

An *ab Initio* Study of the Trimethylamine–Formic Acid and the Trimethylammonium Ion–Formate Anion Complexes, Their Monohydrates, and Continuum Solvation

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Abstract: High-level *ab initio* calculations carried out up to an effective MP4SDQ/6-311+G(3df,2p)//HF/6-31+G* level predict that the trimethylamine–formic acid complex *in vacuo* is favored by 7.0 kcal/mol (ΔG_{298}) relative to the trimethylammonium–formate complex. Interaction with a single water molecule is, according to calculated results, not sufficient to make the ion-pair complex the predominant one, the lowest energy monohydrated neutral complex being favored by 4.7 kcal/mol (ΔG_{298}) in comparison to the lowest energy monohydrated ion-pair. Calculations on the effect of a dielectric continuum on the binary and monohydrated ternary complexes using the Self-Consistent Isodensity Polarized Continuum Model (SCI-PCM) indicate that a strong dielectric continuum with a dielectric constant larger than ca. 9 is required to make the binary ion-pair complex predominant. However, only a relatively weak dielectric continuum with a dielectric constant in the range of 4–6 is required in order to favor the monohydrated ion-pair complex.

Introduction

Interaction between an ammonium ion and a carboxylate anion with the formation of an ion-pair complex is a common and important type of interaction in molecular recognition processes. A large number of examples of such ion-pairs are found in crystal structures of amino acids or of amines co-crystallized with carboxylic acids. In proteins, ammonium ions and carboxylate anions form so-called salt-bridges¹ and the recognition and binding of an amine ligand to an enzyme or receptor often involves or is modeled to involve an ammonium–carboxylate ion-pair. For instance, site-directed mutagenesis studies strongly indicate that aminergic neurotransmitters bind to a highly conserved Asp residue in the putative third trans-membrane helix of their receptors.^{2,3} A number of models of aminergic neurotransmitter receptors have been developed.^{4–8} In all these models an alkylammonium–carboxylate ion-pair interaction is a central feature.

Recently reported high-level *ab initio* calculations on the formic acid–ammonia system *in vacuo* (QCISD(T)/6-311+G**//MP2/6-31+G** level with corrections for higher polarization (3df,2p) and inclusion of zero-point energies) show that the neutral (non-ionized) formic acid–ammonia complex is favored by as much as 11.3 kcal/mol.⁹ There is no local energy minimum on the potential energy surface corresponding to an

ion-pair. The lowest-energy ion-pair was found to be a bifurcated transition-state structure with C_{2v} symmetry. Medium-level *ab initio* calculations (HF/6-31G*) have been performed for methylamine–acetic acid¹⁰ and methylamine–formic acid¹¹ and the corresponding ion-pairs. In these calculations, the neutral complexes were found to be lower in energy than the ion-pair complexes by 18.4 and 21.2 kcal/mol, respectively. These *ab initio* studies indicate that *in vacuo* the ion-pair is strongly disfavored in comparison to the neutral complex. Thus, in order for the ion-pair to be favored as implied in the molecular recognition cases discussed above, the environment must be able to provide a significant preferential stabilization of this complex.

A related case is the problem of the stabilization of the zwitterionic structure of amino acids. For instance, in the glycine case there is no true minimum on the gas phase potential energy surface corresponding to a zwitterion.¹² On the basis of high-level *ab initio* studies on the stabilization of the zwitterion by water molecules, Ding and Krogh-Jespersen¹³ have concluded that a single water molecule bridging the ammonium and carboxylate units is sufficient to make the zwitterion a local minimum on the gas phase potential energy surface. However, this monohydrated glycine zwitterion is calculated to be thermodynamically unstable relative to its non-ionized form plus a water molecule by 6.4 kcal/mol (HF/6-31++G**). In contrast to these results, Jensen and Gordon have found that stabilization by two water molecules is required in order to make the glycine zwitterion a local energy minimum.¹⁴ In this study the zwitterion is less stable than the neutral molecule by 11.6 kcal/mol (MP2/DZP++//RHF/DZP).

Ab initio calculations on the neutral *vs* the ion-pair complex of tertiary alkylamines have not previously been reported. Tertiary alkylamines are commonly found in bioactive substances. There are, for instance, a large number of examples

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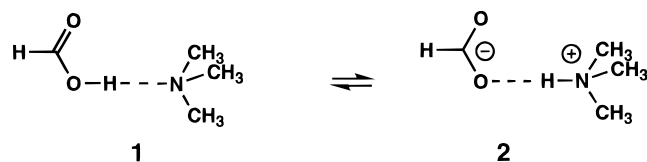
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of tertiary amines being highly potent agonists as well as antagonists for aminergic neurotransmitter receptors such as dopamine and serotonin receptors.¹⁵ The question whether such ligands bind to their receptors in an ionized or non-ionized form has been intensely discussed.¹⁶

Tertiary alkylamines are more basic than ammonia and are the most basic of the alkylamines *in vacuo*.¹⁷ Thus, an ion-pair complex involving the trimethylammonium ion should be significantly more favored with respect to the neutral complex than complexes involving ammonia and it should be the most favored ion-pair complex of an alkylamine and a carboxylic acid *in vacuo*. Thus, by studying the trimethylamine–carboxylic acid case the lower limit of the energy difference between an alkylammonium–carboxylate ion-pair complex and the neutral alkylamine–carboxylic acid complex *in vacuo* may be established.

In order to get insight into the conditions which favor an ion-pair complex between a trialkylammonium ion and carboxylate anion, we have in the present study performed high-level *ab initio* calculations, including correlation energies for the trimethylamine–formic acid (**1**) and the trimethylammonium ion–formate anion (**2**) complexes and their interactions with a single water molecule. In addition, the interactions between complexes **1** and **2** and their monohydrates with a dielectric continuum have been studied.



