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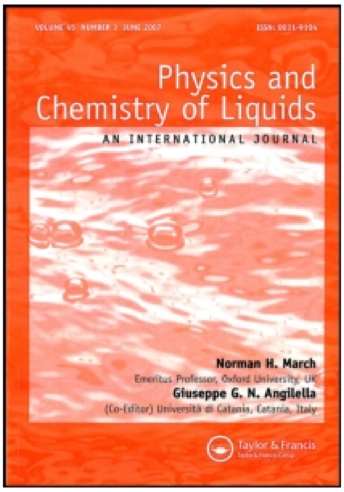

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Hydrophobic Interaction

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Hydrophobic Interaction†

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The motivation for this work comes from Biophysics or, more precisely, from Biopolymer chemistry. It has long been suggested that non-polar molecules, or non-polar groups hung on the skeleton of a biopolymer, tend to adhere to each other in aqueous environment. This phenomenon has been called hydrophobic interaction (HI).[1–4] As it often occurs in science, the very name "HI" has currently replaced the *explanation* of the phenomenon to which it refers. That is, if one observes an attraction between non-polar particles in water, then the "explanation" of this phenomenon is attributed to the existence of HI. The main questions that one may raise in this connection are the following

1) Is there such an effect as HI?

2) If it exists, to what extent it is unique to aqueous environment?

3) How can one relate the phenomenon of HI to what is known on the structure of water?

Figure IX.1 shows some "reactions" that may involve HI. For example, the folding of a polymer in such a way that non-polar groups are removed from the aqueous environment and are transferred to a relatively less polar medium. The most elementary case in which HI may be involved is the system of pure water containing just two simple non-polar solutes, such as methane or argon. One possible question regarding this system is the following: suppose the two particles are allowed to wander about in the total volume V, what is the probability of finding this pair, at some close separation R. This probability distribution is contained in the function $g(R)$, the pair correlation function. An equivalent, and for our purposes a more convenient way, of stating the same problem is to consider a system of N water molecules

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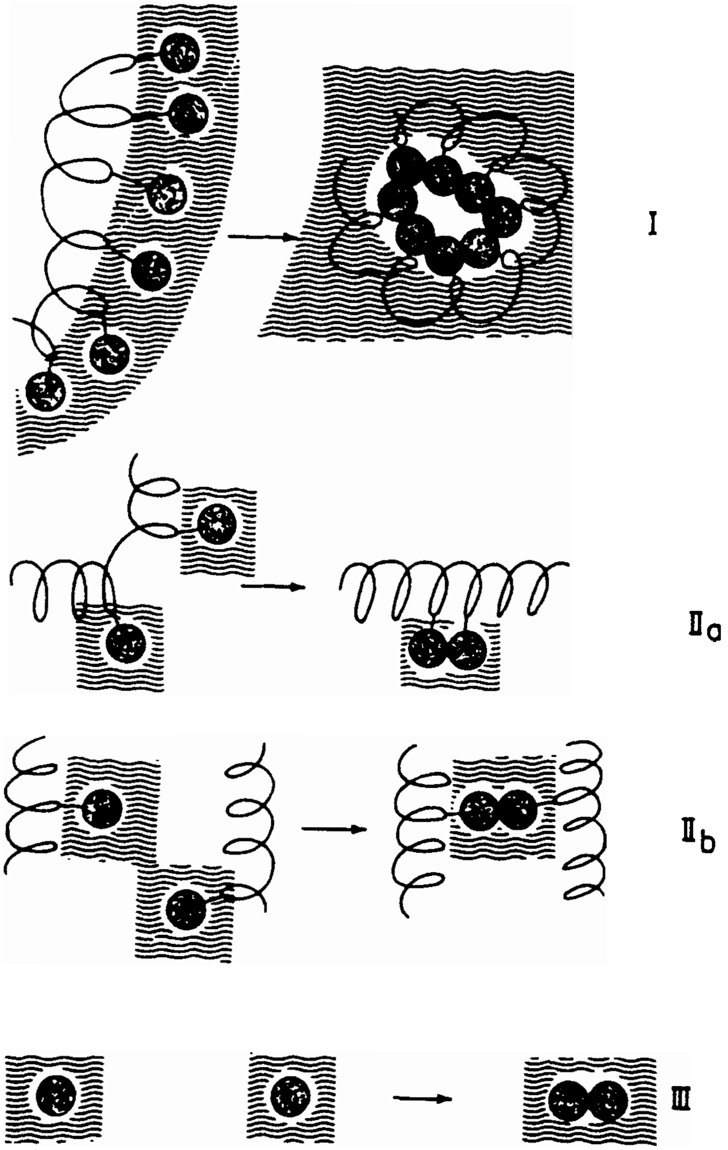

