

Theoretical Methods for the Representation of Solvent

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Received: 21 July 1995 / Accepted: 17 December 1995 / Published: 5 March 1996

Abstract

A review of the theoretical approaches for the representation of the solvent effect on molecular structure and reactivity is presented. The main characteristics of the different methods available for the description of solvation phenomena are outlined. The advantages and shortcomings of the computational approaches are discussed. Comparison of the different methodologies might help a non-expert user select the most suitable method for the treatment of a particular system in solution.

Keywords: solvation, computer simulation, continuum models, discrete methods, quantum mechanics-molecular mechanics methods

Introduction

The complexity of chemical phenomena makes it necessary to use molecular models. A given model must incorporate all the relevant features of the process of interest, so that the results can be interpreted and contrasted with experimental evidence. Choice of the model is made by defining three basic elements: the material constituents or "building-blocks" of the system, the physical rules underlying the chemical process, and the mathematical formalism required to describe such a process according to the physics of the problem. The results provided by the model can be rationalized on the grounds of these elements. Comparison with experiment will show the weaknesses of the model, which must then be revised and improved. The final objective is the development of a theoretical model able to explain the chemical behaviour.

The evolution of theoretical chemistry clearly illustrates this scientific method. Thus, in the early eighties neither theory nor computational resources allowed the study of chemical processes in condensed phases. Reduced systems, in which the solvent was ignored, were used, while large improvements were made in the study of processes in the gas phase. Since then, we have witnessed the impressive increase in computer power, the optimization of computational algorithms available in standard computer programs, and the improvement in the accuracy of quantum chemical techniques. As a result, a very precise quantum mechanical (QM) description of chemical systems in the gas phase can now be achieved. On the other hand, this evolution has been accompanied by the development of sophisticated methods for the representation of solvent, which has provided the theoretical framework and the technical resources required to initiate the study of chemical processes in condensed phases.

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In this paper the most recent methods for the study of solvation are reviewed. First, the nature of the solvent effect and the changes induced in the structure of the solute and in the thermodynamic and kinetic characteristics of chemical interactions are discussed. Second, the classical methods for the description of solvent effects are presented. Finally, the treatment of systems in solution by QM methods are examined. The strengths and weaknesses of the different methods and their range of applicability are discussed.

The nature of the solvent effect

From a rigorous theoretical point of view the concepts of solute and solvent are meaningless, since a dilute solution is an ensemble of molecules which should be treated at the same level, irrespective of their nature and population. The differentiation between solute and solvent obeys to practical considerations, because of the difficulty of treating correctly the bulk solution due to: i) the large number of solvent molecules needed to simulate a dilute solution, and ii) the high level of accuracy often required to describe the solute. In this context, the "solvent effect" can be interpreted as the change experienced by a chemical system (the solute) upon transfer from the gas phase to a dilute solution.

There are different ways in which the solute is influenced by solvation. In the following the solvent effect is examined according to the nature of the changes induced in the solute,

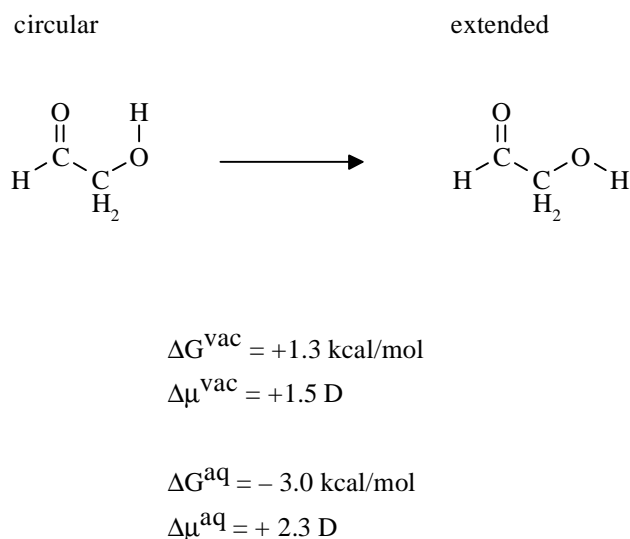


Figure 1. Conformational equilibrium of HCOCH_2OH in gas phase and in aqueous solution. The free energy in solution, ΔG^{aq} , was determined as: $\Delta G^{\text{vac}} + \Delta G_{\text{hyd}}(\text{extended}) - \Delta G_{\text{hyd}}(\text{circular})$, where ΔG^{vac} is the free energy in gas phase at 298 K and ΔG_{hyd} is the free energy of hydration determined from the AM1/MST method using the standard parameters (see text and ref. 45f).

which may affect i) the molecular (nuclear and electronic) structure and ii) the thermodynamics and kinetics of chemical processes. The nature of these effects is quite different and, consequently, the theoretical method chosen to study a given process must be able to capture properly the nature of the factors involved in these effects.

Changes in molecular structure

The solvent can introduce notable changes in the molecular structure, both in terms of nuclear and electronic distributions. Thus, changes in the nuclear configuration may arise from the tendency of polar solvents to stabilize structures with large charge separation (see below). The net effect can be a change in the conformational space of the solute, so that the relative population of the conformers having the largest polarity is increased. An example is the destabilization of the conformations with intramolecular hydrogen-bonds in polar solvents (Figure 1). Another illustrative case is the change in the equilibrium between isomers, as shown by the isomerization of formic acid (Figure 2). Nuclear changes involving the formation or breaking of covalent bonds are also largely dependent on the solvent. There are numerous examples reported in the literature about changes in the preferred species for tautomeric processes [1]. In general, a polar solvent displaces the tautomeric equilibrium so as to increase the population of the most polar tautomer. This effect can revert the stability in gas phase, even for apolar solvents [2]. In all these cases the solvent effect is mainly modulated by classical electrostatic interactions.