Methods

The *ab initio* calculations were carried out using the GAUSSIAN 92¹⁸ or GAUSSIAN 94¹⁹ system of computer programs running on a SGI Indigo2 workstation, PowerIndigo workstation or a Cray92A computer, or the SPARTAN program²⁰ running on a SGI Indigo2 workstation.

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All geometries of binary and ternary complexes were optimized at the HF/6-31+G* level and stationary points were characterized as minima, transition states, etc. using harmonic normal mode analysis. A few geometry optimizations were carried out on the binary complexes using HF/6-31+G** and MP2/6-31+G** calculations. However, in contrast to the results of the geometry optimizations at the HF/6-31+G* level, at these higher levels the ion-pair complex is not a local energy minimum on the potential energy surface. In all cases, geometry optimization results in hydrogen transfer to give the neutral complex. Thus, in order to be able to use the same computational level for all calculations, to avoid using computational constraints which may distort the results and to make it possible to perform a vibrational analysis on the ion-pair complex, we have used the HF/6-31+G* level for all geometry optimizations. Single point calculations were then performed at the HF/6-311+G** and HF/6-311+G(3df,2p) levels and corrections for correlation effects were carried out up to MP4SDQ using the 6-31+G* and 6-311+G* basis sets and up to MP2 using the 6-311+G(3df,2p) basis set. Correlation effects at the MP3/6-311+G(3df,2p) and MP4SDQ/6-311+G(3df,2p) levels were estimated by adding the calculated differences (MP3/6-311+G** – MP2/6-311+G**) and (MP4SDQ/6-311+G** – MP2/6-311+G**), respectively, to the calculated MP2/6-311+G(3df,2p) energies. These calculations are indicated as “MP3/6-311+G(3df,2p)” and “MP4SDQ/6-311+G(3df,2p)”. Corrections for zero-point energy, enthalpy, entropy, and free energy were calculated at the HF/6-31+G* level using frequencies scaled by 0.8929.

In addition to calculations of solvation by a single water molecule, solvation calculations have also been performed by using two dielectric continuum models, AM1-SM2 developed by Cramer and Truhlar,²¹ as implemented in the SPARTAN program, and SCI-PCM (Self-Consistent Isodensity Polarized Continuum Model) implemented in GAUSSIAN 94.²² In these calculations gas phase HF/6-31+G* geometries have been used. SCI-PCM calculations have been performed at the HF/6-31+G* level employing the default isodensity value of 0.0004 au for the cavity surface.

Results and Discussion

Neutral vs Ion-Pair Complex *in vacuo*. At levels below HF/6-31+G* (e.g., HF/3-21+G* or HF/6-31G*) there is only a single minimum on the potential energy surface corresponding to the neutral complex **1** but, in contrast to the ammonia–formic acid case,⁹ the ion-pair **2** is a local energy minimum at the HF/6-31+G* level. However, if polarization functions on hydrogens are included in the energy optimizations, for instance by using the HF/6-31+G** basis set, the ion-pair **2** collapses to the neutral complex **1**. This also occurs in corresponding MP2/6-31+G** optimizations. The collapse of an ammonium–carboxylate ion-pair complex when polarization functions on hydrogens are included has previously been observed by Ding and Krogh-Jespersen in their calculations on glycine in the gas phase.^{12,13}

Thus, the ion-pair complex **2** does not seem to be a “true” energy minimum on the potential energy surface, but in order to be able to characterize the ion-pair complex without having to prevent hydrogen transfer by the use of geometry or symmetry constraints, which may distort the calculations, we have throughout the present study employed HF/6-31+G* calculations for the energy minimizations of the binary as well as the ternary complexes. These optimized geometries have then been used for single point calculations at higher computational levels.

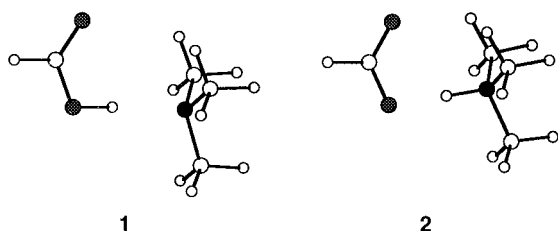
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Table 1. Relative Potential Energies *in Vacuo* and Thermodynamical Corrections Calculated for the Binary Complexes **1** and **2**^a

basis set	1	2
HF/6-31+G*	0.0	8.7
MP2/6-31+G*	0.0	2.3
MP3/6-31+G*	0.0	4.8
MP4SDQ/6-31+G*	0.0	3.9
HF/6-311+G**	0.0	9.6
MP2/6-311+G**	0.0	5.6
MP3/6-311+G**	0.0	8.1
MP4SDQ/6-311+G**	0.0	6.9
HF/6-311+G(3df,2p)	0.0	9.7
MP2/6-311+G(3df,2p)	0.0	4.4
"MP3SDQ/6-311+G(3df,2p)"	0.0	6.9
"MP4SDQ/6-311+G(3df,2p)"	0.0	5.7
ΔZPE^b	0.0	0.3
$\Delta \Delta H_{298}^{c,d}$	0.0	0.2
$-T\Delta \Delta S^{d,e}$	0.0	1.1
$\Delta \Delta G_{298}^d$	0.0	1.3

^a Geometries and thermodynamical contributions are calculated at the HF/6-31+G* level. Energies are in kcal/mol. ^b Zero-point energy. ^c Includes zero-point energy. ^d Correction term to be added to the calculated potential energy. ^e T = 298.15 K.

