

Theoretical Calculation of the Stark Component of the Solute–Solvent Interaction Energy. Validity of the Mean Field Approximation in the Study of Liquids and Solutions

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Received: January 11, 2002; In Final Form: March 13, 2002

We examine the Stark component of the solute–solvent interaction energy and check the validity of the mean field approximation (MFA) in the theoretical study of liquids and solutions. We considered two types of systems: methanol, ethanol, and propanol liquids and formaldehyde, acetaldehyde, and acetone in aqueous solution. We found that, independent of the level of calculation (HF, MP2, or MCSCF), the errors introduced by MFA are less than 5% in the interaction energy and less than 1% in the dipoles. We propose an approximate expression for the Stark component that reduces the errors in the interaction energy to below 1.6%.

I. Introduction

Many of the most frequently used methods for the study of solvent effects make use of the mean field approximation (MFA). The different quantum versions of continuum models (SCRF,¹ PCM,² multipole expansions,³ etc.) or the methods based on Langevin dipoles⁴ are representative examples. In all these methods, the solute is represented quantum mechanically, whereas the solvent response is described classically through very simplified models that completely neglect the microscopic structure of the solvent and the possible presence of specific interactions. Because of this, several methods have been proposed in the past decade that combine MFA with a detailed description of the solvent structure obtained either from integral theories, the reference interaction site method in the case of RISM/HF,⁵ or from simulations, when the averaged solvent electrostatic potential/molecular dynamics method, ASEP/MD,⁶ is used.

In MFA-based methods, the energy and wave function of the solute molecule are obtained in the presence of the averaged perturbation generated by the solvent.^{2b} The main advantage of this approximation is that it notably reduces the number of quantum calculations. For instance, whereas in traditional quantum mechanics/molecular mechanics⁷ (QM/MM) methods (where MFA is not used), it is necessary to perform one quantum calculation for each chosen solvent configuration, ASEP/MD⁶ or RISM/HF⁵ require only 3–10 quantum calculations depending on the number of cycles needed to reach convergence.

As with any other approximation, MFA introduces errors into the evaluation of the solute–solvent interaction energy and the solute properties. These errors are associated with the neglect of the correlation between the motion of the solvent nuclei and the response of the solute electron polarizability; that is, MFA does not allow the solute to polarize in response to a change in the solvent nuclear configuration. This correlation energy is usually known as the Stark component.^{8,9}

Despite the extended use of MFA in solvent effect theories, few studies have focused on the evaluation of the Stark component. Linder,⁸ and later Karlstrom and Halle,⁹ proposed expressions for this component based on continuum models. In both cases, the magnitude of the Stark component was related to the solute polarizability and the difference between the dipole

reaction factors evaluated at zero and optical frequencies:

$$\Delta W_{\text{Stark}} = -\frac{1}{2}K_{\text{B}}T \sum_l \sum_k \alpha_{lk} [g_{lk}(\epsilon_0) - g_{lk}(\epsilon_\infty)] \quad (1)$$

where K_{B} is the Boltzmann constant, T is the absolute temperature, α_{lk} is the lk component of the solute polarizability tensor, and g_{lk} is the lk component of the Onsager factor tensor evaluated at zero and optical frequencies. Like the rest of the expressions based on continuum theories, eq 1 neglects the effects of the microscopic structure of the solvent and of the specific interactions. Furthermore, a value has to have been assigned to the cavity radius that holds the solute molecule, and this is not always easy.^{3b,10}

As was indicated above, the ASEP/MD theory⁶ combines MFA with MD calculations and, hence, does not suffer from the limitations of continuum models. We here use this theory to evaluate the Stark component calculated as the difference between the solute–solvent interaction energy when the MFA is used and when it is not. Our aim is 2-fold. First, we shall evaluate the Stark component for a few representative systems. This is an important preliminary step because the validity of the MFA-based theories depends on the supposition that this component remains small. Second, we shall show how an estimate of this component can easily be obtained from knowledge of the solvent electric field fluctuations at the position occupied by the solute.

The rest of the paper is organized as follows. In sections II and III, we detail the method that we follow in the determination of the magnitude of the Stark component and present an approximate expression that permits a rapid evaluation of this component. Section IV presents the results for various hydrogen-bonded systems using several levels of calculations. Section V presents our conclusions.