The influence of the solvent on the electronic distribution (for a given nuclear configuration) modulates the chemical reactivity. This is reflected in the change of different properties upon solvation, such as the enlargement in the dipole moment for neutral polar molecules [3], the change in the molecular electrostatic potential, the variation in the molecular volume [4], or the displacement in the spectroscopic properties [5]. The magnitude of the polarizing effect is surprisingly large, as noted by increases of 20-30% in dipole moments for neutral solutes in aqueous solution [3]. Furthermore, even in apolar solvents like chloroform the solvent polarization is not negligible, as indicated by increases of 8-10% in the dipole moments determined for neutral molecules from theoretical calculations (see below). In most cases the solvent effect is exerted through the electrostatic perturbation of the solute, but in some cases dispersion interactions are known to play a major effect [5].

Changes in thermodynamics and kinetics of chemical interactions

The best known effect of solvent is the modulation of chemical reactivity, even in the most apolar solvents [6]. This effect is especially relevant for polar solvents like water, where

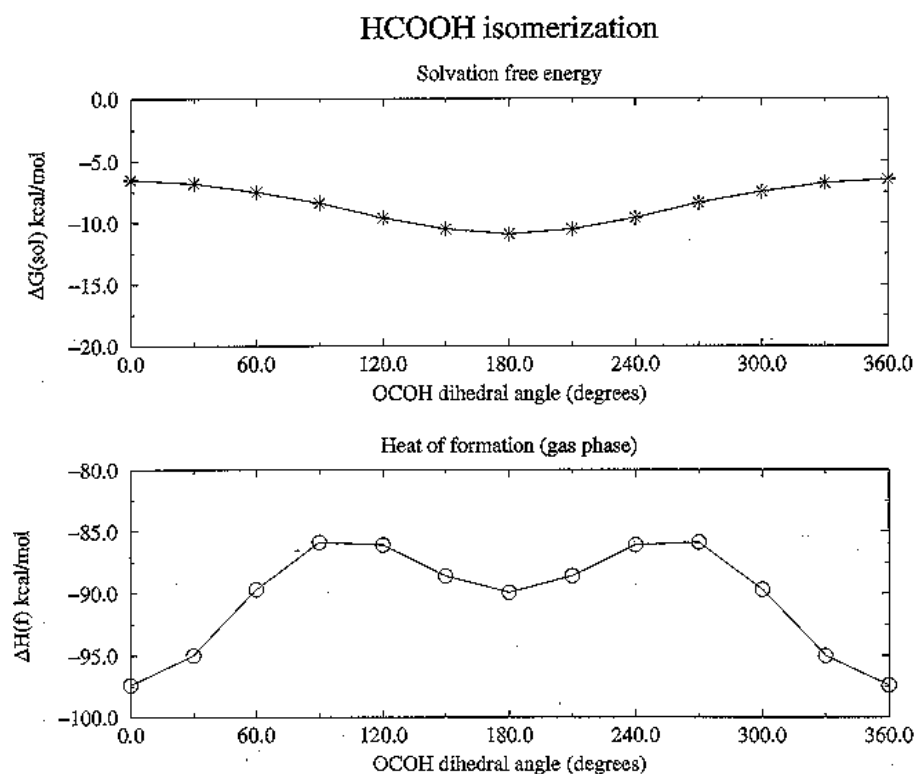


Figure 2. Changes in the heat of formation in gas phase and the free energy of hydration upon rotation of the C-O bond of formic acid. Values of $\Delta H(f)$ and $\Delta G(sol)$ were determined at the AM1 and AM1/MST levels, respectively.

it can invert the sign of the free energy change for a chemical reaction in the gas phase. The solvent has three major effects on the chemical reactivity: i) the modulation of the intrinsic reactive characteristics of reactants; ii) the introduction of viscosity effects; and iii) the direct interaction of solvent molecules with reactants, products, and transition states, which may lead to a differential stabilization of these species.

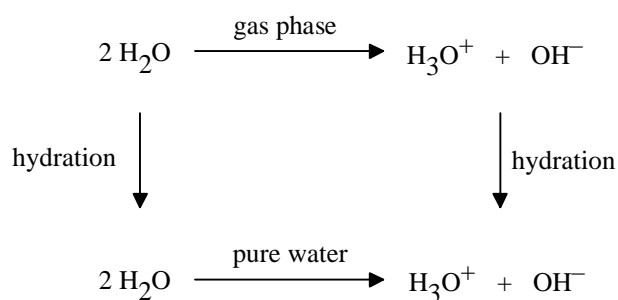
The change in the intrinsic reactive properties is mainly related to the polarization of the solute charge distribution (see above). The inclusion of viscosity effects is expected to modulate greatly the dynamics of the molecular system. This effect is not dramatic for a small and mobile solvent, or for processes with high intrinsic (gas phase) energy barriers, but it can be relevant when the solvent molecules are large and low mobile, or when the energy barrier is small. Indeed, viscosity effects are also involved in processes controlled by diffusion.

The interaction of solvent molecules with reactants, products and transition states may greatly influence the chemical reaction. This effect is especially important for polar solvents like water, where specific interactions, i.e. hydrogen bonds, can be established with the reactive species leading to changes in their relative stabilities. All chemical interactions are susceptible to the solvent effect, but the largest influence may be expected to occur i) when the polarities of reactants, transition state or products are very different, and ii) when the number of specific solute-solvent interactions

(the number of hydrogen-bond donor and acceptors) changes during the interaction. There are a large number of processes that illustrate this effect. Some well-known examples are discussed in this review, but more detailed explanations can be found elsewhere [see, for instance, ref. 7].

