Like-Charge Ion Pairing in Water: An ab Initio Molecular Dynamics Study of Aqueous Guanidinium Cations

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Abstract

The existence of like-charge guanidinium-guanidinium contact ion pairs in water is established by ab initio molecular dynamics simulations. Despite direct electrostatic repulsion a contact ion pair is observed between two guanidinium cations, stabilized primarily by their amphiphilic behavior and van der Waals interactions. In a control simulation performed for two aqueous ammonium cations no such contact ion pair is formed. This is the strongest computational evidence so far for the existence of specific contact ion pairing between guanidinium cations in water, with important implications for biological processes involving arginine-rich proteins.

TOC graphics

Keywords: like-charge ion pairing, guanidinium ions, ammonium ions, solvation, ab initio molecular dynamics, van der Waals interactions
Ion-specific effects play a vital role in living systems. They are important for essential biological functions, such as maintaining the electric potential between cell exterior and interior\(^1\) and enzymatic activity in different ionic solutions.\(^2,3\) A very counter-intuitive example of ion-specific interactions can be found in pairing between like-charged ions. It has been suggested previously that pairing between positively charged arginine residues is abundant in proteins\(^4\) and may be one of the driving forces of formation of protein dimers.\(^5\) Arginine-arginine pairing can also be among the factors responsible for binding between species B adenovirus and its receptor\(^6\) and for the enzymatic activity of cytochrome c oxidase.\(^7\)

Direct experimental detection of like-charge aqueous ion pairs formed by two guanidinium cations (Gdm\(^+\)), with Gdm\(^+\) being the constitutive component of the arginine side chains in proteins, remains elusive.\(^8,9\) Nevertheless, indirect experimental evidence, such as the slow down of electrophoretic mobility of oligoarginines by guanidinium cations,\(^10\) implies that like-charge Gdm\(^+\) ion pairs may indeed be stable in water. Like-charge ion pairing has also been studied by various computational methods, including molecular dynamics,\(^11–14\) Monte Carlo simulations,\(^13,15\) and quantum chemical calculations,\(^16,17\) which indicate that Gdm\(^+\) forms contact ion pairs in water. However, since the molecular dynamics simulations with different force fields show varying ion-pairing strength between the two guanidinium cations,\(^18\) it is important to address this issue also using ab initio approaches. A very recent quantum mechanical cluster study\(^16\) showed that the Gdm\(^+\)-Gdm\(^+\) contact ion pair with twelve water molecules represents a weakly stable (by about 0.04 eV) minimal structure, while in an aqueous bulk continuum this ion pair was calculated to be stabilized by about 0.09 eV.\(^17\) In order to obtain more conclusive computational evidence and characterize the electronic structural origin of the stability of the Gdm\(^+\)-Gdm\(^+\) like-charge ion pair, we present here the results from extensive ab initio molecular dynamics (AIMD) simulations of a pair of guanidinium cations in ambient liquid water, contrasting its behavior to a control system consisting of two aqueous ammonium cations.

AIMD simulations were performed for two guanidinium cations and two chloride anions dissolved in 62 water molecules in the unit cell. In parallel, simulations where the guanidiniums were
replaced by two ammonium cations, were also performed. Two different starting configurations were prepared; in the first one, Gdm$^+$ cations were put in a stacked configuration at a distance of 3.4 Å and then hydrated. In the second one, guanidinium cations were placed further apart, at the distance of 6 Å and, in contrast to the first starting configuration, water molecules were placed also in-between guanidinium cations. A similar starting condition was also prepared for the ammonium cations. Each of the trajectories was propagated for 50 ps with a time step of 0.5 fs. We employed the B-LYP density functional\textsuperscript{19} with an empirical dispersion correction (B-LYP-D),\textsuperscript{20} with the electronic density converged in each step (Born-Oppenheimer dynamics). As shown previously, dispersion is important for correct energetics of the interaction between guanidinium cations.\textsuperscript{16} Pseudopotentials\textsuperscript{21} replaced the core electrons. The Kohn-Sham orbitals were expanded into an atom centered double-zeta quality DZVP-MOLOPT-GTH basis set\textsuperscript{22} in conjunction with an auxiliary plane wave basis set with a cutoff of 280 Å for the electronic density.\textsuperscript{23} Periodic boundary conditions were used with fixed unit cell of dimensions of 12.65 Å $\times$ 12.65 Å $\times$ 12.65 Å. Simulations were performed at 300 K\textsuperscript{24} using the CP2K program package.\textsuperscript{25}

For the purpose of testing the reliability of the B-LYP-D method used in AIMD simulations, we first benchmarked it against more accurate perturbative MP2 and coupled cluster CCSD(T) calculations on small Gdm$^+$-water clusters. These calculations were performed using the Gaussian09 program.\textsuperscript{26} Results for the complexation energy $\Delta E_c$ between Gdm$^+$ and one or three water molecules using different basis sets are presented in Table 1. The comparison in Table 1 shows

Table 1: Complexation energies $\Delta E_c$ for guanidinium cation and one water molecule (Gdm + 1W) and guanidinium ion pair with three water molecules (given in kcal mol$^{-1}$), respectively, obtained by B-LYP-D and MP2 geometry optimizations with different basis sets. CCSD(T) single point energy calculations were performed at the MP2 geometry with a given basis set.

