

Stability of Like and Oppositely Charged Organic Ion Pairs in Aqueous Solution

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Abstract: To investigate the stability of ionic pairs in aqueous solution, polarizable continuum-model (PCM) *ab initio* molecular orbital calculations were carried out. Ion pairs formed from three organic ions, methylacetate, methylammonium, and guanidinium, were treated. The methylacetate ion pair forms a stable complex when the two methyl groups are in contact. When the charged groups of methylacetate and methylammonium are in contact, this pair does not form a stable complex in aqueous solution. When the methyl group of methylacetate is in contact with that of methylammonium, the ionic groups are far apart, and a stable complex is not formed, even though the complex involves a strong attractive electrostatic interaction. The guanidinium pair forms a stable complex in aqueous solution at all conformations investigated in this work even though a strong repulsive electrostatic interaction is present in this complex.

Introduction

Electrostatic interactions play an important role in determining the structure and function of proteins.^{1–4} Charged groups located on the exterior of the protein domain are crucial for expressing its surface properties,^{5,6} for example, biological activities as reflected in active sites. Charged groups located in the interior of the protein domain are also important for understanding protein folding and stabilization of protein conformation.⁴

The ion pairs observed in proteins are mainly oppositely charged.^{7–9} About 10% of all protein structures exhibit at least one charge cluster, mostly of the mixed type involving about equally anionic and cationic residues. However, in some cases, pairing of like-charged groups is also found in crystal data.^{10–13} From a survey of the Cambridge Structure Database (CSD), Gao et al.¹⁴ found that chloride pairs in contact are common in the crystalline state. The environments around the chloride pair

are very polar. The attraction arising from the polarization effect can exceed the electrostatic repulsion between chloride ions. Magalhaes et al.¹³ investigated the stability of arginine-arginine pairs with both a Brookhaven Protein Data Bank survey and semiempirical molecular orbital (MO) calculations. In several proteins, two arginine residues, more precisely two guanidiniums, are in close contact. Most of the Arg-Arg pairs are found in the vicinity of the surfaces of the proteins. The solvation of the ion pair leads to the stabilization of the like-charged pair.

Buckner and Jorgensen¹⁵ carried out Monte-Carlo simulations to investigate the energetics and hydration of the constituent ion pairs of tetramethylammonium chloride. According to the simulation, the potential of mean force (PMF) of $(\text{CH}_3)_4\text{N}^+\cdots\text{Cl}^-$ has two minima along the interionic distance, $r_{\text{N}\cdots\text{Cl}}$, and the PMF of $\text{Cl}^-\cdots\text{Cl}^-$ has deep minima at $r_{\text{N}\cdots\text{Cl}} = 4.8 \text{ \AA}$, -4.2 kcal/mol whereas the PMF of $(\text{CH}_3)_4\text{N}^+\cdots(\text{CH}_3)_4\text{N}^+$ does not have a minimum. From the simulation, they found a tendency for the hydration of the oppositely-charged pairs to become less favorable as the ions approach each other. On the other hand, the hydration of like-charged ion pairs becomes more favorable as the ions approach each other.¹⁵

Boudon et al.¹⁶ carried out Monte-Carlo simulations with a guanidinium-guanidinium ion pair in water to evaluate effective interactions in water at short distances. The PMF plotted along the C \cdots C distance shows a deep minimum of 9.5 kcal/mol at a C \cdots C distance of 3.3 Å. They concluded that guanidinium ions attract locally because of related induced solvent effects contrary to the simple electrostatic picture in the absence of solvent.

The association of ions, whether they have opposite or like charges, is influenced by the size and charge distribution of the ions, and by the environments around the ions, which can be a solvent effect or a local field effect produced by the polar groups of the protein.