Ion-ion interactions are particularly influenced by the solvent. The shielding of electrostatic interactions in polar solvents can stabilize two species equally charged (with the same sign) and separated by a finite distance, but this situation would obviously be unstable in gas phase [8]. Close anion-cation interactions are extremely stable in the gas phase, but the configurations corresponding to a solvent-separated ion pair are favored in polar solvents [8]. This difference ultimately stems from the preferential stabilization of the isolated (or solvent-separated) ions by the solvent. An additional example is the ionization of acids and bases. A simple calculation (Figure 3) based on the experimental proton affinities of water and the hydroxyl anion [9] suggests that the free energy of ionization of water in gas phase at 298 K is around 218 kcal/mol. In contrast, the free energy in aqueous solution, as determined from the experimental pKa, is around 24 kcal/mol, and that determined from the thermodynamic cycle in Figure 3 using experimental free energies of hydration [10] is around 21 kcal/mol.

The effect of polar solvents on ion-molecule interactions has also been the subject of a large number of experimental and theoretical studies [7c,11]. A classical process is the SN^2 reaction, in which water molecules induce large changes in



$$\Delta G^{\text{vac}} \approx 218 \text{ kcal/mol}$$

(from experimental proton affinities)

$$\Delta \Delta G^{\text{sol}} \approx -197 \text{ kcal/mol}$$

(from experimental free energies of hydration)

$$\Delta G^{\text{aq}} \approx 21 \text{ kcal/mol (from thermodynamic cycle)}$$

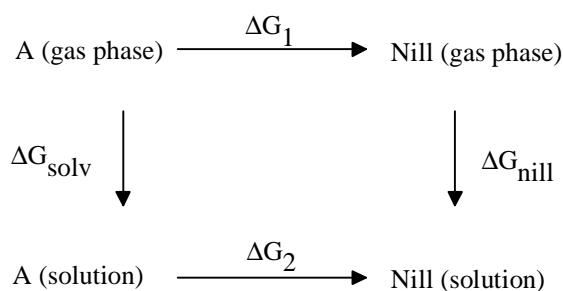
$$\Delta G^{\text{aq}} \approx 24 \text{ kcal/mol (from experimental pKa)}$$

Figure 3. Thermodynamic cycle for the ionization of water in gas phase and in aqueous solution (see text for details).

the kinetic and thermodynamic characteristics. A remarkable example is the nucleophilic attack of a hydroxyl group to a carbonyl center. This reaction is very exothermic and occurs without activation barrier in the gas phase (for instance, see ref. 11e,i and references therein), but it is clearly endothermic in aqueous solution, and the activation barrier is largely due to the preferential solvation of reactants with respect to transition state and products [11e]. Similar considerations apply

Table 1. Differences in free energy of hydration ($\Delta \Delta G_{\text{hyd}}$) related to hydrogen-bond formation in aqueous solution. Geometries for hydrogen-bond structures were determined at the AM1 level in the gas phase. Values of ΔG_{hyd} were computed using the standard AM1-MST method. Errors in hydrogen-bond geometries are not expected to introduce dramatic changes in the evaluation of $\Delta \Delta G_{\text{hyd}}$. All the values are in kcal/mol. $\Delta \Delta G_{\text{hyd}}$ is defined as $\Delta G_{\text{hyd}}(\text{bound}) - \Delta G_{\text{hyd}}(\text{unbound})$.

Donor	Acceptor	$\Delta \Delta G_{\text{hyd}}$
H ₂ O	H ₂ O	+2.4
H ₂ O	NH ₃	+3.1
NH ₃	NH ₃	+1.9
NH ₃	H ₂ O	+1.3
HF	H ₂ O	+3.2
HF	NH ₃	+4.5



$$\Delta G_{\text{solv}} = \Delta G_1 + \Delta G_{\text{nill}} - \Delta G_2 = \Delta G_1 - \Delta G_2$$

Figure 4. Thermodynamic cycle used to compute the free energy of solvation.

for the attack of other nucleophilic agents to carbonyl centers [see, for instance, ref. 11g,h].

In addition to ion-ion and ion-molecule interactions, other chemical reactions are highly susceptible to the solvent. In particular, attention has been paid to the solvent effect on Claisen rearrangements [7b,12], Diels-Alder reactions [13], benzoin condensation [14], reduction reactions [15], racemization [16] and aldolic condensations [17], among others [for details of solvent effects on chemical reactions, see ref. 7]. In all cases the solvent plays an important role in the thermodynamics and kinetics of each reaction.

Finally, non-bonded interactions, specially hydrogen-bonds, are significantly affected by polar solvents. Thus, the formation of hydrogen-bonded structures in aqueous solution is largely disfavored due to efficient competition of water molecules for the hydrogen-bond donor and acceptor groups. A prototypical example is the hydrogen-bond association of nucleic acid bases, which is exothermic in the gas phase, while the weak stacking interaction is preferred in aqueous solution [18]. The reason for this behavior stems from the differences in the free energy of hydration of the hydrogen-bonded complexes of nucleic bases with respect to the free bases.

A more general picture of the influence of polar solvent on hydrogen-bond interactions can be obtained from inspection of Table 1, where the solvent effect on the formation of several hydrogen-bond complexes was determined using theoretical methods (see below). The results show the large disturbing effect of water, as noted by the positive values of the differences in free energy of hydration for the formation of the hydrogen-bond complex, which can revert the sign of the free energy of association in the gas phase. The implications of these results on molecular recognition in aqueous solution, specially in biological systems, cannot be underestimated.

Theoretical calculation of solvent effects

As noted before, the solvent may influence the nuclear and electronic distributions of the solute, as well as the chemical reactivity and intermolecular interactions. In the last 20 years different methods have been developed to gain insight into these effects. All these methods can broadly be grouped into two main categories depending on the treatment of the solute: i) classical methods and ii) QM methods. In both cases, the solvent is described classically, either in terms of discrete particles (the microscopic level) or as a continuum medium (the macroscopic level).

