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A quantum mechanical study of the ionic interactions in model compounds of polyelectrolyte–surfactant complexes derived from polypeptides

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Abstract

A quantum mechanical study on the interactions of alkyltrimethylammonium–acetate (with alkyl = methyl, ethyl, propyl and butyl), methylammonium–methyl sulfate and methylammonium–acetate ion pairs in the gas phase and in solution is presented. These are model complexes for the ionic interactions of self-assembled polyelectrolyte–surfactant complexes derived from polypeptides. Two different solvents (water and chloroform) were used to analyze the effects of varying the dielectric constant of the surrounding media on the ionic interactions. The stability of the methylammonium–methyl sulfate and methylammonium–acetate ion pairs was compared to that of the corresponding non-ionic hydrogen-bonded forms. © 2000 Published by Elsevier Science B.V. All rights reserved.

1. Introduction

Salt bridges are among the more thoroughly investigated interactions in biological chemistry. Such interactions are due to the important and often quite specific functions played by ion pairs [1]. They act as binding sites in enzymes [2], mediate molecular recognition [3] and modulate the allosteric behavior of proteins [4]. Their role in determining the stability of secondary-structural elements has been also considered [5]. Indeed, several studies on model peptides

have shown that the character and position of salt-bridging groups affect helix formation [6]. Salt bridges are also involved in connecting different subunits of proteins [7] or in the control of the equilibrium between various conformational states [8]. As a consequence a number of theoretical studies about the energetic of salt bridges [9–12] and the contribution of this interaction to protein stability has been reported for the last years.

For the last decade ion-pair interactions have also attracted considerable interest in polymer science. They have been used to design materials consisting of polyelectrolytes and oppositely charged surfactants [13–19]. Such complexes assemble in aqueous

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solutions through the electrostatic interactions between polyion chain units and oppositely charged surfactant ions, being stabilized by hydrophobic interactions of the surfactant alkyl side chains in water. Stoichiometric polyelectrolyte–surfactant complexes are insoluble in water but can be dissolved in some common organic solvents of low polarity without dissociation [13,17]. Complexation of polymers with oppositely charged low-molecular-weight compounds may result in stiffening leading to the formation of main chain liquid crystals in organic solvents [20].

Most work in this area has involved biopolymers, which can form a variety of highly ordered secondary structures, offering polymer–surfactant complexes with useful properties. Complexes formed by the synthetic sodium poly(α ,L-glutamate) and the oppositely charged alkyltrimethylammonium surfactants [13,18] have been reported. In these complexes the polymer chains adopt an α -helix conformation in the solid state. Conversely, the alkyl chains of surfactant are extended but positionally disordered if contains 16 or less carbon atoms in the alkyl groups while those with 18 carbon atoms crystallize in a hexagonal lattice. This behavior is similar to that observed in poly(γ -alkyl- α ,L-glutamate)s, which have been widely investigated as liquid crystals [21]. On the other hand, complexes formed by poly(L-lysine) hydrobromide and alkyl sulfate anions have been also reported [19]. Polypeptide chains in the solid complex can adopt either β -helix or β -sheet conformations whereas the surfactants present an extended conformation forming a layer with tail-to-tail arrangements.

Here we present a theoretical study on the stability of the ionic interactions involved in self-assembled complexes derived from polypeptides. A number of small model complexes have been used to mimic the interactions between charged polypeptides and the oppositely charged surfactants. Binding free energies were computed in the gas phase using high-level *ab initio* calculations. Calculations in solution were performed using a self-consistent reaction-field (SCRF) method allowing to get insight into the effect of the bulk solvent on the ionic interactions. Two different solvents (water and chloroform) were used to analyze the effect of varying the dielectric constant of the surrounding media.

2. Methods

2.1. Gas-phase calculations

Full geometry optimizations were performed at the HF, MP2 and DFT levels of theory using the 6-31 + G(d) [22] basis set. All the DFT calculations were carried out using the Becke's three-parameter hybrid functional with gradient corrections provided by the LYP functional (B3LYP) [23,24]. Force constant analyses were performed to verify the minimum energy state of the optimized geometries. Single-point calculations were performed using the 6-31 + G(d) and 6-311 + G(d,p) [22] basis sets. The basis set superposition error (BSSE) was corrected following Boys and Bernardi [25]. The binding energies were corrected by the addition of the thermal and entropic (298 K) effects using the standard procedures in GAUSSIAN-94 [26] program in order to obtain the Gibbs free energy. Thus, to conduct the thermodynamical analysis we confined ourselves to the harmonic approximation.