To investigate solutions computationally, generally two approaches are mainly used: the first are the classical ensemble treatments including individual solvent molecules and the second are the continuum models in which the solvent is treated as a

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continuous unstructured dielectric with a given dielectric constant. The classical ensemble treatments are molecular dynamics (MD) simulations,^{17–19} Monte-Carlo (MC) simulations,^{20,21} free energy perturbation combined with MD or MC,^{22–24} and the Langevin dipole method.²⁵ The continuum treatment includes empirical hydration models such as a hydration shell model^{26–28} and a surface area model^{29–36} and quantum mechanical continuum models such as the self-consistent-reaction-field (SCRf)^{37–40} model, which is based on the Onsager reaction field model.⁴¹

Recently, a new infinite-order solvation scheme, isoelectron-density polarizable continuum model (IPCM), which defines the cavity of the solute in a solvent with an isoelectron density surface of the solute, was proposed by Foresman et al.⁴² IPCM is a modification of the polarizable continuum model (PCM) developed by Tomasi and co-workers.⁴³

In this work, the stabilities of some organic ion pairs in water, both opposite and like-charged ion pairs, are determined with PCM MO calculations. Since the PCM method leads to good convergence in the calculation of the binding energy for ion-pair pairs in water at any interionic distance, the PCM method is used in this work.

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Method

Ion Pair Models. In this work, we treat three kinds of organic ions which appear most frequently in the amino acid side chains of proteins. These are $-\text{CO}_2^-$, $-\text{NH}_3^+$, and guanidinium [$^+\text{C}(\text{NH}_2)_3$]. To determine the stability of like- and oppositely-charged ion pairs in aqueous solution, eleven ion pair models were investigated (Figure 1, a to k). The geometries of each ion were optimized with HF and SCI-PCM^{43b,44} HF *ab initio* MO calculations for the gas and aqueous phases, respectively, with a 6-31+G* basis set. The isodensity level of the electron distribution 0.0004 was employed. The optimized geometries of the ions are described in Figure 1.

Binding Energy Calculation. In the PCM,⁴³ the free energy of a solvated system is described as

$$G(\Psi) = \langle \Psi | H_0 | \Psi \rangle + \langle \Psi | H_{\text{pol}} | \Psi \rangle \quad (1)$$

where the first term represents the solute Hamiltonian, which is modified by the electric field of the solvent, and the second term includes both the solvent–solute stabilization energy as well as the reversible work needed to polarize the solvent. In the PCM,⁴³ the second term was evaluated from the induced charges on the reaction field cavity surface.

$$H_{\text{pol}} = \sum_a \sum_j Z_a |R_a - r_j^s|^{-1} - \sum_i \sum_j q_p^j |r_i - r_j^s|^{-1} \quad (2)$$

where Z_a and R_a represent the charges and coordinates of the nuclei, and r_i is the location of the charge distribution arising from the electrons of the solute. The induced charge q_p^j at the grid point j at the cavity surface r_j^s can be calculated from the electric field and the area of the curved patches surrounding the grid point. Equation 1 can be solved with an SCF calculation in which the new solute electron density is used to update H_{pol} . Tomasi and co-workers⁴³ suggested that the appropriate radii of the cavities are 20% greater than the van der Waals radii.

Since the PCM has no convergence problem at any interionic distances, the PCM was introduced in this work for the ion–ion interaction calculation in water. The calculations were carried out with the 6-31+G* basis set at the HF level for each ion pair along the interatomic coordinate defined in Figure 1. All the calculations were carried out with the Gaussian 94⁴⁴ program in which the PCM was incorporated in the HF *ab initio* calculation. For the PCM parameters, the number of grid points per sphere was 500 and the dielectric constant of the medium was 78.3. Both gas phase and aqueous solution calculations were carried out along the same coordinates and with the same basis set. The geometries of the ions in the gas phase and in aqueous solution were fixed at the optimized geometries in the gas phase and aqueous solution, respectively, during the calculation of the energies of the ion pairs.

In this work, the stability of an ion pair, $E_{A-B}^{S,X}(r_{AB})$, was taken as the stabilization energy defined as follows.

$$E_{A-B}^{S,X}(r_{AB}) = E_{A-B}^X(r_{AB}) - (E_A^X + E_B^X) \quad (3)$$

where A and B represent the ions A and B , respectively, and X is the index for the phase; it can be gas phase (g) or aqueous solution (aq). r_{AB} is the distance between ions A and B . $E_{A-B}^X(r_{AB})$ is the ion pair energy at the separation r_{AB} in phase X . E_A^X and E_B^X are the energies of ions A and B , respectively, in phase X . The sum of E_A^X and E_B^X corresponds to the reference state of the energy of ion pair $A-B$ in phase X . The superscript S stands for *stabilization energy*. When X is an aqueous solution, the energies were obtained from PCM *ab initio* MO

