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Theoretical Study of Proton and Solvent Effects on Molecular Stacking

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Molecular stacking between π-electron systems was analyzed in connection with effects of external charge and solvent. A perturbation approach was used for calculating intermolecular energies and a discrete plus continuum model was used for solvent effects. The solvent favors stacking in unprotonated systems by hydrophobic forces. In the presence of an external charge the solvent induces dissociative effects on the molecular pairs by electrostatic solvation forces.

It is well known that molecular stacking plays an important role in many biological processes. Indeed, intramolecular stacking favors conformational preferences in large flexible molecules (FAD, NAD, *etc.*), while intermolecular stacking is one of the causes for binding of molecules to enzymes, base pairing, *etc.* Generally, these molecular systems are characterized by large π-electron systems which interact with one another essentially through van der Waals-type forces. Since in biological environments these large systems are imbedded in a liquid or quasi-liquid (membrane) medium, and frequently they are in a protonated form ($NAD\text{-}H^+$, $FAD\text{-}H^+$), we think it to be interesting to study associated effects of proton-charge and of solvent on interactions among some π-electron systems.

Following an approach already adopted by us,[1] we select simple systems which partially simulate relevant characteristics of more complex biological systems. Consequently, in the present work we study, both in vacuum and in water, interactions between two π-electron clouds, unperturbed as well as perturbed by a proton localized in a site. In the present approach we study interactions in vacuum between two π-systems, one of which is affected by the presence of a neighboring proton. Successively, we add solvation energy, which allows us to examine effects of both hydrophobic interactions and electrostatic solvation energies on the association of these π-systems.

Intermolecular forces, which are responsible for stacking, can be efficiently described in the framework of the second order perturbation approach of Murrell *et al.*[2] This method is particularly suitable for studying medium- and long-range forces; moreover, it allows an insight into different natures of working intermolecular forces. Practically, to interaction energies we add solvation energies calculated according to the discrete plus continuum model, and draw the trend of total energies at various intermolecular distances.

Description of the Method

The following pair systems were considered in the present work: i) protonated ethylene–ethylene, ii) protonated ethylene–benzene, and iii) protonated benzene–ethylene, each case including the corresponding unprotonated pair. The approaching pathways for the neutral pairs are shown in Fig. 1, where the variable parameters are also defined. The positive charge is located at 1.1 Å[3] from the ethylene plane for systems i) and ii), and at 0.85 Å from the benzene plane†† for system iii). In all cases it is located along the principal symmetry axis outside the intermolecular space. In evaluating the solvent effect for the unprotonated systems the continuum model was adopted. For the protonated systems the discrete plus continuum model was used; that is, a planar H_3O^+ molecule, perpendicular to the ethylene or benzene plane, was bound to the π-system inside an elliptic cavity of a continuum dielectric medium. Geometrical parameters of H_3O^+ and of the neutral molecules were taken from Refs. 4 and 5. For each value of intermolecular distance, R, and for some relative spatial arrangements, the interaction energy was first calculated, and then the corresponding solvation energy was added.

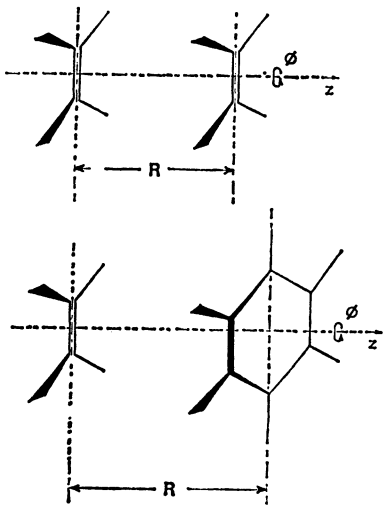

Fig. 1. Approach pathways and variable parameters for ethylene–ethylene and benzene–ethylene pair systems.

The intermolecular interaction energy was calculated by the second order perturbation theory of Murrell *et al.*,[2] developed on the LCAO approximation by Fueno *et al.*;[6] this method has been utilized successfully by several authors.[1d,7,8] The method describes quite well the medium and long range forces and allows a useful energy partitioning into five contributions: coulombic (E_Q), exchange repulsion (E_K), induction (E_I), dispersion (E_D), and charge transfer (E_{CT}) energies. The approximations, used in calculating intermolecular integrals, and the structure of the computer

†† This value was optimized by a MINDO/3 calculation.

program used were described in a previous paper.[1d]

Solvation energy was evaluated by means of an approximation††† which divides it into electrostatic, cavitation, dispersion, and short-range contributions. The first contribution was calculated on the reaction field approximation, taking into account the elliptic shape of cavity and the actual position of charges inside. Supermolecule dipole moment was evaluated as the dipole moment induced by a positive charge on polarizable molecules. Polarizability components were evaluated according to a perturbative approach.[9] Cavity contribution was related to the surface tension and to the elliptic surface of solute.[10] Dispersion and short-range energies were calculated by

$$E_{\mathrm{disp}} = \frac{\delta}{2}\int_{\sigma}^{\infty} U(\rho)g^{(2)}(\rho)\langle A(\rho)\rangle d\rho,$$

where δ is the number density of solvent and $U(\rho)$ is a Lennard-Jones potential corrected for the three-body interaction.[11] The coefficient of potential $U(\rho)$ was put equal to

$$\frac{3}{2}\bar{\alpha}_{\mathrm{w}}\bar{\alpha}_{\mathrm{s}}\frac{I_{\mathrm{w}}I_{\mathrm{s}}}{I_{\mathrm{w}}+I_{\mathrm{s}}}(2\sigma)^{-6}.$$