**Figure 1.** HF/6-31+G* optimized structures of the trimethylamine–formic acid (**1**) and the trimethylammonium–formate (**2**) complexes *in vacuo*.**Table 2.** Selected Calculated Geometrical Data for **1** and **2**^a

	1	2
N---O	2.842	2.590
N--H/N--H	1.866	1.073 (1.009)
O--H/O--H	0.977 (0.954)	1.517
N--H--O/N--H--O	178.4	179.5

^a The values within parentheses are the corresponding values for uncomplexed trimethylammonium ion and formic acid. Geometries were optimized at the HF/6-31+G* level. Distances are in angstroms, angles are in degrees.

The calculated relative potential energies for the complexes **1** and **2** are given in Table 1. The optimized structures of **1** and **2** are shown in Figure 1, and selected calculated geometrical data are given in Table 2.

At all computational levels shown in Table 1, the neutral complex **1** is calculated to be significantly lower in energy than the ion-pair complex **2**. At the Hartree–Fock level, the energy difference is 8.7–9.7 kcal/mol and the effects of including more basis functions and higher polarization are small, at most 1.0 kcal/mol. However, addition of electron correlation (MP2, MP3, and MP4SDQ) leads to a significant preferential stabilization of the ion-pair complex **2**. At the MP4SDQ level the energy difference between **1** and **2** is decreased by 2.7–4.8 kcal/mol, but in all cases the neutral complex **1** is still the most stable one. At the MP2/6-311+G**, MP3/6-311+G**, and MP4SDQ/6-311+G** levels the energy difference between **1** and **2** is 7.6, 8.3, and 6.5 kcal/mol lower than those calculated for the ammonia–formic acid system⁹ at comparable levels (MP2/6-311+G**, MP3/6-311+G**, and MP4/6-311+G** with geometries optimized at the MP2/6-31+G* level).

As shown in Table 1, differences in zero-point energies and ΔH_{298} for **1** and **2** are small while the $T\Delta S$ term favors the neutral complex. The free energy difference ($\Delta G = \Delta H - T\Delta S$) between **1** and **2** is calculated to be 1.3 kcal/mol higher than indicated by the calculated potential energies. Thus, at our highest computational level “MP4SDQ/6-311+G(3df,2p)” the free energy differences between **1** and **2** is estimated to be 7.0 kcal/mol in favor of the neutral complex **1**. The lower entropy of the ion-pair complex **2** is due to the greater “tightness” of this complex. As indicated by the shorter N–O distance in **2** (Table 2), this is a consequence of a more restricted rotation about the N–O axis in complex **2** than in **1** (calculated to 58 cm⁻¹ for **2** as opposed to 30 cm⁻¹ for **1**). The numerical value for the entropy contributions from these low-energy modes may be in error due to the harmonic approximation used in the calculations, but the conclusion that the neutral complex is preferentially stabilized by the entropy is most probably valid.

The calculated geometrical data in Table 2 show that both complexes have essentially linear hydrogen bonds and that the OH bond in formic acid increases by 0.023 Å on complexation with trimethylamine in **1**, while the corresponding increase of the NH bond in the trimethylammonium ion in **2** is somewhat larger, 0.064 Å.

The calculations described above indicate that in order for the ion-pair complex **2** to be favored, the environment must be able to provide a preferential stabilization of this complex by at least 6 (enthalpy) or 7 kcal/mol (free energy). This should be compared to the energy required for the bifurcated C_{2v} ion-pair structure of the ammonium ion–formate anion to be favored in comparison to the neutral ammonia–formic acid complex. The calculations reported in ref 9 indicate that a preferential stabilization of the ion-pair by at least 11.3 kcal/mol (potential energy + ZPE) is required. It may be safe to assume that the corresponding energies required for favoring the ion-pairs involving the methylammonium ion and the dimethylammonium ion fall in between the values given above.

Ternary Complexes of 1 and 2 with H₂O. In contrast to the ammonia and the primary and secondary alkylamine cases, the lack of N–H bonds in trimethylamine precludes the ion-pair to be stabilized by water *via* hydrogen bond interactions to NH atoms. Only stabilization *via* hydrogen bond donation to the carboxylate oxygens is feasible. This reduces the area of the potential energy surface to be searched for stable ternary complexes.

Several ternary complexes of trimethylammonium–formate–water and trimethylamine–formic acid–water, in which a single water molecule interacts with the formate anion/formic acid from different directions, were optimized at the HF/6-31+G* level. All ternary complexes were first optimized by using C_s symmetry constraints. It was then checked if the structures were energy minima or not. Those structures which were not energy minima were reoptimized without symmetry constraints to yield energy minima with C₁ symmetry.

Five energy minima were found and the optimized structures are shown in Figure 2. The ternary complexes are organized in Figure 2 so that the ion-pair and neutral complexes involving the same direction of interaction to the water molecule may be directly compared. This may be a useful way of considering the neutral *vs* ion-pair equilibrium in connection with the possibility of stabilization of the binary complex with a water molecule or a hydrogen bond donating amino acid residue in the ligand binding site of enzymes and receptors.