2.2. Solvation calculations

SCRF calculations were performed to incorporate the solvent effects on the stability of the complexes investigated. These methods have been successfully used to investigate related topics [27]. In order to examine the influence of the permittivity of the medium on the stability of the complexes investigated, calculations were performed in water and chloroform. The semiempirical AM1 version [28,29] of the polarizable continuum model formulated by Miertus, Scrocco and Tomasi [30] (MST) was used to determine the electrostatic component of the free energy of solvation (ΔG_{sol}). The cavitation contribution was introduced following Pierotti's scaled particle theory [28,29], and the van der Waals component was calculated by using an optimized linear relationship with the atomic surface area. The solute cavity was built up using the standard procedure [29], but it was reduced by a factor of 0.92 for calculations involving charged species [28]. In these calculations *ab initio* gas-phase geometries were used. It should be emphasized that because of the semiempirical formulation of the method, the root mean square deviation between the experimental and MST/AM1

ΔG_{sol} values is only 1.0 and 0.4 kcal/mol for aqueous and chloroform solutions, respectively [28,29]. Calculations were performed with an adapted version of MOPAC93 Revision 2 program [31].

3. Results and discussion

3.1. Ion-pair complexes in the gas phase

The complexes constituted by the acetate anion and the alkyltrimethylammonium cation (complexes **I**) with alkyl = methyl (**Ia**), ethyl (**Ib**), propyl (**Ic**) and butyl (**Id**) have been calculated to model the interactions that appear in the self-assembled complexes formed by poly(α ,L-glutamate) and alkyltrimethylammonium ions.

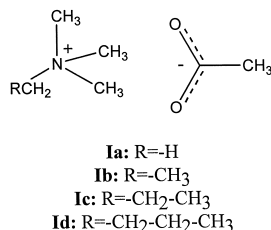


Fig. 1 shows the most relevant intermolecular parameters for the complexes **Ia**, **Ib**, **Ic** and **Id** optimized at the HF/6-31 + G(d) level. Intermolecular distances obtained for these complexes are very similar, the largest difference being 0.040 Å. However, a detailed inspection to Fig. 1 reveals that intermolecular distances present a systematic variation. Thus, they increase with the size of the alkyl group in the alkyltrimethylammonium cation suggesting a reduction in the strength of the binding. Table 1 reports the gas-phase binding energies (ΔE), which were corrected for BSSE, obtained for the four complexes at both HF/6-31 + G(d) and MP2/6-31 + G(d) levels of theory. The results provided by the two computational levels are in excellent agreement, the differences between them being ~ 2 –3 kcal/mol, i.e. lower than 3%.

Table 1 shows the gas-phase binding enthalpies (ΔH^{298}), which were obtained by adding the differ-

