

Strong Decrease of the Benzene–Ammonium Ion Interaction upon Complexation with a Carboxylate Anion

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Abstract: The ternary complex between benzene, ammonium ion, and formate ion has been investigated computationally. The total interaction energy is found to be much lower than the sum of the three pairwise interactions, due to nonadditive polarizations (intra- and intermolecular). The interaction with a benzene cannot stabilize the ammonium–formate complex sufficiently to avoid gas-phase collapse to the neutral formic acid–ammonia complex.

Introduction

The interaction between ammonium groups and various electron-rich moieties is very important in many biological systems. Salt bridges in the form of ammonium carboxylate salts have been proposed as important stabilizing factors both in proteins themselves¹ and in their interactions with various ligands.² The ammonium ion and its mono- and trialkylated derivatives have also been shown to bind strongly to aromatic systems, with gas-phase interaction enthalpies of 9–19 kcal/mol, respectively.³ The latter type of interaction has also been invoked as a major contributor to binding of ligands to enzymes.⁴ It has been speculated that both types of interactions contribute to ligand binding in aminergic neurotransmitter receptors.² In a very recent DFT study, Inoue et al. argue that the interaction of ammonium carboxylate ion pairs with aromatic moieties could play an important role in biological systems.⁵

From a theoretical point of view, it is well-known that ammonium carboxylates (including amino acid zwitterions) are unstable in the gas phase, reverting to the thermodynamically favored carboxylic acid–amine complex. For the parent complex, ammonium formate, the ion pair form is not even a minimum, but a saddle point ca. 11 kcal/mol above the hydrogen-bonded formic acid–ammonia complex.⁶ Despite this, it is well-known that in polar solvents (in particular in water), the ion pair form is strongly favored. The effect of water on the proton transfer in glycine has been studied at high levels of theory.⁷ Using a combination of microsolvation and continuum solvation, we have previously investigated the trimethylammonium–formate system computationally to elucidate the level

of stabilization required to shift the equilibrium to the ion pair form.⁸ It was found that a single water molecule as a hydrogen bond donor in combination with a weakly dielectric surrounding was sufficient to shift the equilibrium to the ion pair.

To better understand the important ammonium interactions, and to enable accurate modeling of them, several questions must still be answered. In this work, we will address the following questions: Do aromatic moieties provide sufficient stabilization to the ammonium–carboxylate complex to shift the equilibrium from neutral to ion pair form? How does the magnitude of the stabilization of an ion pair compare to the interaction of an aromatic moiety with a cation? What are the geometric requirements for interaction of aromatic moieties with ammonium ions and ion pairs? What is the nature of the stabilization, and can it be modeled by current force fields?

As our model system, we have chosen formic acid for the carboxylic moiety, ammonia for the amine, and benzene as the basic aromatic unit. The complexation and proton transfer equilibria for the ionized forms are depicted in Scheme 1.

Methods

All calculations were performed in Gaussian94.⁹ Optimized geometries were calculated at HF/6-311G**. The optimized structures were subjected to a normal-mode analysis at the same level. Thermodynamic quantities were calculated with $T = 298.15$ K (default). Single point energies were evaluated up to MP4SDQ/6-311G**.

The ion pair complexes (**1** and **3**) were not minima at any of the levels tested, reverting to the neutral forms (**6** and **7**) by proton transfer without any apparent barrier. To allow determination of gas-phase geometries, it was necessary to impose constraints.¹⁰ We have chosen to utilize only symmetry constraints. Thus, the ion pairs were evaluated in the bifurcated form, with two equivalent hydrogen bonds. The parent

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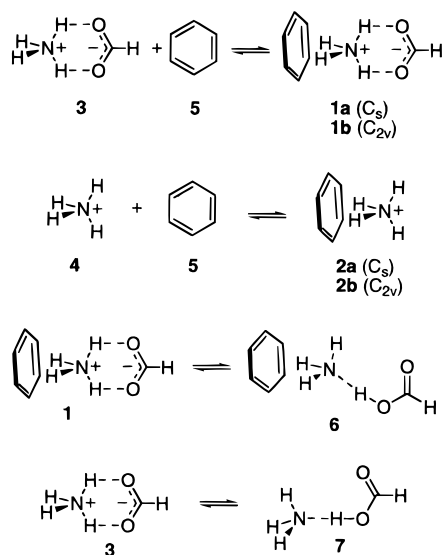
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Table 1. Interaction Energies for the Complexation Equilibria in Scheme 1 (kcal/mol)