Two energy minima, **4a** and **4c** (Figure 2), were found for the ternary complexes involving an ion-pair. Complex **4b** is found to be a transition state structure with C_s symmetry. This

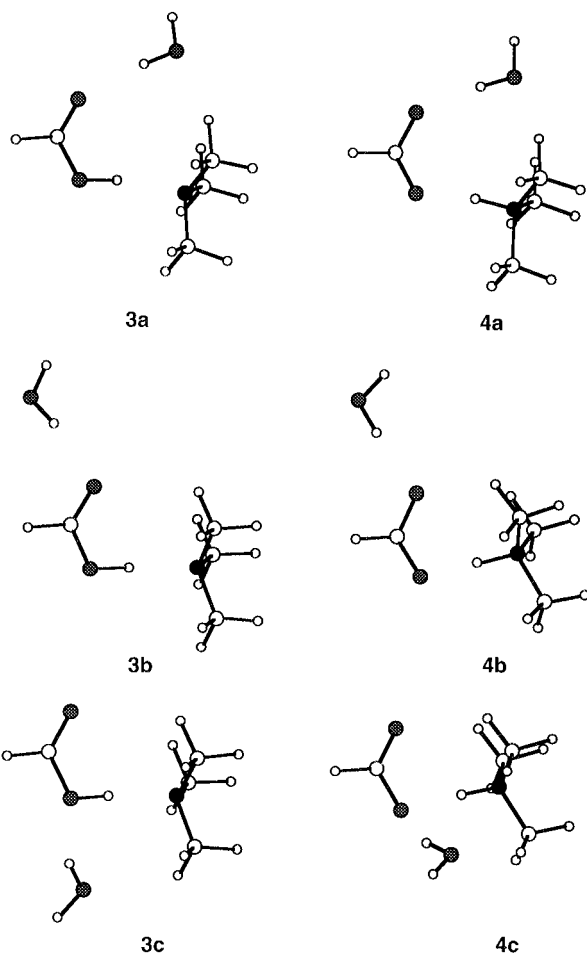


Figure 2. HF/6-31+G* optimized geometries of ternary complexes **3a–c** and **4a–c**. The energy minima **3a** and **4a** have C_s symmetries while structures **3b**, **3c**, and **4c** have C_1 symmetry. Structure **4b** is a transition state structure with C_s symmetry.

structure minimizes to **4a** if the symmetry constraints are removed. For the neutral case, three energy minima were found, **3a–c** (Figure 2), corresponding to the three available lone pair directions on the carboxylic acid oxygens. An attempt to optimize the ternary complex **4a** (C_s symmetry) at the MP2/6-311+G** level resulted in a collapse of the ion-pair giving the neutral complex **3a**. Due to the excessive amount of cpu time involved in these calculations we have not investigated if the other ion-pair complexes are energy minima at levels higher than HF/6-31+G*, but considering the results for **4a** and the results described above for **2** it is not likely that the ternary complexes involving an ion-pair are energy minima when polarization functions on hydrogen are included in the calculations.

Relative energies calculated at various computational levels for the six ternary complexes **3a–c** and **4a–c** are given in Table 3. At the Hartree–Fock level, the neutral ternary complex **3a** is the most favored one for all basis sets employed, followed by the two other neutral complexes **3b** and **3c**. The ion-pair complexes are, ignoring the high energy transition state structure **4b**, ca. 4 (HF/6-31+G*), 5 (HF/6-311+G**), and 6 kcal/mol (HF/6-311+G(3df,2p)) higher in energy than the lowest energy neutral complex **3a**. Comparing the calculated results in Table 3 with those for the binary complexes (Table 1), a single water molecule is calculated to preferentially stabilize the ion-pair **2** in the ternary complexes **4a** and **4b** relative to the stabilization of **3a** by essentially the same amount of energy at a given computational level, 4.7–4.8 (HF/6-31+G*), 4.2–4.4 (HF/6-311+G**), and 3.7–3.8 kcal/mol (HF/6-311+G(3df,2p)), but

Table 3. Relative Potential Energies *in Vacuo* and Thermodynamical Corrections Calculated for Complexes **3a–c** and **4a–c**^a

computational level	3a	3b	3c	4a	4b ^b	4c
HF/6-31+G*	0.0	1.1	2.4	4.0	7.3	3.9
MP2/6-31+G*	2.6	4.6	4.3	0.8	4.7	0.0
MP3/6-31+G*	0.4	2.2	2.1	0.9	4.6	0.0
MP4SDQ/6-31+G*	1.3	3.2	3.0	0.9	4.7	0.0
HF/6-311+G**	0.0	1.1	2.3	5.2	8.4	5.4
MP2/6-311+G**	0.0	1.9	1.3	2.2	5.5	1.6
MP3/6-311+G**	0.0	1.8	1.5	4.5	7.7	3.9
MP4SDQ/6-311+G**	0.0	1.8	1.4	3.3	6.6	2.7
HF/6-311+G(3df,2p)	0.0	0.8	2.3	5.9	8.4	6.0
MP2/6-311+G(3df,2p)	0.0	1.7	1.8	1.3	4.2	0.7
“MP3/6-311+G(3df,2p)”	0.0	1.6	1.9	3.6	6.5	3.0
“MP4SDQ/6-311+G(3df,2p)”	0.0	1.6	1.8	2.5	5.4	1.8
ΔZPE^c	0.4	0.2	0.0	1.5	0.9	1.7
$\Delta\Delta H_{298}^{d,e}$	0.2	0.2	0.0	0.9	0.1	1.2
$-T\Delta\Delta S^{e,f}$	2.0	0.0	1.0	3.1	3.3	3.8
$\Delta\Delta G_{298}^e$	2.0	0.0	0.8	3.8	3.2	4.8

^a Geometries and thermodynamical corrections are calculated at the HF/6-31+G* level. Energies are in kcal/mol. ^b Transition state structure. ^c Zero-point energy. ^d Includes zero-point energy. ^e Correction term to be added to the calculated potential energy. ^f $T = 298.15$ K.

this is not sufficient to make the ion-pair complex favored at any of these levels.