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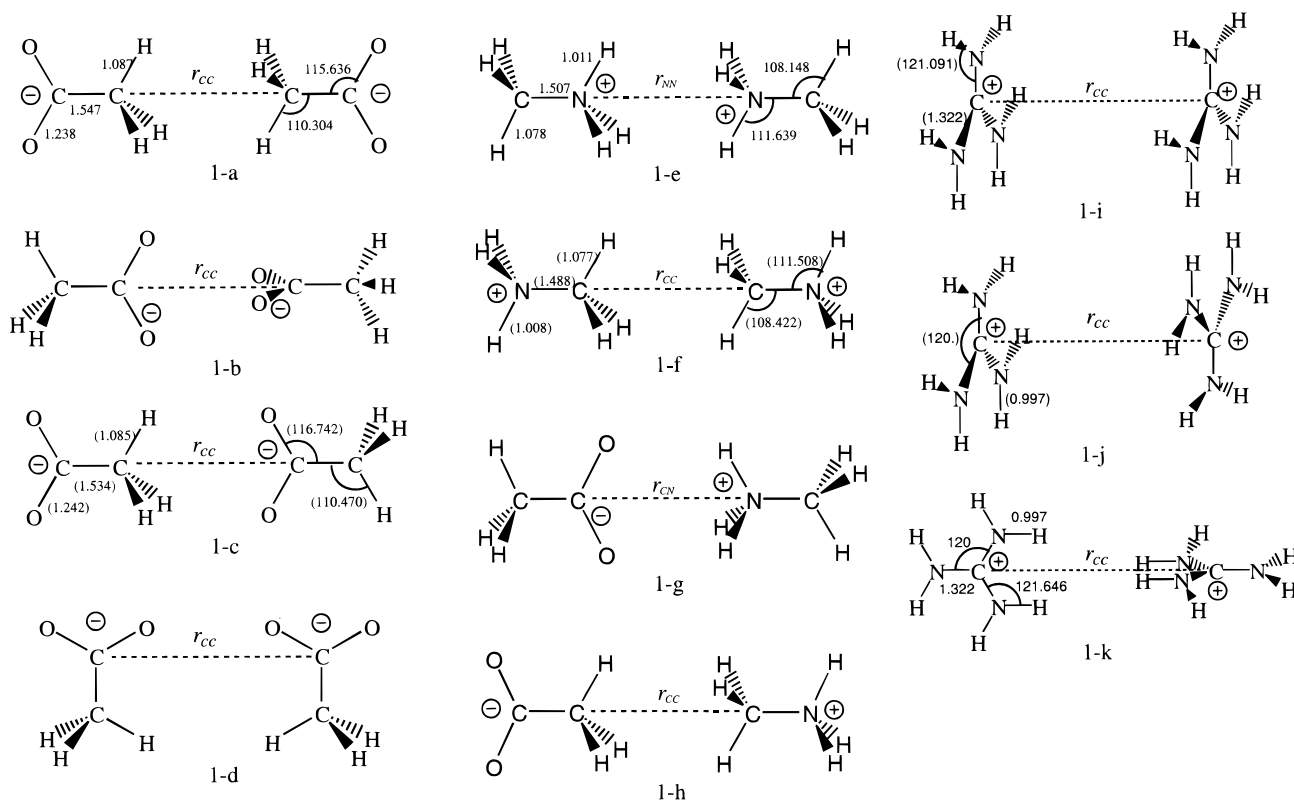


Figure 1. Methylacetate pair with (a) two methyl groups in contact, model OC...CO, (b) two carboxylates in contact, model CO...OC, (c) two dipoles in head-to-tail arrangement, model CO...CO, and (d) two dipoles in parallel arrangement, model CO...CO parallel, configurations. Methylammonium pair with (e) two ammonium groups in contact, model CN...NC, and (f) two methyl groups in contact, model NC...CN, configurations. Methylacetate and methylammonium with (g) oppositely-charged groups in contact, model, CO...NC, and (h) methyl groups in contact, model OC...CN. Two guanidiniums in (i) eclipsed arrangement, model G-G eclipsed, (j) staggered arrangement, model G-G staggered, and (k) perpendicular arrangement, model G-G perpendicular, configurations. The bond lengths and bond angles in parentheses are the optimized geometries in water; those not in parentheses pertain to the gas phase.

calculations. The reference states of ion pair A and B in the gas phase and in aqueous solution are $(E_A^g + E_B^g)$ and $(E_A^{aq} + E_B^{aq})$, respectively.