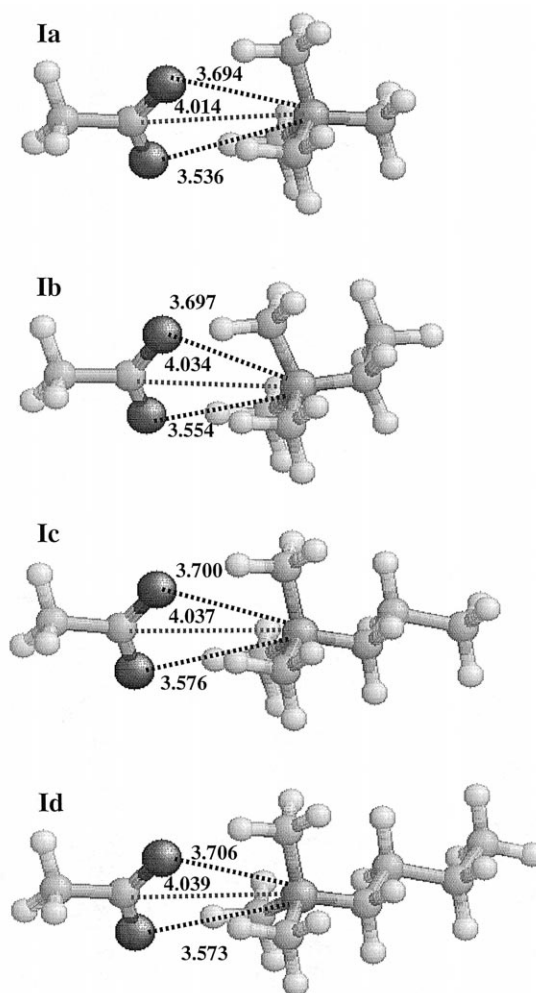


Fig. 1. Optimized geometries for the tetramethylammonium–acetate (**Ia**), ethyltrimethylammonium–acetate (**Ib**), propyltrimethylammonium–acetate (**Ic**) and butyltrimethylammonium–acetate (**Id**) ion pairs. Selected intermolecular parameters are displayed.

ences between the values of zero-point energy and thermal corrections of the complex and the ions to the ΔE computed at the MP2/6-31 + G(d) level, and the entropic corrections ($-T\Delta S$) for complexes **I**. As it can be seen, the zero – point energies and thermal corrections upon binding lead to a destabilization of ~ 10.7 – 11.2 kcal/mol. On the other hand, the unfavorable contribution arising from the entropic term ranges from 9.0 to 9.7 kcal/mol. As a result, the binding free energy ($\Delta G^{298} = \Delta H^{298} -$

Table 1

Energy^a (E ; in a.u.), number of imaginary frequencies (ν_i), binding energy^{a,b} (ΔE ; in kcal/mol), binding enthalpy^{a,b,c} (ΔH^{298} ; in kcal/mol), entropic contribution ($-T\Delta S$; in kcal/mol) and binding free energy (ΔG^{298} ; in kcal/mol) calculated in the gas phase for the investigated ion pairs

Complex	E HF/6-31 + G(d)	ν_i	E MP2/6-31 + G(d)	ΔE HF/6-31 + G(d)	ΔE^a MP2/6-31 + G(d)	ΔH^{298}	$-T\Delta S$	ΔG^{298}
Ia	−440.086779	0	−441.419566	−95.6	−97.4	−86.7	9.0	−77.7
Ib	−479.120325	0	−480.587564	−94.2	−96.9	−86.2	9.1	−77.1
Ic	−518.155215	0	−519.755127	−93.5	−95.4	−84.7	9.1	−75.6
Id	−557.190396	0	−558.922629	−93.1	−95.0	−83.8	9.7	−74.1
II	−757.463900	0	−758.597757	−114.8	−116.5	−105.4	10.0	−95.4
III^d	−323.022624	1	−323.952754	−127.6	−128.2	−114.2	14.0	−100.2

^a Geometries calculated at the HF/6-31 + G(d) level.

^b Thermodynamical contributions at 298 K calculated at the HF/6-31 + G(d) level.

^c The differences between the values of zero-point energy and thermal corrections of the complex and the separated ions were added to the ΔE computed at the MP2/6-31 + G(d) level.

^d The imaginary frequency obtained in complex **III** (see text) was not considered for the calculation of thermodynamic contributions.

$T\Delta S$) between alkyltrimethylammonium and acetate ions varies from −77.7 to −74.1 kcal/mol.

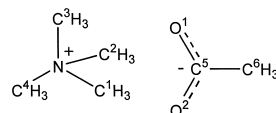
An interesting feature can be extracted from the results obtained for these four complexes. This is that the gas-phase binding free energy of the complexes varies as follows: **Ia** > **Ib** > **Ic** > **Id**. Thus, the binding free energy drops 3.6 kcal/mol when the alkyl group changes from methyl to butyl. The reduction in the binding free energy is consistent with the variation observed for the intermolecular parameters confirming that the strength of this ionic interac-

tion decreases when the size of the alkyl group in the alkyltrimethylammonium cation increases. This feature clearly illustrates the electron leasing associated to the alkyl chains in classical organic chemistry. It is worth noting that the difference in the binding free energies for **Ic** and **Id** is 1.5 kcal/mol, suggesting that the ionic interaction for complexes with an alkyl group larger than butyl should provide a lower stabilization than that obtained for **Id**.

