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MEDIUM POLARIZATION EFFECT ON PROTON POTENTIAL SHAPE S.A SCRF-MO CNDO/2 study of methanol and methanethiol H-bonded to imidazol

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ABSTRACT.

The theoretical calculations carried out with the self-consistent reaction field theory of solvent (medium) effects,have shown that the proton potential curve shapes of the above mentioned H-bonded systems are remarkably dependant upon the reaction field susceptibility parameter.The results show that the imidazol system would display different pK's at different sites of a given globular protein.Moreover, a proton translocation process is shown to be an essentially medium driven effect.

1. INTRODUCTION.

The self-consistent reaction field (SCRF) calculations of some simple H-bonded systems have disclosed a dependance of the shape of their proton potentials upon the coupling with a polarizable medium[1,2]. While these systems, e.g., water dimers and trimers, do have a biochemical and/or biophysical relevance they are far from being a faithful representation of more realistic H-bridges as they are found in enzyme structures Indeed, the growth of information on the three dimensional structure of enzymes[3] has lead, among other things, to the discovery of charge-relay systems involving proton translocation across H-bridges. Furthermore,these structures have been recognized as possible sources of catalytic activity as, for instance, for chymotrypsin[4], trypsin[5], elastase[6], papain[7] liver alcohol dehydrogenase[8], etc. It is quite remarkable that for all

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these H-bridges, histidine is proving to be of prime importance, and it seems natural to extend our SCRF calculations to examine a model histidine system, imidazol, H-bonded with methanol (serine model) and methanethiol (cysteine model). The former is a portion of the serine proteases and of the LADHase proton relay systems, while the latter may be considered as a model for a portion of the papain charge relay system. The aim of this work is to look at the extent to which a polarizable medium may change these proton potential curves (PPCs). The answer is not evident since as we have found recently, some carbonyl-water H-bonded complexes do not display a double well potential even for large reaction field (RF) susceptibilities[9]. However, on the experimental side it has been shown that the acidity or basicity of the histidine is a function of the local environment at different sites of an enzyme[10].

In a recent paper[9] it has been shown that a representation of the medium produced by a globular protein and acting at a given site inside the protein may be accomplished within the SCRF theory of solvent effects[11]. The site system-surrounding medium coupling parameter g derived from this theory is related to the RF susceptibility at that particular site and is produced by the folded polypeptide main chain[9]. A change of this parameter may be associated with variations of the folded state of the protein. The effect of superimposed electric fields which do have a component along the RF may be understood as a change (positive or negative) of the g-value at a given site. The present study is therefore relevant in connection with the enzymic activity of the above mentioned systems.

The PPCs of imidazol-methanol and imidazol-methanethiol have been studied as a function of the intermolecular distance and the g-parameter. It is interesting to notice that both systems have already been the object of quantum mechanical studies in connection with enzymic reaction mechanisms of the α-chymotrypsin[12], trypsin[13] and

papain[14]. Neither of these calculations have taken the medium polarization effects into account. While the scope of the study herewith reported is much narrower, the results obtained might be of relevance in this respect. The calculations have been carried out within the CNDO/2 computational scheme. The reader is referred to refs.(9) and (11) for a discussion of the approximation involved.