Solute ionization potential (I_s) and polarizability (α_s) have been theoretically calculated;[9] the ethylene σ value was taken from Ref. 7, while the other values were evaluated from density data.[12,13] $\langle A(\rho)\rangle$ is the spherical average surface of solute, and $g^{(2)}(\rho)$ is the distribution function, here set equal to zero for $\rho<\sigma$ and 1 otherwise.

Results in Gas Phase

Table 1 shows perturbation interaction energy values for the ethylene–ethylene and protonated ethylene–ethylene systems, together with single energy contributions. It can be noted that for the former system, at shorter distances, the exchange repulsion contribution (E_K) is the most important, whereas the coulombic (E_Q) and dispersion (E_D) energies nearly balance each other; at longer distances the total energy arises essentially from the dispersion term, the figures being in agreement with previous calculations.[7] Further calculations showed that the total energy is not affected by rotation of one ethylene molecule around the intermolecular symmetry axis.

When a proton is added (the latter system), we note an increase in E_K and a decrease in E_Q, while the induction (E_I) and charge transfer (E_{CT}) terms are appreciable. Then the total energy shows, with respect to the unprotonated system, a slight deepening of the minimum, which now lies at nearly the same

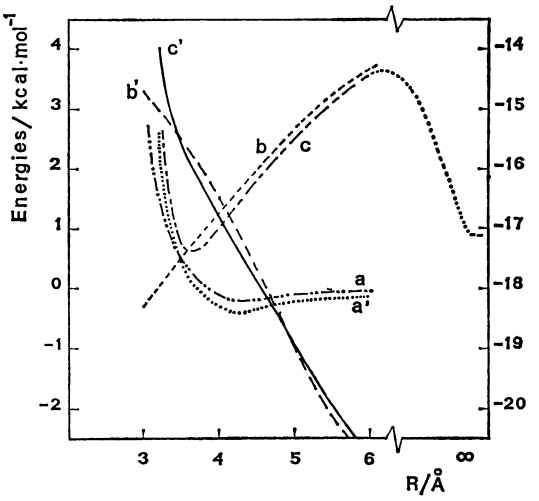

Fig. 2. Ethylene–Ethylene system.
a: Gas-phase energy, unprotonated, a′: gas-phase energy, protonated, b: solvation energy, unprotonated, b′: solvation energy, protonated, c: total energy, unprotonated, c′: total energy, protonated. Scale on the right refers to b′ and c′ curves (1 cal=4.184 J).

Table 1. Perturbation interaction energy terms

R/Å	E_Q / kcal mol^{-1}	E_K / kcal mol^{-1}	E_I / kcal mol^{-1}	E_D / kcal mol^{-1}	E_{CT} / kcal mol^{-1}	$E_{tot.}$ / kcal mol^{-1}
			Ethylene–Ethylene			
2.8	2.32	5.93	0	−1.13	0	7.12
3.0	1.02	3.17	0	−0.80	0	3.39
3.2	0.42	1.63	0	−0.57	0	1.48
3.4	0.18	0.81	0	−0.42	0	0.57
4.0	0.01	0.08	0	−0.18	0	−0.09
5.0	0	0	0	−0.05	0	−0.05
6.0	0	0	0	−0.02	0	−0.02
			H$^+$-Ethylene–Ethylene			
2.8	1.80	11.64	−0.18	−0.93	−0.48	11.85
3.0	0.36	6.13	−0.14	−0.66	−0.25	5.44
3.2	0.02	3.12	−0.10	−0.47	−0.13	2.44
3.4	−0.17	1.54	−0.08	−0.35	−0.06	0.89
4.0	−0.23	0.16	−0.04	−0.15	−0.01	−0.26
5.0	−0.13	0	−0.01	−0.04	0	−0.19
6.0	−0.08	0	−0.01	−0.02	0	−0.11

††† Details of the method are described in Ref. 1b.

distance as in the neutral system (Fig. 2, a and a' curves).

At first sight it could appear strange that, in Table 1, the coulombic terms vary rapidly with distance as compared with the corresponding exchange terms. However, we must bear in mind that in the ethylene–ethylene system the first nonvanishing term of coulomb interaction is the quadrupole-quadrupole term. A similar situation occurs in the protonated ethylene–ethylene system, where the monopole-quadrupole term is nearly zero on symmetry ground.

Calculations were carried out to test the effect due to the proton–ethylene distance on each energy term: The main effect (at 1—2 Å) is a small increasing of E_K nearly balanced by a small lowering of E_Q when the proton–ethylene distance decreases.