The effects of both the computational procedure and the basis set in the ionic interactions subject of

Table 2

Selected intermolecular parameters^a determined from geometry optimizations of complex **Ia** at different levels of theory



Parameter	HF/6-31 + G(d)	MP2/6-31 + G(d)	B3LYP/6-31 + G(d)
$d(\text{N} \cdots \text{C}5)$	4.014	3.958	3.996
$d(\text{N} \cdots \text{O}1)$	3.536	3.466	3.434
$d(\text{N} \cdots \text{O}2)$	4.014	3.643	3.755
$d(\text{C}1 \cdots \text{C}5)$	3.681	3.590	3.777
$d(\text{C}2 \cdots \text{C}5)$	3.781	3.722	3.714
$d(\text{C}3 \cdots \text{C}5)$	3.870	3.863	3.776
$\angle \text{N} \cdots \text{C}5\text{--C}6$	175.8	175.3	171.9
$\angle \text{C}4\text{--N} \cdots \text{C}5\text{--C}6$	110.4	99.8	177.1

^a Distances and angles in ångströms and degrees, respectively.

study have been determined for **Ia**. Table 2 summarizes selected intermolecular parameters for **Ia** of the geometries optimized at the HF, MP2 and B3LYP levels of theory. All these structures were optimized using the 6-31 + G(d) basis set. The intermolecular distances determined from both HF and B3LYP calculations are in good agreement with those predicted at the MP2 level. Thus, the values obtained at the latter level of theory are the smallest ones but the differences with respect to the values predicted at the HF and B3LYP levels can be considered acceptable. However, inspection to the dihedral angle defined by the atoms $\angle C4-N \cdots C5-C6$ (see Table 2) reveals that the arrangement of the acetate anion with respect to the tetramethylammonium cation provided by the HF and MP2 methods differs from that predicted at the B3LYP level. Thus, HF and MP2 geometry optimizations lead to a geometry where the oxygen atoms of the acetate alternate with respect to the methyl groups of the tetramethylammonium (**case A**). Conversely, the B3LYP minimum presents an eclipsed arrangement between one oxygen atom of the acetate and one methyl group of the tetramethylammonium (**case B**) suggesting a failure of this functional. These two arrangements, i.e. **cases A** and **B**, are illustrated in the following scheme where the

hydrogen atoms have been neglected to make clearer the representation.

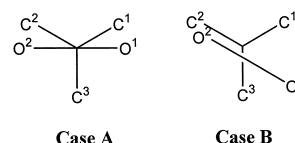


Table 3 shows the binding energies computed at the HF/6-31 + G(d), HF/6-311 + G(d,p), MP2/6-31 + G(d), MP2/6-311 + G(d,p), B3LYP/6-31 + G(d) and B3LYP/6-311 + G(d,p) levels using the geometries of **Ia** optimized at the HF/6-31 + G(d), MP2/6-31 + G(d) and B3LYP/6-31 + G(d) levels. The calculated binding energy is not dependent on the basis set. Thus, the largest difference between the 6-31 + G(d) and 6-311 + G(d,p) results is 0.1, 0.5 and 0.6 kcal/mol at the HF, MP2 and B3LYP levels of theory. On the other hand, a larger dependence may be traced with the level of theory. Thus, comparison of the HF/6-311 + G(d,p) and B3LYP/6-311 + G(d,p) binding energies with the MP2/6-311 + G(d,p) ones shows that the largest difference is 2.5 and 0.8 kcal/mol, respectively. The overall of

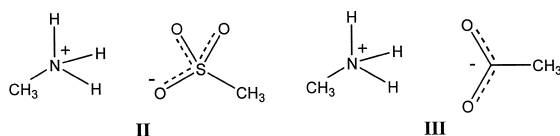
Table 3

Energies (E ; in a.u.) and binding energies (ΔE ; in kcal/mol) calculated in the gas phase for the complex **Ia** at different levels of theory^a

