REGULAR ARTICLE

On the effect of external perturbation on amino acid salt bridge: a DFT study

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Abstract. Effect of external perturbation (in terms of external electric field and solvents) on the stability of lysine-aspartic acid salt bridge was analyzed by density functional theory. Because of solvation, interaction energy in the aqueous phase is much lower as compared to gas phase. Interaction energy as well as stability (measured in terms of global hardness, HOMO energy and total electronic energy) are observed to be sensitive towards the strength and direction of the applied electric field. Gap between HOMO energy of the acids and salt bridge also points towards the feasibility of hydrogen bonding.

Keywords. Salt bridge; DFT; DFRT; Electric field; PCM.

1. Introduction

The stabilization of molecular conformations by the attractive interaction between oppositely charged ions (e.g., salt bridges) is of relevance in many areas of science. In particular, biological systems such as proteins, often contain salt bridges between ionic side chains that govern their structure and functions.^{1,2} Salt bridges can occur intra-molecularly, between a charged amino acid side chain and other groups within the protein; or inter-molecularly, between the amino acid side chain and charged groups on a ligand or other biomolecules.³ Salt bridges are instrumental in determining binding specificity during protein–protein association and it contributes to the energetic as well. Moreover, a salt bridge compensates to the free energy requirement for binding.^{4–7} Lysine (lys) often forms salt bridge with aspartic acid (asp) and the salt bridge plays crucial role in the structure of the proteins. During salt bridge formation, hydrogen bonding between the $-\text{NH}_3^+$ (of lys) group and $-\text{COO}^-$ (of asp) contribute to the strength of the salt bridge.

In recent years, Density Functional Theory (DFT) has found enormous application in the interpretation of chemical reactivity.^{8–14} Density Functional Reactivity Theory (DFRT) can be used to estimate reactivity parameters. These parameters, called reactivity descriptors, defined within the framework of density functional

theory are global hardness (also called chemical hardness), electrophilicity, chemical potential, local softness, Fukui functions, *etc.*¹⁵ These descriptors have been tested by several research groups and are found to be very useful in rationalizing the reactivity patterns in the molecular systems.^{16–20} Geerlings *et al.*, and Chattaraj *et al.*, have reviewed the theoretical basis for these descriptors and their applicability.^{21,22} Some of the recent developments and applications of these descriptors are highly impressive.^{23–27}

The ionic environment in cellular environment imparts some sort of electric field which affects the reactivity of the biomolecules. In a cellular environment, the biomolecules may experience electric field and their reactivity pattern as well as stability may be altered. Moreover, when tissue is exposed to external electric field, it gets damaged.²⁸ Effect of external electric field on the stability and reactivity of different molecular systems have been studied earlier.^{29–31} Effect of external electric field on chemical reactions is also familiar.^{32–35} The effect of electric field on the chemical reactivity has been carried out in a number of occasions.^{36–46} Chattaraj and co-workers have observed the effect of electric field on the global and local reactivity indices and confirmed that electric field considerably affects all the local reactivity indices and thereby the site selectivity of attack.^{37–39} Pal and co-workers have studied the behaviour of these descriptors in presence of external electric field as well as in solvent media.^{39–42} Accordingly, introduction of electric field influences both physical and chemical properties

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of various molecular systems. In addition, a number of studies describe the effect of external electric field on biological molecules.^{43–46} Moreover, the aqueous environment within the cell is expected to contribute to the stabilized the salt bridge.

Herein we have made an attempt to gauge the stability of the lysine-aspartic acid salt bridge (lys-asp) in terms of interaction energy and reactivity descriptors in presence of external perturbation by external electric field and solvents by using DFT and DFRT. As the structure of proteins is extremely important in biology, understanding the stability of the salt bridge in biological environment (which is mainly the polar and charged ions that produce the electric field) is thus expected to make an insight on to the structure of the proteins and hence bears importance.