The former methods treat the solute as a classical particle, whose interactions are determined by classical force-fields, which difficults a correct representation of the solvent-induced changes on solute properties. The QM methods account for solvent polarization, and accordingly for changes in structure and reactivity upon solvation. Unfortunately, they are computationally very expensive and this impedes their application to large systems. The (classical or QM) methods based on a microscopic description of the solvent determine the average representation of the system in solution from the ensemble of configurations collected from Monte Carlo (MC) or Molecular Dynamics (MD) simulations. Quite accurate estimates of the change in the free energy of reaction in solution when MD or MC simulations are coupled to statistical mechanical algorithms [19]. The expensiveness of these simulations is, nevertheless, a critical factor for large systems, or when the solute is represented quantum mechanically. In this context, the treatment of the solvent as a continuum medium is advantageous, since the degrees of freedom of the solvent are not longer considered.

Table 2 Comparative characteristics of Monte Carlo and Molecular Dynamics for the study of solvated systems.

Properties	Monte Carlo	Molecular Dynamics
Control of T, P	Easy	Difficult (weak coupling methods)
Conf. variables	Internals	Cartesians
Reduction of configurational space	Easy	Difficult (holonomic constrains)
Sampling for small solutes	Easy	Easy
Sampling for large solutes	Very difficult	Average difficulty
Study of time-dependent processes	Very difficult	Average difficulty
Setup of the simulation system	Average difficulty	Easy

Treating the solvent as a continuum medium, however, implies the lack of a detailed description of solute-solvent interactions. Nevertheless, precise results can be obtained through a well-balanced selection of the properties that characterize the solvent continuum model.

Classical methods

The classical methods determine the free energy of solvation (the reversible work needed to transfer a molecule from gas phase to solution) as the difference between the works required to annihilate the molecule in gas phase and in dilute solution (Figure 4). If the work involved in the annihilation of intramolecular interactions is the same in gas phase and in solution, i.e. the molecule has a similar electronic and nuclear configuration in the two phases, the thermodynamic cycle in Figure 4 can be simplified, and the free energy of solvation can be determined from the work required to annihilate the intermolecular interactions of the solute in solution. The annihilation is usually performed in two steps (electrostatic decoupling), where the steric interactions are annihilated after removing the electrostatic interactions .

The calculation of electrostatic and steric contributions to the free energy of solvation can be performed considering the solvent as a finite set of discrete particles (discrete methods) or as a continuum which reacts against the solute (continuum methods).

Classical discrete methods

The microscopic description of solute and solvent is encoded in the force-field [19,20], which has different energy terms for bonded (stretching, bending, torsion) and non-bonded (electrostatic, van der Waals) interactions. These terms adopt

very simple expressions, which facilitates the evaluation of the potential energy of the system. The averaged representation of the solute-solvent system is obtained from MD and MC techniques [21].

The sampling of the solute-solvent configurational space by MD is performed from the trajectories determined by integration of the equations of motion, which can be performed following Newton, Lagrange or Hamilton formalisms (for review, see ref. 21). MC samplings are obtained from the application of Boltzmann probabilistic rules to a very large set of randomly selected configurations. In principle, MD and MC samplings should be identical for infinite simulations if the system is in equilibrium. However, the use of MD and MC techniques present several differences for their application to computational simulations, a concise summary of them being given in Table 2.

In general, MD and MC have a similar efficiency in the sampling of the configurational space for small solutes. MD techniques offer the advantage that the time evolution of the system may be analyzed, which is often interesting to study time-correlation functions or transport properties. On the other hand, MC calculations allow complete control of the simulation system and an easy reduction of configurational variables, although caution must be taken to avoid an artefactual simplification of the configurational space. When the solute is large and flexible, MD techniques are preferred, since in these cases the sampling in internal coordinates used in standard MC simulations is inefficient. Strategies to increase the reliability of MC techniques in the sampling of conformational movements in large solutes have been discussed elsewhere [21f]. Both MD and MC techniques provide Boltzmann-averaged samplings, which can be used to determine the free energy of solvation. This can be done following two different strategies based on: i) linear free energy response (LFER) theory, or ii) statistical mechanical (SM) methods.

According to LFER (for details see ref. 22), the electrostatic component of the free energy of solvation is half the magnitude of the averaged solute-solvent electrostatic interaction energy (E_{sx} in eq.1). The steric components can be computed upon a proper scaling of the solute-solvent van der Waals interaction (E_{vw} in eq. 2) or by using parametric equations expressed in terms of the molecular volume, the solvent accessible surface or similar descriptors (ζ in eq. 2). In eq. 2 the brackets mean that the averages are done for Boltzmann samplings, and the scaling parameters (α , β) are adjustable variables fitted to reproduce dispersion-repulsion and cavitation contributions to the free energy of solvation. Parametrized LFER-based discrete methods provide good estimates of free energy of hydration, and its application in molecular modeling studies is promising [23].

$$\Delta G_{ele} = \frac{1}{2} \langle E_{sx} \rangle \quad (1)$$

$$\Delta G_{ster} = \alpha \langle E_{vw} \rangle + \beta \langle \zeta \rangle \quad (2)$$

Some of the most powerful techniques available for the study of systems in solution have emerged from the coupling of SM theory with MD and MC simulations. Among them, free energy perturbation (FEP) and thermodynamic integration (TI) are of special interest for the calculation of the free energy of solvation [24]. It is not our purpose to explain in detail these methods, but just to present briefly their essential characteristics. For a detailed explanation on these and related techniques, we address the reader to the original works in ref. 24, and to other recent reviews [19].