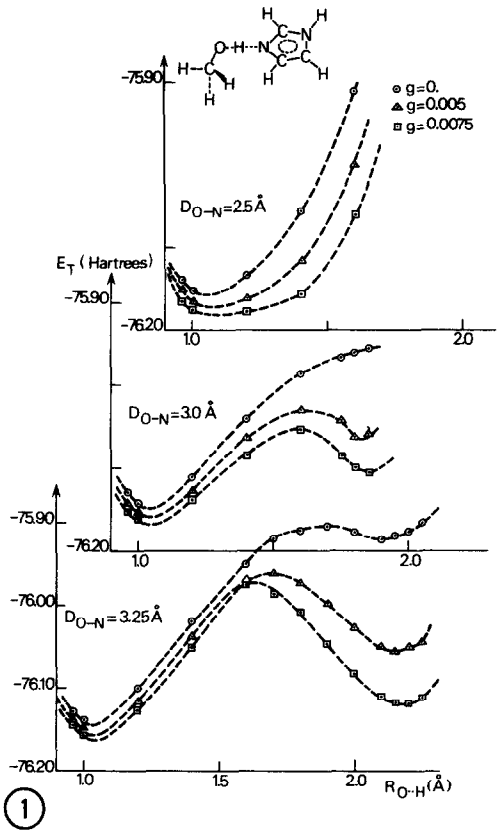
2. THE MODELS.

The relative orientations chosen for the partners are displayed in the figures. The geometrical parameters of methanol are taken from ref. (15), while those for imidazol and methanethiol have been borrowed from ref.(14). To find out the minimum of the intermolecular potential for the chosen orientations, calculations were carried out at $g = 0.$ ($bohr^{-3}$). They furned out to be at 2.55 Å for the methanol association and at 3.0 Å for the methanethiol complex. As it has already been established[1,2,9], the PPCs hardly display a double well pattern for intermolecular distances shorter than that corresponding to the equilibrium point. Accordingly the PPCs for methanol/imidazol have been calculated at 2.5Å, 3.0Å and 3.25Å whereas for the methanethiol complex the distances chosen are 3.0Å, 3.25Å and 3.35Å.

3. RESULTS AND DISCUSSION.

In fig. 1 and 2 for methanol-imidazol and methanethiol-imidazol respectively, the total energy of the system, which does include the medium polarization energy[16], is plotted as a function of the proton coordinate for the chosen manifold of intermolecular distances and RF susceptibility parameters.

The appearance of a double well potential is due to the combined action of a proper intermolecular distance and RF susceptibility The global pattern is then a function of environmental properties.



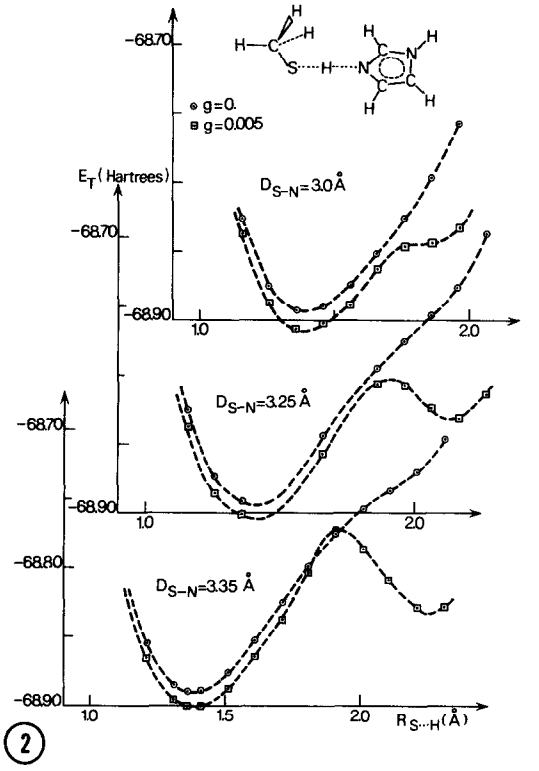


Fig. 1

Proton potential curves of the imidazol-methanol HB system.

D_{O-N} stands for the intermolecular distance; R_{O-H} indicates the position coordinate of the proton in the bridge. The reaction field strenghts associated to g=0.005 (bohr^{-3}) calculated at R_{O-H} = 1.0 Å nearby the HB minimum are 0.77 V/Å at D_{O-N} = 2.5 Å; 0.66 V/Å at D_{O-N} = 3.0 Å; and 0.64 V/Å at D_{O-N} = 3.25 Å. For g=0.0075 (bohr^{-3}) one gets the following results: 1.3 V/Å at D_{O-N} = 2.5 Å; 1.1 V/Å at D_{O-N} = 3.0 Å; and 1.1 V/Å at D_{O-N}=3.25 Å.