2. Theoretical and computational details

In DFT, global hardness (η) is defined as the second derivative of energy with respect to the number of electrons respectively.^{47,48} Use of finite difference approximation and Koopmans' theorem⁴⁹ lead to the working formulae for η as:

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2} \quad (1)$$

where, E_{HOMO} is the energy of the HOMO (highest occupied molecular orbital) and E_{LUMO} is energy of the lowest unoccupied molecular orbital. The geometrical minima of the species are obtained using 6-31+G(d,p) basis set with Becke three parameter exchange and Lee, Yang and Parr correlation functional (B3LYP)^{50,51} and is confirmed by the absence of any negative frequency. After locating the minima, single point energy calculations have been carried out at different external electric field values applied along six directions (positive and negative directions of x , y and z axis; the sign + means that the field is applied along + direction of the axis and – sign means that the field is applied along the – direction of the axis). It was shown that the strength of biological systems such as DNA base pairs can experience intense local electric

fields close to the order of $\sim 10^{10} \text{ Vm}^{-1}$.³² Therefore, chosen strength of the external field ranges from 0.00 a.u. to 0.01 a.u. [1 a.u. = $51.4 \text{ V/\AA} = 51.4 \times 10^{10} \text{ Vm}^{-1}$].

Strength of hydrogen bonds is expressed in terms of interaction energy (ΔE_{int}) which is calculated using super molecular approach [for $A + B \rightarrow AB$, $\Delta E_{\text{int}} = (E_{AB}) - (E_A + E_B)$, where, E is the total energy of the corresponding species]. When interaction energies are calculated, basis set superposition error (BSSE) is taken into account by using counterpoise = N.^{32,52} To observe the impact of solvent media, we repeated our observations in aqueous phase using PCM (Polarizable Continuum Model).^{53–55} All the calculations have been carried out using Gaussian09.⁵⁶

3. Results and Discussion

Hydrogen bonding interaction is primarily electrostatic in nature and electrostatic potential in an outer surface of a molecule will therefore be well suited for predicting the nature of this kind of interaction. Figure 1 presents the isosurface diagram (with 0.001 a.u. density) of lys and asp which depicts a negative charge region around the $-\text{COO}^-$ group, acting as H-acceptor and a positive charge on the $-\text{NH}_3^+$ group which facilitate hydrogen bond formation between the two moieties.

It is important to note that the $-\text{COO}^-$ group of asp accepts hydrogen from the $-\text{NH}_3^+$ group of lys. The N-H bond length in isolated lys molecule is 1.03 Å and in the salt bridge with asp this distance becomes 1.63 Å and the O-H bond length is observed to be 1.04 Å, (Figure 2). Thus, a single linear hydrogen bond formation is observed with $\theta(\angle\text{NHO}) = 174.75^\circ$.

3.1 Variation of total electronic energy and interaction energy

The time-independent nonrelativistic electronic Hamiltonian, under the Born–Oppenheimer approximation can be written as:

Figure 1. Isosurface diagram of lys and asp.

Figure 2. Gas phase optimised structure of the lys-asp salt bridge.

$$\hat{H} = -\frac{1}{2} \sum_{i=1}^N \nabla_i^2 - \sum_{i,A=1}^N \frac{Z_A}{r_{iA}} + \sum_{i<j}^N \frac{1}{r_{ij}} \quad (2)$$

In the Hamiltonian, the external electric field is introduced as a perturbation parameter. The dipolar interaction of the Hamiltonian with the electric field, F can be written as,

$$\hat{H} = \hat{H}_0 - \hat{d} \cdot \vec{F} \quad (3)$$

where, $\hat{H}_0$ is the unperturbed Hamiltonian and $\hat{d}$ is the dipole moment operator. In the presence of external perturbation like external electric field, the total energy of the system can be written as,

$$E = E_0 - \sum_i d_i F_i \quad (4)$$

where, E_0 is the energy of the system at zero field, d_i is the permanent dipole moment and F_i is the strength of the field. The effect of the external electric field on total electronic energy can easily be estimated using equation (4). Total electronic energy (E_{el}) of a system is a measure of stability of a system; accordingly, we studied the variation of total electronic energies of the salt bridge. It is interesting to note that application of external electric field on salt bridge in both gas and aqueous phases perturbs the E_{el} of the system, (Figure 3).