<table>
<thead>
<tr>
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<th>Gdm + 1W</th>
<th>Gdm-Gdm + 3W$^a$</th>
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<tr>
<td></td>
<td>$\Delta E_c$</td>
<td>B-LYP-D</td>
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<tr>
<td>cc-pVDZ</td>
<td>-25.3</td>
<td>-22.2</td>
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<tr>
<td>aug-cc-pVDZ</td>
<td>-17.4</td>
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<tr>
<td>cc-pVTZ</td>
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<tr>
<td>aug-cc-pVTZ</td>
<td>-16.9</td>
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$^a$ taken from reference 16.
that augmentation of the basis set by diffuse functions is essential for proper description of the interaction between Gdm\(^+\) cation and surrounding water molecules. Thus, we chose to use in the production runs the DZVP-MOLOPT-GTH basis set, which is comparable in size to the aug-cc-pVDZ basis set and also contains diffuse functions.\(^22\) The comparison of complexation energies \(\Delta E_c\) shown in Table 1 indicates that the BLYP-D/DZVP-MOLOPT-GTH level of theory is adequate for the purpose of the present study.

Spatial distribution functions of co-ions and water around Gdm\(^+\) or NH\(_4^+\) ion from aqueous bulk AIMD simulations are depicted in Figure 1. In case of Gdm\(^+\) (left panel), another Gdm\(^+\) ion is found with high occurrence in close proximity, forming a contact ion pair with no water molecules between them. Water molecules (and occasionally also chloride counter-ions) form hydrogen bonds with Gdm\(^+\) exclusively in the molecular plane of the ion, being repelled from the hydrophobic faces of Gdm\(^+\). In the control case of two ammonium cations (right panel), no such contact ion pair is formed, with the other NH\(_4^+\) being separated by water molecule(s). The relatively high occurrence of the ammonium solvent-separated ion pair is to a large extent an artifact due to the periodicity of a relatively small system, which does not allow for separations of the two ions larger than half the unit cell size in each dimension. The present system is, nevertheless, large enough to safely distinguish between contact and solvent separated ion pairs, with guanidinium (but not ammonium) cations clearly preferring the former arrangement.

The difference in co-ion pairing and the hydration structure of Gdm\(^+\) vs. NH\(_4^+\) ions can be further inferred from radial distribution functions (RDFs) with respect to the carbon atom of Gdm\(^+\) and nitrogen atoms of NH\(_4^+\), presented in Figure 2. For a pair of Gdm\(^+\), the peak in the RDF is located at 3.7 Å which is the same distance as that at which also the peak in the RDF for water oxygen atoms is located (left panel). This implies that there is no water in-between paired guanidinium ions. These RDFs thus represent a clear signature of formation of a like-charge Gdm\(^+\) contact ion pair. The situation is completely different for the ammonium ion pair where the first peak in the RDF of central nitrogen atoms only appears at distance of 4.7 Å. Since the first peak in the RDF between NH\(_4^+\) and water oxygens occurs at 2.9 Å only solvent separated NH\(_4^+\)-NH\(_4^+\)-
Figure 1: Spatial distribution functions around Gdm$^+$ ion (left; Gdm$^+$ - blue, water oxygen - red, and water hydrogen - white) and NH$_4^+$ (right; NH$_4^+$ - blue, water oxygen - red, and water hydrogen - white). Black arrow points to a water molecule(s) occupying space between two NH$_4^+$.

ion pairs exist with no formation of contact pairs.