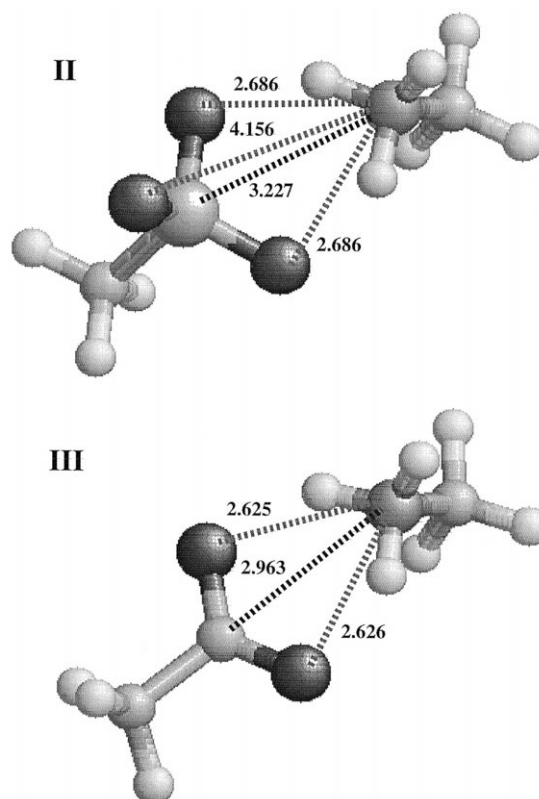
Level of theory	E	ΔE
HF/6-31 + G(d)/HF/6-31 + G(d)	−440.086779	−95.6
HF/6-311 + G(d,p)/HF/6-31 + G(d)	−440.201746	−95.7
MP2/6-31 + G(d)/HF/6-31 + G(d)	−441.419566	−97.4
MP2/6-311 + G(d,p)/HF/6-31 + G(d)	−441.700611	−97.8
B3LYP/6-31 + G(d)/HF/6-31 + G(d)	−442.858179	−97.5
B3LYP/6-311 + G(d,p)/HF/6-31 + G(d)	−442.978946	−98.0
HF/6-31 + G(d)/MP2/6-31 + G(d)	−440.081461	−96.2
HF/6-311 + G(d,p)/MP2/6-31 + G(d)	−440.195900	−96.2
MP2/6-31 + G(d)/MP2/6-31 + G(d)	−441.424500	−98.3
MP2/6-311 + G(d,p)/MP2/6-31 + G(d)	−441.704088	−98.7
B3LYP/6-31 + G(d)/MP2/6-31 + G(d)	−442.861898	−98.6
B3LYP/6-311 + G(d,p)/MP2/6-31 + G(d)	−442.981152	−99.2
HF/6-31 + G(d)/B3LYP/6-31 + G(d)	−440.082027	−95.9
HF/6-311 + G(d,p)/B3LYP/6-31 + G(d)	−440.196591	−96.0
MP2/6-31 + G(d)/B3LYP/6-31 + G(d)	−441.423852	−98.0
MP2/6-311 + G(d,p)/B3LYP/6-31 + G(d)	−441.703817	−98.5
B3LYP/6-31 + G(d)/B3LYP/6-31 + G(d)	−442.862843	−98.7
B3LYP/6-311 + G(d,p)/B3LYP/6-31 + G(d)	−442.982149	−99.3

^a Level of energy calculation//level of geometry optimization.

The interaction between poly(L-lysine) cation and the oppositely charged surfactant alkyl sulfate has been modeled by a complex formed by methylammonium and methyl sulfate ions (complex **II**). The ion-pair constituted by methylammonium cation and acetate anion (complex **III**) has been also considered for comparison.



The binding energies of complexes **II** and **III** estimated at the MP2/6-31 + G(d) levels are -116.5 and -128.2 kcal/mol, respectively. On the other hand, the binding free energies are -95.4 and -100.2 kcal/mol, respectively. It should be emphasized that both the binding enthalpy and binding free energy values listed in Table 1 for **III** are slightly



overestimated due to the apparition of two imaginary frequencies. The interaction of methylammonium with acetate is preferred by ~ 4.8 kcal/mol with respect to the interaction with the methyl sulfate. Moreover, the binding in complexes with alkyltrimethylammonium is $\sim 18\text{--}26$ kcal/mol less stabilized than in complexes with methylammonium. This feature is probably due to the larger concentration of the positive charge in the latter cation as revealed the analysis of the atomic charges.