The calculations including electron correlation show a preferential stabilization of the ion-pair complex by an energy amount similar to that shown at the HF levels. As the energy difference between the binary complexes **1** and **2** are calculated to be significantly smaller at correlated levels (see Table 1) this results in smaller energy differences between the monohydrated ion-pair and the corresponding neutral complex. At the 6-31+G* level, the calculations including electron correlation give the monohydrated ion-pair **4c** to be the most stable. However, at the 6-311+G** as well as the 6-311+G(3df,2p) levels the corresponding calculations give the neutral complex **3a** as the most stable one, with the best monohydrated ion-pair at the MP4SDQ level being 2.7 kcal/mol (MP4SDQ/6-311+G**) and 1.8 kcal/mol (“MP4SDQ/6-311+G(3df,2p)”) higher in energy.

On comparing pairs of monohydrated structures with the hydrogen bond from the water molecule coming from the same direction, **3a** vs **4a**, **3b** vs **4b**, and **3c** vs **4c**, the results in Table 2 show that at the 6-311+G** and 6-311+G(3df,2p) levels, **3a** and **3b** are always favored in comparison to **4a** and **4b**, respectively. In the correlated 6-311+G(3df,2p) calculations, **3c** and **4c** are close in energy. MP2 calculations at this level show the ion-pair **4c** to be the most stable while MP4SDQ calculations result in identical energies for **3c** and **4c**. This equalization of energies is most probably due to the relatively weak hydrogen bond between water and the “ether” oxygen in **3c**.

The thermodynamical corrections shown in Table 3 favor the neutral ternary complexes. Adding these contributions to our “best” potential energies (“MP4SDQ/6-311+G(3df,2p)”) it is clear that all three neutral ternary complexes have significantly lower free energies than any of the ion-pair complexes. However, the main part of the contributions to the free energy differences in Table 3 comes from the $T\Delta S$ terms. Since the lowest frequency in the ternary complexes are very low (13–23 cm^{-1} for the neutral complexes **3a–c**, slightly higher, 19–46 cm^{-1} , for the ionic complexes **4a–c**), the entropy calculated may be significantly in error due to harmonic approximation employed. Thus, the entropic and free energy contributions in Table 3 should be used with caution.

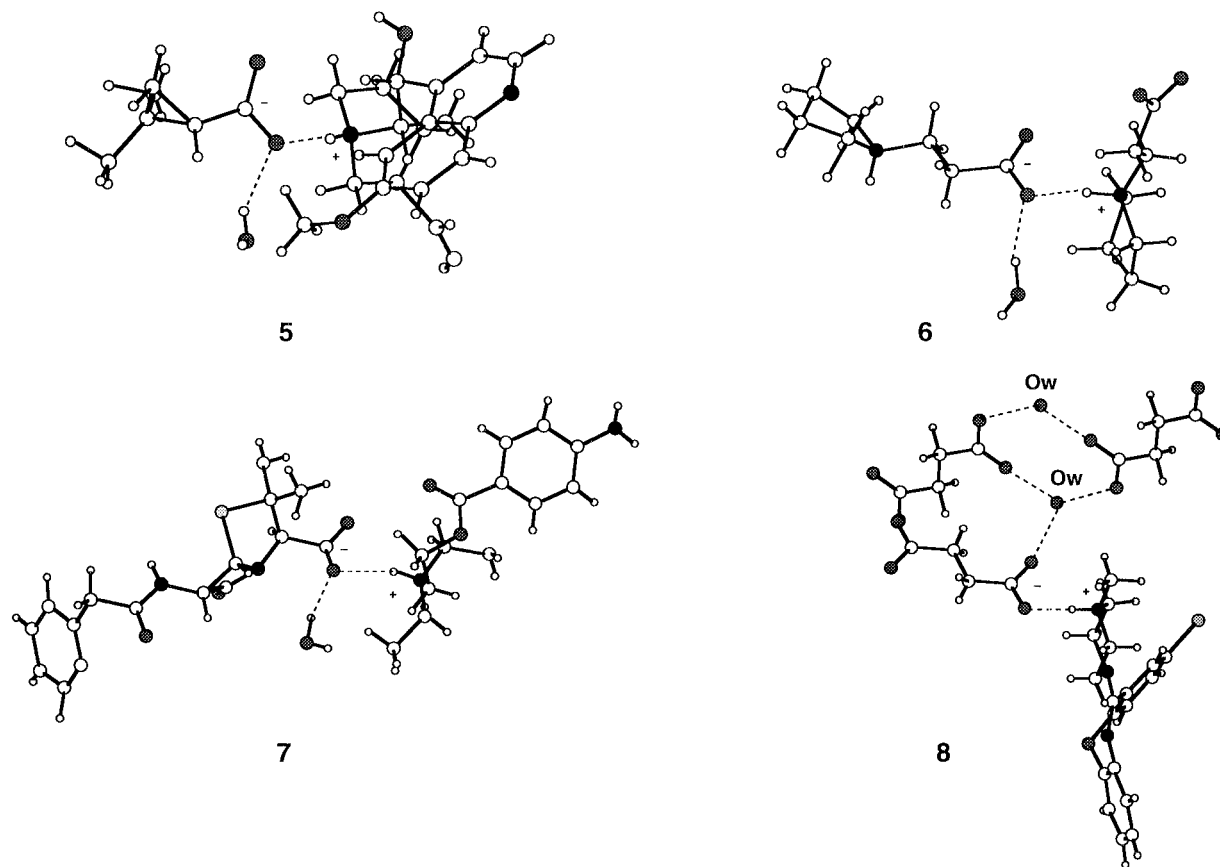


Figure 3. X-ray structures of trialkylammonium ion-carboxylate anion complexes stabilized by a single water molecule, extracted from the Cambridge Structural Database. Ow denotes oxygen in a water molecule. Codes for **5–8** are FIJSUM, BINRIZ, PRPENG, and LOXSUC10, respectively.