The RDFs in Figure 2 are statistically significant and meaningful, nevertheless, AIMD sim-

ulations may be computationally too demanding to allow for a fully converged sampling of the distribution of distances between the two guanidinium cations. In order to check the potential effect of the choice of initial geometry, two very different starting configurations of the two guanidinium ions were prepared. Starting from the first initial geometry, where the two guanidinium ions were in a stacked contact ion pair, this close contact was maintained throughout the whole 50
ps of the simulation. In case of the other initial configuration, where the guanidinium ions were separated by water molecules, a T-shape Gdm$^+$ ion pair was formed first. This T-shaped ion pair with an average central carbon distance of 4.7 Å persisted for another 20 ps (Figure 3), after which a stacked contact ion pair was formed and persisted. This was accompanied with shortening of the carbon-carbon distance and energy stabilization (Figure 3). Accordingly, the angle between the two Gdm$^+$ planes steadily decreased from the value of about 80° which corresponds to the T-shape structure, to values much closer to zero, which in turn correlate with the stacked structure. Note that the existence of the T-shape structure as a local minimum on the potential energy surface was also predicted by model calculations of a guanidinium ion pair in a dielectric continuum representing water, with the stacked contact ion pair being a global minimum.\textsuperscript{17}

![Figure 3: Time evolution of the the angle (green) between the two guanidinium ions and the total potential energy $\Delta E_{\text{pot}}$ (blue). Plotted values are running averages averaged over 2000 fs. The AIMD simulation was started from a solvent separated Gdm$^+$-Gdm$^+$ ion pair, and first unequilibrated 10 ps were discarded from the plot. Representative snapshots of a T-shaped Gdm$^+$ and stacked Gdm$^+$ contact ion pair with characteristic distances between central carbon atoms are presented. The transition between these two structures is indicated by a dashed vertical line.](image)

Recently, a very useful analysis of noncovalent interactions (NCI) has been developed based on the electronic density and its reduced gradient $s = (1/(2(3\pi^2)^{1/3})) |\nabla \rho|/\rho^{4/3})$.\textsuperscript{27} This approach is based on the fact that the reduced gradient describes deviations from the homogeneous electronic distribution.\textsuperscript{28} Low density and low gradient regions in a system, together with the sign of
a second derivative component of the electronic density $\lambda_2$, are then identified with various types of non-covalent interactions, i.e., hydrogen bonds, van der Waals (vdW) interactions, and sterical clashes. These interactions differ in the value of $\text{sign}(\lambda_2) \times \rho$, which is positive for steric clashes, negative for hydrogen bonds, and slightly negative for vdW interactions. We performed the NCI analysis for a set of snapshots from the AIMD for aqueous Gdm$^+$ and NH$_4^+$ ion pairs (Figure 4). In case of the Gdm$^+$ ion pair, the green color of the isosurfaces, which indicates vdW interactions,

Figure 4: Gradient isosurfaces ($s = 0.6$ au) for Gdm$^+$ (upper panel) and NH$_4^+$ ion pairs (lower panel) are displayed for the selected AIMD snapshots. The surfaces are colored on a color scale according to values of $\text{sign}(\lambda_2) \times \rho$ (shown on right), ranging from -0.05 to +0.05 au.

is present in all of the displayed snapshots. These interactions get stronger upon closer contacts of the stacked guanidinium cations (compare snapshots at 30 vs. 45 ps). In contrast to the guanidinium ion pair, green color (or any other color) isosurfaces between NH$_4^+$ cations practically do not occur, which further points to the fact that like-charge contacts are not stabilized for the control system of the pair of aqueous ammonium cations.

The present extensive AIMD demonstrate that a stacked like-charge ion pair forms between two guanidinium cations and, once formed, is stable for the duration of the simulation. The key behind the unusual stability of this "electrostatics-defying" structure$^5$ lies in the amphiphilic nature of the guanidinium (Gdm$^+$) cation. Due to its planarity, aromaticity, and non-uniform charge distribution, the faces of Gdm$^+$ cation are hydrophobic and weakly hydrated, with guanidinium
forming hydrogen bonds with water molecules exclusively in the plane.\textsuperscript{29} This also leads to further stabilization by van der Waals interactions, as evidenced by the present noncovalent interaction analysis. It is important to note that in the case of water separated initial configuration, a T-shape structure was formed first. This structure represents a local minimum on the potential energy surface, with an energetically more favorable stacked structure being formed subsequently and being then stable for the rest of the simulation. Formation of like-charge contact ion pairs requires specific geometric and electronic structure properties - planarity and a delocalized inhomogeneous electronic distribution, such as that present for guanidinium cations. "Normal" ions, such as the control ammonium cations, clearly do not form like-charged contact ion pair, but at best solvent separated pairs, the occurrence of which was enhanced by the finite size of the simulated cell. The present findings, based on an electronic structure description of a bulk aqueous guanidinium solution at ambient conditions, provide the most direct and strongest computational evidence so far for the remarkable and counter-intuitive formation of like-charge Gdm\textsuperscript{+}-Gdm\textsuperscript{+} contact ion pairs in water. Establishing this phenomenon with a solid computational, as well as experimental backing, will allow us to better understand and rationalize biological processes involving interactions within and between arginine-rich proteins.

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