II. Methods

(a) Direct Determination of the Stark Component. For a direct determination of the magnitude of the errors introduced by the MFA, we have to compare a full calculation of the energy and properties of a solute molecule in solution with the result when the MFA is introduced.

We use a QM/MM method to obtain the solute wave function in solution. The solvent effect theory involving coupling between a quantum and a classical system has been widely discussed.⁷ For clarity, we shall summarize the main points of the implementation of the method.

The Hamiltonian model is partitioned in the usual way:

$$H = H_{\text{QM}} + H_{\text{MM}} + H_{\text{QM/MM}} \quad (2)$$

with terms that correspond to the quantum part, H_{QM} , the classical part, H_{MM} , and the interaction between them, $H_{\text{QM/MM}}$. In our case, the quantum part is formed by the solute molecule, whereas the classical part includes all of the solvent molecules.

The energy and wave function of the solvated solute molecule are obtained by solving the effective Schrödinger equation for each configuration:

$$(H_{\text{QM}} + H_{\text{QM/MM}})|\Psi\rangle = E|\Psi\rangle \quad (3)$$

The interaction term, $H_{\text{QM/MM}}$, takes the following form:

$$\hat{H}_{\text{QM/MM}} = H_{\text{QM/MM}}^{\text{elect}} + H_{\text{QM/MM}}^{\text{vdw}} \quad (4)$$

$$\hat{H}_{\text{QM/MM}}^{\text{elect}} = \int dr \hat{\rho} \cdot \hat{V}_S(r; X_i) \quad (5)$$

where $\hat{\rho}$ is the solute charge density and $\hat{V}_S(r; X)$ is the electrostatic potential generated at the position r by the solvent configuration X_i . If the solvent is regarded as nonpolarizable, then this potential is nothing more than the electrostatic potential generated by the charges that represent the solvent molecules during the simulation. If the solvent is polarizable, we have also to include the contribution from the induced dipoles. The term $H_{\text{QM/MM}}^{\text{vdw}}$ is the Hamiltonian for the van der Waals interaction, which is generally represented by a Lennard-Jones potential. Schrödinger's equation has to be solved for each point of configuration space, usually by sampling through molecular dynamics or Monte Carlo simulations.¹¹

The desired properties are then obtained by averaging over the N solvent configurations

$$\langle A \rangle = \frac{1}{N} \sum_{i=1}^N A(X_i) \quad (6)$$

where the different $A(X_i)$ values are obtained from the solute wave function, $\Psi(X_i)$, calculated in the presence of the solvent configuration X_i .

On the contrary, in MFA, one averages the solvent perturbation, $\hat{H}_{\text{QM/MM}}^{\text{elect}}$:

$$\hat{H}_{\text{QM/MM}}^{\text{elect}} = \int dr \hat{\rho} \cdot \langle \hat{V}_S(r) \rangle \quad (7)$$

where the brackets denote a statistical average. The term $\langle \hat{V}_S(r) \rangle$ is usually known as the averaged solvent electrostatic potential (ASEP). Substituting (7) into (4) and (3), we obtain the energy, E_{MFA} , and wave function, Ψ_{MFA} , of the solute in the presence of the averaged solvent configuration. The obvious advantage of this approximation is that only one quantum calculation has to be performed. The Stark component is then calculated as the difference between the energies obtained with eqs 6 and 7, that is, $W_{\text{Stark}} = \langle E \rangle - E_{\text{MFA}}$.

Different mean field models can be obtained if we vary the description of the solute–solvent interaction term (point charges, point charges + polarizabilities, multipole expansion, pseudo-potentials, etc.) or the way in which the different solvent configurations are obtained (MD, MC, integral theories, etc.)

In our case, we obtain the solvent configuration from MD, and the ASEP is represented by a set of point charges chosen in the following way.

1. We include the charges belonging to solvent molecules that, in any of the MD configurations, lie within a sphere of radius R chosen in such a way that it includes the first solvation shell. The value of any charge is then divided by the number of solvent configurations included in the calculation of the ASEP.

