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# The role of proton affinity, acidity, and electrostatics on the stability of neutral versus ion-pair forms of molecular dimers

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## Abstract

Ion-pair formation via proton transfer from an acidic hydrogen of one functional group to a basic functional group plays an important role in the structure and reactivity of biomolecules in the gas phase. The relative stabilities of the ion-pair and the neutral-pair forms of five dimers composed of a basic molecule and a trifluoroacetic acid molecule were compared using density-functional calculations. The proton affinity of the basic molecules investigated ranged from 246 to 254 kcal/mol. The gas phase acidity of trifluoroacetic acid is 323.8 kcal/mol. The results of the B3LYP (6−311++G**) calculations indicate that the structures of the dimers change from a neutral pair to an ion pair as the proton affinity of the bases increases. This result is consistent with previous blackbody infrared radiative dissociation experiments on protonated trimolecular complexes (or trimers) consisting of two basic molecules and trifluoroacetic acid, which indicates that the predominant structure of the trimer changes from a charge-solvation structure to a salt bridge structure with the increasing gas phase basicity of the base. The electrostatic character of the interaction between the basic molecule and the trifluoroacetic acid molecule was determined using the natural energy-decomposition analysis (NEDA) program. In the ion pair, a majority (69%–77%) of the attractive energy of the dimer is comprised of the electrostatic component. Two models are derived that include the acidity of the acidic molecule, the proton affinity of the basic molecule, and an electrostatic binding term for both the ion pair and the neutral pair. Several nonelectrostatic interaction terms can be replaced by a single correction or constant term so that both models, one using NEDA electrostatic terms and the other using integration of point-charge interactions, provide reasonably accurate results. This indicates that electrostatic models similar to the ones used here may be useful in studying salt bridge formation in larger molecules. (Int J Mass Spectrom 212 (2001) 287–300) © 2001 Elsevier Science B.V.

## 1. Introduction

For over a century, it has been recognized that amino acids exhibit amphoteric properties (thus can exist as acid or base) in aqueous solution [1,2]. The structure of amino acids was deduced largely from the solution behavior of these compounds under the influence of electric fields. In 1894, Georg Bredig suggested that betaine exists as an “inneres salz” (inner salt) containing both a positive and a negative charge in the same molecule. A few years later, Küster [3] recognized that the pH-dependant color change of methylorange arises from the transition between the anionic form and inner salt form ($H^+ (CH_3)_2N\text{-}C_6H_4\text{-}N_2\text{-}C_6H_4\text{-}SO_3^+$). The inner salt compound is ionized in aqueous solution, yet it does not conduct current under an electric field. Küster termed this nonconducting ion a “zwitterion” [3]. All amino acids were later found to exist in their zwitterionic state under physiological conditions [2].

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Dedicated to R. Graham Cooks on the occasion of his sixtieth birthday.

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Intramolecular electric fields also have important effects on the structure of amino acids [2]. The acidity of the carboxylic acid functional group in a polar amino acid can also be perturbed by its ionizable side chain [2]. The pH range at which a peptide is a zwitterion can be affected by the distance between the carboxylic acid and the amino group [2]. Peptides also interact with the surrounding solvent molecules via electrostatic interactions. Typically, the largest amount of hydration of a protein occurs when it is at its isoelectric point [4,5].

With the advent of structurally informative techniques, such as X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy, and computational models for biomolecules, such as Born and Poisson-Boltzmann solvation, the effects of ionic interactions both within proteins and on protein–protein interactions have been extensively investigated [6–12]. Ionic interactions take place between oppositely charged side chains of amino acids. These interactions are usually referred to as salt bridges [6]. A salt bridge is stabilizing if the energy gained from the interaction between the oppositely charged groups is larger than that gained from the interaction of these groups with the solvent. A computational study on the arginine–phosphate and histidine–aspartate interactions indicates that salt bridges are slightly stabilizing, lowering the total energy of an 18-residue $\alpha$-helical peptide by 1–5 kJ/mol [7]. However, an experimental study on two pentapeptides (AcTrp-Lys-X-Lys-Lys, X = Arg and Lys) in octanol, which was used to simulate the environment of the interior of a protein, showed that salt bridges do not contribute to the stability of these peptides [8]. Other computational studies indicate that some salt bridges are destabilizing [9,10]. Poisson-Boltzmann solvation models rely largely on approximate electrostatic interaction terms of intramolecular bonding and solvent interactions. Important charge-transfer interactions are not treated. Thus, it appears that there is no general rule that governs the amount of energy that a salt bridge contributes to protein stability.

*Ab initio* calculations can also be used to investigate zwitterion and salt bridge formation [13–18]. These calculations include the effects of charge transfer and dispersion interactions between the acidic and basic groups. While these calculations are more accurate, the systems to which *ab initio* methods can be applied are typically limited to $\lesssim$100 atoms [19]. Most of the *ab initio*–based studies on zwitterion (ion-pair) formation have focused on the relative stability of the ionized and nonionized forms [14–17]. Although some aspects of the electrostatic nature of the bonding within salt bridges have been reported [14], there has been little discussion of the relative contributions of electrostatic and nonelectrostatic interactions. Information about the contributions of these components would be useful in judging the level of accuracy obtainable for simulations based solely on electrostatic interactions.