Results and Discussion

In Figure 2, the stabilization energies of the ion pairs in the gas phase are plotted along the interionic distances defined in Figure 1.

Methylacetate Ion Pairs. In Figure 3a, the stabilization energies of the methylacetate ion pairs in aqueous solution at four different orientations are plotted along the interionic distances. For model OC...CO (Figure 1a) two methyl groups are headed toward each other and the two carboxylate ions are far apart; a weak complex is formed when $r_{C...C}$ is about 4.5 Å and $E^{S,aq}$ is -0.34 kcal/mol (Figure 3a). This anion pair is more stable when the two ionic groups are in close contact than when they are far apart [reference state; $(E_{CO}^{aq} + E_{CO}^{aq})$] in aqueous solution.

For model CO...OC, Figure 1b, two acetate ions are headed toward each other and the two methyl groups are far apart and maximally exposed to water; a stable complex is not formed. $E^{S,aq}(r_{O...O})$ is 13.6 kcal/mol when $r_{O...O}$ is 4.5 Å (Figure 3a). Although this ion pair can not form a stable complex, it is stabilized considerably by hydration. In the gas phase, the value of $E^{S,g}$ for this ion pair at 4.5-Å separation is +88 kcal/mol (Figure 2a).

For model CO...CO, Figure 1c, two methyl acetate ions are in contact in head-to-tail orientation; no stable complex is formed. The value of $E_{CO...CO}^{X,g}$ for this ion pair at 4.5 Å is about +52 kcal/mol; the ions are repulsive (Figure 2a). In

aqueous solution, the value of $E^{S,aq}$ is about 2.5 kcal/mol higher than the reference state at 4.5-Å separation of $r_{O...O}$ (Figure 3a).

For model CO...CO parallel, Figure 1-d, two methyl acetates are in parallel orientation; the value of $E^{S,aq}$ is 4.5 kcal/mol (Figure 3a) whereas the value of $E^{S,g}$ is +61 kcal/mol (Figure 2a) at $r_{O...O} = 6$ Å. In this configuration, both acetate ions and methyl groups are much exposed to water except for the contact surfaces between ionic groups and between methyl groups.

Methylammonium Pairs. For two methylammonium ions with their ammonium groups facing each other, model CN...NC, Figure 1e, the value of $E^{S,X}$ is 5.9 and +70 kcal/mol at $r_{N...N} = 4.5$ Å in aqueous solution (Figure 3b) and in the gas phase (Figure 2b), respectively. Although two positive ions are in close contact at 4.5 Å in the aqueous phase, $E^{S,aq}$ is only 5.9 kcal/mol higher than the reference state.

When two methyl groups face each other, model NC...CN, Figure 1f, $E^{S,aq}(r_{C...C})$ has a minimum at $r_{C...C} = 3.5$ Å (Figure 3b). The value of $E^{S,aq}$ is 2.1 kcal/mol in aqueous solution (Figure 3b), whereas this ion pair is highly repulsive, +61 kcal/mol, in the gas phase at 3.5-Å separation (Figure 2b).

Buckner and Jorgensen¹⁵ found, from an MC simulation of $(CH_3)_4NCl$ in aqueous solution, that $(CH_3)_4N^+ \cdots (CH_3)_4N^+$ is purely repulsive. There is experimental evidence⁴⁵ for tetraalkylammonium ion pairing especially when the size of the alkyl group increases. Buckner and Jorgensen mentioned that,