Calculations on the benzene–ethylene system evidenced a higher dispersion energy than the ethylene–ethylene one owing to the increased π-system size, in addition to decreases in E_Q and E_K.** The benzene–ethylene energy curve is shown in Fig. 3 (curve a), together with the corresponding curve for the protonated benzene–ethylene system (curve a').*** We can see that the unprotonated benzene–ethylene system shows a minimum more pronounced and at shorter distances than the ethylene dimer.

Protonation has a stabilizing effect, though small (0.3 kcal mol^{-1}) (1 cal=4.184 J); the energy curves appear deeper and wider with the minima lying at slightly greater distances than in the corresponding unprotonated systems. Indeed, the stabilization should be more extensive; in fact, it is well known that the limited basis set will cause underestimation of dispersive forces,[14,15] so that a more negative dispersion energy is to be expected.

Results in Aqueous Solution

Since the energies involved in these molecular associations are small, we expect that solvation energy plays an important role in determining the stability of molecular pairs. Following the scheme outlined in the calculation section, we added the solvation energy to the energy for the gas phase and constructed curves for the resulting total energy *vs.* intermolecular distance. Figures 2 and 3 show solvation and total energy for the pair systems studied.

The solvation energy for the unprotonated systems (curves b) increases with intermolecular distance, R, the cavitation term prevailing and the dispersion term being nearly constant;§ the slope is greater in the wider benzene–ethylene system (Fig. 3) than in the ethylene dimer (Fig. 2). The solvation causes drastic deepening of the potential well in the short distance range in both the cases (curves c). Moreover, for

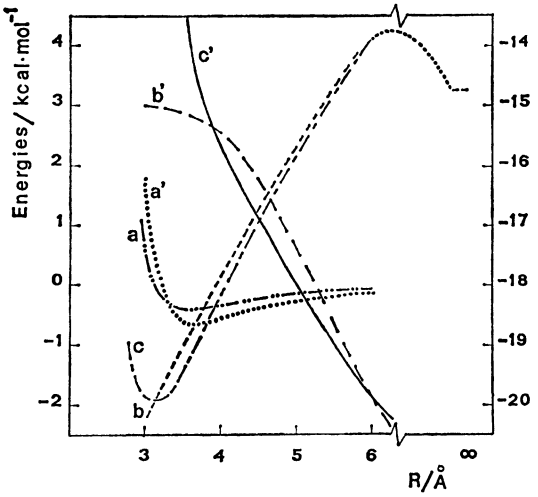

Fig. 3. Benzene–Ethylene system.
a: Gas-phase energy, unprotonated a': gas-phase energy, protonated; b: solvation energy, unprotonated, b': solvation energy, protonated, c: total energy, unprotonated; c': total energy, protonated. Scale on the right refers to b' and c' curves.

each pair in solution the energy minimum is lower than the energy of the two single solvated components at infinite distance. Therefore, to dissociate these unprotonated pairs, we must overcome a potential barrier. This explains how hydrophobic forces induce the stacking of π-electron molecular systems in solution.

The present approach is not capable of allowing us to calculate the exact dissociation barrier, leaving the intermolecular potential variable in a periodic fashion with intermolecular distance as far as this distance is comparable, or greater than, solvent molecular radii.[16,17] However, from an inspection of the curves we expect barriers of 2—3 kcal mol^{-1} for the ethylene–ethylene pair and 5—6 kcal mol^{-1} for the benzene–ethylene one.

When the proton is bound to one of pairing molecules, main consequences from the solvent effect are the disappearence of short range minima and the strong dissociative power in all the cases considered (curves c'). This is accounted for in terms of the appreciable electrostatic contribution to solvation energy. This contribution increases greatly with intermolecular distance because the charge is located in the proximity of cavity wall; this geometric fashion makes remarkable the effect of ellipticity on the electrostatic solvation energy. Such increase in electrostatic solvation energy has been pointed out by several authors[18,19] and evidenced by us in our previous work.[1b] On this ground the cavitation energy here plays a minor role, in contrast to the unprotonated systems.

By comparing the shapes of the solvation energy curves (b') in Figs. 2 and 3, it can be deduced that increasing the size of unsaturated systems will result in lowering the slope of solvation energy curves at short distances. We, therefore, think that the interaction between very extended unsaturated systems could cause inversion in the slope of the above curves for protonated systems so that stacking effects induced by

** No values of the energy components are reported because their trend is quite similar to that of the corresponding ethylene–ethylene system.

*** The curve for the protonated ethylene–benzene system, not reported here, is nearly equal to curve a', apart from a slight destabilization.

§ No significant variations were observed on changing the rotation angle ϕ (see Fig. 1).

the solvent could be reliable. No curves for the protonated ethylene–benzene (both in the gas phase and in solution) are reported in Fig. 3; they are similar to those for the protonated benzene–ethylene system.

We can conclude that in water solution the stacking effect, though weak, can occur between unsaturated molecules, provided that no proton is bound to anyone of the interacting molecules (hydrophobic stacking). On the contrary, when a net charge is held by one of the two molecules, any stacking effects are not possible; at the most, only in very extended unsaturated systems they should be taken into account.

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