FIGURE IX.1

with two non-polar solutes at infinite separation. The quantity of interest is what is the work (say at TVN constant) for the process of bringing the two particles from infinity to a distance R within the liquid. This work can always be split as

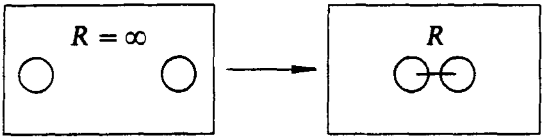

FIGURE IX.2

$$\Delta A(R) = U(R) + \delta A^{HI}(R)$$

where $U(R)$ is the direct pair potential operating between the two particles. $\delta A^{HI}(R)$ is the indirect part of the work and will be referred to as the hydrophobic interaction between the two particles at distance R. We have used the superscript "HI" on the $\delta A^{HI}(R)$ because we are mainly interested in water, though this quantity has a similar meaning in any other solvent. We first recognize the fact that $U(R)$ is the uninteresting part of the work, as far as we are concerned with the properties of the solvent. The assumption is made that $U(R)$ is the same in water and in other fluids. Therefore, if we can get rid of $U(R)$ we shall be left with the important quantity δA^{HI} which, we expect, may be unique for liquid water. This can be easily achieved by using the cyclic process described in Figure IX.3. The idea is now to repeat the same

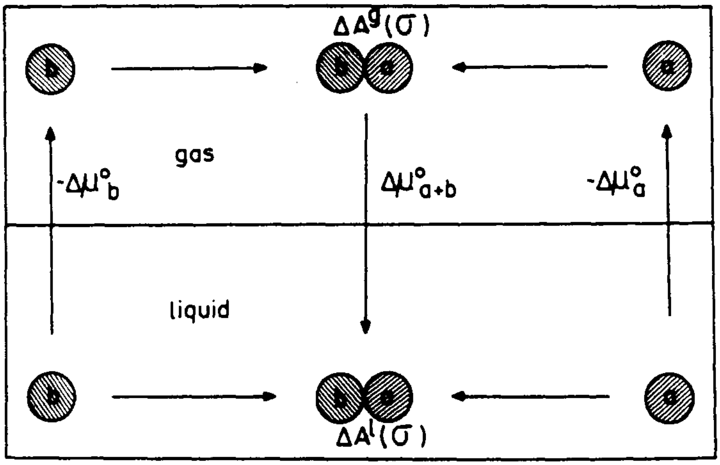

FIGURE IX.3

process in the gaseous phase. As may be seen from the figure we have the following equality:

$$\Delta A(R) = U(R) + \delta A^{HI}(R) = \Delta\mu^0_{a+b} - \Delta\mu^0_a - \Delta\mu^0_b + U(R)$$

or

$$\delta A^{HI}(R) = \Delta\mu^0_{a+b} - \Delta\mu^0_a - \Delta\mu^0_b.$$

$\Delta\mu^0_i$ is the standard free energy of solution of the solute *i*. The last equation almost achieves a relation between the required quantity $\delta A^{HI}(R)$ and experimental quantities. However it is still not complete, the quantity $\Delta\mu^0_{a+b}$ is not measurable since we do not have a molecule that has been denoted by $a + b$ and therefore we cannot measure $\Delta\mu^0_{a+b}$. To overcome this difficulty we have employed a "trick" to fool—so to speak—the water molecules around the solute molecules. It may be shown[5,6] that $\Delta\mu^0_i$ is essentially the work required to introduce a solute into the solvent at some fixed position *R*. Now, as far as the solvent is concerned, we can produce a field of force originated from *R*, which is equivalent to the field of force produced by the solute. If we do that, the solvent cannot distinguish between the two fields of forces. It can be shown that $\Delta\mu^0_i$ is essentially the work required to "build up" or to create a field of force equivalent to the one produced by the solute *i*. Without getting into the details of the computations we note that the advantage of using this replacement of the field of force is especially useful for two solute particles. Whereas for two *real* solute particles we are limited to a separation of closest approach $R > \sigma$, (σ being the diamater of the solute