	$3 + 5 \rightleftharpoons 1a$	$4 + 5 \rightleftharpoons 2a$	$3 + 5 \rightleftharpoons 1b$	$4 + 5 \rightleftharpoons 2b$
HF/6-311G** geometries				
HF/6-311G**	-4.5	-14.9	-4.4	-14.8
MP2/6-311G**	-5.9	-18.2	-5.5	-18.0
MP2/6-311G** geometries				
MP2/6-311G**			-6.0	-19.1
MP3/6-311G**			-5.4	-17.8
MP4SDQ/6-311G**			-5.2	-17.3
MP2/6-311+G(2d,2p)			-6.7	-19.8
"MP4SDQ/6-311+G(2d,2p)"			-5.9	-18.0
$\Delta(E + ZPE)^a$			-5.2	-17.1
ΔH^a			-4.9	-17.2
ΔG^a			1.8	-9.6

^a "MP4SDQ/6-311+G(2d,2p)" energies (eq 1) with thermodynamic contributions calculated at HF/6-311G**.

Scheme 1. Calculated Equilibria^a

^a In the C_{2v} -symmetric complexes (**1b** and **2b**), two ammonium hydrogens are interacting equally with bond midpoints in the benzene. The C_s complexes (**1a** and **2a**) are tilted so that only one hydrogen points toward the benzene.

ammonium formate (**3**) adopts a C_{2v} -symmetric geometry when one symmetry plane is imposed. Adding a benzene to this complex, it is then possible to retain both or only one mirror plane, yielding complexes of C_{2v} or C_s symmetry, respectively.¹¹ Both possibilities were investigated (complexes **1a** and **1b**). The monomers **4** and **5** were optimized in C_{2v} symmetry only.¹² According to the normal-mode analysis, the ion pairs **1b** and **3** display negative eigenvalues, showing that in the gas phase they are transition states for proton transfer between equivalent forms of **6** and **7**, as expected.⁶ In addition, the C_{2v} -symmetric forms **1b** and **2b** also show very weakly negative eigenvalues corresponding to a break of C_{2v} symmetry (leading to C_s -symmetric forms **1a** and **2a**, respectively). All other structures were true minima without negative eigenvalues.

The computationally cheap C_{2v} -symmetric systems were also optimized at the MP2/6-311G** level, with single point energies calculated up to MP4SDQ/6-311G** and MP2/6-311+G(2d,2p). Final potential energies were calculated by extrapolation to the "MP4SDQ/6-311+G-

(10) This is in contrast to the previous theoretical study on this type of systems, where no constraints were imposed; instead, the calculations were simply stopped when the proton started migrating in the energy minimization (ref 5).

(11) It is in fact possible to form two types of ternary complexes of each symmetry. At the HF level in C_{2v} symmetry, the forms with hydrogen bonds to the midpoints of benzene bonds were more stable than those where the ammonium hydrogens interacted with benzene carbon atoms. The former were therefore used throughout.

(12) The final structures of **4** and **5** ended up very close to T_d and D_{6h} symmetry, as expected.

Table 2. Proton Transfer Energies (kcal/mol, HF/6-311G** Geometries)

	$1a \rightleftharpoons 6$	$3 \rightleftharpoons 7$
HF/6-311G**	-18.7	-20.7
MP2/6-311G**	-13.7	-14.8
$\Delta(E + ZPE)^a$	-13.6	-14.4
ΔH^a	-12.1	-13.5
ΔG^a	-15.7	-16.3

^a MP2/6-311G**//HF/6-311G** energies with thermodynamic contributions calculated at HF/6-311G**.