Several gas phase experiments on salt bridge formation and stability have been reported [20–29]. By investigating these interactions in the gas phase, their intrinsic behavior can be completely separated from the influence of solvent. Experiments [20,24,26,29] and theory [19] indicate that salt bridges can influence both the dissociation energies and the pathways of peptide ions. Experiments on protonated betaine–base dimers [20] using blackbody infrared radiative dissociation (BIRD), and experiments on base–haloacid [21] complexes with rotational spectroscopy indicate that zwitterion or ion-pair formation becomes more spontaneous with increasing gas-phase basicity (GB) of the bases. Studies of Bowers and coworkers [22] indicate that the stability of the salt-bridge form relative to the stability of the charge-solvation form of some cationized amino acids is nearly proportional to the proton affinity (PA) of the amino acid. Experiments conducted on a series of trimer ions of the general formula $(B_2AH + H)^+$, when B is a basic molecule and AH is trifluoroacetic acid, indicate that the structure converts from a charge-solvated structure to a salt bridge when B has a GB $\gtrsim$244 kcal/mol [23]. Both the threshold dissociation energies and the dissociation pathways of the trimer ions are strongly correlated with the GB of the base. The trimers consisting of the bases with a GB higher than 244 kcal/mol dissociate to $BH^+$ with a threshold dissociation energy ($E_0$) of approximately $\sim$1.4 eV [23]. The trimers consisting of bases with a GB $<$241 kcal/mol

Table 1
Energetics of dimer formation

| Base | PA (Base)[a] | $BE^{A\cdot BH}$ | $BE^{A^-\cdot BH^+}$ | $\Delta E$ | $\Delta H_r$ (350 K)[a] | $\Delta G_r$ (350 K)[a] |
|---|---|---|---|---|---|---|
| MTBD | 254.0 | −21.3 | −84.7 | −2.9 | −2.9 | −1.0 |
| TBD | 252.1 | −23.7 | −96.6 | −10.0 | −9.6 | −8.3 |
| DBU | 250.5 | −19.7 | −88.8 | −6.2 | −5.9 | −3.7 |
| DBN | 248.2 | −21.7 | 89.8 | −1.7 | −1.5 | +0.1 |
| TMG | 246.6 | −20.2 | −87.9 | +0.6 | +1.0 | +3.0 |

[a] Zero point, internal vibrational, and entropy correction calculated with mechanics (Merck molecular force field).

Note. Proton affinity of the basic molecules from the NIST thermochemical database. Interaction energies (BE) for $AH \cdot B$ and $A^- \cdot BH^+$ calculated at the B3LYP 6−311++G**//6−31+G** level (AH is trifluoroacetic acid). $\Delta E$, $E(A^- \cdot BH^+) - E(AH \cdot B)$, is the difference in energy between the ion pair and neutral pair (in kcal/mol).

MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

dissociate directly to $B \cdot BH^+$ with an $E_0$ of ~1.1–1.2 eV. The base with an intermediate GB dissociates through both pathways, with an $E_0 = 1.20$ eV [23]. These findings are consistent with a change in the structure of the protonated trimer, from a simple charge-solvated complex ($B \cdot BH^+ \cdot AH$) to a salt bridge complex ($BH^+ \cdot A^- \cdot BH^+$) within increasing GB of the basic molecule.

The charge-solvated form of the trimer can convert to the salt bridge by proton transfer from AH to B, forming $BH^+ \cdot A^-$. The presence of a charged basic molecule, a metal ion, or an electric field applied coincident to the base–acid axis, can stabilize the ion-pair form [30]. Here, we investigate the stability of the ion-pair and neutral-pair forms of the acid–base substructure in the absence of the additional protonated base using density-functional calculations. From calculations on the dimer, information on how the interaction of $BH^+$ influences the structure of the $B \cdot AH$ dimer present in the trimer ions can be obtained. In addition, a simplified model for the formation of an ion pair based on electrostatics interaction, PA of the basic molecule, and $\Delta H_{acid}$ of the acidic molecule is presented and discussed.

## 2. Methods

### Acid–base pair structure

Calculations were performed on a series of five dimers, $B \cdot AH$, where B is a basic molecule with a PA ranging from 246 to 254 kcal/mol [31] (listed in Table 1) and AH is trifluoroacetic acid ($\Delta H_{acid} = 323.8$ kcal/mol) [31]. The five basic molecules were chosen in our original study on protonated trimers [23] because of their strong gas-phase basicity, which facilitates proton transfer when bonded to an acidic molecule. Trifluoroacetic acid is among the strongest proton donors in the gas phase that contain a carboxylic acid group. This computational study investigates the structure of the acid–base pair in the absence of a protonated base. This investigation provides information complimentary to that which has been reported previously [23]. The IUPAC names for the basic molecules are tetramethylguanidine (TMG), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The dimers were modeled both as neutral pairs and as ion pairs. Low-energy structures for each of these dimers were found using internal coordinate-conformation searching. Initial structures were built in the Macromodel software program (Columbia University, NY). A 500-step conformational search using the Monte Carlo method [32] was performed for each dimer, using the Merck molecular force field (MMFF) [33]. For all conformation searches, no new conformers were found during the final 100 steps. This indicates that the lowest-energy structures, within the limits of accuracy of the force field used, were found. Density functional calculations were performed on the lowest-energy structures of the two forms of the dimers, using the Qchem computational program [34]. The relative stabilities of these two forms of the dimers were calculated at the B3LYP 6−311++G**// BHH-LYP6−31+G** level (BHH-LYP = Becke half-and-half functional). For TBD · TFA and MTBD · TFA, the proton-transfer barrier was particularly low and the proton transferred from the acid to the base during geometry optimizations on the neutral pair, resulting in the formation of the ion pair. For these neutral pairs, a constrained optimization was performed, where the O–H bond distance in trifluoroacetic acid was fixed at 1.0 Å. Zero-point and thermal-energy corrections were calculated using mechanics frequencies. Zero-point and internal energies calculated using density-functional and mechanics frequencies are expected to be similar [35]. Entropy was calculated from the sum of vibrational entropy and rotational entropy (with the rigid rotor approximation), using molecular mechanics.