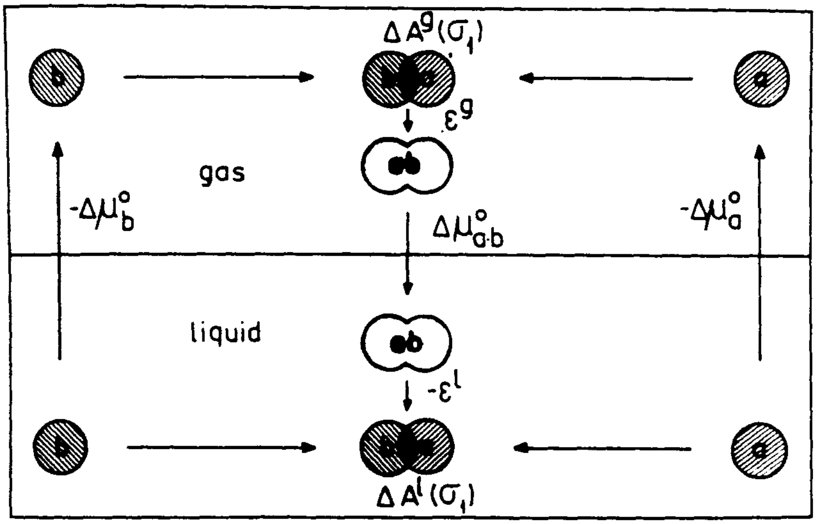

FIGURE IX.4

particles), this limitation does not exist when we consider the field of force originates from two centers, say R_1 and R_2.

In Figure IX.4, we show a modified cyclic process which leads to a better relation between the molecular quantity δA^{HI} and experimental quantities. As usual, the benefit we get by this modification requires some expense. What we gain is replacing a "hypothetical" molecule, $a + b$ by a "real" molecule. We sacrifice however the freedom of choice of the distance, i.e., we are restricted to $R = \sigma_1 = 1.53$ Å, the C–C distance in ethane. The final relation obtained from the new cycle is

$$\delta A^{HI}(\sigma_1) = \Delta\mu^0{}_{\text{thane}} - 2\Delta\mu^0{}_{\text{ethane}}$$

Of course one can choose other pairs of solutes for which experimental results are available. Figure IX.5 shows some values of HI in water and a