Table 4. Selected Calculated Geometrical Data for **3a–c** and **4a–c**^a

	3a	3b	3c	4a	4b	4c
N---O	2.805	2.819	2.788	2.603	2.610	2.692
O---Ow ^b	2.931	2.959	3.004	2.766	2.878	2.788
Ow-H---O	173.9	170.7	156.0	174.1	176.2	157.8
N-H---O/ N-H---O	167.5	177.6	174.0	167.3	179.4	175.7
O-C-O---Ow	0.0	176.8	113.7	0.0	180.0	88.2

^a Geometries optimized at the HF/6-31+G* level. Distances in angstroms, angles in degrees. ^b Ow denotes oxygen in water molecule.

Geometries of Ternary Complexes. Selected calculated geometrical features for the ternary complexes **3a–c** and **4a–c** are given in Table 4. The effect on the N--O distance of hydrogen bonding to water is opposite in the neutral and ion-pair cases. The N--O distances in the neutral ternary complexes **3a–c** are calculated to be 0.023–0.054 Å *shorter* than the corresponding distance in the binary complex **1**, whereas these distances are 0.013–0.102 Å *longer* in **4a–c** in comparison with **2**. Hydrogen bonding to water withdraws electron density from the acid and makes the acid in the neutral complex a better hydrogen bond donor (more acidic) resulting in a shorter N--O distance. In contrast, hydrogen bonding by water to the carboxylate anion gives a less basic anion and a weaker hydrogen bond acceptor resulting in a longer N--O distance.

The distances between the water oxygen and carboxylate oxygen in the ion-pair complexes are, as expected, significantly shorter than the corresponding distances in the neutral complexes. It should also be noted that the water molecule in **3c** and **4c** is located significantly out of the carboxylic acid/carboxylate plane. This is due to relaxation of the eclipsing of the O-H and N-CH₃ bonds in the planar arrangement. The

Ow-H---O angle in these complexes also deviates significantly from the "ideal" 180 degrees.

The ternary ion-pair complex **4c** displays a hydrogen bonding pattern in which the water molecule and the trimethylammonium ion are interacting with the same oxygen atom of the carboxylate group (Figure 2). Interestingly, this complex is calculated to have a lower potential energy and enthalpy than the other monohydrated ion-pair complexes and has essentially the same free energy as the complex **4a** and much lower than **4b** (Table 3). In a search of the Cambridge Structural Data Base²³ we found four examples of trialkylammonium ion-carboxylate anion complexes with N--O distances less than 3.5 Å and interacting with a single water molecule. These structures are shown in Figure 3. In three of the structures, **5**, **6**, and **7**, the same hydrogen bond pattern as in **4c** is observed. Structure **8** displays the alternative pattern corresponding to **4a**. In structure **8** the water molecule interacting with the ion-pair complex is also involved in bridging two dicarboxylic acids making it more acidic than normal.

It would be highly interesting to study such ion-pair interactions in ligand-protein complexes. Searching the Brookhaven Protein Data Bank files,²⁴ we have not been able to find any ligand-protein complex involving a trialkylammonium ion interacting with a carboxylate ion. However, there are a large number of examples of primary ammonium ion-carboxylate ion interactions. In the cases we have examined, the ion-pair is clearly strongly hydrated. For instance, in the complex

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(24) Protein Data Bank, Chemistry Department, Building 555, Brookhaven National Laboratory, Upton, NY 11973.

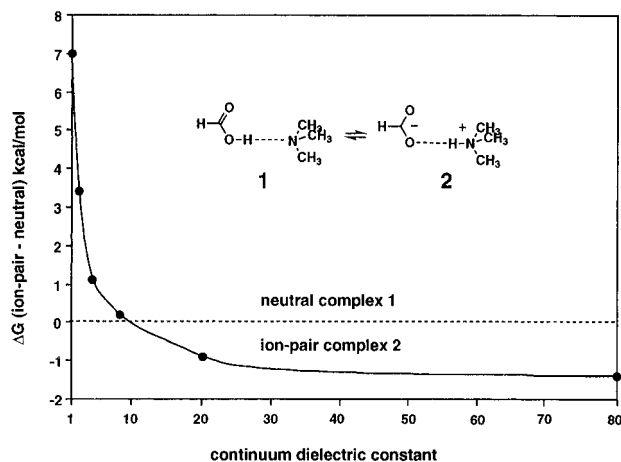


Figure 4. Calculated free energy differences between the ion-pair complex **2** and the neutral complex **1** in a dielectric continuum, as a function of the dielectric constant. The calculations are made at the "MP4SDQ/6-311+G(3df,2p)//HF/6-31+G*" level including solvation contributions calculated by SCI-PCM/6-31+G*.

between lysine and the periplasmatic lysine/arginine/ornithine-binding protein²⁵ both ammonium groups of lysine are interacting with carboxylate groups of aspartate residues. These interactions are presumably ion-pair interactions. In both cases the carboxylate ion of the aspartate is hydrated by at least two water molecules. Furthermore, in a series of six complexes involving small ligands containing an ammonium group interacting with Asp189 of trypsin, the carboxylate group of Asp189 is hydrated by two water molecules which are conserved in all complexes.²⁶

Solvation by a Dielectric Continuum. In order to investigate the relative stabilization of complexes **1** and **2** by a dielectric continuum, calculations using the Self-Consistent Isodensity Polarized Continuum Model (SCI-PCM) calculations were performed using HF/6-31+G* geometries and wave functions. The calculated free energy difference including solvation effects between the ion-pair complex (**2**) and the neutral complex (**1**) as a function of the continuum dielectric constant is shown in Figure 4. The free energy difference for the binary complexes *in vacuo* (7.0 kcal/mol) is taken from the "MP4SDQ/6-311+G(3df,2p)" calculations in Table 1, including thermodynamic contributions calculated at the HF/6-31+G* level. The SCI-PCM calculations yield the electrostatic contribution to the solvation energies, but considering the structural similarities of complexes **1** and **2** it may be assumed that the differences in the calculated solvation energies can be taken as free energy differences.