Another interesting point concerning ion-pair complexes is the difference in stability between ion-pair and non-ionic hydrogen-bonded forms. In order to get insight into this point the complexes **IV** and **V**,

which are the hydrogen-bonded forms of **II** and **III**, respectively, were investigated.

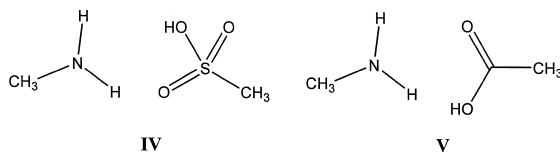


Fig. 3 shows the geometries optimized at the HF/6-31 + G(d) level, where selected geometrical data are included. Table 4 lists the free energy difference between the ion-pair and hydrogen-bonded complexes. It is worth noting that the hydrogen-bonded forms are lower in energy than the corresponding ion-pair complexes. Moreover, **V** is significantly more stabilized with respect to **III** than **IV** with respect to **II**.

These results obtained for methylammonium–acetate and methylamine–acetic acid complexes are in satisfactory agreement with the values reported in the literature for related systems, even although our free energy difference is slightly overestimated due to the constraints imposed in the geometry optimiza-

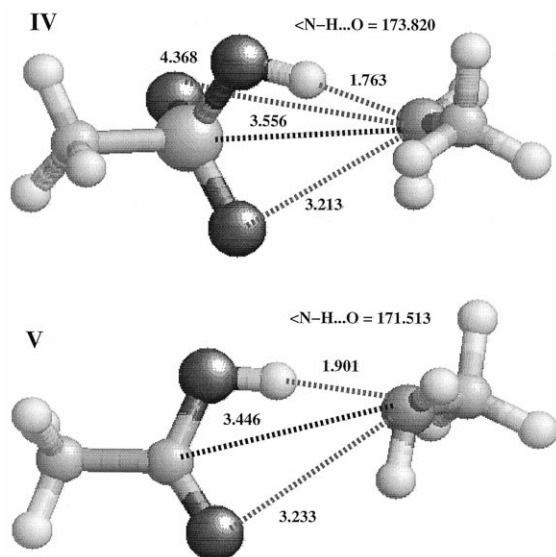


Fig. 3. Optimized geometries for the methylamine methylsulfuric acid (**IV**) and methylamine acetic acid (**V**) hydrogen-bonded complexes. Selected intermolecular parameters are displayed.

Table 4

Free energy differences (in kcal/mol) between the ion-pair and hydrogen-bonded complexes in the gas phase, aqueous solution and chloroform solution

Environment	II–IV	III–V
Gas phase ^a	1.0	17.6
Aqueous solution ^b	–21.8	–2.2
Chloroform solution ^b	–0.9	11.1

^a The free energy difference in the gas phase was computed using the energies obtained at the MP2/6-31 + G(d) level and the thermodynamical corrections estimated at the HF/6-31 + G(d) level.

^b The free energy difference in solution is obtained by adding the binding free energy difference in the gas phase to the difference between the free energies of solvation of the ion-pair and the non-ionic hydrogen-bonded complexes.

tion of **III**. Thus, the neutral formic acid–ammonia [9] and formic acid–trimethylamine [10] non-ionic complexes were estimated to be 11.3 and 7.0 kcal/mol favored with respect to the formate–ammonium and formate–trimethylammonium ion pairs, respectively, using very high levels of theory (up to QCISD(T)/6-311 + G(d, p) and MP4SDQ/6-311 + G(3df, 2p), respectively). On the other hand, the methylguanidinium–acetate ion pair was predicted to be 1.7–8.3 kcal/mol less stable than the corresponding hydrogen-bonded complex at the MP2/6-31 + G(d) level [13].

3.3. Ion-pair complexes in aqueous and chloroform solutions

The free energies of solvation and the binding free energies in aqueous and chloroform solution for the ion pairs investigated are reported in Table 5. As expected, in all cases complexes are less solvated than isolated ions. This effect is mainly due to the partial annihilation of the net charges upon complexation. The formation of ion-pair complexes is strongly destabilized by the solvent in all cases, the destabilization being larger in water than in chloroform. Thus, the solvation of the isolated ions in bulk water is very favorable due to the strong electrostatic interactions between the solute and the solvent. The strength of these electrostatic interactions decreases with the dielectric constant of the solvent.