2. Next, a second set of charges is obtained by a least-squares fit to the values of the electrostatic potential originated by the solvent molecules lying beyond the first solvation shell.¹⁶ The details have been given elsewhere.^{6a,6d}

The total number of charges introduced into the perturbation Hamiltonian is about 5000.

(b) Approximate Evaluation of the Stark Component. A very simple formula to evaluate the magnitude of the Stark component can be obtained if we represent the solute charge distribution by a dipole moment. In this case, the electrostatic solute–solvent interaction energy is

$$W(X_i) = \mu_0 E(X_i) + \frac{1}{2} (\alpha E(X_i)) E(X_i) = \mu_0 E(X_i) + \frac{1}{2} \alpha : [E(X_i) \otimes E(X_i)] \quad (8)$$

where E is the electric field generated by the solvent in the position occupied by the solute when the solvent is at the configuration X_i , α is the solute electronic polarizability tensor, “:” is the double scalar product of two second-order tensors defined as $A:B = \sum_i \sum_j A_{ij} B_{ij}$, and “ \otimes ” denotes the tensor product.

The final energy is obtained by averaging over all of the configurations:

$$\langle W \rangle = \mu_0 \langle E \rangle + \frac{1}{2} \alpha : \langle E \otimes E \rangle \quad (9)$$

where the brackets denote averaged values.

In MFA, we calculate the energy of the averaged solvent configuration as

$$W = (\mu_0 + \frac{1}{2} \alpha \langle E \rangle) \langle E \rangle = \mu_0 \langle E \rangle + \frac{1}{2} \alpha : \langle E \rangle \otimes \langle E \rangle \quad (10)$$

The difference between (9) and (10) yields an approximate formula for the Stark component that is valid when the solute charge distribution is well described by a dipole moment:

$$\Delta W_{\text{Stark}} = \frac{1}{2} \alpha : (\langle E \otimes E \rangle - \langle E \rangle \otimes \langle E \rangle) \quad (11)$$

$$= \frac{1}{2} \sum_i \sum_j \alpha_{ij} (\langle E_i E_j \rangle - \langle E_i \rangle \langle E_j \rangle) \quad (12)$$

Equation 12 is obtained from eq 11 by resolving the double scalar and the tensor product. One sees that in this expression ΔW_{Stark} is proportional to the solute polarizability and to the fluctuations of the electric field generated by the solvent at the position occupied by the solute.

III. Details of the Calculations

We studied two types of systems, pure liquids and solutions. As examples of liquids, we considered methanol, ethanol, and propanol, and as examples of solutions, we considered formaldehyde, acetaldehyde, and acetone in aqueous solution. In all these cases, there are strong hydrogen bond interactions.

In the three pure liquid systems, the geometries were taken from Jorgensen et al.¹² and the basis set used was the aug-cc-pVDZ from Dunning et al.¹³ This basis set yields values for

TABLE 1: In Vacuo Dipole Moments and Polarizabilities of the Methanol, Ethanol, and Propanol Molecules^a

	μ^0	α^0	$\mu^0(\text{exp})^{26,27}$	$\alpha^0(\text{exp})^{28,29}$
methanol	1.81	19.52	1.70	21.79
ethanol	1.72	31.00	1.68	34.48
propanol	1.65	42.12	1.55	45.49

^a Dipole moments are in debyes. Polarizabilities are in au.

TABLE 2: In Vacuo Dipole Moments and Polarizabilities of the Formaldehyde, Acetaldehyde, and Acetone Molecules^a

	μ^0	α^0	$\mu^0(\text{exp})$	$\alpha^0(\text{exp})$
formaldehyde	2.35	14.40	2.36 ^b	16.53 ^c
acetaldehyde	2.76	25.38	2.75 ^d	31.04 ^c
acetone	2.90	35.58	2.93 ^e	42.52 ^f

^a Dipole moments are in debyes. Polarizabilities are in au. ^b Reference 30. ^c Reference 29. ^d Reference 31. ^e Reference 32. ^f Reference 33.

the in vacuo dipole moment and polarizability close to the experimental values (see Table 1). The dipole moments are overestimated by about 0.1 D, and the polarizabilities are underestimated by about 3 au. The experimental trends of decreasing dipole moments and increasing polarizabilities with the size of the alkyl groups are well reproduced. Wave functions and energies were calculated at Hartree–Fock (HF) level, and second-order Møller–Plesset (MP2) perturbation theory corrections to the energy (PTE) were added when indicated.

