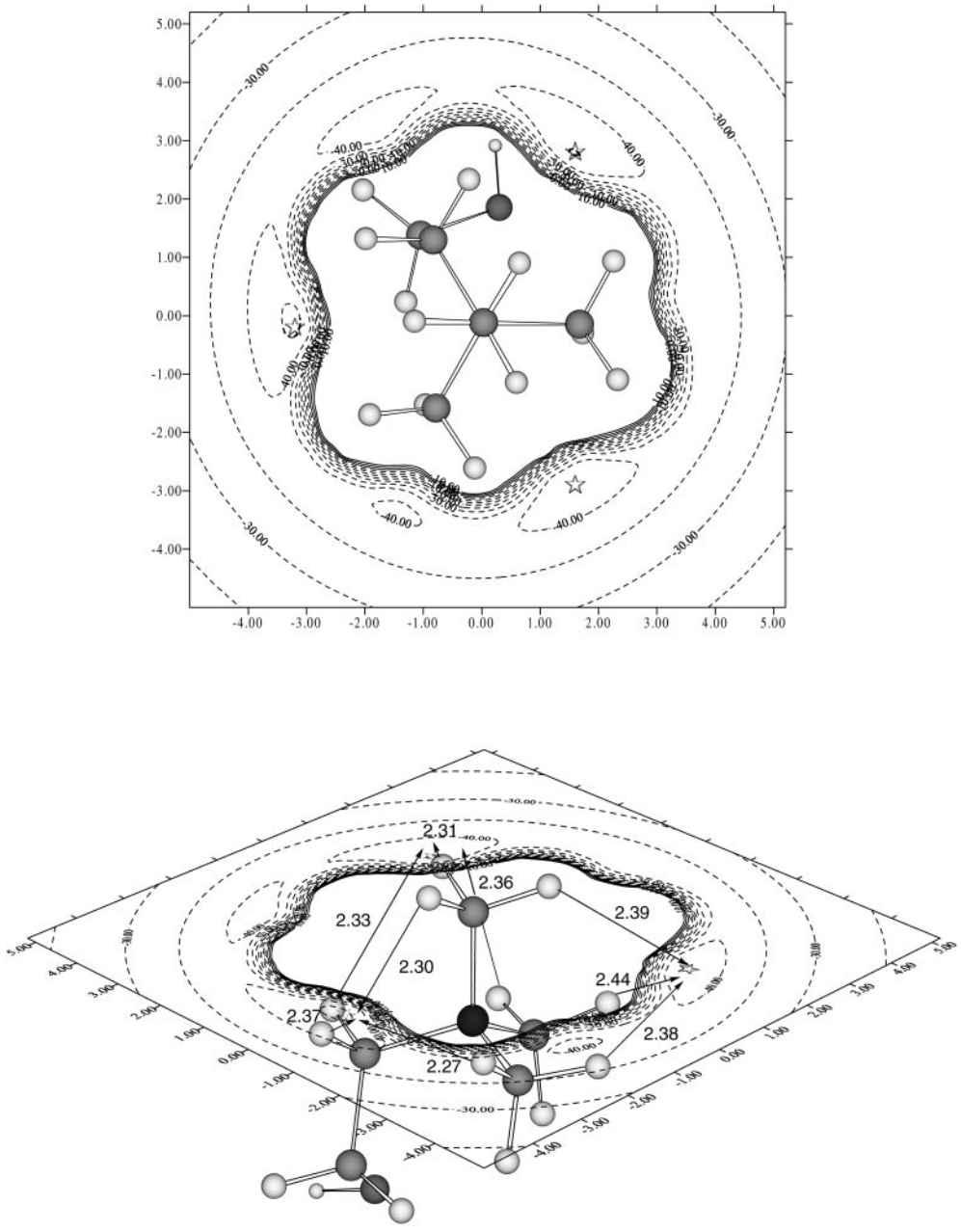


Fig. 15. *Upper* and *perspective view* of MIP (½ O^-) energy maps for cation **2d**, at an *x*-coordinate value of 1.2 Å. *Isocontour lines* are shown every 5 kcal/mol. The axes of the Cartesian coordinates are in atomic units. *Distances* between minima, represented by *stars*, and hydrogen atoms are given in angstrom

Acknowledgements. We are grateful to M. Orozco and J.F. Luque for making available their version of the MOPETE program and for helpful discussions and to Ghislain Des longchamps for valuable suggestions. Gratitude is expressed to the DGICYT (project PB96-0143 and PB95-0341) for financial support. We also thank the Centre de Supercomputació de Catalunya for computational facilities. A.F. wishes to thank the MEC for a postdoctoral grant. D.Q. wishes to thank the Universitat de les Illes Balears for a predoctoral fellowship.

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