FEP and TI techniques compute the free energy of solvation using the thermodynamic cycle in Figure 4. The free energy of solvation is determined as the difference in the works involved in the annihilation of the solute in gas phase and in solution (ΔG_1 and ΔG_2 in Figure 4) through a reversible pathway. The requisite of reversibility for the A(solute)->B(dummy) interconversion implies that such a mutation has to be divided into smaller steps: A->A'->A''->...->B''->B'->B, in such a way that the change in every step is small enough as to make every (micro)process reversible. In practical simulations this is achieved through the use of a "coupling" parameter (λ), which controls the change between the Hamiltonians for the two states, A and B (eq. 3; $\lambda=0$: state A, $\lambda=1$: state B).

$$H_\lambda = (1-\lambda)H_A + \lambda H_B \quad (3)$$

The use of the coupling parameter within the FEP framework allows the calculation of the free energy of solvation according to eq. 4. The equivalent expression obtained from TI theory is shown in eq. 5. The Boltzmann averages are obtained from MD or MC samplings, and $\Delta\lambda$ defines the number of steps (windows) involved in the annihilation process ($\lambda:0 \rightarrow 1$).

$$\Delta G_{solv} = \sum_{\lambda=0}^{1-\Delta\lambda} RT \ln \left\langle \exp \left[-\frac{(E_{\lambda+\Delta\lambda} - E_\lambda)}{RT} \right] \right\rangle_\lambda \quad (4)$$

$$\Delta G_{solv} = - \sum_{\lambda=0}^{1-\Delta\lambda} \left[\int_\lambda^{\lambda+\Delta\lambda} \left\langle \frac{\partial E_{\lambda'}}{\partial \lambda'} \right\rangle_{\lambda'} d\lambda' \right] \quad (5)$$

Other related algorithms have been suggested. Among them, slow growth (SG, [25]), where a very small window ($\Delta\lambda=d\lambda$) is sampled only with a single configuration, the muticonfigurational thermodynamic integration (MCTI, [26]), which is based on a discontinuous integration of $(\partial E/\partial\lambda)$, and the finite difference thermodynamic integration (FDTI, [27]), which has shown an excellent performance in different studies of complex solutes [1f,27]. This latter algorithm, which combines TI and FEP methods, computes the free energy of solvation according to the expression given by eq. 6.

$$\Delta G_{\text{solv}} = - \int_{\lambda=0}^{\lambda=1} \left(\frac{\partial}{\partial \lambda} \left[-RT \ln \left\langle \exp \left(-\frac{(E_{\lambda+\delta\lambda} - E_{\lambda})}{RT} \right) \right\rangle_{\lambda} \right] \right) d\lambda \quad (6)$$

The SM methods have been successfully used in the study of solvation in different solvents, as well as in the calculation of transfer free energies between immiscible solvents [28]. A couple of recent studies have shown that the method can provide, without any specific ad hoc parametrization, free energies of solvation with an average error of 1 kcal/mol from experimental data for neutral polar solutes [29]. However, it should be noted that the goodness of the results is guaranteed only when: i) a reliable force-field is used, ii) polarization effects are not very important, and iii) MD or MC simulations are large enough to provide representative Boltzmann samplings at every step of the simulation.

Classical continuum methods

These methods treat the solvent as a continuum medium which reacts against the (unperturbed) solute charge distribution. Calculation of the electrostatic free energy of solvation can be done following the theory of polarizable solvents [22a] at different degrees of complexity. Extension of the method to incorporate other components of the free energy of solvation (dispersion-repulsion and cavitation) is not difficult.

The classical continuum models can be classified according to two main characteristics: i) the shape of the cavity that defines the solute/solvent interface, and ii) the description of the solute charge distribution and the solvent reaction field. With regard to the solute/solvent interface, a large number of cavities have been used. The simplest methods define cavities of regular shape, such as spheres, ellipsoids or cylinders, while the most accurate methods use cavities adapted to the actual molecular shape. Regarding the treatment of the solute charge distribution and the solvent reaction field, Tomasi and Persico in their recent and exhaustive review [30] categorized the different treatments in five formalisms: i) *multipole expansions*, ii) *apparent surface charge*, iii) *image charge*, iv) *finite difference*, and v) *finite elements*. It is not our purpose to review all the methods, but just to comment on the most popular ones. The reader is referred to ref. 30 and 31 for a more complete discussion.

Methods based on multipole expansions are probably the simplest ones. They typically use a regular cavity and the multipole expansion is truncated at different levels: monopole (Born model, eq. 7 [32]), dipole (Bell and Onsager, eqs. 8-9 [33]) or higher order terms [27]. In eqs. 7-9, ϵ is the dielectric constant, q and μ are the charge and dipole moment, R is the radius of the cavity and α is the solute polarizability.

$$\Delta G_{\text{ele}} = - \frac{\epsilon - 1}{2\epsilon} \left[\frac{q^2}{R} \right] \quad (7)$$

$$\Delta G_{\text{ele}} = - \frac{\epsilon - 1}{2\epsilon + 1} \left[\frac{\mu^2}{R^3} \right] \quad (8)$$

$$\Delta G_{\text{ele}} = - \frac{\epsilon - 1}{2\epsilon + 1} \left[\frac{\mu^2}{R^3} \left(1 - \frac{\epsilon - 1}{2\epsilon + 1} \frac{2\alpha}{R^3} \right)^{-1} \right] \quad (9)$$

Born and Bell-Onsager models have been very popular because of their simplicity, even though the quantitative quality of the results may not very good when complex molecules are dealt with. These two expressions have been recently applied to account for long range interactions in MD and MC simulations, where cutoff techniques are used to evaluate non-bonded interactions [19-21].