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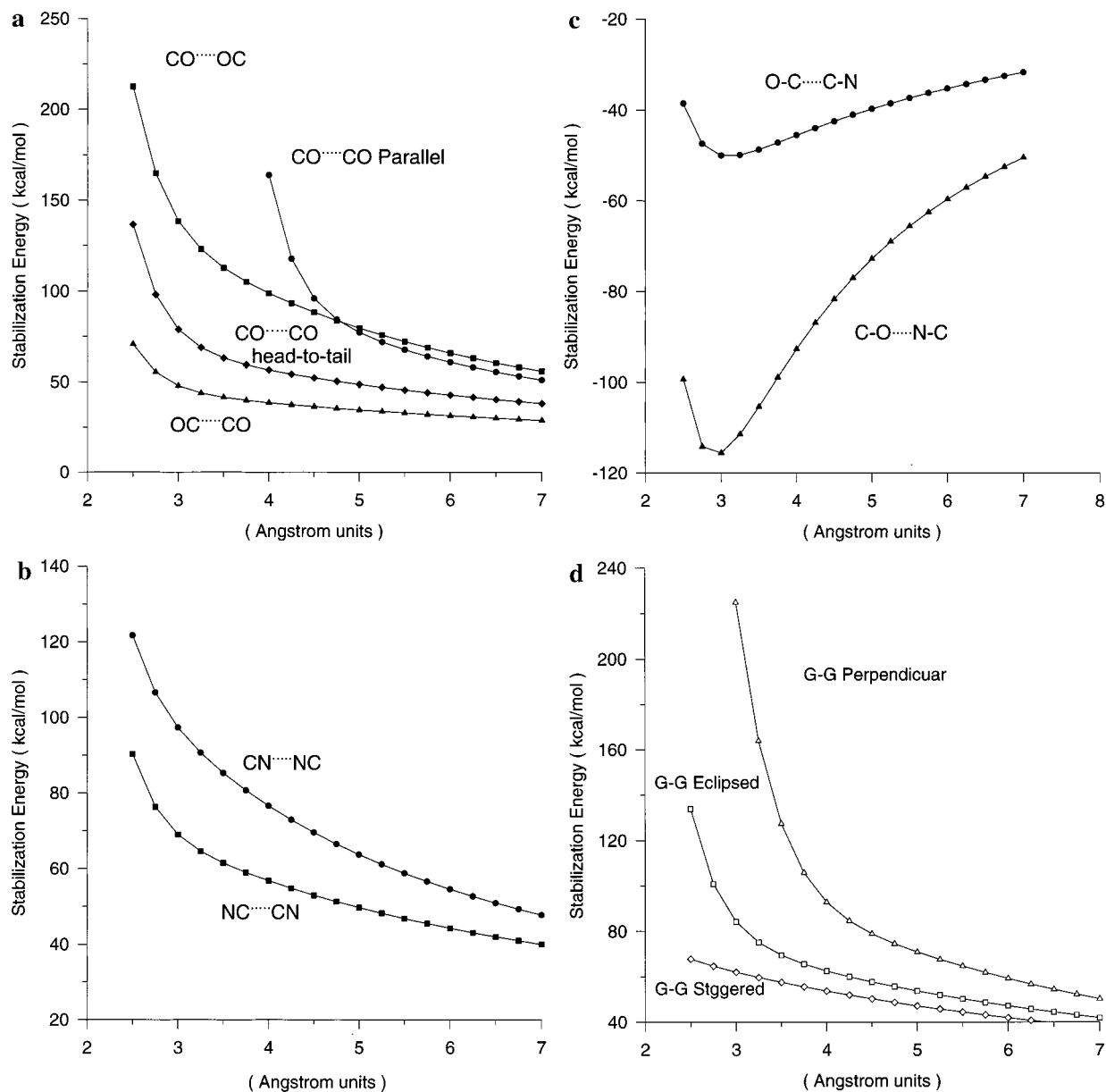


Figure 2. The gas phase stabilization energy, $E^{S,g}$, of (a) methylacetate pairs, (b) methylammonium pairs, (c) methylacetate and methylammonium pairs, and (d) guanidinium pairs.

for the large tetraalkylammonium, hydrophobicity is claimed to overcome the electrostatic repulsion. But, in the case of $(\text{CH}_3)_4\text{N}^+$, the two forces are apparently more in balance.

Methylacetate–Methylammonium Pair. When the charged groups of two oppositely charged ions, methylacetate and methylammonium, are in contact, as carboxylate and ammonium in model $\text{CO}\cdots\text{NC}$, Figure 1g, a stable complex is not formed in aqueous solution (Figure 3c) whereas a very stable complex is formed in the gas phase (Figure 2c). The value of $E^{S,X}_{\text{CO}\cdots\text{NC}}$ of the complex is 18.0 and -105 kcal/mol at $r_{\text{O}\cdots\text{N}} = 3.5$ Å in aqueous solution and in the gas phase, respectively. In aqueous solution, this ion pair does not form a stable complex although two oppositely charged ions are in close contact. In aqueous solution, this ion pair has an energy minimum although it is higher than the reference state. In this complex, two methyl groups are maximally exposed to water, and the ionic groups are least exposed to water.