For formaldehyde,¹⁴ acetaldehyde,¹⁵ and acetone,¹⁶ the experimental geometries and generally contracted basis sets of the atomic natural orbital (ANO) type¹⁷ were used. The latter were obtained from 14s9p4d/8s primitive sets and contracted to 4s3p1d/2s. For each molecule, a Hartree–Fock (HF) calculation was first performed. The corresponding orbitals were used as starting orbitals in the subsequent CASSCF (complete active space self-consistent field) calculations. The active space is spanned by all of the configurations arising from six valence electrons in four orbitals. Table 2 gives the in vacuo dipole moments and polarizabilities for these molecules. The dipole moments are very well reproduced, but the polarizabilities are underestimated.

All of the quantum calculations were performed using the Gaussian 94 package.¹⁸

The MD calculations were performed using the program MOLDY.¹⁹ In each case 128 (alcohols) or 215 (carbonyls) molecules were simulated at fixed intramolecular geometry by combining Lennard-Jones interatomic interactions^{12,20} with electrostatic interactions. In the carbonyl–water system, the 214 solvent molecules were simulated by the TIP3P²¹ model at fixed intramolecular geometry. Periodic boundary conditions were applied, and spherical cutoffs were used to truncate the molecular interactions at 9.0, 11.5, and 12.5 Å for methanol, ethanol, and propanol, respectively, and 9 Å for formaldehyde, acetaldehyde, and acetone. A time step of 0.5 fs was used. The electrostatic interaction was calculated with the Ewald method.²² The temperature was fixed at 298 K by using a Nosé–Hoover²³ thermostat. Each simulation of the self-consistent process was run for 150 000 time steps (50 000 equilibration, 100 000 production). The solute and solvent coordinates were dumped at every 100 or 1000 steps for further analysis.

Once the different solvent configurations have been obtained, we calculate the solute–solvent interaction energy in the two ways indicated above. In the first, we perform a quantum calculation for each of the N solvent configurations and obtain N values of the interaction energy and the dipole moment. Next, the mean value is obtained (values in brackets). In the second

TABLE 3: Interaction Energy (in kcal/mol) and Dipole Moment (in debyes) of a Methanol Molecule in the Liquid State as a Function of the Number of Configurations Included in the Calculation of the Average^a

N configurations	$\langle E \rangle$	$\langle \mu \rangle$	N configurations	$\langle E \rangle$	$\langle \mu \rangle$
50	−19.28	2.47	333	−19.02	2.46
100	−19.07	2.46	500	−19.01	2.46
200	−19.02	2.46	1000	−19.01	2.46
250	−19.02	2.46			

^a Results obtained at the Hartree–Fock level.

TABLE 4: Interaction Energy (in kcal/mol) and Dipole Moment (in debyes) of a Methanol Molecule in the Liquid State as a Function of the Time Window Chosen to Calculate the Average^a

interval (ps)	$\langle E \rangle$	$\langle \mu \rangle$	interval (ps)	$\langle E \rangle$	$\langle \mu \rangle$	interval (ps)	$\langle E \rangle$	$\langle \mu \rangle$
0:5	18.95	2.41	20:25	18.73	2.48	35:40	20.13	2.49
5:10	18.78	2.44	25:30	19.26	2.50	40:45	20.64	2.52
10:15	17.44	2.39	30:35	20.79	2.56	45:50	17.59	2.38
15:20	17.86	2.46						

^a Results obtained at the Hartree–Fock level.

type of calculation, from the N configurations, we obtain the averaged potential, ASEP, which is then introduced into the solute molecular Hamiltonian. By solving the Schrödinger equation, we get the values of the interaction energy and dipole moment in the mean field approximation.