Fig. 2

Proton potential curves of the imidazol-methanethiol HB system. The reaction field strengts associated to g = 0.005 (bohr^{-3}) calculated at each HB minimum are 1.06 V/Å at D_{S-N} = 3.0 Å; 0.94 V/Å at D_{S-N}= 3.25 Å and 0.91 V/Å at D_{S-N}= 3.35 Å.

Similarly to other model systems studied[9]., the RF strength decreases with the intermolecular distance at the HB-region (region I) and increases at the ion-pair zone (region II). At this latter zone the relative gain

of the polarization energy is not enough to explain the depth increment. In fact, as was already discussed, it is the behavior of the corresponding Coulomb integral (within the charge-transfer model for the H-bond) with the intermolecular distance that allows for an explanation[9]. Essentially, at region II the charge-transfer configuration descends in the energy scale at a lower level than the non-bonded configuration. This in turn causes a decrement of the Coulomb integral due to an increment of the intermolecular distance to be expressed in an increased weight of the charge-transfer component in the total wave function. The opposite is found at region I. Thus, in a certain sense, the RF susceptibility g acts as a sensitizer of the site system so that the computational scheme tends to produce negative ions (in an ion-pair) such as methoxide and thiolate showing reasonable proton affinities. This is exactly the opposite behavior to minimum basis set ab-initio calculations[13] that do not take medium polarization fields into account.

The results reported support the experimental finding of the site dependance of pK in the enzymes. The energy difference between both minima of the PPCs, $\Delta E(g,R)$, wich would be one of the factors affecting the equilibrium between the acids and bases, may be varied over wide ranges depending upon the intermolecular distance R and the susceptibility. It is qualitatively clear that different sites might have associated different g and R values.

Let us make a brief comment on the charge relay systems of trypsine[13] and papaine[14]. From the computational standpoint one should bear in mind that the former has a terminal proton acceptor which is negatively charged (Asp 102) while the latter has a neutral carbonyl group (Asn 175). Thus, a double well proton potential can be obtained for the former within an ab-initio minimal basis set calculation due essentially to an error cancellation[13], whereas in the latter

system a double well proton potential for the simultaneous motion may be absent due to basis set drawback[14]. However, we believe that the appearance of a medium driven double well pattern in the PPCs is closely related to a proper representation of the surrounding medium polarization effects. Thus, a simple solvation model recently proposed[17] shows that for $H_3N...HF$, the hydration has a profound effect on the potential energy surface favoring a proton transfer structure $H_3NH^+...F^-$. Turning back to the papaine system, calculations of the carbonyl-water proton potential, within the SCRF scheme, as a function of R and g have shown that the C = O group is a much poorer proton acceptor[9], thus, a simultaneous proton motion a cross the bridge might be unfavorable, so that one can conjecture that the Asn 175 is only assisting through H-bonding, the formation of the ion-pair $-S^-...ImH^+$, which in turn is allowed for by environmental effects.

To sum up, the study reported here substantiates the statement made by Warshel and Levitt[18] that the medium polarization effect is one of the key mechanisms to understanding the sources for enzyme activity. We are of course aware of the limitations of both the computational scheme, and the approximation made by taking a homogeneous RF over the site system. Nevertheless, it is believed that the portion of polarization effect taken into account is meaningful and relevant. These effects can be introduced in a number of ways into the quantum chemical scheme (see ref. (19) for a recent review). We have chosen to explore the effect of inhomogeneities over the site system on the energy surfaces. However whichever technique is used to represent the environement the conclusion of this work is that it cannot be avoided if meaningful results in connection with enzyme activity of charge relay systems are sought.

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