More elaborated methods have been developed based on multipole expansions. Among them, the Generalized Born Model (GBM; eq.10) [34] treats the solute as a set of monopoles (centered at nuclei), each independently solvated. Empirical corrections are introduced to correct the overestimation of the free energy of solvation, which arises from the direct incremental application of the Born formalism (eqs. 11-13). GBM and other methods based on multipole expansion are available in the QM framework (see below).

$$\Delta G_{\text{ele}} = - \frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \sum_{i,j} \frac{q_i q_j}{f_{\text{GB}}} \quad (10)$$

$$f_{\text{GB}} = \left(r_{ij} + \alpha_{ij}^2 e^{-D} \right)^{0.5} \quad (11)$$

$$\alpha_{ij} = \left(\alpha_i \alpha_j \right)^{0.5} \quad (12)$$

$$D = \frac{r_{ij}^2}{(2\alpha_{ij})^2} \quad (13)$$

r_{ij} : distance between two atoms (center of charges)
 α_i : Born radii of atom -i.

Methods based on the apparent surface charge are also widely used and different QM formalisms are available (see below). In these methods the reaction field is represented in terms of an imaginary surface charge spread over the cavity, and the electrostatic free energy of solvation can be repre-

sented with expressions analogous to eq. 14 [35], where σ is the apparent surface charge distribution, ρ is the solute charge distribution, Φ_ρ is the solute electrostatic potential on the cavity surface, and Φ_σ is the solvent reaction potential. At the classical level the polarization of the solute charge distribution by the solvent is typically ignored, i.e. $\rho = \rho(o)$.

$$\Delta G_{\text{ele}} = \frac{1}{2} \int_S \sigma \Phi_\rho dS = \frac{1}{2} \int \Phi_\sigma \rho dr \quad (14)$$

The above expression, which arises from the application of Poisson and Laplace equations with the appropriate boundary conditions at the cavity surface, can be used to obtain fast estimates of the electrostatic free energy of solvation, as suggested in the eighties by Tomasi and coworkers [35]. Recent studies have confirmed the goodness of this strategy [36] for the calculation of free energies of solvation in a large series of prototypical solutes. In addition, new strategies have been suggested that, upon a detailed expansion of eq. 14, can capture at least partially the mutual solute<->solvent polarization effects [36b].

Finite difference methods (FDM) are very popular for the study of the free energy of solvation of large systems [37]. The electrostatic component is determined according to eq. 15. Here the internal electrostatic potential (Φ_i^{intra}) is determined from the unperturbed solute charge distribution, while the total electrostatic potential (Φ_i^{tot}) is determined by solving the Poisson equation, where the dielectric constant is considered to be a function of the distance (eq. 16; Φ is the total potential).

$$\Delta G_{\text{ele}} = \frac{1}{2} \sum_i q_i (\Phi_i^{\text{tot}} - \Phi_i^{\text{intra}}) \quad (15)$$

$$\nabla[\epsilon(r)\nabla\Phi(r)] = -4\pi(\rho_{\text{int}}(r) + \rho_{\text{ext}}(r)) \quad (16)$$

The solution of the Poisson equation can be found at a linear or nonlinear level, depending on the complexity of the relationship between the external charge distribution (ρ_{ext}) and the electrostatic potential (Φ). In any case, the analytical solution is not feasible, it being necessary to use finite difference methods. This is accomplished by using finite grids to map the entire space, including solute and solvent. The electrostatic potential at each point is then determined as a function of the potentials at the nearest grid points. The process is repeated until convergence.

FDM provides good estimates of the free energy of solvation for small molecules [38] provided that the grid of points is dense enough. Otherwise, rather inaccurate results are obtained. Alternative strategies have been devised to alleviate this problem, such as the focusing procedure [39]. Furthermore, some of the FDM algorithms, like DelPhi [37c], have been extensively applied to the study of solvation in macromolecules. When large systems are considered, cau-

tion is needed due to the large magnitude of the solvation free energy, the difficulties in defining a priori the dielectric constant inside the macromolecule, and the use of a rigid set of charges for the solute charge distribution.

The most advanced classical continuum theories have widespread application in the study of biochemical systems, where efficient algorithms are necessary. They are also becoming very useful when coupled to MD and MC simulations, where they are used to simulate the environment effect beyond the cutoff used for the non-bonded interactions. However, the shortcomings of these methods have to be properly considered. In most cases non-electrostatic contributions to the free energy of solvation are neglected, and a detailed treatment of the solvent-induced polarization of the solute is difficult. Indeed, the description of the solute charge distribution and the definition of the cavity may not be accurate enough. Finally, specific solute-solvent interactions are not dealt with.

Quantum mechanical methods

The treatment of the solute-solvent system at the QM level is impossible with the current computational resources. The cost of this approach limits the description of the solvent to a few molecules within the supermolecule approach, mainly to analyze specific interactions with the solute. Thus, the general approach is to treat the solute at the QM level, while the solvent is represented classically using discrete or continuum representations. In the discrete models the free energy of solvation is computed from the work needed to annihilate the coupling interactions between the solute and the solvent Hamiltonian (see below). In the continuum models the free energy of solvation is determined as the work necessary to build up the solute in the solvent minus the work necessary to perturb nuclear and electron distributions upon transfer from gas phase to solution. It is worth noting that in both strategies the solvent-induced polarization of the solute is explicitly introduced.

Quantum discrete methods

These methods use a classical force field to represent the solvent interactions [40]. The total Hamiltonian of the solute-solvent system is decomposed into three terms (eq. 17): i) a QM Hamiltonian for the intramolecular solute interactions (QM); ii) a classical Hamiltonian for the solvent-solvent (intra and intermolecular) interactions (MM); and iii) a coupling term to account for the solute-solvent interactions (QM/MM).

$$\hat{H}^{\text{ef}} = \hat{H}^{\text{MM}} + \hat{H}^{\text{QM}} + \hat{H}^{\text{QM/MM}} \quad (17)$$

Owing to the expense of QM calculations, most algorithms use semiempirical Hamiltonians for the solute [40,41], but recently methods based on density functional theory, and also at the *ab initio* level with small basis sets have been developed [42]. Furthermore, all the methods consider that the only change on the solute electron distribution results from electrostatic interactions, neglecting changes due to dispersion. Indeed, the solvent is usually assumed to be self-polarized, the specific solute->solvent polarization being, accordingly, typically neglected at the molecular level. Finally, rigid models are used to represent simple solvents like water, avoiding the need of an intramolecular term in the force field of the solvent.