IV. Results

Let us begin by analyzing the effect of the number of configurations used to calculate the averages on the values of the desired properties. Table 3 gives the results for methanol. It is necessary to clarify that, independent of their number, the configurations were chosen so as to span the complete time of the simulation, 50 ps. With 50 configurations (and hence 50 quantum calculations) the error (when compared with the 1000 configuration value) is only 0.3 kcal/mol in the energy and 0.01 D in the dipole moment. With 100 configurations, the errors decrease to 0.06 kcal/mol and 0.00 D, respectively. With 200 configurations the results have almost converged. It is evident that if the chosen configurations are uncorrelated,²⁴ as is the case, the results should converge very quickly. A very small number of configurations is enough to obtain an adequate description of the average properties of the system. The results do not depend on the particular set of configurations used as long as they span the same simulation time (different sets yield interaction energies that differ by less than 0.15 kcal/mol). The same conclusions were obtained by Coutinho et al.²⁴ in a study of the solvatochromic shifts of the lowest transition of benzene in several solvents. Because of the small magnitude of the errors obtained with 100 configurations, and in order to save computational time, in the rest of the paper the mean values are calculated by averaging over 100 configurations.

The results showed larger variations when different time windows were used to calculate the averages. For instance, in methanol, variations of about 3 kcal/mol in the electrostatic interaction energy can be found if the averages are calculated taken different windows of 5.0 ps (see Table 4). For the dipole moments, the differences can be 0.2 D. As expected, these fluctuations in the mean values decrease when we increase the size of the time window. From the results given in Tables 3 and 4, one can conclude that, to obtain good averaged values, more important than including many configurations is to choose the configurations so as to span the largest possible time interval.

TABLE 5: Interaction Energy, Stark Component (in kcal/mol), and Dipole Moment (in debyes) of Alcohols in the Liquid State Calculated as a Mean Value ($\langle E \rangle$ and $\langle \mu \rangle$) or with the Mean Field Approximation (E_{MFA} and μ_{MFA})

	$\langle E \rangle$	E_{MFA}	W_{Stark}	$\langle \mu \rangle$	μ_{MFA}	$\langle \mu \rangle - \mu_{\text{MFA}}$
HF						
methanol 1000	-19.0	-18.6	0.4 (2.1%)	2.46	2.45	0.01 (0.4%)
methanol 100	-19.1	-18.7	0.4 (2.1%)	2.46	2.45	0.01 (0.4%)
ethanol 100	-16.5	-16.0	0.5 (3.0%)	2.27	2.25	0.02 (0.9%)
propanol 100	-14.3	-14.0	0.3 (2.1%)	2.15	2.13	0.02 (0.9%)
MP2						
methanol 1000	-18.3	-17.9	0.4 (2.2%)			
methanol 100	-18.3	-17.9	0.4 (2.2%)			
ethanol 100	-15.8	-15.4	0.4 (2.5%)			
propanol 100	-13.7	-13.5	0.2 (1.5%)			

TABLE 6: Interaction Energy, Stark Component (in kcal/mol), and Dipole Moment (in debyes) of Carbonyl Compounds in Aqueous Solution Calculated as a Mean Value ($\langle E \rangle$ and $\langle \mu \rangle$) or with the Mean Field Approximation (E_{MFA} and μ_{MFA})

	$\langle E \rangle$	E_{MFA}	W_{Stark}	$\langle \mu \rangle$	μ_{MFA}	$\langle \mu \rangle - \mu_{\text{MFA}}$
CASSCF/ANO						
formaldehyde	-9.2	-8.8	0.4 (4.3%)	2.99	2.99	0.00 (0.0%)
acetaldehyde	-8.9	-8.5	0.4 (4.5%)	3.46	3.46	0.00 (0.0%)
acetone	-21.9	-21.1	0.8 (3.6%)	4.48	4.47	0.01 (0.2%)

We shall next analyze the validity of the MFA. Table 5 gives the values of the Stark energy for the liquid alcohols. For methanol, the results are for 1000 and 100 configurations. For ethanol and propanol, only 100 configurations were used. The Stark energy ranges between 0.3 and 0.8 kcal/mol, representing less than 5% in all of the cases. The differences in dipole moments are even lower: 0.01–0.02 D representing 0.4–1%. The inclusion of the electron correlation decreases the interaction energy, a fact already found in studies performed with continuum models,²⁵ but has very little effect on the value of the Stark component, which is unchanged or slightly lower.