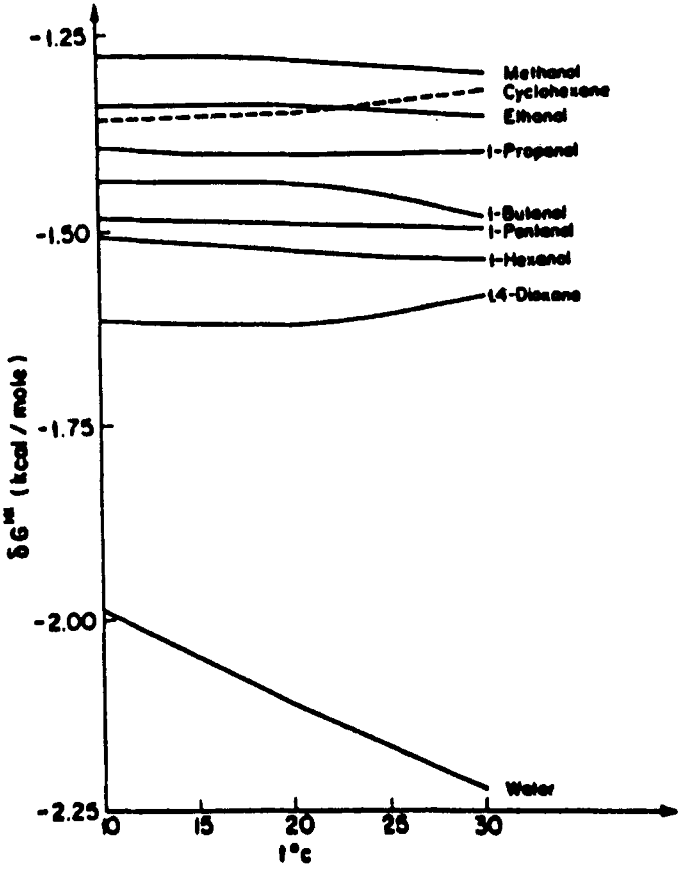

FIGURE IX.5

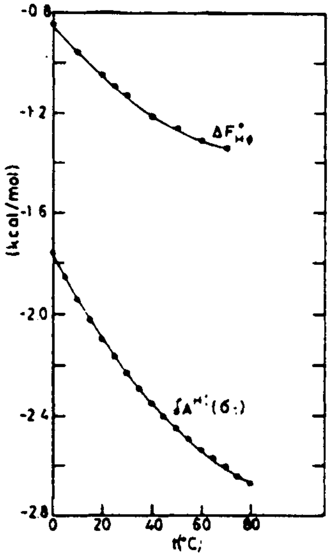

FIGURE IX.6

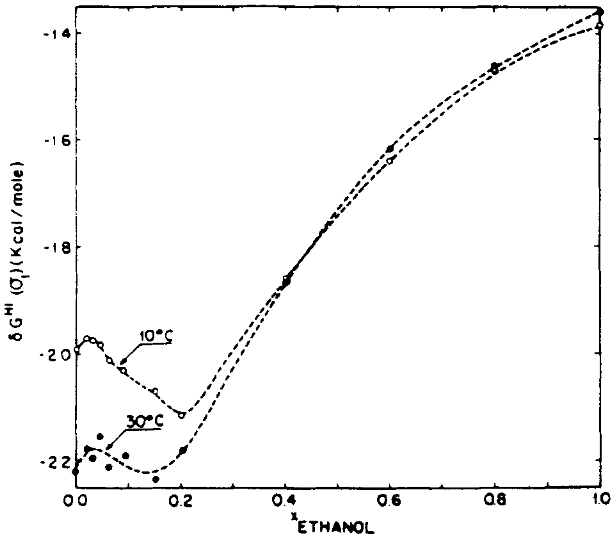

FIGURE IX.7

series of alcohols. It should be noted that, in the first place, the strength of HI is much greater in water than in the alcohols. This difference is significant since it is a little larger than kT at these temperatures. Secondly we note the difference in the temperature dependance of HI. In water there is a strong negative temperature dependence, whereas in other liquids we find either a positive, or a negligible temperature dependence.

The temperature dependence of HI is shown in Figure IX.6. We see that the HI becomes stronger as temperature increases. This behavior seems to diminish at high temperatures.

In Figure IX.7 we demonstrate the variation of HI in mixtures of water and ethanol. Note the inversion of the temperature dependence in the alcohol-rich region. In Figure IX.8 the entropy of the process of HI is shown for water-alcohol system. Note the large positive value of δS^{HI} in water, and the almost zero value in the alcohol-rich region.

The procedure we have presented can easily be generalized to three, four, etc. particles. It is interesting to note that the HI between a group of particles becomes almost constant when we divide the HI by the number of bonds in the molecule. There are various other possible applications of this method. The idea is that one can improve the approximation by using bulkier

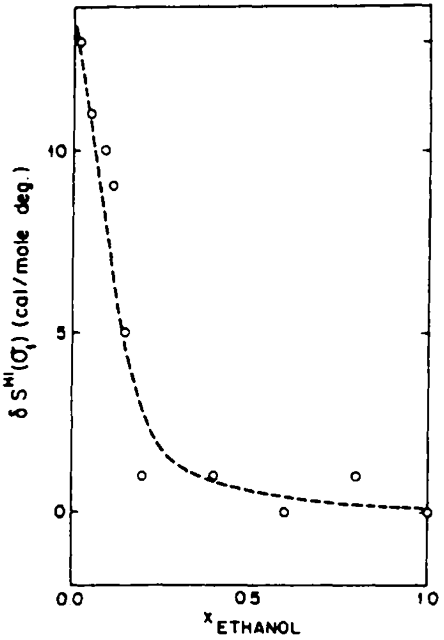

FIGURE IX.8

molecules in such a way that the water molecules do not feel the field of force produced by the central molecule.

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M. Mandel Although I liked very much your approach to the hydrophobic interactions, I am somewhat worried by the fact that in calculating your δA^{HI} you used a distance of closest approach between two molecules which is different from the real one. Now, as your δA^{HI} is in fact connected to the pair-correlation function $g(R)$ and this quantity depends strongly on R near its first maximum, what effect will your choice of the distance of closest approach have in calculating the former quantity?