Atomic charges were determined using the Natural Population Analysis [36] subprogram within Qchem. Accurate proton-transfer barriers are important for charge to be partitioned correctly between the acid and the base. The BHH/LYP method accurately represents proton-transfer barriers between hydrogen-bound species [37]. The BHH/LYP calculations were performed at the 6−31+G** level for each acid–base dimer, and natural charges that reside on each atom in the dimer were determined using the population-analysis subprogram. A program was written in C++ to retrieve the charges for each atom from the output of the Qchem program and to then determine the charge stabilization between the acid–base pair. The energy stabilization was computed using the Cartesian coordinates of each atom and of its corresponding charge. The total charge stabilization was taken as the sum of the charge–charge interactions from each pairwise atom interaction.

### 2.2. Natural energy decomposition analysis

For a bimolecular complex of the general form, X · Y, the natural energy-decomposition analysis program of Glendening and Streitwieser [38,39] can be used to determine the relative amounts of stabilization from charge transfer, electrostatic, and deformation interactions. The deformation energy arises from the Pauli exclusion principle that causes repulsion between molecule X and molecule Y. The charge-transfer interaction stabilizes the X · Y complex and is roughly defined as the energy gained from the delocalization of the wavefunctions of X and Y over the molecular complex. The electrostatic interaction calculated by NEDA corresponds to the static and induced electric interaction between the two molecules. A small component of the electrostatic interaction is exchange energy between X and Y.

## Results and Discussion

### 3.1. Low-energy structures

Conformational searching using molecular mechanics was done to find low-energy structures. The lowest-energy structure of each dimer was subsequently minimized at the BHH-LYP 6−31+G** level. The structures of the ion-pair form ($BH^+ \cdot A^-$) and the neutral-pair form (B · AH) of the dimers are shown in Fig. 1 and 2, respectively. A general characteristic of all of the structures in Fig. 1 is that the oxygens of the trifluoroacetate anion coordinate the acidic proton on B. For the dimers with TMG, DBN, and TBD, the position and orientation of the TFA molecule is practically unchanged in going from the ion-pair to the neural-pair form. For MTBD and DBU-containing dimers, the TFA molecule is positioned above the plane of the basic molecule in the neutral-pair form. MTBD · TFA is unique in that the TFA molecule lies above the plane of the base in both the ion-pair and neutral-pair forms. This is most likely caused by the steric repulsion from the methyl substituent on the bicyclic ring of MTBD. Both forms of the dimers containing TMG, DBN, and TBD have planar geometries.

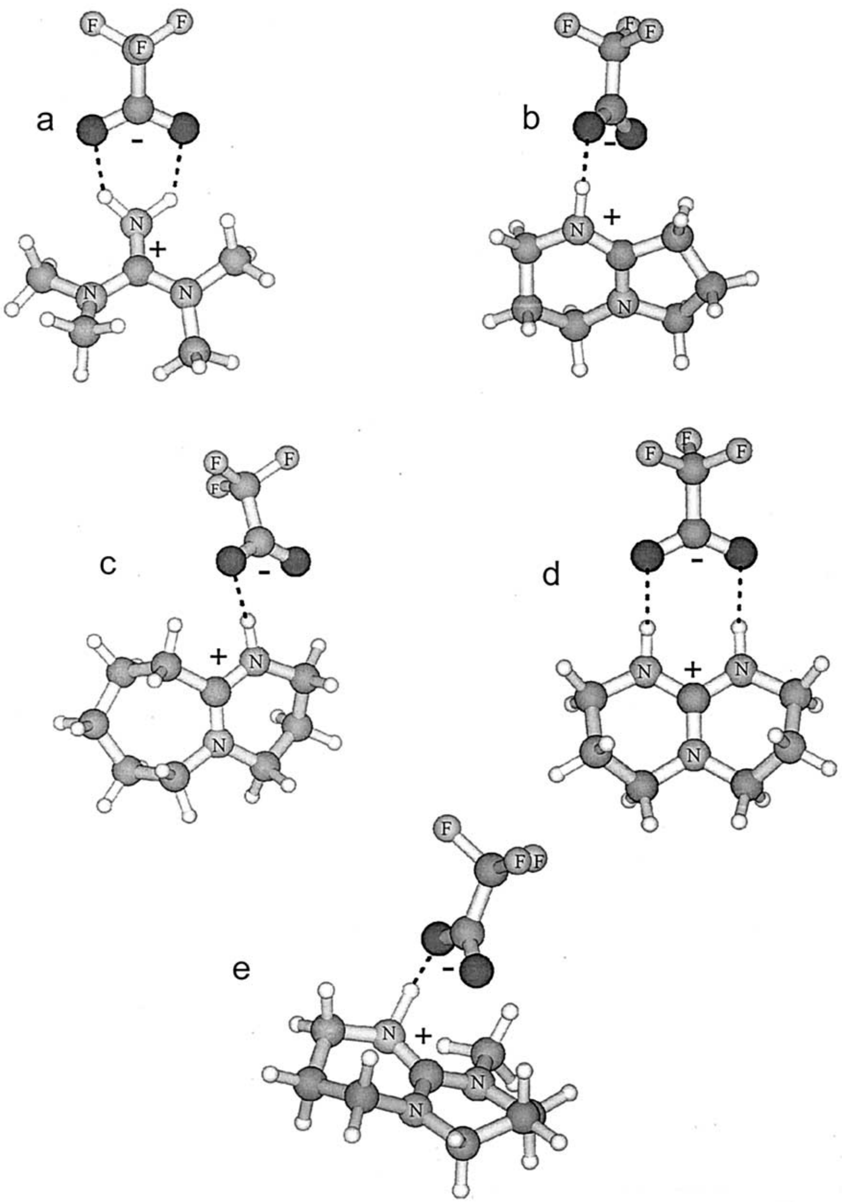


Fig. 1. Structures of the ion-pair form of the dimers of trifluoroactetic acid and (a) TMG, (b) DBN, (c) DBU, (d) TBD, (e) MTBD. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

