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A Simple Electrostatic Model of Solvation for Large Molecules within the SCF MO Theory

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A very simple electrostatic model of solvation in which the solvent molecules are represented by point dipoles has been applied to simulate the hydration effect on molecular systems within the CNDO/2 method. The limitations of the model compared to the previous approaches as well as its feasible application to the study of tautomeric equilibria of cytosine and adenine in aqueous solution are discussed.

Key words: Hydration effect, point dipole model of – Tautomeric equilibria shifts

1. Introduction

There is an increasing number of papers dealing with the solvation phenomena within the quantum chemistry methods during the recent few years as an attempt to break through the difficulties which do appear when comparing the experimental results with the theoretical ones. The problem is particularly important in the case of biomolecules, for which the most important experimental results refer to measurements in solution.

Theoretical description of the solvation phenomena for large biomolecules is however handicapped by two main difficulties: the size of the molecules imposing the need of approximate methods (of decreased accuracy) and the lack of an unambiguous general theory describing the liquid state in general or liquid water in particular (the purely statistical approach being not tractable for the practical case). Thus all the "theoretical" results so far available must be treated with a caution,

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remembering that the approximations of the quantum chemical methods are superimposed on the approximate models and the fundamental problems still remain unresolved.

The traditional continuous, supermolecule and mixed super-continuous models developed during the last few years have been recently reviewed in a number of papers [1–3]. In spite of their obvious shortcomings, there is hope that the models proposed so far may be suitable for describing, at least partially, some of the features of the solvation phenomena. In this respect, it seems that the supermolecule approach has been most extensively and systematically exploited. The most difficult practical problem, when using the supermolecule model, lies in determining the number of solvent molecules, which should be simultaneously considered around the solute molecule as well as their positions and rotational degrees of freedom. The very recent papers of Clementi *et al.* [4–8] represent an attempt to overcome the above difficulties by applying the Monte Carlo technique for solvation of biomolecules. Even though this type of calculation seems to be promising, the papers do reveal the crucial difficulties concerning the effective pair potential approximation involved in such a procedure.

Thus at present, considering the practical need to continue studies in this field on the one hand and having at one's disposal a variety of results obtained within different model approaches on the other, it would be interesting to investigate the possibility of obtaining simplified models being to some extent reliable extrapolations of more sophisticated ones, which due to their simplicity might be applied in a straightforward manner to some experimental data for large biomolecules. For this reason, in this paper a simple model of solvation, namely an extrapolation of the electrostatic approaches described in the literature, is proposed. An application of the model (within the CNDO/2 method) to the study of the hydration schemes of molecules and evaluation of water influence on the tautomeric equilibria of some nucleic acid bases (cystosine, adenine) is presented.

2. Model Assumptions

The reliability of the electrostatic approximation, assuming that in the interaction energy between the solute and polar solvent the predominating contribution at increasing distances is of the electrostatic type, seems to be well established [9–11]. The model presented here is an extrapolated electrostatic approach with the following assumptions being made.

1) The presence of the solvent modifies the solute's Hamiltonian via an electrostatic interaction contribution described by the classical formula

$$E_{\text{int}} = \frac{1}{f} \sum_{A<B} \frac{Q_A Q_B}{r_{AB}}, \tag{1}$$

where Q_A, Q_B denote charge distributions for the solvent (A) and solute (B), respectively, r_{AB} is their mutual distance and f is a parameter describing the decrease of the energy in solution. Formally, the latter might be treated as a function of the

dielectric constant, for instance in a fashion similar to that used in several papers on the electrostatic solvation models (e.g. [12–16]). But since the use of the macroscopic dielectric constant is not fully justified in such models (e.g. [17]), we have decided to treat f as a scaling factor and determine its value by comparing the results of the model calculations with appropriate supermolecule results.

2) The multipole expansion is applied for the potential due to the solvent. The first term of the expansion describing the charge interaction is omitted and only the dipole moments contribution is explicitly dealt with. The above approximation may be physically justified only for those distances for which it can be assumed that the solvent molecule may be treated as a neutral entity. In such a case the solvent becomes the source of a dipole field and the solvent molecules are treated as point dipoles.