(2d,2p)//MP2/6-311G** level from single point energies at the MP2/6-311G** geometries with use of eq 1.

$$E = E[\text{MP4SDQ/6-311G**}] + E[\text{MP2/6-311+G(2d,2p)}] - E[\text{MP2/6-311G**}] \quad (1)$$

The distance dependence of the stabilization afforded by a benzene molecule was investigated by constrained optimizations of the C_{2v} -symmetric complexes **1b** and **2b** at the MP2/6-311G** level of theory. All carbons of the benzene ring were kept in the xy -plane by fixing the z -coordinate to zero. The z -coordinate of the ammonium nitrogen was fixed at successively higher values, whereupon all remaining degrees of freedom were allowed to relax.

Results

Energies and thermodynamic contributions for all complexes are available as Supporting Information. The energies of C_{2v} - and C_s -symmetric forms are very similar, varying by less than 0.001 hartree. The computationally less demanding C_{2v} -symmetric systems were also investigated at higher levels of theory. The stabilization energy afforded by benzene to ammonium ion and the ammonium formate ion pair are shown in Table 1 at some selected levels of theory. The proton-transfer energies for going from neutral to ion pair form with and without benzene stabilization are shown in Table 2.

Discussion

The calculated energies show a nice convergence. In Table 1, it can be seen that already at the MP2/6-311G**//HF/6-311G** level, the results are sufficiently converged for all conclusions drawn in this work. It can also be seen that the effect of extending the basis set from 6-311G** to 6-311+G(2d,2p) is very small, indicating that basis set superposition errors (BSSE) can be neglected. Looking first at the proton-transfer equilibria depicted in Scheme 1, it is apparent from the data in Table 2 that stabilization by benzene is insufficient to shift the equilibrium to the ion pair form. The proton transfer takes place without a barrier, as evidenced both by geometry optimization of C_1 -symmetric systems and from the normal-mode analysis of ion pair complexes. Benzene does afford some

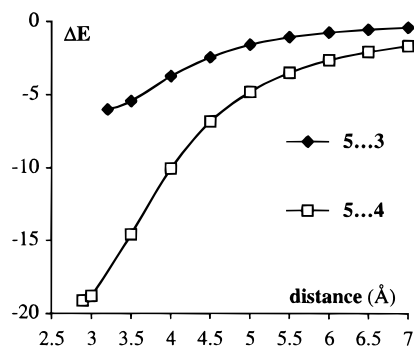


Figure 1. Interaction energy (kcal/mol) as a function of distance between benzene centroid and ammonium nitrogen, C_{2v} symmetry, MP2/6-311G**.

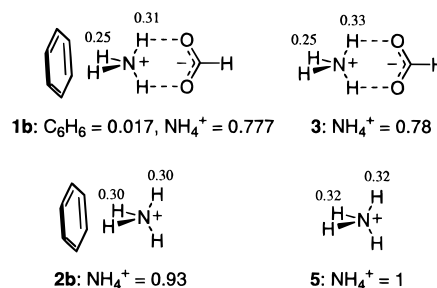
selective stabilization of the ion pair form, but not sufficient to overcome the strong disfavoring of charge separation in the gas phase. Additional stabilization by, for example, hydrogen bonding to the carboxylate ion⁸ would be required for the ion pair to be favored over the neutral form.

The interaction enthalpy between an ammonium ion and benzene in the gas phase has been determined to be 19.3 kcal/mol.³ Computational results are in close agreement with this value.¹³ In the current study, we find interaction energies in the range 17–19 kcal/mol depending on computational level. In contrast, the stabilization of the ion pair by benzene is calculated to be only ca. 6 kcal/mol (Table 1; a similar result was obtained by DFT⁵). As stated above, this stabilization is not sufficient to prevent collapse to the neutral form.

In Figure 1 is depicted the stabilization energy in **1b** and **2b** as a function of the distance from benzene to ammonium. It can be seen that the interaction energy falls off rapidly with distance. Also, the falloff with distance has a similar shape for complexes **1** and **2**. It is clear that for the interaction to contribute significantly to binding (in cases where additional stabilization of the carboxylate enable ion pair formation⁸), a very close proximity must be possible between the aromatic moiety and the ammonium group.