Table 5

Free energies of solvation (ΔG_{sol} ; in kcal/mol) and binding free energies^a (ΔG_{bind} ; in kcal/mol) for the complexes investigated in aqueous and chloroform solutions

Complex	Aqueous solution		Chloroform solution	
	ΔG_{sol}	ΔG_{bind}	ΔG_{sol}	ΔG_{bind}
Ia	−31.2	26.0	−19.5	−3.4
Ib	−31.5	23.7	−19.9	−3.9
Ic	−31.6	23.1	−20.3	−3.4
Id	−32.0	25.8	−21.1	−2.3
II	−38.0	33.3	−19.2	−9.4
III	−25.5	41.1	−14.1	−6.7

^a The binding free energy in solution was obtained by adding the binding free energy in the gas phase to the difference between the free energy of solvation of the complex and the separated ions.

The results indicate that the environment plays a crucial role to the binding free energy of ion-pair complexes. The complexation process is destabilized in aqueous solution for all the ion pairs investigated. Thus, the large energy penalty arising upon desolvation of the interacting ions is not counterbalanced by the gas-phase binding free energy. The binding free energy in aqueous solution of **II** and **III** is ~ 7 – 18 kcal/mol less favored than those of complexes **I**. Thus, the free energies of solvation of the ions are more favored for the former complexes since there are more polar groups accessible to the solvent. The destabilizing effect of chloroform, although less important than that of water, is still significant. Thus, the change in the free energy of solvation between the complex and the separated ions amounts to ~ 72 – 74 , 86 and 93 kcal/mol for **I**, **II** and **III**, respectively. As a consequence, the binding of the ion-pair species in chloroform solution is stabilized by ~ 2 – 9 kcal/mol due to the favorable gas-phase contribution.

3.4. Relative stability between ion-pair and hydrogen-bonded complexes in aqueous and chloroform solutions

The free energy difference in aqueous and chloroform solutions between the ion-pair and non-ionic hydrogen-bonded complexes are displayed in Table 4. As it can be seen, the environment makes a decisive contribution to the relative stability of ionic

and hydrogen-bonded complexes. In the gas phase, the complexation process is greatly favored, and the hydrogen-bonded complex is more stable than the ion pair. However, water destabilizes the hydrogen-bonded complexes with respect to the ion pairs. However, as was discussed before the binding in aqueous solution is strongly unfavored (see Table 5). Accordingly, it can be concluded that water does not stabilize neither the ionic nor hydrogen-bonded complexes owing to the large energy penalty arising upon desolvation of the interacting monomers. The situation, nevertheless, is quite different in chloroform, where the binding of ionic species occurs. Moreover, the preference of the neutral complex over the ion pair is largely reduced or even reversed. Thus, the ion pair **II** is 0.9 kcal/mol favored with respect to **IV** whereas the neutral form **V** is ~ 11.1 kcal/mol more stable than **III**, the latter free energy difference being 5.5 kcal/mol lower than in the gas phase.

4. Summary

Gas-phase *ab initio* calculations show that the binding free energy of complexes formed by acetate anion and alkyltrimethylammonium cation ranges from -74.1 to -77.7 kcal/mol, depending on the size of the alkyl group. On the other hand, the binding free energy in the gas phase of methylammonium–methyl sulfate and methylammonium–acetate ion pairs is -95.4 and -100.2 kcal/mol, respectively. Accordingly, the strength of this stabilizing interaction decreases when the number and size of the alkyl groups increase. Calculations in aqueous solution reveal that the complexation process is unfavored for all the ion pairs investigated due to the large energy cost associated to the desolvation of the separated ions. This energy penalty is lower in chloroform, being partially compensated by the strong interaction between the ions. Accordingly, the assembly of the oppositely charged ions is favored in chloroform solution by ~ 2 – 9 kcal/mol.

The free energy differences between the ion-pair and the non-ionic hydrogen-bonded forms indicate that the latter are favored in the gas phase whereas the former are most stable in aqueous solution. Thus, a comparison of the results obtained in aqueous and

chloroform solutions shows how the stability of the ion pairs increases with the dielectric constant of the solvent. However, the binding process only occurs in solvents with a relative low dielectric constant due to the large energy penalty arising upon desolvation of the separated ions in polar solvents like water.

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