Finally, in the Hamiltonian prior to the SCF procedure the following additional term must be considered

$$\hat{v} = -\frac{1}{f}\left(\sum_{d}^{D}\sum_{i}^{N}\frac{\vec{\mu}_d\vec{r}_{di}}{r_{di}^3} - \sum_{d}^{D}\sum_{n}^{M}\frac{z_n\vec{\mu}_d\vec{r}_{dn}}{r_{dn}^3}\right), \tag{2}$$

where $\vec{\mu}_d$ is the dipole moment of the solvent molecule (here the experimental value of 1.85 D for H_2O has been taken [18]), $\vec{r}_{di}$, $\vec{r}_{dn}$ are the dipole–electron and dipole–nucleus distances, respectively, and the summation runs over all dipoles (D), nuclei (M) and electrons (N).

The additional one-electron integrals of the type $\langle\chi_A|x/r_C^3|\chi_B\rangle$ appearing in the Hartree–Fock matrix elements may be calculated analytically both in the GTO [19, 20] and STO [21] basis. Thus the model may be applied at both the *ab initio* and semiempirical levels of calculation. In particular, however, having in mind a tentative test of its efficiency for large molecules within a semiempirical scheme (making use of the ZDO approximations), one may easily calculate the appearing integrals on the basis of Roothaan's analytical formulas for the integrals of the type $\langle\chi_A|1/r_C|\chi_A\rangle$ [22]. In the present paper we have taken advantage of the latter approach in the frame of the CNDO/2 method. Formally, such a model in a limited context of application owing to its simplicity allows to perform in an unexpensive way preliminary calculations, in which many solvent molecules at different positions and orientations may be simultaneously considered around the solute molecule.

The reliability of the model, however, depends on answers to the following questions. Is it possible to obtain a measurable effect (in a computational sense) of the solvent influence on the system's energy within the model? Assuming the model is correct when it allows to reproduce qualitatively the results of the *ab initio* calculations in the supermolecule approach, is there a possibility to treat the corresponding supermolecule predictions as a basic information concerning the most favourable positions and orientations of the dipoles around a specific solute molecule? Is it possible to formulate general rules providing an effective application of the model for series of molecules with similar functional groups also in case no references to more sophisticated calculations for the systems are available?

3. Applications

3.1. The Reliability of the Model

It is assumed that the demonstration of the reliability of the model is to be accomplished by comparison with the supermolecule results. Formamide and water have been chosen as reference molecules in this respect. Preliminary calculations within the CNDO/2 scheme made for water and formamide monohydrates indicated that the use of standard CNDO/2 core charge values Z for estimation of the dipoles nuclei contributions led to incorrect results. Namely, the effect of destabilization was obtained for systems being stabilized by water in the supermolecule approach (at both the *ab initio* and CNDO/2 levels of calculations). Therefore, additional nuclei shielding due to valence electrons has been considered in the term describing dipoles–nuclei energy contribution (comp. Eq. (2)). It has been assumed that the shielding depends on mutual dipoles–nuclei distances r and the effective charge Z_{eff} is represented by a function of the type $Z_{\text{eff}} = Z \exp(-r)$. It seems that the need of the latter assumption is strictly connected with the CNDO/2 method, for which, in particular, the internuclear potential energy estimation is a crucial point (comp. e.g. [23]).

The preliminary results indicate that the dipole field contributions to the Hartree–Fock matrix elements may cause quite significant changes in the electronic energies of the molecules (up to several electron volts for $f=1$, see Eq. (1), depending on the dipoles positions). Thus the effect is "measurable" in the computational sense. However, to obtain the model results for the total energies quantitatively comparable with the supermolecule ones, it has been found reasonable to assume the value of the scaling factor f being equal to 25 (this value is consequently used for all the investigated systems).