A. Ben-Naïm I agree that the method I have shown is restricted to one separation $R = \sigma_1$ only. However by using further approximations one can extend the method to obtain information on the hydrophobic interaction at $R = \sigma$. The main idea (for more details see reference 5) is that the function

$$y(R) = e^{+BU(R)}g(R)$$

is almost linear with R in the region $U \leqslant R \leqslant \sigma$. This is known either from the exact solution of the Percus-Yevick equation or from numerical computations. Now this information can be utilized to extrapolate values of $\delta A^{HI}(\sigma)$ from information on $\delta A^{HI}(\sigma_1)$ and $\delta A^{HI}(O)$ (i.e., at zero separation). It may be worth to mention that in principle one can compute the full function $g(R)$ or $\Delta A(R)$ by any of the "computer experiments." In fact we have been studying this problem on a two dimensional system of water-like particles.

J. E. B. Randles Dr. Ben-Naïm uses the method he has described, to estimate the free energy of association into pairs of solute molecules in an alcoholic or aqueous solvent. Would it not be possible to measure this by a careful study of the thermodynamics of the solutions? The deviation from ideality could be interpreted as a first approximation as due to pairwise interactions and the free energy of pair formation could be deduced.

A. Ben-Naïm The investigation of non-ideally in terms of hydrophobic interaction has in fact been studied by Kozak, Knight and Kauzmann.[4] One may look at the second virial coefficient of the density expansion of the osmotic pressure, namely

$$\frac{\pi}{kT} = S_S + B_2^* S_S^2 + \ldots.$$

where B_2^* is essentially a measure of the overall solute-solute interaction between the two solute particles. There is however an essential difficulty to this method because it is difficult to obtain experimental values of B_2^* for very simple solutes. On the other hand for those solutes for which there exist experimental results, the solute-solute interaction usually involves more factors than simply the hydrophobic interaction. One could of course get B_2^* for methane if we dissolve the gas under high pressure. However, in this case we may miss the effect we are looking for, since at high pressures the structure of water may be altered to a large extent.

H. G. Hertz There exists now a method to study hydrophobic association directly: consider a solution of $DOOCCH_2CD_3$ in D_2O.

The intermolecular proton relaxation rate in the aqueous solution, as a function of propionic acid content, may be compared with the intermolecular relaxation rate, as expected from the theory. In the theory, it is assumed that we have uniform distribution of the acid molecules in the solution. Experimentally, it was found that the intermolecular relaxation rate exceeded the theoretical one. This shows that the acid molecule are associated to a certain degree. Next, the same experiment was performed with the propionic acid $DOOCCD_2CH_3$. It turned out that the proton intermolecular relaxation rate was less for this species. One concludes that the point of association for two propionic acid molecules is closer to the methylene group than to the methyl group. Next, the mixture of the two acid species (dissolved in water) was studied. Preliminary results indicate that intermolecular methylene-methyl interactions are about as strong as methylene-methylene interactions. This tells us that the methylene group of one molecule is located between the methylene and methyl group of the other molecule.

Similar experiments were made with D_2O solutions of the three butyric acids:

$DOOCCH_2CD_2CD_3$
$DOOCCD_2CH_2CD_3$
$DOOCCD_2CD_2CH_3$

A. Ben-Naïm I think this is a very direct way of looking at the hydrophobic interaction. I would like to raise only two comments:

1) the fact that the solutes contain carboxylic groups imposes some geometry to whatever dimer that is formed and therefore the distance between the two non-polar groups is already confined to a certain extent

2) the two non-polar groups in these compounds "see" each other through an already perturbed medium, because of the presence of the polar group. In this respect the study of the hydrophobic interaction between two simple molecules is advantageous since the perturbation to the structure of water is minimal (at least as far as polarization effects are concerned).

H. A. Resing Dr. Ben-Naïm, have you considered what part the flexibility of the molecule might play in the hydrophobic interaction? i.e., curling of the molecules would further decrease contact with the water?

A. Ben-Naïm We have evaluated also the hydrophobic interaction for cyclic hydrocarbons. It was found that the HI per-bond tends to a constant value as we increase the chain length of the molecule.