When two methyl groups face each other, the two methyl groups are least exposed to water, model $\text{OC}\cdots\text{CN}$, Figure 1h,

the complex has an energy minimum around $r_{\text{C}\cdots\text{C}} = 3.5$ Å in aqueous solution, and the value of $E^{S,ag}_{\text{CO}\cdots\text{CN}}$ (at $r_{\text{C}\cdots\text{C}} = 3.5$ Å) is much higher than the reference state ($E_{\text{CO}}^{aq} + E_{\text{CN}}^{aq}$), $+35.5$ kcal/mol, whereas in the gas phase, a very stable complex is formed at 3.5 Å, and the value of $E^{S,g}_{\text{CO}\cdots\text{CN}}$ (at $r_{\text{C}\cdots\text{C}} = 3.5$ Å) is -49 kcal/mol.

For oppositely charged ion pairs, $(\text{CH}_3)_3\text{C}^+\cdots\text{Cl}^-$ and $(\text{CH}_3)_4\text{N}^+\cdots\text{Cl}^-$ were investigated by Jorgensen et al.^{15,46} with MC simulations. The PMF of the $(\text{CH}_3)_3\text{C}^+\cdots\text{Cl}^-$ ion pair has a well-defined minimum for a contact ion pair at a $\text{C}\cdots\text{Cl}$ distance of 2.9 Å, $+2$ kcal/mol, and another broad minimum for the solvent-separated form occurs at 5.75 Å, -2 kcal/mol. The shape of the PMF of the $(\text{CH}_3)_4\text{N}^+\cdots\text{Cl}^-$ is similar to that for the $(\text{CH}_3)_3\text{C}^+\cdots\text{Cl}^-$ ion pair. The first minimum is located at an $\text{N}^+\cdots\text{Cl}^-$ distance of 6.25 Å, about -0.3 kcal/mol, and the second is located at 7.75 Å, about -1.4 kcal/mol. As in our calculations, the oppositely charged ion pairs do not form stable complexes in spite of the strong electrostatic attractive interaction between the ions.

Guanidinium Pair. For the guanidinium pair, three configurations, model G-G staggered, G-G eclipsed, and G-G perpen-

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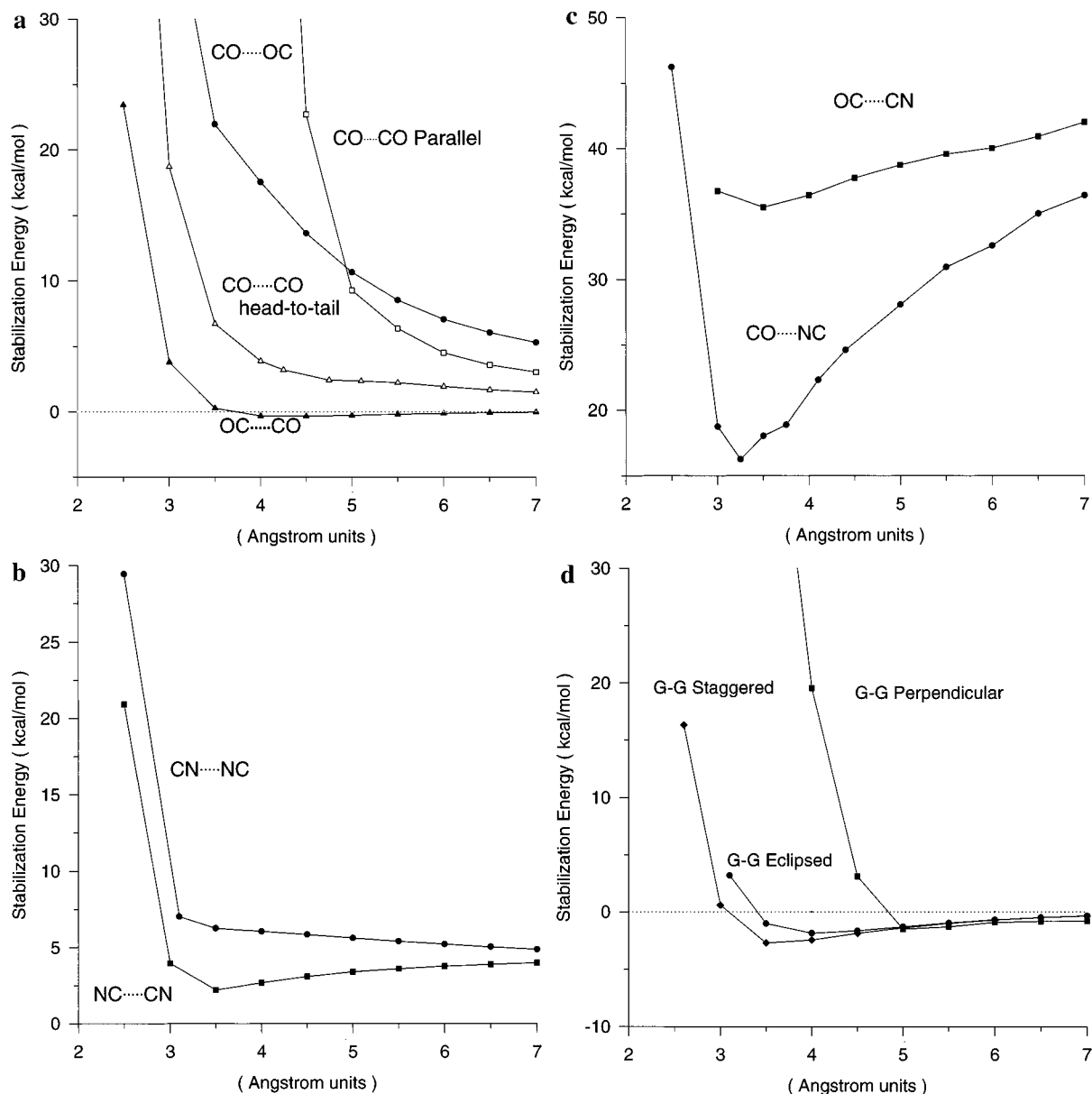