The crucial problem, which appeared in the calculations, concerns the point dipoles positions and orientations. Even though it is commonly accepted that the electrostatic models may be treated as reliable ones at the distances larger than the corresponding equilibria distances of the complex system (i.e. solute molecule + solvent molecule), one cannot simply take the appropriate supermolecule predictions as a reference since the latter do strongly depend on the level of calculations being employed. For example, for the complex of 4-pyridone + H_2O the supermolecule approach predicts the equilibrium distances at ~ 2.9 Å on the *ab initio* SCF level [24, 25] comparing to the distance of ~ 2.5 Å on the CNDO/2 level for one in-plane configuration, while for another out-of-plane configuration it yields distances of ~ 3.2 Å and ~ 2.5 Å, respectively. It has also been found that the orientations, predicted by the supermolecule approach as the most favourable ones, do not always correspond to those in the point dipoles model (e.g. for formamide in some cases the differences are up to more than 90°). To some extent such a result should not be unexpectable owing to the simplicity of the point model, but still the differences had not been anticipated to be so drastic. In fact our result confirms the conclusion found for water molecules interactions (comp. [26] and Ref. therein) according to which the truncation of the permanent multipole expansion for electrostatic interactions yields an inadequate molecular symmetry giving rise to

erroneous energy values being strongly orientationally dependent. In general, it seems that the relevant problem of a correct selection of preferred orientations in simplified electrostatic models (both the point charge ones [27–29] and the overlap multipole expansion (OMTP) one [11, 30]) with respect to the supermolecule predictions requires a further detailed research. Considering the above, we come to the conclusions that on one hand the supermolecule predictions concerning the optimal positions and orientations of the solvent molecules cannot be applied in the point dipole model in a straightforward manner and on the other hand an optimizing procedure for orientations solely within the point dipole model would neither be justified nor reliable. That is why the problem of a reasonable *a priori* choice of point dipole positions and orientations arises.

In this respect, after tentative calculations we have found the following rules to be acceptable: the point dipoles are oriented on the nearest atoms and the dipole-atoms (hydrogens including) distances are equal to 2.85 Å. The latter is the constant distance assumed *a priori* between the oxygen of water and the second row atoms in the pioneer electrostatic treatments of water-DNA bases interactions [30].

The "effectiveness" and to some extent the justification of the above rules may be illustrated on the calculations made for water and formamide. Table 1 presents the results obtained in the *ab initio* perturbation calculations [10] for two interacting water molecules: the electrostatic interaction energy and the dipole–dipole interaction contribution for different oxygen–oxygen distances ($R_{O\text{-}O}$) are compared with the energies resulting from the point dipole model (for the same geometry). As it can be seen, the latter qualitatively reproduce the electrostatic interaction energies only for the $R_{O\text{-}O}$ distances larger than 3.70 Å (this justifies the distance of $\sim$2.85 Å between the dipole and hydrogen atom). For smaller distances the model's values may be comparable only with the dipole–dipole terms.

In the case of formamide hydrates, where orientation of the dipoles does play an important role, the above rules of orientation give the hydration picture qualitatively comparable with that of the supermolecule approach. The results for

Table 1. Interaction energies (in kcal/mole) between two water molecules versus the oxygen–oxygen distance ($R_{O\text{-}O}$ in Å) in different approximated approaches

$R_{O\text{-}O}$	Electrostatic interaction [10]	Dipole–dipole interaction [10]	Point dipole model (present study on CNDO/2 level)
2.12	−43.09	−9.33	−9.90
2.33	−27.10	−7.01	−8.23
2.54	−17.07	−5.40	−6.91
2.75	−11.10	−4.25	−5.86
3.00	−7.12	−3.28	−4.89
3.70	−2.79	−1.74	−3.16
4.76	−1.12	−0.82	−1.88
7.94	−0.21	−0.18	−0.66

Table 2. Hydration of formamide–stabilization energies (in kcal/mole)

Position of water[a]	Supermolecule approach on an *ab initio* level [27]	Electrostatic approaches: Point charges, *ab initio* [27]	Electrostatic approaches: Point dipole model (present study on CNDO/2 level)
I	9.4	6.5	7.9
II	9.2	8.3	8.2
III	8.2	9.4	8.4
IV	7.2	8.4	7.7
V	3.0	3.5	5.9
VI	1.8	1.4	5.8

[a] For the positions of water molecule relative to formamide see Ref. [27].

formamide monohydrates corresponding to six different complexes according to geometrical parameters of Ref. [27] in both the supermolecule and point charge models are presented in Table 2 together with the point dipole model results, where the suggested rules of orientation have been applied (while keeping the distances equal to those of Ref. [27]). In Table 3 the results for gradual total hydration of formamide are given, both as obtained in the supermolecule approach [31] and the present model. It is seen that in the case of monohydrates the respective differences in the stabilization energies for the sequential species (I–VI) resulting from the point dipoles model are definitely smaller than those from either the supermolecule or point charge models. In general also the differences in stabilization energies caused by a change of mutual solute–solvent distances are smaller for the point dipoles model than for the supermolecule one. This seems understandable, if one considers that in the former only the dipole moments are explicitly dealt with (comp. Table 1). On the other hand, as far as the total hydration is concerned, the stabilization energy values are approximately of the same range in both the supermolecule and point dipoles approaches.