J. E. Mayer I would like to ask Mr. Ben-Naïm if he does not think that the change of local entropy density of water around a solvent entity, ion or molecule, may not be a better quantity to fix attention on, than the vague concepts of structure making or structure breaking. I do not understand what the "structure" of water is. I understand less what distinguishes a "broken" structure from a "made" structure. If structure "breaking" means greater freedom of motion of the water degree of freedom, both of the center of mass of the molecules and of the rotational and vibrational coordinates, it will manifest itself in a greater local entropy density. If structure making means tightening an already present structure, then local entropy will decrease.

My trouble is that "structure" in water is a multi-dimensional object. It is not only an arrangement of fixed positions in a three dimensional space, but a probability density in a space of three dimensions for each atom of a large number of molecules when their probabilities of position in phase space are highly correlated. I have great difficulty in visualizing such an object, much less hoping to determine it in any precise way.

I can visualize, to some extent at least, a single number related to the integral in phase space of this probability density times its logarithm which is proportional to the negative entropy divided by Boltzmann's constant. True, that since the stretching motion of the H-atom must be quantum mechanical, I have to treat this degree of freedom by something like the Wigner representation in $p - q$ space of the density matrix, but I do not believe that this completely distorts the picture.

H. G.Hertz But there is a vibrational contribution to the entropy. Thus, if one tries to define the structure of water through its entropy, then this statement may not only imply configurational properties. Let us consider water slightly above the temperature of maximum density: with increasing pressure, the entropy decreases. But the translational and rotational diffusion coefficients increase, generally one says: we have a breaking of hydrogen bonds, i.e., a structure breaking effect contrary to a statement given by the entropy change.

J. E. Mayer It is because of the quantum mechanical vibrational entropy that I remarked about using the density matrix formulation; for low enough frequencies the vibrational entropy can be handled as classical and then have a purely configurational interpretation.

The effect of pressure remarked by Hertz would indicate exactly the difficulty I perceive. One would have to understand the contribution of the different degrees of freedom separately, that of the centers of mass of the molecules may show increased structure whereas that of orientation show decreased structure.

J. E. B. Randles As I understand, the calculation was not simply based on the dipole moment alone, but on the dipole plus the quadrupole, and this, of course, does give a dissymetry which will cause a preferential orientation of molecules. But the fact is that the magnitude, even the sign, of the quadrupole moment depends on the choice of the origin of your coordinates; this origin ought to be at the center of the spherical cavity which the molecule occupies, I think.

A. Ben-Naïm The distribution of point charges was constructed so that the dipole moment of water but not the quadrupole moment was correct. Of course once we have a distribution of point charges at finite distances then one has all the multipoles, and not simply the first few ideal multipoles.

J. E. B. Randles The point is that the dipole moment in itself has a field which, as far as the intensity is concerned, is identical at the two ends. Therefore, it provides no reason for preferential orientation in a region of gradient of dielectric constant.

If you can add a quadrupolar moment, then it develops a preferred orientation in one way, but can one really trust any calculation of it?

A. Ben-Naïm I am almost sure that, in order to simulate the interaction between two water molecules, one should use more then just the dipole and the quadrupole moments, in fact the main idea of the pair potential for water molecules was to simulate the preference of water molecules to arrange in the tetrahedral configuration. To achieve that by a few multipoles would certainly be quite difficult.

J. E. B. Randles Just one more sentence: it seems to me that this is an example of the extreme unsatisfactoriness of treating regions of molecular dimension in water, in terms of the dielectric constant. I mean we should be attempting to look at the detailed interaction between water molecules, taking a tetrahedral structure.

There must be, I feel, a difference between the center of what you can call a sphere of occupation of the water molecule, and maybe the center with respect to the dipole of the molecule, or even the center of gravity of the molecule.

A. Ben-Naïm The model is certainly a very crude one. The charge distribution along the O-H direction is surely different from the charge distribution along the "lone-pair" directions. This should be taken into consideration in future work, and information on the details of the charge distribution will eventually come from quantum mechanical calculations.

J. E. Mayer One needs not only a quantum mechanical calculations on one more molecule in the gas, but also a question of approach of another molecule.

A. Ben-Naïm I would like to add one comment on the interaction between a pair of water molecules in the gaseous phase compared with the liquid. It is almost certain that the pair potential is modified to a large extent by the presence of other molecules. Therefore, for the study of water we have been talking on an effective pair potential which takes into account the non-additivity of the total potential energy.