Assuming the previous considerations and the validity of an empirical model for the solvent intermolecular interactions, the Hamiltonian for the solute-solvent system can be expanded as shown in eq. 18, where a set of charges and van der Waals parameters is used to represent the solvent molecules. In eq.18 s denotes the solvent charge sites, m and i refer to the solute nuclei and electrons, N is the number of doubly occupied molecular orbitals, and E_{vw} is the solute-solvent van der Waals interaction energy as determined from standard force-fields. The average representation of the solute-solvent system is obtained through MC or MD simulations. Modified equations have been suggested by Warshel and coworkers for aqueous solution, where the electrostatic properties of water are represented by means of a polarizable dipole [40a-d,h] instead of a set of rigid charges.

$$\hat{H}^{ef} = \hat{H}^{MM} + \hat{H}^{QM} + \sum_{s=1}^S \sum_{i=1}^{2N} \frac{eq_s}{R_{si}} + \sum_{s=1}^S \sum_{i=1}^{2N} \frac{Z_m q_s}{R_{sm}} + E_{vw} \quad (18)$$

For a particular nuclear configuration the energy is obtained by solving the corresponding pseudo-Schrödinger equation (eq. 19), where the effective Hamiltonian, H_{ef} , includes the QM Hamiltonian of the solute and the solute-solvent coupling term. It should be stressed that every nuclear movement requires a self-consistent field calculation to be performed. This requires an enormous computational effort, which explains the use of very simple Hamiltonians.

$$\hat{H}^{ef} \Psi = E \Psi \quad (19)$$

The calculation of free energy of solvation can be done using either FEP or TI theory [24]. As noted before, in practical simulations the annihilation of the interactions between the solute and solvent molecule is controlled by a parameter (λ) that modulates the contribution of the QM/MM term to the total Hamiltonian (eq. 20). Indeed, electrostatic decoupling [25] is usually performed in the annihilation process.

$$\hat{H}^{ef}(\lambda) = \hat{H}^{QM} + \hat{H}^{MM} + \lambda \hat{H}^{QM/MM} \quad (20)$$

Quantum discrete models are very attractive from a conceptual point of view and have a wide range of potential applications. It should be emphasized that the QM treatment of the solute avoids the errors in the intramolecular energy terms inherent to force fields. Indeed, solute-solvent polarization effects can be considered. Moreover, the solvent is represented at a discrete level, allowing for analysis of specific solute-solvent interactions. Finally, the sampling of solute (and solvent) configurational space is enabled by MD and MC methods. The usefulness of these methods is, nevertheless, limited by their computational cost, which makes it necessary to use non-polarizable force fields for the solvent and simple Hamiltonians for the solute. It also limits the extension of the configurational sampling. However, these simplifications may affect the accuracy of the results. An additional source of uncertainty arises from the different nature of the van der Waals interactions in classical and quantum discrete models [43], and ideally the transfer of van der Waals parameters from classical force-fields should be avoided. The newest methods, which use a specific parametrization of van der Waals interactions for solutes, should improve the quality of results [42b,43].

Quantum continuum methods

These methods combine the QM treatment of the solute with a continuum description of the solvent. As in classical continuum methods, the free energy of solvation is determined from the addition of three contributions: cavitation, dispersion+repulsion, and electrostatic. The steric term, which is considered independent of the solute electron distribution, is computed for a given nuclear configuration by using classical equations, often parametrized from discrete simulations or from fitting to experimental data [44,45]. A large number of models are available, and several of them have been implemented in *ab initio* and semiempirical QM packages. The main differences between these methods lie in: i) the formalism used to account for the electrostatic free energy of solvation; ii) the shape of the solute/solvent interface; and iii) the procedure adopted for the steric contribution to the free energy of solvation.

The electrostatic term is essentially determined according to the same principles defined for classical continuum models: the dielectric continuum reacts against the solute charge distribution generating a reaction field, which in turn interacts with the solute. Nevertheless, because of the QM treatment of the solute, i) a rigorous representation of the charge distribution is achieved, ii) the mutual solute-<->solvent polarization can be accurately incorporated, and iii) the

solvent-induced changes in the molecular properties of the solute can be evaluated.

The solvent reaction field is generally described in terms of a multipole expansion or by an apparent surface charge, even though other formalisms are available [30]. The reaction field is introduced into the solute Hamiltonian (eq. 21) in a way analogous to that used for discrete QM methods (see above). It is worth noting that in continuum methods the solute wavefunction and the solvent reaction field are coupled *via* the perturbation operator, \hat{R} , which usually requires the use of self-consistent strategies. Only few of the large number of quantum continuum methods will be outlined here. The reader is addressed to the review by Tomasi and Persico [30] for a thorough explanation of the different models.

$$(\hat{H}^0 + \hat{R})\Psi^{\text{sol}} = E_{\text{aq}}\Psi^{\text{sol}} \quad (21)$$

Methods based on multipole expansions can be easily implemented within the QM framework following the formalisms developed by Rivail [7f,31a,46], Tapia [31d,47], Katritzky and Zerner (48), among others [30,49]. The simplest method corresponds to the Bell-Onsager model, where the solute charge distribution is represented by a simple dipole and the solute cavity is spherical. Important improvements arise from the inclusion of higher order terms in the multipolar expansion. In this context, it is important to note the high-level treatment developed by Rivail and coworkers. The method, implemented in classical, semiempirical and *ab initio* QM frameworks, uses a multipole expansion up to the 7th order to represent the solute charge distribution. Moreover, extension to multicenter expansions is also considered. Further refinements also stem from the extension of this method to improved cavity models [46e]. In addition, the code developed in Nancy on the basis of the formalism of reaction field factors has been extended to the Density Functional theory [46f], and also allows the possibility of performing post-Hartree-Fock calculations [7f,46g].