### *3.2. Density-functional calculations*

The energy of $AH \cdot B$ relative to $AH + B$ at infinite separation was calculated at the B3LYP6−311++G** level for each of the bases (Table 1). The energy of $A^- \cdot BH^+$ relative to $A^- + BH^+$ was calculated at this same level of theory (Table 1). The intermolecular stabilization for the neutral-pair and the ion-pair forms of the dimer is ~20 kcal/mol and ≈90 kcal/mol, respectively. Also

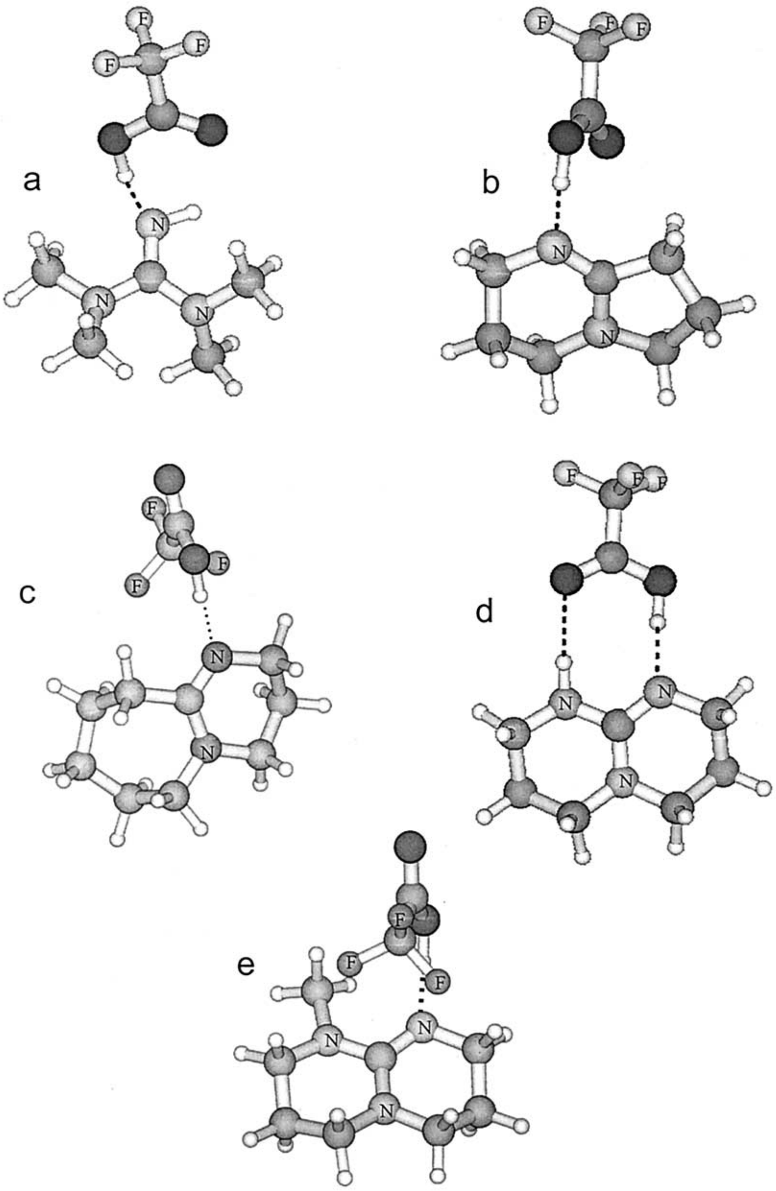


Fig. 2. Structures of the neutral-pair form of the dimers of trifluoroactetic acid and (a) TMG, (b) DBN, (c) DBU, (d) TBD, (e) MTBD. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

included in Table 1 is the difference in energy between $A^- \cdot BH^+$ and $AH \cdot B$ (a negative number means that the ion-pair is more stable). These differences were calculated using energies from B3LYP6−311++G** calculations ($\Delta E = E_{B3LYP}[A^- \cdot BH^+] - E_{B3LYP}[AH \cdot B]$). The 0 K energies indicate that the ion-pair form is more stable for all the bases except TMG.

The enthalpy and free-energy differences were calculated at $T = 350$ K. This is the midpoint of the temperature range used in the experiments on the protonated trimers, $(B_2AH + H)^+$. The enthalpy was calculated using zero-point energies, $E_{ZP}$, and the internal vibrational energies, $E_{vib}$, and the free energy was calculated using entropies, $S$, for both ion pair and the neutral pair:

$$\Delta H_r = \Delta E + E_{ZP}(A^- \cdot BH^+) - E_{ZP}(AH \cdot B) + E_{vib}(A^- \cdot BH^+) - E_{vib}(AH \cdot B), \quad (1a)$$

$$\Delta G_r = \Delta H_r - T[S(A^- \cdot BH^+) - S(AH \cdot B)]. \quad (1b)$$

The relative ΔG values at 350 K indicate that the ion-pair form of dimers consisting of TFA and the three most basic molecules, MTBD, TBD, and DBU, is more stable but the neutral form of dimers consisting of TFA and the two least-basic molecules, DBN and TMG, is more stable. These energy differences are small, but there appears to be a trend in the relative stability of these two forms of the dimer with the PA of the base.