Table 3. Total hydration of formamide–stabilization energies (in kcal/mole)

System[a]	Supermolecule approach on an *ab initio* level [31]	Point dipole model (present study on CNDO/2 level)
F+H_2O (I)	6.8	7.9
F+$2H_2O$ (I, II)	13.4	16.0
F+$3H_2O$ (I, II, III)	28.4	24.4
F+$4H_2O$ (I, II, III, IV)	36.1	32.2
F+$5H_2O$ (I, II, III, IV, V)	40.2	38.7

[a] F-formamide. For the positions of water molecules relative to formamide see Refs. [27, 31].

It should be stressed that the suggested rules for point dipole positions and orientations may sometimes lead to physically unrealistic situations (in particular concerning the point dipole orientations, which may be opposite to those predicted by the supermolecule approach). But even in such cases the application of the rules keeps the final results reasonable, since the obtained stabilization energy values allow to select the hydration sites being qualitatively comparable with those of both the supermolecule model and the electrostatic molecular potential one [9] (see below our results for cytosine and adenine).

3.2. The Tautomeric Equilibria Study

The essential difficulty in the study of tautomeric equilibria by means of the approximate quantum chemical methods is connected with a strong dependence of the total energy values on the geometrical parameters assumed in the calculations [32–34]. On the other hand, it does seem that the use of experimental geometry input when applying e.g. a method of the CNDO/2 type, is more reasonable than carrying out an optimizing procedure for geometry within the frame of the method [35, 36]. In the case of rare tautomeric forms, however, experimental geometries are usually not available. The situation is still more complicated when considering the tautomeric equilibria in aqueous solution, since the use of experimental data usually derived from crystallographic measurements is not fully justified in such a case.

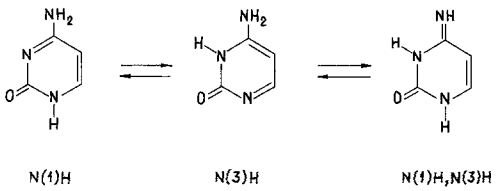
Therefore, it seems reasonable, in spite of a different approach being suggested in the literature (e.g. [25, 37, 38]), to compare only the stabilization energies with respect to the corresponding isolated forms and to neglect in the final conclusions the energy differences between the isolated species (since the latter may be significantly changed when using different geometries in the calculations). Such an approach is presented here.

Finding that the model described here gives a reasonable picture of preferred hydration sites, we have been encouraged to apply it to the study of water environmental effect on the shift of the tautomeric equilibria in a manner similar to that being used within the supermolecule approach [25, 37, 38]. Preliminary calculations have been carried out for 2- and 4-hydroxypyridines. The equilibria between the lactim and lactam tautomers of these pyridine derivatives are known to be strongly solvent dependent and they have been the subject of recent theoretical studies [24, 25, 38]. These studies based on the supermolecule approach (at the *ab initio* and CNDO/2 levels) have confirmed the experimental effect of stronger stabilization for the lactam forms of both the derivatives in aqueous solution.

The hydration schemes predicted here for both tautomeric forms of the 2- and 4-hydroxypyridines are qualitatively similar to those found previously [24, 25, 38]. For example, the positions of the sequential point dipoles surrounding the solute molecules coincide with the most probable ones predicted for the water molecules by the supermolecule approach [38]. Fixing a few water molecules represented by the point dipoles at the most favourable sites of hydration surfaces of both

tautomeric forms of the molecules[1] we easily estimated, as previously, that the lactam tautomers are more stabilized by water than the corresponding lactim ones (in both cases by ~ 3 kcal/mole). Thus the resulting polyhydration picture remains qualitatively comparable with the previous one [24, 25, 38].