Application of the electric field along $-x$, $-y$ and $+z$ directions stabilizes the salt bridge by lowering (more negative) the E_{el} of the system in both the phases. A field of strength 0.010 a.u. applied along $-x$ direction drop the gas phase E_{el} by 0.047748 a.u. (29.96 kcal/mol) and application of the same field strength along $-y$ and $+z$ directions results in drop of E_{el} in gas phase by 0.008196 a.u. (5.14 kcal/mol) and 0.021563 a.u. (13.53 kcal/mol) respectively, (Figure 3a). The dipole moment of the salt bridge is calculated to be 10.5 D and is aligned along the x -axis, Figure 2. As can be realized from equation (4), that in presence of EEF, the E_{el} energy of a molecular system, depends on the dipole moment of the system. It is observed that the total electronic energy of the salt bridge is much sensitive towards the electric field applied along x -axis as compared to y - or z -axes. In essence, one must not ignore the effect of electric field while dealing with systems possessing high dipole moment. As the biomolecules possess substantial dipole moment and the presence of ions as well as the polar sugar-phosphate backbone and charged histones exert some electric field within the cellular environment,⁵⁷ the obtained results confirm a significant role of electric

Figure 3. Variation of total electronic energy of the lys-asp salt bridge in, (a) gas and (b) aqueous phase with external electric field. (■-along x -axis, ●-along y -axis, Δ-along z -axis).

field on the energy of the molecular systems and hence on their stability.

Incorporation of aqueous phase does not play any significant role on the variation pattern of E_{el} , albeit, the aqueous phase energies are higher (more negative) than the gas phase values (Figure 3a–3b). For example, a field of strength 0.01 a.u. applied along $-x$, $-y$ and $+z$ directions lowers the E_{el} values by 0.0564 a.u. (35.43 kcal/mol), 0.008208 a.u. (5.15 kcal/mol) and 0.025705 a.u. (16.13 kcal/mol) respectively, (Figure 3b). Thus, the electronic energy of the system is observed to be sensitive towards the strength and orientation of the applied field and incorporation of aqueous phase stabilizes the salt bridge to some extent.

The gas phase interaction energies (ΔE_{int}) are calculated to be too high; -115.83 kcal/mol. However, incorporation of aqueous phase results a spiky reduction in ΔE_{int} (obtained from single point calculation in aqueous phase) owing to extensive solvation of the constituents and is calculated to be -13.31 kcal/mol. The considered amino acids bear charges (+1 charge in lys and -1 charge on asp) and the salt bridge bears no charge. An obvious impact of presence of charges on the amino acids is that the constituent amino acids undergo extensive solvation compared to the salt bridge which results a sharp fall in interaction energy. Usually, molecular systems involving charges or high dipole moment undergo extensive solvation in polar solvent media which leads to a sharp decrease in interaction energy. Earlier study also witnessed similar conclusion in case of interaction between aziridinium ion and nucleophiles.⁵⁸ Further, to check the effect of aqueous medium on the proton transfer in the salt bridge, we re-optimized the geometry in the same solvent. The re-optimized geometry witnessed slight shifting of the proton to the O site. In gas phase, the $N \cdots H$ and $O \cdots H$ distances are 1.63 and 1.04 Å,

respectively, which advocates transfer of the NH proton towards the O site in gas phase, and in the re-optimized structure in solvent phase these distances become 1.48 and 1.08 Å, respectively. Interaction energy calculated from the re-optimized geometry is -12.24 kcal/mol, not far apart from that obtained from single point calculation (-13.31 kcal/mol).

This result infers a hefty impact of a polar solvent on the interaction between the two components. Importantly, in both the phases (gas and aqueous) ΔE_{int} of the salt bridge is well affected by the application of the electric field; pattern of variation of ΔE_{int} with applied field strength in both gas and aqueous phase are similar (Figure 4).