A comparison between these results for $AH \cdot B$ and the structure of the dimer based on the results of the BIRD experiments on the protonated trimer, $(B_2AH + H)^+$, is complicated by the presence of the charged base in the trimers. The results of these experiments are summarized in Scheme 1 and are described in full detail elsewhere [23]. The electric field generated by the protonated base in the trimer can stabilize the ion-pair form relative to the neutral-pair form of the $AH \cdot B$ dimer. BIRD experiments indicated that protonated trimers consisting of the bases of the highest PA (MTBD and TBD) exist as salt bridges in which both basic molecules are protonated and in which TFA is deprotonated [23]. In contrast, the trimers consisting of the bases of lowest PA (DBN and TMG) exist as charge-solvated structures [23]. Our calculations on acid–base dimers are consistent with the BIRD observations for these bases. The results for DBU are more ambiguous. The experimental results indicate that the protonated trimer is a salt bridge but that the neutral form of the acid–base dimer is more stable when the charged base is separated from the acid–base dimer. The calculations reported here indicate that the ion-pair form of the acid–base pair is more stable for this base. This minor discrepancy can be attributed to the expected uncertainty of these calculations. However, both experiment and theory consistently show that the ion-pair form is increasingly stabilized with increasing PA of the bases examined in this study.

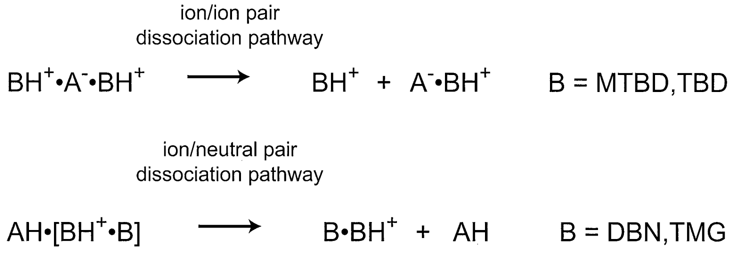
### 3.3. Energetics of ion-pair formation

The reactions of interest for the formation of an ion pair between an acidic and a basic molecule are given below:

$$B + AH = BH^+ + A^- \quad \Delta H = \Delta H_{acid}(A) - PA(B); \quad (2a)$$

$$BH^+ + A^- = A^- \cdot BH^+ \quad \Delta H = \Delta H^{A^- \cdot BH^+}, \quad (2b)$$

where PA is the gas phase proton affinity of B and $\Delta H_{acid}$ is gas phase acidity of AH. Reaction (2a)



DBU dissociates by both pathways (structure ambiguous)

Scheme 1

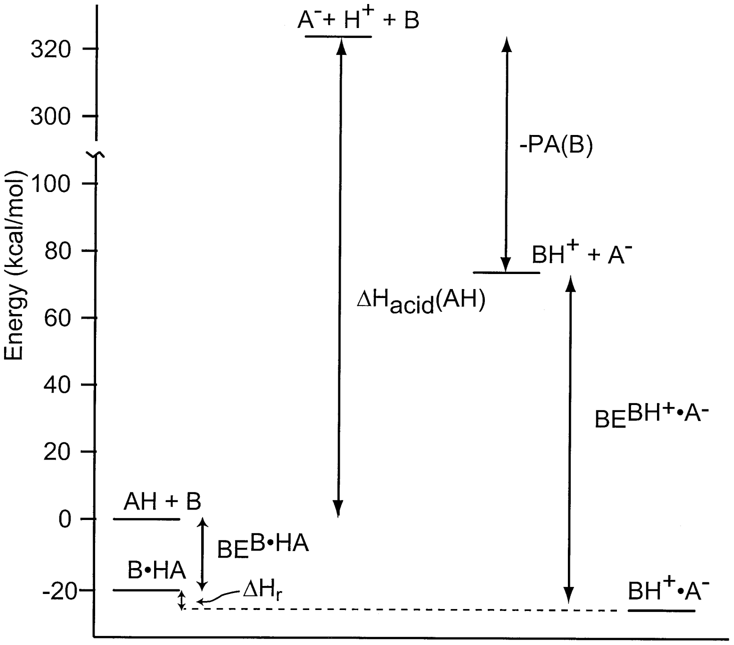


Fig. 3. Diagram showing the energetics of proton transfer from an acidic molecule to a basic molecule in the gas phase.

corresponds to proton transfer between AH and B with the products at infinite distance. Reaction (2b) corresponds to bringing these ionic products to their equilibrium distance. The term $\Delta H^{A^- \cdot BH^+}$ is the interaction energy of the ion-pair form of the dimer formed from its ionic components at infinite separation. Similarly, the energetics for the neutral-pair are given by

$$B + AH = B \cdot AH; \Delta H = \Delta H^{B \cdot AH}, \qquad (3)$$

where $\Delta H^{B \cdot AH}$ is the interaction energy of the two neutral molecules brought from infinite separation to their equilibrium geometry.

A general energy diagram for these processes is shown in Fig 3. Removing a proton from TFA requires considerably more energy than that gained one by protonating a base. For the bases used in this study, $\Delta H_{acid}(TFA) - PA(B) > 70-80$ kcal/mol. Thus, for ion-pair formation to be exothermic, >70–80 kcal/mol stabilization energy from intermolecular interactions in $BH^+ \cdot A^-$ must be gained. As $B \cdot AH$ is also stabilized by intermolecular interactions, an additional amount of energy corresponding to binding energy of $B \cdot AH$ or $BE^{B \cdot AH}$ must also be gained for the ion pair to be more stable than the neutral form.

### 3.3. Interaction energies

Although density-functional calculations give a very good way of comparing the stability between the ion-pair and neutral-pair forms, DFT calculations become untenable for large molecules such as proteins. If the interaction in ion pairs is largely electrostatic, a simple proton-transfer model could be constructed based on the $\Delta H_{acid}$ of AH, the PA of the base, and a Coulomb or electrostatic term. Such a model, even if only moderately accurate, could greatly simplify the effort needed to model ionic interactions in proteins. The accuracy depends on the extent to which the interaction between $BH^+$ and $A^-$ is electrostatic in origin.