Table 6 gives the values calculated for the Stark component in solutions of carbonyl compounds in liquid water. The properties are calculated now at the MCSCF level and with a basis set of ANO quality. The trend is very similar to that found for the alcohols: differences less than 4% in the energies and then 0.02 D in the dipole moments.

In sum, for all the systems considered and independent of the level of calculation (HF, MP2, or MCSCF), the Stark component ranges between 0.2 and 0.8 kcal/mol, with percentages representing 1.5 and 4.5%, respectively. It is clear that the Stark energy represents a very small part of the solute–solvent interaction energy. The behavior of the MFA is even better in the prediction of the molecular properties where the errors are less than 0.02 D (1%). As a consequence, one can conclude that, for the present systems, MFA is a very good approximation that does not introduce significant errors either in the energy or in molecular properties, and that permits a notable saving of computation time.

Although the values of the solute polarizabilities given in Tables 1 and 2 range between 14 and 36 au³, the magnitude of the Stark component, Tables 3 and 4, is almost constant and independent of the system or method of calculation. From eq 11, it is clear that the Stark component is proportional to the polarizability of the solute molecule, so that in principle, an increase in polarizability should be followed by an increase in the Stark energy. However, for a given series of compounds, alcohols for instance, increasing polarizability is associated with the increase in the size of the alkyl group. Because of volume effects of these groups, the solvent reaction field decreases as

TABLE 7: Polarizability (in au), Electric Field Fluctuation (in au), and Comparison between the Values of the Stark Component Calculated Exactly, ΔW_{Stark} , (kcal/mol) and with the Approximate Formula, eq 11

	α	$[\langle E^2 \rangle - \langle E \rangle^2]10^5$	ΔW_{Stark}	ΔW_{Stark} (eq 11)
methanol 1000	19.45	3.87	0.44	0.20
methanol 100	19.45	4.10	0.40	0.20
ethanol	31.00	2.77	0.51	0.25
propanol	42.11	1.15	0.29	0.15
formaldehyde	14.40	6.60	0.4	0.28
acetaldehyde	25.28	3.24	0.4	0.25
acetone	35.58	4.18	0.78	0.45

also do its fluctuations. These two factors, polarizability and electric field fluctuations, seem to mutually compensate, resulting in values of the Stark component that are almost independent of the polarizability.

Last, Table 7 presents the values obtained for the Stark component when the approximate formula, eq 11, was used. In general, the approximate values are one-half the exact values. The reason is that eq 11 neglects the effect of terms of higher order than the dipole. If the Stark component obtained with the approximate formula is added to the mean field value, E_{MFA} , the difference from the true energy, $\langle E \rangle$, reduces to 0.35–0.1 kcal/mol, representing less than 1.5%. These results, together with the small differences found in the dipoles, 0.02 D ($\approx 1\%$), are evidence for the validity of the mean field approximation in the study of molecules in solution.

V. Conclusions

The use of the mean field approximation has become standard in solvent effect theories. Its main advantage is that it requires notably fewer quantum calculations. The cost to pay is the loss of any information associated with the fluctuations of the solvent electric field. Furthermore, it is not clear to what extent the mean energy of different solute–solvent configurations can be replaced by the energy of an averaged configuration. In this work, we have shown that, for all of the systems studied, the mean field approximation introduces only small errors in the interaction energies, and negligible differences in dipole moments. We found that, independent of the system studied, the Stark component is close to 0.5 kcal/mol, a value that can be neglected when compared with the rest of the approximations (neglect of intermolecular electron exchange, parametrization of the Lennard-Jones potential, etc.) introduced in most QM/MM methods. Furthermore, the small errors in the energy introduced by this approximation can easily be corrected through the use of the approximate formula, eq 11, whose behavior is very good, especially given that is a very easy and rapid way to obtain an estimate of the Stark component.

Acknowledgment. This research was sponsored by the Dirección General de Investigación Científica y Técnica (Project No. BQU2000-0243) and by the Consejería de Educación Ciencia Y Tecnología de la Junta de Extremadura (Project No. 2PR01A010).

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