Figure 3. The stabilization energy in aqueous solution, $E^{S,aq}$, of (a) methylacetate pairs, (b) methylammonium pairs, (c) methylacetate and methylammonium pairs, and (d) guanidinium pairs.

dicular, Figure 1i, j, and k, respectively, were investigated. For all these configurations, the guanidinium pairs form stable complexes in aqueous solution (Figure 3d) whereas all the ion pairs are very repulsive in the gas phase (Figure 2d). The eclipsed form has a minimum at $r_{C...C} = 4 \text{ \AA}$, with $E_{G...G}^{S,aq} = -1.9 \text{ kcal/mol}$, and the staggered form has a minimum at $r_{C...C} = 3.5 \text{ \AA}$, with $E_{G...G}^{S,aq} = -2.7 \text{ kcal/mol}$. The perpendicular configuration, Figure 1k, also forms a stable complex when $r_{C...C}$ is 5.0 \AA , with $E_{G...G}^{S,aq} = -1.5 \text{ kcal/mol}$.

With MC simulations, Bouden et al.¹⁶ obtained a broad minimum in the PMF for the contact guanidinium pair, occurring at $r_{C...C} = 3.3 \text{ \AA}$ in aqueous solution. The difference between the minimum free energy at the contact ion pair and at the maximum free energy point at $r_{C...C} = 5.5 \text{ \AA}$ in their PMF is about 9.5 kcal/mol ; the minimum free energy configuration is a staggered-like form. They concluded that the interaction between guanidinium ions in aqueous solution may be dominated by a hydrophobic interaction. In our calculation, the value of $E^{S,aq}$ of the G-G staggered model at $r_{C...C} = 3.5 \text{ \AA}$ was found to be -2.7 kcal/mol . From the results of Bouden et al.,¹⁶ Magalhaes et al.,¹³ and this work, it can be concluded that

two guanidinium ions located near the protein surface can be stabilized by hydration and can form a stable cluster.

Magalhaes et al.¹³ concluded that the behavior of the electrostatic potential around the ion pair, compared with that of the separated ions, reflects the bridging role of the water molecules that keep the two guanidinium ions close to each other.