The interaction is reminiscent of hydrogen bonding, and might be modeled as such or as a charge-dipole interaction between the cationic ammonium moiety and the benzene C–H dipoles.¹⁴ However, a more detailed analysis indicates that the interaction may be impossible to model directly in most current force fields. The large difference between stabilizations of ammonium ion and the ion pair shows that the interactions of carboxylate and benzene with ammonium are nonadditive. This was verified by MP2/6-311G** single point calculations on all possible combinations of moieties in the ternary complex **1a** (at the exact geometry of all moieties found in **1a**).¹⁵ Thus, the energy loss of removing benzene from **1a** is 6.6 kcal/mol, whereas if carboxylate is first removed, subsequent removal of benzene from ammonium ion causes an energy loss of 14.1 kcal/mol (these values are lower than those in Table 1, due to the lack of

Chart 1. Mulliken Charges, Single Moieties, and Ammonium Hydrogens



geometry relaxation). The difference is -7.5 kcal/mol, whereas the destabilizing interaction between benzene and carboxylate in the geometry of **1a** is only -1.3 kcal/mol, showing clearly that the low influence of benzene in **1a** compared to **2a** cannot be rationalized by simple pairwise interactions. In most current force fields, only pairwise interactions are included, wherefore a combination of interaction energies as described above must correspond exactly. Nonadditivity must be the result of many-body interactions. Such interactions have been included in some recent force fields, for example in the form of polarizability.¹⁶

The charge distributions in the different complexes were investigated to elucidate the actual effects responsible for the nonadditivity.¹⁷ The Mulliken populations on ammonium hydrogens and on single moieties in some complexes are shown in Chart 1.

It is immediately obvious from Chart 1 that intermolecular charge transfer plays an important role in these systems. This is most noticeable in ammonium formate (**3**), where 0.22 e^- have been transferred to the cation. Interestingly, the nitrogen and the hydrogens proximal to the formate are almost unaffected by complexation, whereas the distal hydrogens are distinctly less positive in the complex compared to free ammonium ion **4**. As the distal hydrogens are involved in complexation to benzene, the charge transfer offers a rationale for the lowering in interaction energy. In the pure ammonium–benzene complex (**2b**), there is also a small contribution from charge transfer to the ammonium ion, ca. 0.07 e^- . In the ternary complex (**1b**), the charge transfer from formate to ammonium is virtually unchanged from **3**, whereas the charge transfer from benzene to ammonium is almost absent ($<0.02 e^-$), indicating that the charge accepting ability of the ammonium ion has been saturated by formate complexation. The charge distribution within the ammonium ion is also very similar in **1b** and **3**, again indicating that benzene has only a marginal influence in **1b**.

Conclusions

Despite the fact that the interaction energy between benzene (**5**) and ammonium ion (**4**) in itself is large enough to compensate the energy loss when ammonium formate (**3**) is formed from the ammonia–formic acid complex (**7**) in the gas phase, the interaction of ion pair **3** with **5** is insufficiently strong to favor the ion pair complex **1** over the neutral form **6**. This result cannot be rationalized by pairwise interactions, but is the result of strong intermolecular polarization (charge transfer) from formate to ammonium in **3**, negating the ability of the ammonium moiety to form additional complexes.

The total interaction energy between benzene and ion pair is of the same order as in a hydrogen bond, as previously

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(15) Single point calculations at one fixed geometry were performed for reasons of comparison to force fields, not to get the total contributions: the latter are found in Table 1. If geometries are allowed to relax, even simple force fields may give nonadditive results, masking the underlying contributions we want to elucidate here. All results are available as Supporting Information.

observed.⁵ The interaction could therefore plausibly have an importance in biological systems, but only if sufficient additional stabilization is offered by the environment to favor the ion pair over the neutral form.⁸

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Supporting Information Available: Tables of calculated energies at several levels of theory and Cartesian coordinates for all structures (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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