The tautomeric equilibria of cytosine in aqueous solution have not been systematically studied by theoretical methods, but there exist experimental data revealing an important influence of water on the tautomeric equilibria N(1)H $\rightleftarrows$ N(3)H and N(1)H,N(3)H $\rightleftarrows$ N(3)H. It has been shown [39] by the temperature-jump spectroscopy method that in aqueous solution the amino–oxo



N(1)H N(3)H N(1)H,N(3)H

tautomer N(1)H is the predominating form (the equilibrium constant $K=[\mathrm{N(3)H}]/[\mathrm{N(1)H}]$ being equal to $(2.5\pm0.5)10^{-3}$ at 25°). As far as the tautomeric reactions N(3)H $\rightleftarrows$ N(1)H,N(3)H is concerned the experimental data for 3-methylcytosine [39] indicate that the imine–oxo form N(1)H,N(3)H predominates in nonpolar solution, while in water the amine–oxo tautomer N(3)H becomes the major form (with the equilibrium constant $K=[\mathrm{N(1)H,N(3)H}]/[\mathrm{N(1)H}]\sim 3\cdot 10^{-2}$ at 25°). The CNDO/2 calculations of the total energies for the isolated species indicate the following sequence of stabilization: N(1)H > N(1)H,N(3)H > N(3)H (this, in particular, seems to confirm the predominance of the N(1)H,N(3)H form with respect to the N(3)H one in nonpolar solvents [39]). To estimate the water influence on the above tautomeric equilibria, we have performed calculations in the frame of the suggested electrostatic model. Figure 1 presents the point dipole

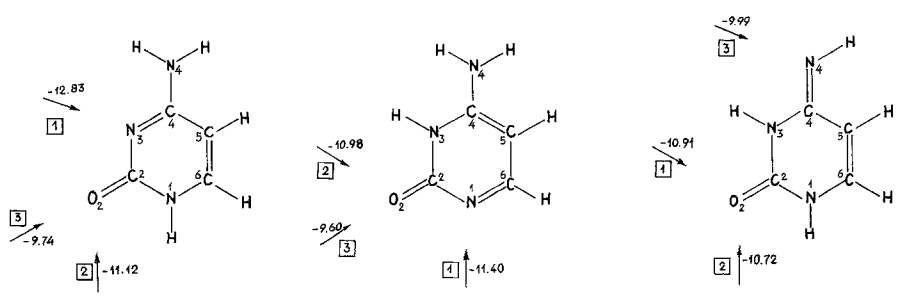


Fig. 1. Hydration of the tautomers of cytosine in the point dipole model. Stabilization energies in kcal/mole

[1] The location of the water molecules on the hydration surfaces of the molecules should be made with caution, remembering water–water interaction as well as limitations of the method used to describe these interactions (see [25, 38]).

positions around the solute molecules, for which the maximum stabilization effects have been found. It is worth to remark here that in the case of the amino–oxo form the selection of the hydration sites, resulting from the point dipole model, fairly agrees with the predictions of the supermolecule and electrostatic (OMTP) approaches [11, 30] as well as an approximate perturbation treatment [40]. The results for gradual hydration of the tautomers (i.e. with considering two and three water molecules being simultaneously placed in the corresponding hydration sites of Fig. 1) are given in Table 4. As can be seen, there are differences of the

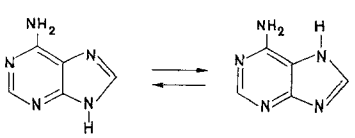
Table 4. Hydration of tautomeric forms of cytosine and adenine (point dipole model within the CNDO/2 method)–stabilization energies in kcal/mole

Number of water molecules[a]			
	Cytosine		
	N(1)H	N(3)H	N(1)H,N(3)H
1	12.8	11.4	10.9
2	23.9	22.3	21.7
3	33.6	31.9	31.5
	Adenine		
	N(9)H	N(7)H	
1	12.9	13.1	
2	25.4	25.7	
3	37.8	37.7	

[a] For the location of water molecules around the tautomers of cytosine and adenine see Figs. 1 and 2, respectively.

stabilization effects for the tautomeric species. The strongest stabilization effect may be observed for the N(1)H tautomer (the difference with respect to the N(3)H form being about 2 kcal/mole). Thus, the predominance of the N(1)H form in the water solution, checked experimentally, has been confirmed by the model calculations. Even though there is only a slight difference (of about 0.5 kcal/mole) between the stabilization energies of the N(3)H form and the imino–oxo N(1)H,N(3)H one, in favour of the former, the trend of the stabilization may be considered as qualitatively correct in this case too, when comparing with the experimental data.