As expected, a dielectric continuum preferentially stabilizes the ion-pair complex and at a dielectric constant of ca. 9 the two complexes become isoenergetic. Thus, at dielectric constants larger than 9 the ion-pair complex should predominate. In this context it is of interest to note that Denisov and Golubev²⁷ have observed an ion-pair complex between trimethylammonium ion and acetate anion by ¹H NMR at low temperatures in aprotic CDF₂Cl/CDFCl₂ solution (dielectric constant ca. 6).

The AM1-SM2 method²¹ is widely used for dielectric continuum calculations of free energies of hydration. In the

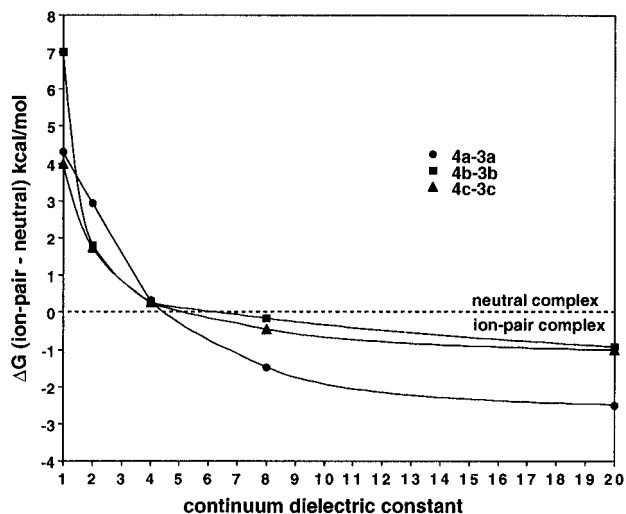


Figure 5. Calculated free energy differences for the monohydrated complex pairs **4a-3a**, **4b-3b**, and **4c-3c** in a dielectric continuum, as a function of the dielectric constant. The calculations are performed at the "MP4SDQ/6-311+G(3df,2p)//HF/6-31+G*" level including solvation contributions calculated by SCI-PCM/6-31+G*.

present case the free energy of hydration, as calculated by the AM1-SM2 method, favors the ion-pair complex by 6.2 kcal/mol. Using a dielectric constant of 80 the corresponding number calculated by using SCI-PCM is somewhat larger, 8.4 kcal/mol. It should be noted that AM1-SM2 is a parametrized method and no ion-pair complexes have been included in the parametrization procedure.

As discussed above, stabilization by a single water molecule is not sufficient to make the ion-pair complex in the equilibrium between **1** and **2** the most favored one (Table 3). In order to investigate at which dielectric constant the monohydrated ion-pair complex may predominate in a dielectric continuum we have used the SCI-PCM method to calculate the stabilization of the ternary complexes (**3a-c** and **4a-c**). Calculated free energy differences including solvation effects for **4a-3a**, **4b-3b**, and **4c-3c** as a function of the continuum dielectric constant are shown in Figure 5.

For all pairs, the ion-pair complex predominates at dielectric constants larger than ca. 6. The crossover takes place at a dielectric constant of 4–5 for **4a-3a**, and **4c-3c**, whereas **4b-3b** requires a dielectric constant of ca. 6. In the latter case the dielectric constant *vs* ΔG curve is extremely flat in the range of 4–8. At a dielectric constant of 4 the neutral complex **3b** is lower in free energy by 0.3 kcal/mol, and at a value of 8 the ion-pair complex **4b** is lower in free energy by 0.2 kcal/mol.

At dielectric constants higher than 2, **3b** is the lowest energy neutral complex, whereas **4b** is the lowest energy ion-pair complex (for calculated solvation energies see Supporting Information). Thus, as shown in Figure 5, if the comparison is made between the best neutral and the best ion-pair complex, the crossover point occurs at a dielectric constant of 6–7. However, it should be noted that **4b** is not a minimum, but a transition state at the potential energy surface (Table 3), and thus the thermodynamic contributions calculated for **4b-3b** are not exactly comparable with those for the pairs **4a-3a** and **4c-3c**.

As discussed above, the entropy values calculated for the monohydrated complexes are somewhat uncertain and should be used with caution. In particular, the largest contribution to the entropies originates from motions of the water molecule. When the movement of the additional hydrogen bond donor is restricted (as will be the case in a crystal or in a ligand binding

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(26) (a) Kurinov, I.; Harrison, R. W. *Nature Struct. Biol.* **1994**, *1*, 735. (b) Kurinov, I.; Harrison, R. W.; Brookhaven Protein Data Bank entries 1TNG, 1TNH, 1TNI, 1TNJ, 1TNK, 1TNL for complexes between trypsin and 2-aminocyclohexane, 4-fluorobenzylamine, 4-phenylbutylamine, 2-phenylethylamine, 3-phenylpropylamine, and tranlycypromine, respectively.