Although there appears to be no ideal method of determining the electrostatic nature of a bond, the method of Glendening and Streitwieser [38] appears to be promising for weak hydrogen bonding, strongly

Table 2
Natural energy decomposition analysis calculated at the Hartree-Fock level for B · AH dimers (AH is trifluoroacetic acid)

| $BH^+$ | Basis | ES | CT | DEF ($A^-$) | DEF ($BH^+$) | $\Delta E^{BH^+\cdot A^-}$ |
|---|---|---|---|---|---|---|
| MTBD | 6−31G* | −137.5 | −46.2 | 64.6 | 28.4 | −90.7 |
| TBD | 6−31G* | −147.6 | −67.5 | 82.4 | 32.8 | −99.9 |
| DBU | 6−31G* | −139.5 | −56.6 | 72.8 | 32.1 | −91.2 |
| DBN | 6−31G* | −137.3 | −53.2 | 66.5 | 29.9 | −94.2 |
| TMG | 6−31G* | −136.4 | −40.2 | 55.3 | 27.7 | −93.5 |
| Guanidine | 6−31G* | −149.3 | −52.6 | 61.8 | 19.7 | −120.4 |
| Guanidine | 6−31G+** | −152.3 | −51.6 | 62.6 | 24.3 | −117.0 |

Note. The electrostatic (ES), charge transfer (CT), and deformation (DEF) energies are given in kcal/mol. The interaction energy ($\Delta E^{BH^+\cdot A^-}$) is the stabilization achieved when the two oppositely charged ions are brought from infinite distance to equilibrium distance.

MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diaza-bicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

ionic, and moderate donor-acceptor interactions. In their NEDA program, the self-consistent-field interaction energies are divided into charge transfer (CT), electrostatic (ES), and deformation (DEF) components. These calculations were performed for all five dimers, which were modeled both as ion pairs and as neutral pairs. With NEDA calculations, all atomic orbitals must be stored on hard disk during the HF calculation and NEDA partitioning. This requires a large amount of storage space. Because of the limits of our computational ability, calculations with only the moderate 6−31G* basis were performed.

The amounts of stabilization from ES, CT, and DEF for the ion-pair forms of the five dimers are listed in Table 2. The ionic character of the intermolecular bond can be determined from the ratio of ES to ES + CT. For the dimers in Table 2, the ionic character is between 69% and 77% of the total attractive interaction energy. This fraction is much less than that for inorganic salts (>95%) [39]. Thus, it appears that nonelectrostatic interactions make a significant contribution to ion-pair stability and that a purely electrostatic model for binding would not reproduce the energetics of ion-pair formation without parameterization or additional terms.

The magnitude of the parameterization can be determined from the following analysis. The energy difference between the ion pair and neutral pair forms of the dimer ($\Delta H_r$) is given by equation (4);

$$\Delta H_r = \Delta H_{acid} - \Delta H^{AH\cdot B} - PA(B) + \Delta H^{A^-\cdot BH^+}. \tag{4}$$

The intermolecular interaction terms can be separated into their ES, CT, and DEF components:

$$\Delta H_r = \Delta H_{acid} - [ES^{AH\cdot B} + CT^{AH\cdot B} + DEF^{AH} + DEF^{B}] - PA(B) + [ES^{A^-\cdot BH^+} + CT^{A^-\cdot BH^+} + DEF^{A\cdot} + DEF^{BH^+}. \tag{5}$$

Equation (5) can be simplified by identifying trends and cancellations between the terms. The NEDA breakdown components for the ion pair (Table 2) are presented graphically in Fig. 4. The ES and DEF($BH^+$) terms change relatively little between the dimers consisting of different bases. The CT and DEF($A^-$) terms vary more significantly. However, the values of DEF($A^-$) are correlated to the values of CT. The values of DEF($A^-$) are consistently ~15 kcal/mol larger than the values of CT. Stronger CT interactions in a bimolecular complex should bring the two molecules closer together, thereby increasing the Pauli repulsion or the DEF energy. Thus, the $CT^{A^-\cdot BH^+}$ and $DEF^{A^-}$ terms in Eq. (5) can be approximated by a constant value of 15 kcal/mol:

$$\Delta H_r \approx \Delta H_{acid} - [ES^{AH\cdot B} + CT^{AH\cdot B} + DEF^{AH} + DEF^{B}] - PA(B) + [ES^{A^-\cdot BH^+} + DEF^{BH^+} + 15\ \text{kcal/mol}. \tag{6}$$

The NEDA breakdown for the neutral pair is given in Table 3 and also in Fig. 5. The CT and DEF(AH)

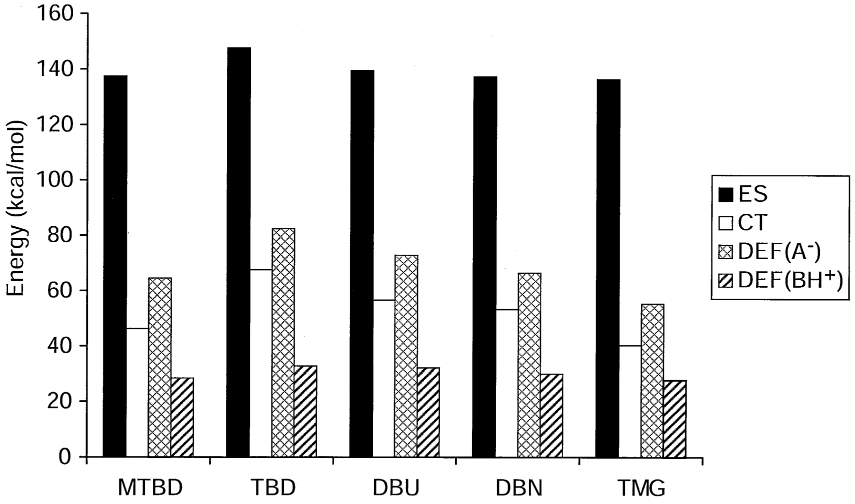


Fig. 4. Bar graph of the breakdown of the interaction energy derived from the national energy decomposition analysis program for the ion-pair form of the five dimers. The breakdown consists of the absolute values of the ES (electrostatic), CT (charge transfer), and deformation (DEF) energy components. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