In both the phases, maximum variation in ΔE_{int} is observed when the field is applied along x or z -axis. Interestingly, it is evident that the interaction energy sharply increases on changing the direction of applied field from $+x$ to $-x$ and from $-z$ to $+z$ direction. Application of the field along y axis also leads to a variation in the interaction energy; however, variation is not as sharp as compared to the x or z -axis. In aqueous phase, application of the field along $+x$ and $+z$ direction leads to a repulsive interaction and concomitant destabilization of the salt bridge. Thus, the direction of the applied field makes an important contribution towards ΔE_{int} . In aqueous phase, application of the field (of strength 0.01 a.u.) along $-x$, $+y$ and $+z$ directions increase the ΔE_{int} to -0.06735 a.u. (-42.26 kcal/mol), -0.02691 a.u. (-16.88 kcal/mol) and -0.05094 a.u. (-31.96 kcal/mol). The reverse is observed when the field is along $+x$, $-y$ and $-z$ directions; and at high field strength applied along $+x$ and $-z$ directions, a repulsive interaction is observed (positive ΔE_{int}), 0.026677 a.u. (16.74 kcal/mol) and 0.007676 a.u. (4.81 kcal/mol), respectively. Therefore, an inescapable role of solvent

Figure 4. Variation of interaction energy in lys-asp in, (a) gas and (b) aqueous phase with external electric field, (c) variation of interaction energies with the separation distances between the two amino acid moieties. (■)-along x -axis, (●)-along y -axis, (Δ)-along z -axis).

Figure 5. Change in the ESP surface in presence of electric field.

phase even in presence of external electric field can be construed from the calculated ΔE_{int} values.

Response of the ΔE_{int} towards external electric field and solvent phase are different. A sharp drop in interaction energy is evident in presence of aqueous phase, whereas the impact of an external electric field on ΔE_{int} (rise/fall) depends on the orientation and strength of the applied field. This is on account of the directional nature of the electric field which is absent in case of the solvent. Results obtained advocate that the protein structure is affected in presence of external field as well as solvent phase. Further, we analyzed the variation of the interaction energy as a function of separation distances between the two amino acid moieties in gas phase and in presence of electric field of strength 0.0020 a.u. applied along $+x$ and $-x$ directions (Figure 4c). It is to be noted that as the two moieties approach each other, interaction energy increases and gets a maximum value at 1.04 Å.

The applied electric field interacts with the electron cloud and redistribution of the electron cloud may take place in presence of external electric field. This can easily be visualized with the help of ESP surface. A comparison of the ESP surfaces in absence of the electric field and at a field of strength 0.010 a.u. applied along $-x$ direction are shown in Figure 5. It can be seen from Figure 5 that electron cloud is redistributed in presence of the electric field and its impact on the interaction energy can be quantified using equation (4).

3.2 Variation of reactivity parameters of the salt bridge

Reactivity parameter of a system is indicative of their chemical stability and hence is important from chemical viewpoint. Variation of the global hardness of the salt bridge gas and aqueous phase with applied field strength along the three axes are presented in Figure 6a–b.

The gas phase global hardness of the salt bridge decreases noticeably on both sides of the axes. Upon application of external electric field along x , y and z axes, the global hardness decreases along both the direc-

tions. But upon application of a field strength of 0.002 a.u. along $-x$, $-y$ and $+z$ directions, the global hardness increases slightly. Variation of the global hardness follows the same trend in both gas and aqueous phases, although aqueous phase hardness values are higher than those in the gas phase, indicating greater stability to the salt bridge in aqueous phase. For example, application of field strength of 0.01 a.u. along $-x$ direction raised the global hardness by 0.018485 a.u. (11.59 kcal/mol) in aqueous phase. According to the maximum hardness principle (MHP), maximum hardness leads to maximum stability. Here, in accordance with this principle, greater stability in the aqueous phase may be attributed to the dipole-dipole interaction between the salt bridge and solvent. MHP is found to be applicable in a wide range of molecular species.^{59–67} Earlier studies also confirmed that the MHP worked well in illustrating the chemical reactivity of drug molecules in ground state in presence of external electric field.⁶⁸

This observation advocates that irrespective of increase/decrease of the total E_{el} , the overall stability of the salt bridges decreases on application of external electric field. However, unlike the variation of total E_{el} , reactivity parameter does not depend on the direction of the applied electric field but depends on the field strength only.