(27) Denisov, G. S.; Golubev, N. S. *J. Mol. Struct.* **1981**, *75*, 311.

to a protein, especially if the hydrogen bond donor is not a water molecule), these contributions will be reduced. The limiting case of negligible entropy differences between the pairs **4a**–**3a**, **4b**–**3b**, and **4c**–**3c** is obtained if the ΔH values are used instead of ΔG values in Figure 5. In this case the ion-pair complexes predominate already at dielectric constants larger than 2–3.

Accuracy. There are no experimental data for the free energy difference of complexes of type **1** and **2**. In the absence of experimental data, the accuracy of the calculations must be assessed from the convergence of the calculations. It is not expected that the levels of theory employed in this work should be sufficient to calculate accurate absolute energies, and indeed the results in “Supporting Information” show that the energy is lowered by 100–200 kcal/mol on going from the 6-311+G** to the 6-311+G(3df,2p) basis set, and by 10–20 kcal/mol by going from MP3 to MP4SDQ correlation. However, all conclusions in this work have been drawn from relative energies between complexes with equal numbers of atoms and very similar bonding and geometry. It can be seen in Tables 1 and 3 that the relative energies are nicely converged to within 1–2 kcal/mol with respect to basis set as well as correlation. This, together with the highly similar geometries of all complexes employed in pairwise comparisons, makes it plausible that basis set deficiencies and superposition errors, as well as additional correlation, can be neglected. We have avoided discussion of complexation energies as these are much more susceptible to deficiencies in the underlying theory (especially BSSE in the MP calculations).

The computational convergence may be evaluated by comparison to experimental data for acid–base equilibria. The total number of bonds change in these equilibria, so the accuracy is not expected to be quite as good as for the proton transfer above, but the results may at least give a high estimate of the expected errors. The gas phase proton affinity of trimethylamine²⁸ and the acid strength of formic acid²⁹ are available in the literature and can be obtained from our calculated data for the monomeric species. At the final level used in the current work [ΔE (“MP4SDQ/6-311+G(3df,2p)”) + thermodynamic corrections at 298 K from HF/6-31+G*], we obtain the following for trimethylamine: $\Delta G^{\circ}_{\text{calc}} = 219.2$, $\Delta G^{\circ}_{\text{exp}} = 216.5$; $\Delta H^{\circ}_{\text{calc}} = 226.6$, $\Delta H^{\circ}_{\text{exp}} = 224.3$ (all values in kcal/mol, calculated values corrected for $T\Delta S^{\circ}$ of a free proton, 7.75 kcal/mol²⁸). Correspondingly, for formic acid, we obtain the following: $\Delta G^{\circ}_{\text{calc}} = 336.5$, $\Delta G^{\circ}_{\text{exp}} = 338.2$; $\Delta H^{\circ}_{\text{calc}} = 343.5$, $\Delta H^{\circ}_{\text{exp}} = 345.2$. For these small molecule equilibria, it was shown that the error in ΔE due to extrapolation is ca. 0.5 kcal/mol (from comparison with true MP4SDQ/6-311+G(3df,2p) calculations). It can be seen that the highest discrepancy between experimental and calculated values is less than 3 kcal/mol. It should be noted that the experimental values are obtained from a series of measurements of relative energies. Aue and Bowers state that in the assignment of absolute values, “errors up to several kcal/

mol are possible”.²⁸ Unfortunately, the quite large uncertainty in the experimental absolute energies makes it less meaningful to use these data to discuss the errors in the calculations.

A potential source of error is the use of gas phase HF/6-31+G* geometries in all calculations. This choice was forced by the fact that the ion-pair complexes collapse to neutral complexes at medium levels of theory. Our results indicate that it should be possible to characterize the ion-pair complexes if minimized at, for example, the MP2/G-311+G** level in conjunction with a continuum solvation model. Such a verification would be highly desirable, but is unfortunately currently well beyond our computational resources.

Conclusions

High-level *ab initio* calculations including electron correlation, carried out up to an effective MP4SDQ/6-311+G(3df,2p) level, using geometries optimized at the HF/6-31+G* level show that the trimethylamine–formic acid complex, at the highest computational level employed, is favored *in vacuo* by 5.9 (ΔH_{298}) or by 7.0 kcal/mol (ΔG_{298}) in comparison to the trimethylammonium–formate complex.

Interaction with a single water molecule is not sufficient to shift the equilibrium to favor the ion-pair, as the lowest energy ternary neutral complex is still favored by 2.8 kcal/mol (ΔH_{298}) or by 4.7 kcal/mol (ΔG_{298}) in comparison with the most favored monohydrated ion-pair. This difference decreases to 1.2 (ΔH_{298}) and 4.0 kcal/mol (ΔG_{298}) if interactions with water from the same direction are compared (**3c** vs **4c**). The monohydrated ion-pair structure with lowest potential energy and enthalpy (**4c**) displays a hydrogen bonding pattern in which the water molecule and the trimethylammonium ion are hydrogen bonded to the same oxygen of the carboxylate anion. A search of the Cambridge Structural Database reveals that this hydrogen bonding pattern is the most common one in monohydrated trialkylammonium–carboxylate complexes in the solid phase.

Calculations on the effect of a dielectric continuum on the binary (**1** and **2**) and ternary complexes (**3** and **4**) using the SCI-PCM method indicate that a strong dielectric continuum (a dielectric constant larger than 9) is required to make the binary ion-pair complex the predominant one. However, only a relatively weak dielectric continuum (dielectric constant larger than 4–6) is required in order to favor the monohydrated ion-pair complex.

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Supporting Information Available: A listing of calculated results, including absolute energies, solvation energies, lowest frequencies, and thermodynamic quantities (2 pages). See any current masthead page for ordering and Internet access instructions.

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