The tautomerism involving ring atoms of adenine represents an interesting case from the point of view of water influence estimation. The temperature-jump relaxation methods [41] have indicated that in water two tautomeric forms of adenine N(7)H and N(9)H exist in comparable amounts (the constant being $K=[\mathrm{N(7)H}]/[\mathrm{N(9)H}]=0.28$ at 20°).



N(9)H N(7)H

The calculations made for isolated forms indicate a stronger stabilization of the N(9)H form and also reveal a rather large difference between the dipole moment values of both tautomeric forms. Namely, the calculated values of the dipole moments are 2.60 and 7.8 D for the N(9)H and N(7)H forms, respectively. According to a commonly accepted opinion, being drawn in fact from the classical reaction field theory (comp. e.g. [42]), one might expect that the tautomer of a larger dipole moment's value would be more stabilized in aqueous solution (in fact, in many cases such a situation does occur). On the other hand, the experimental equilibrium constant seems to suggest comparable stabilization energies for both the tautomers in water.

To see how this case is interpreted by means of the presented electrostatic model, we have performed calculations for adenine tautomers, finding the most probable hydration sites, as presented in Fig. 2. It may be remarked here that the hydration picture for the N(9)H form in Fig. 2 remains in agreement with those resulting from other electrostatic models (the electrostatic molecular potential [9] and the overlap multipole expansion one [30]). The results of the calculations, in which simultaneously two and three water molecules (placed at the most probable hydration sites, Fig. 2) were considered are presented in Table 4. As it can be seen, the obtained stabilization energies for both the tautomers are comparable. Thus the dipole model confirms the observed analogy in the stabilization of two tautomers by water. This

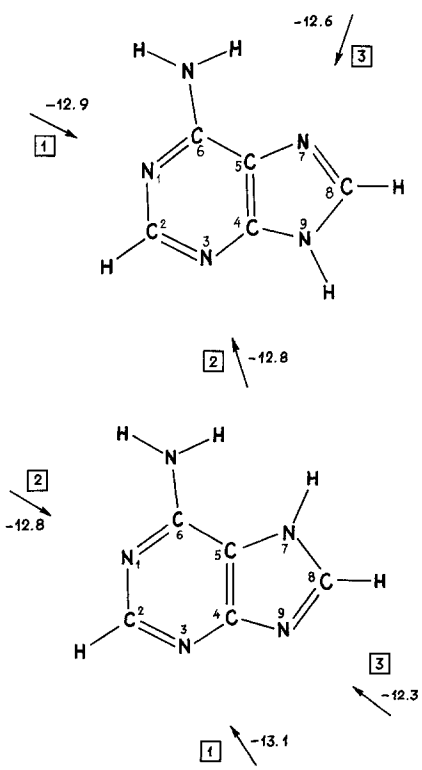


Fig. 2. Hydration of the tautomers of adenine in the point dipole model. Stabilization energies in kcal/mole

result indicates that the difference in the dipole moment values does not always provide an evidence concerning the solvent effect stabilization.

4. Conclusions

The suggested point dipole model for solvation of large biomolecules applied within the CNDO/2 procedure, in spite of its obvious drawbacks, owing to crude simplifications in both the model and the calculations scheme, seems to satisfy the basic desiderata for such a model, since in a limited context of application, it qualitatively reproduces the results of more sophisticated methods and the model's results seem to be in agreement with the available experimental data.

The practical advantage of the model is that it requires a minimal numerical effort – when starting with the isolated system's functions in most cases only 2–4 additional iterations have to be done within the SCF procedure.

To find the essential shortcomings of the model, imposed by the approximations of the CNDO/2 method, we are planning to test its efficiency at the *ab initio* level of calculation, also having in mind the possibility of including higher order multipoles.

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