3.3 HOMO-LUMO perspective

To scrutinize the role of hydrogen bonding in the salt bridge formation, we have calculated the energy of the LUMO of lys (considering it as a H-donor); energy of HOMO of asp (considering it as a H acceptor). In the synergic effect of hydrogen bonding interactions of the type, $B + HA \leftrightarrow BHA$ (where B is lys; HA is asp, BHA is the salt bridge), intermolecular hydrogen bond formation is favoured when the HOMO of the BHA has lower energy than the HOMO of B or LUMO of HA. Subsequently, the energy of separation, $\Delta E (= E_{\text{HOMO}, BHA} - E_{\text{HOMO}, B})$ in the absence of any external electric field, is calculated. Results are presented in

Figure 6. Variation of global hardness along three axes. (a) in gas phase; (b) in aqueous phase (■-along x -axis, ●-along y -axis, △-along z -axis).

Figure 7. (a) Schematic presentation for energy separation of HOMO and LUMO during formation of salt-bridge; (b) LUMO of lys; (c) HOMO of asp.

Figure 7a. The observed gas phase ΔE values for asp is -114.71 kcal/mol and in aqueous phase it is reduced to -22.60 kcal/mol. Earlier, Sarma *et al.* reported a correlation between ΔE values and ΔE_{int} (in case of hydrogen bonded system) which showed an increase in ΔE_{int} with an increment in ΔE values.⁶⁹ Here, a large gas phase ΔE value complements to high magnitude of gas phase ΔE_{int} (>-100 kcal/mol). Incorporation of aqueous phase lowers ΔE values (~ -20 kcal/mol), thus supporting the observed lowering in ΔE_{int} (-13.33 kcal/mol). Sharp drop in ΔE is due to the fact that the salt bridge possesses large dipole moment (10.5 D) and strong dipole-dipole interaction between solvent and the salt bridge stabilizes the E_{HOMO} of the salt bridge and results in much lower ΔE value in aqueous phase compared to the gas phase value. However, no linear relationship between ΔE and ΔE_{int} is observed. Apart from ΔE values, it is worthwhile to study the shape of the LUMO of the donor and HOMO of the acceptor. Figure 7b-c reveal that LUMO of lys is localized over the $-\text{NH}_3^+$ group, and this facilitates the $-\text{NH}_3^+$ group to participate in hydro-

gen bonding as a hydrogen donor. Moreover, HOMO of asp is spreading over $-\text{COO}^-$ group (Figure 7c), which makes them hydrogen acceptor during hydrogen bonding formation. Importantly, the HOMO of the salt bridge is lying far below the LUMO of lys, favouring hydrogen bond formation from the HOMO-LUMO energy perspectives.

It is expected that the HOMO of the salt bridge and asp are affected by the presence of electric field. Figure 8 shows the variation of HOMO energy of asp and the corresponding lys-asp salt bridge. It is also seen that the HOMO of the salt bridge is well affected by the presence of electric field. In both gas and aqueous phases, we observe destabilization of the HOMO (Figure 8a,b). In contrast to the salt bridge, variation of HOMO of asp follows a different pattern; drop in HOMO energy is observed upon application of the field along $-x$ and $-z$ directions in asp. Interestingly, presence of aqueous phase does not change the variation pattern (Figure 8c,d). However, a drop in E_{HOMO} and therefore, a more stable HOMO results in aqueous

Figure 8. Variation of HOMO energy with external electric field. (a) lys-asp salt bridge in gas phase; (b) lys-asp salt bridge in aqueous phase; (c) asp in gas phase; and (d) asp in aqueous phase. (■-along x -axis, ●-along y -axis, Δ -along z -axis).

phase. This variation explains why ΔE value (Figure 7a) is perturbed in the presence of external electric field which in turn affects the strength of the hydrogen bonding in the salt bridge.

4. Conclusions

Our study found out some important aspects on the stability of amino acid salt bridge of lys and asp upon application of external electric field and in aqueous phase. Calculated interaction energies confirm formation of salt bridge in the gas phase. Incorporation of aqueous phase reduces the interaction energies considerably. Total electronic energy and interaction energies are observed to be sensitive towards the strength and direction of the applied electric field; however, presence of aqueous phase does not alter the variation pattern. Variation of global hardness suggests that application

of external electric field imparts instability to the salt bridge. The study also delineates the inherent feasibility of formation of hydrogen bonding during formation of salt bridge. Generic conclusion that can be drawn from this study is that aqueous phase and external electric field essentially contribute to the stability of the salt bridge and hence it is expected that the structure and the stability of the protein are also affected by the presence of such external perturbation.

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