Like-charged ion pairs at some special configuration form stable complexes in aqueous solution, Figure 1, a and i to k. Even when the like-charged groups are in contact (Figure 1, b, d, and e), the degree of repulsion in aqueous solution is weak, compared with the repulsion in the gas phase. This tendency can be explained by stabilization by the water molecules around the solvent cavity formed by the ion pair. Once two like-charged ions approach closely, the water molecules at the surface of the cavity feel the electric field produced by the two ions. Therefore, the water molecules located around the cavity are stabilized by the stronger electrostatic field which is produced by the two ions than by the one singly charged ion. Especially, in the case of Figures 1a and 1f, the ionic groups are maximally exposed to water, whereas the nonpolar groups, $-\text{CH}_3$, are least

exposed to water. In this kind of configuration, the favorable water–ionic group contacts are maximized and the unfavorable water–nonpolar group contacts are minimized. The latter is the origin of the hydrophobic interaction.

The instability of the models CO···NC (Figure 1g) and OC···CN (Figure 1h) can be explained in similar terms as above. The water molecules located around the cavities of the model CO···NC and OC···CN complexes are less stabilized compared with the water around the cavity of the separate ions, CH₃CO₂[−] or CH₃NH₃⁺. The electric fields around the ion pair cavity are cancelled because the two ions are oppositely charged. When the two ions are in contact at the methyl groups, Figure 1h, the complex can be regarded as a dipole in which one positive and one negative charge center is located at each end of the complex. The electric field around this complex dipole is weaker than those around the CH₃CO₂[−] or CH₃NH₃⁺. Although the electrostatic interaction energy for $-\text{CO}_2^- \cdots \text{H}_3\text{N}^+$ of the model CO···NC is very large, this electrostatic interaction cannot overcome the destabilization of the water molecules around the cavity due to the cancellation of the electrostatic field. Therefore, it cannot form a stable complex. For Figure 1h, although the ionic groups are maximally exposed and the methyl groups are least exposed to water, a stable complex is not formed because the water molecules around the cavity are destabilized because the electric fields produced by the oppositely charged ions are cancelled.

From a comparison of models OC···CO and NC···CN with OC···CN, it is evident that one cannot predict the stabilization of ion-ion pairs in aqueous solution only with the sums of the interactions between nonpolar groups and between polar groups. The stabilization of the solute pair depends strongly on the stabilization of the environments around the interacting molecules.

For the polar solutes, the *solvent-induced attraction* arises mainly from (i) the stabilization of the water molecules around the molecular complex by the electrostatic field produced by the solute molecules, and (ii) the tendency to reduce the degree of exposure of nonpolar groups to water. The sum of (i) and (ii) becomes the origin of a *solvent-induced attraction* between solutes. It may be convenient to define the sum of all the interaction terms in the solution as an “effective solute–solute interaction”. If one plots it along some intersolute coordinate, it becomes a PMF. The nonbonded (van der Waals) interaction between nonpolar groups contributes only a small amount to this *effective solute–solute interaction*. The aggregation of nonpolar molecules can occur in aqueous solution although they have only weak nonbonded interaction.^{47–50} To maximize the

solvent-induced attraction, the electrostatic field around the molecular pair must be maximized and the exposure of nonpolar groups to water minimized. Since several factors work cooperatively to produce the effective solute–solute interaction, especially between polar solutes, it is not a simple matter to predict the stability of the solute pair in aqueous solution.

Although the PCM calculation cannot explain the conformation of the explicit water molecules around an ion pair, it can be used for the study of the ion-ion interaction in solution and the role of the solvent as a polarizable medium.

Conclusion

We have calculated the stabilization energy of some organic ion pairs which appear frequently in proteins. To include the effect of the aqueous solution, PCM *ab initio* MO calculations were carried out. The methylacetate pair can form a weak complex in aqueous solution even though it encounters strong electrostatic repulsion. When the ionic groups of methylacetate and methylammonium are in contact, they cannot form a stable complex although this ion pair has very strong electrostatic attraction in the gas phase, -105 kcal/mol at 3.5 Å. If two methyl groups are in contact in this ion pair, a stable complex cannot form. A guanidinium pair can form stable complexes at several configurations in aqueous solution even though these pairs are electrostatically very repulsive in the gas phase. From the analysis of the results, it can be said that the pairing of ions in aqueous solution cannot be explained simply by the sums of the interactions of the nonpolar groups and the electrostatic interaction of the ionic groups. This problem can be solved by introducing the water in the calculations of aqueous solutions whether it is an explicit or implicit expression of the water solvation.

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Supporting Information Available: Tables of energy and structure data (11 pages). See any current masthead page for ordering and Internet access instructions.

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