interactions are roughly equal in magnitude (but of opposite signs) and nearly cancel. Also, DEF($BH^+$) and DEF(B) also roughly cancel out in Eq. (6). Thus, Eq. (6) becomes;

$$\Delta H_r \approx \Delta H_{acid} - [ES^{AH\cdot B}] - PA(B) + [ES^{A^-\cdot BH^+}] + 15\ \text{kcal/mol}; \quad (7a)$$

$$\Delta H_r \approx \Delta H_{acid} - PA(B) + [ES^{A^-\cdot BH^+} - ES^{AH\cdot B}] + 15\ \text{kcal/mol} = \Delta H^{ES(NEDA)}. \quad (7b)$$

The values for $\Delta H^{ES(NEDA)}$ were calculated and are listed in Table 4. All of the values are negative, indicating exothermic reactions for the formation of the ion pair. Although this is certainly not consistent with the results of the DFT calculations, the average absolute difference is only 4.4 kcal/mol. This indicates that an electrostatic model can provide a moderately accurate way to predict the formation of an ion pair in the gas phase.

In Eq. (7), the constant that accounts for the effect

Table 3
Natural energy decomposition analysis calculated at the Hartree-Fock level for B · AH dimers (AH is trifluoroacetic acid)

| B | Basis | ES | CT | DEF (AH) | DEF (B) | $\Delta E^{B\cdot AH}$ |
|---|---|---|---|---|---|---|
| MTBD | 6−31G* | −52.1 | −38.1 | 39.6 | 29.6 | −21.0 |
| TBD | 6−31G* | −57.3 | −58.6 | 51.8 | 43.6 | −20.6 |
| DBU | 6−31G* | −50.3 | −50.0 | 50.5 | 35.0 | −14.8 |
| DBN | 6−31G* | −42.0 | −39.4 | 40.1 | 25.4 | −15.9 |
| TMG | 6−31G* | −37.8 | −36.0 | 38.6 | 22.5 | −12.6 |
| Guanidine | 6−31G* | −50.5 | −47.2 | 41.7 | 38.5 | −17.5 |
| Guanidine | 6−31G+** | −52.0 | −48.7 | 45.0 | 39.2 | −16.4 |

Note. The electrostatic (ES), charge transfer (CT), and deformation (DEF) energies are given in kcal/mol. The interaction energy ($\Delta E^{B\cdot AH}$) is the stabilization achieved when the two molecules are brought from infinite distance to equilibrium distance.

MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

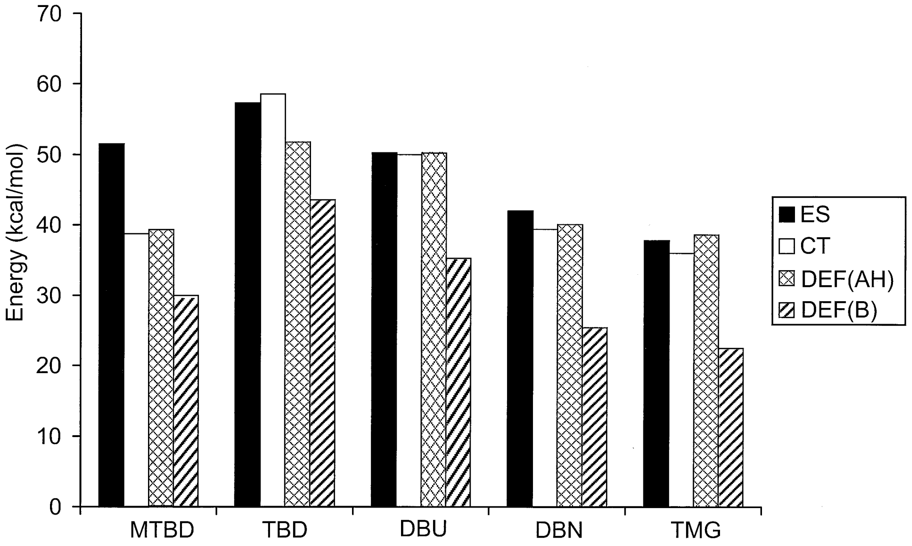


Figure 5. Bar graph similar to that in Fig. 4 for the neutral-pair form of the dimers. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

of CT and DEF has no dependence on intermolecular distance or geometry. This simplification is surely not valid at distances different from the equilibrium distance. At larger distances, this term will decrease to zero, as both DEF and CT are large only when the electron clouds of the two molecules are close to each other. A term with a functional dependence on the intermolecular distance would be appropriate in Eq. (7) for calculations at nonequilibrium geometries.

Table 4
Reaction enthalpy (in kcal/mol) calculated using proton affinity of B, $\Delta H_{acid}$ of TFA, and an electrostatic term from the national energy decompression analysis (NEDA) calculations (Eq. [7]).

| B | $\Delta H^{ES(NEDA)}$ |
|---|---|
| MTBD | −0.6 |
| TBD | −3.6 |
| DBU | −0.9 |
| DBN | −4.7 |
| TMG | −6.4 |

[a] From reference [31].

Note. MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

The amount of variation in the ES, CT, and DEF energies with basis set was investigated on the guanidinium–acetate and the guanidine–acetic acid dimers. These two dimers contain fewer heavy atoms than the five dimers in Table 1, and therefore, NEDA calculations can be performed using larger basis sets. ES, CT, and DEF change little between the 6−31+G** and the 6−31G* levels of theory. The 6−31G* basis appears to be an adequate level to determine NEDA energies.

### 3.3. Coulomb interaction

The question of whether a point-charge interaction could be used instead of the NEDA ES term was investigated. A potential advantage of a point-charge model is that point charges can be easily calculated with most *ab initio* packages. A disadvantage is that the charge distribution is reduced to atom center charges and the effect of Pauli exclusion repulsion and charge redistribution between the dimers is not included. To the extent that the interaction energy in $BH^+ \cdot A^-$ can be approximated by a classical Cou-

Table 5
Electrostatic interaction energies (in kcal/mol) calculated from the sum of the Coulomb interactions between the natural charges of the basic molecule and those of the acidic molecule

| Base | $\Sigma\Sigma q_i q_j/4\pi\varepsilon_0 r_{ij}$ | $\Sigma\Sigma q_k q_l/4\pi\varepsilon_0 r_k$ | $\Delta H^{ES(\mathrm{coulomb})}$ ($C = 0$) | $\Delta H^{ES(\mathrm{coulomb})}$ ($C = -16$) |
|---|---|---|---|---|
| MTBD | −74.2 | −25.8 | 21.4 | 5.4 |
| TBD | −83.7 | −24.6 | 12.6 | −3.4 |
| DBU | −82.9 | −26.9 | 17.3 | 1.3 |
| DBN | −81.6 | −23.5 | 17.5 | 1.5 |
| TMG | −88.4 | −25.2 | 14 | −2.0 |

Note. This calculation was done for both the ion pair and neutral pair (see text). A reaction enthalpy, $\Delta H^{ES(\mathrm{coulomb})}$, is calculated from these electrostatic interactions, PA, $\Delta H_{\mathrm{acid}}$, and empirical correction term, $C$ (Eq. [8]). MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN = 1,5-diazabicyclo[4.3.0]non-5-ene; TMG = tetramethylguanidine.

lomb electrostatic interaction, the reaction enthalpy for conversion of the neutral pair to the ion pair can be approximated by Eq. 8:

$$\Delta H_r \approx \Delta H_{acid} - PA + \sum_i \sum_j \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} - \sum_k \sum_l \frac{q_k q_l}{4\pi\varepsilon_0 r_{kl}} + C = \Delta H^{ES(Coulomb)}, \tag{8}$$

where the first summation term is the sum of the electrostatic interactions of the $i$th charge of the deprotonated acid and the $j$th charge on the protonated base at a distance, $r_{ij}$, apart; $\varepsilon_0$ is the permittivity of vacuum, and $C$ is an empirical correction term. Similarly, the Coulomb term for the neutral pair is the sum of the electrostatic interactions of the $k$th charge of the acid and the $l$th charge on the base at a distance, $r_k$, apart. The values of $\Delta H^{ES(Coulomb)}$ are given in Table 5. These values are all positive, indicating that ion-pair formation is endothermic for all the dimers. To bring this simple model into agreement with the results of DFT calculations, an empirical correction term ($C$) of approximately −16 kcal/mol is required. This correction is approximately equal in magnitude but opposite in sign to the NEDA-derived correction in Eq. (7a) and (7b). However, no significance is attributed to the fact that the correction terms are equal in magnitude in the two models. Instead, this appears to be only coincidental. Also, electrostatic interactions calculated from point charges are smaller than that calculated using the NEDA method, indicating that the ES and DEF terms are not correctly partitioned in the point-charge model.

## 4. Conclusions

The effect of proton affinity on the structure of five dimers consisting of one trifluoroacetic acid molecule and one of five different bases was investigated using ab initio calculations. The structures of these dimers change from neutral pairs to ion pairs with increasing proton affinity of the bases. These results are in reasonable agreement with results of BIRD experiments on related protonated trimer ions consisting of these same bases and one trifluoroacetic acid molecule. These experiments indicate that the structure of the trimers changes from charge-solvated to salt bridge structures with the increasing gas-phase basicity of the bases.

The interaction energies between the molecules in both the neutral and ion-pair forms of these dimers was investigated using the NEDA Hartree-Fock partitioning scheme. Although the electrostatic interaction in the ion pair is large (between 69% and 77% of the total attractive energy), it is much less than that for inorganic salts (>95%).

Charge transfer also plays a significant role in these dimers.

Two models, which include the acidity of AH, the proton affinity of B, and an electrostatic term, are derived to determine when ion-pair formation occurs. One, based on separation of interactions using the NEDA program, provides very good agreement with moderate level DFT calculations. A second, similar, model based on point-charge electrostatic interactions can be combined with an empirical correction term to make it reasonably accurate. The former model requires that molecular wavefunctions are calculated so that the effects of deformation and charge transfer can be separated from electrostatics. The latter method also requires *ab initio* calculations so that point charges can be obtained. Another method of calculating electrically based intermolecular potentials is one based on tensor calculus of the molecular multipoles. The pertinent mathematical formulation is given by Dykstra [40]. This method could be used to calculate electrostatic interactions for larger molecules, such as proteins. This would require an *ab initio* calculation of the multipole expansion for individual polar side chains or amino acid residues. Minimization and energy calculations of proteins containing these residues can be performed using molecular mechanics–based techniques. The use of multipole moments calculations in molecular mechanics has been successfully implemented by Ponder et al. [41]. This could be useful for calculating salt bridge interactions in peptides and proteins in the absence of solvent, using molecular mechanics–based simulations.

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