Another method based on multipole expansions is AMSOL [45a-c], developed by Cramer and Truhlar. AMSOL uses semiempirical Hamiltonians for the solute, and the molecular-shaped cavity is built up from the Born radii of the atoms. Steric factors are considered from an empirical linear relationship with the solvent accessible area (eq. 22), where the tension parameters (σ_i) are obtained from empirical fitting. The electrostatic component is based on the GBM method. Empirically fitted parameters are also used in the calculation of the coulombic integrals (γ_{kl}) to guarantee the quality of the results.

$$\Delta G_{\text{ster}} = -\sum_{i=1}^N \sigma_i A_i \quad (22)$$

AMSOL was parametrized using a large series of molecules. The final RMS error in the fitting was less than 1 kcal/mol [45a-c]. Early versions of the method may underestimate the electrostatic free energy of solvation due to the use of Mulliken charges, whose shortcomings are well known [50]. However, this problem has been largely corrected in the newest versions of the method [50c-d]. The recent extension of AMSOL to non-aqueous solvents increases the potential applications of this program [51], which is distributed by QCPE.

Among the algorithms based on the apparent surface charge, we limit our attention to i) the Polarizable Continuum Model (PCM) developed by Pisa's group [35a,b], and ii) COSMOS (conductor-like screening model), developed by Klamt and Schuurman [52]. The PCM method, also denoted as MST (Miertus-Scrocco-Tomasi) in other versions developed by our group, is available in both semiempirical and *ab initio* [35a,b,45d-f,53] formalisms, while COSMOS is available only at the semiempirical level.

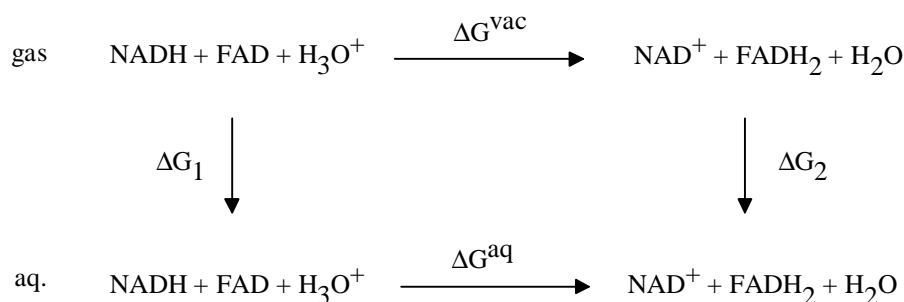
The newest versions of the PCM method uses the scaled particle theory [54], modified in a suitable way to deal with cavities adapted to the molecular shape, to compute the cavitation contribution. The van der Waals component can be determined using different classical formalisms, which range from polynomial expansions [44a] to linear relationships with molecular surface [45d-f]. In the latest case the tension parameters (eq. 23) are parametrized from experimental data [45d-f]. Molecular-shaped algorithms are used to determine the solute/solvent interface [55]. The electrostatic free energy is computed according to eq. 24, where the reaction field operator (\hat{V}_R) is evaluated from eqs. 25-26. It is worth noting that the apparent surface charge is determined *via* the electrostatic potential (both solute and solvent contributions are included), which avoids the use of truncated expansions. Proper attention is also paid to the tails in the electronic distribution outside the cavity.

$$\Delta G_{\text{VW}} = -\sum_{i=1}^N \zeta_i A_i \quad (23)$$

$$\Delta G_{\text{ele}} = \langle \Phi^{\text{sol}} | \hat{H}^0 + \hat{V}^0 | \Phi^{\text{sol}} \rangle - \langle \Phi^0 | \hat{H}^0 | \Phi^0 \rangle - \frac{1}{2} \left[\langle \Phi^{\text{sol}} | \hat{V}_R | \Phi^{\text{sol}} \rangle + \int \rho_{\text{nuc}} V_{\sigma}(s) ds \right] \quad (24)$$

$$\hat{V}_R = \sum_{i=1}^M \frac{\sigma_i S_i}{|r_i - r|} \quad (25)$$

$$\sigma_i = -\frac{\epsilon - 1}{4\pi\epsilon} \left(\frac{\delta(V_{\sigma} + V_{\rho})}{\delta n} \right)_i \quad (26)$$



$$\Delta G^{\text{aq}} = \Delta G^{\text{vac}} + \Delta G_2 - \Delta G_1 = \Delta G^{\text{vac}} + \Delta\Delta G_{2-1}$$

$$\Delta G^{\text{aq}} = -71 \text{ kcal/mol} + 55 \text{ kcal/mol} = -16 \text{ kcal/mol}$$

$$\Delta G^{\text{aq}} \text{ (exp from redox potentials)} = \text{from } -15 \text{ to } -5 \text{ kcal/mol [a]}$$

[a] Depending on protein environment

Figure 5. Thermodynamic cycle for the electron transfer between NADH and FAD. Values in gas phase and in aqueous solution were determined from AM1 and AM1/MST calculations. The cavity for charged species was reduced following the standard procedure (see text and ref. 45g).

The PCM method has been successfully applied to a large variety of phenomena in solution, like the description of free energies of hydration, solvent effects in chemical reactions, and solvent-induced changes in molecular properties [30 and references therein]. Besides several *ab initio* implementations at the HF and multiconfigurational levels [35a,b,45d,53a-c] and a recent implementation in the Density Functional framework [53d], different semiempirical versions are available [45e-f,56]. The MST version developed by our group, which is available within the MOPAC-93 package [57], yields to free energies of hydration with an expected RMS around 1 kcal/mol for neutral solutes. Recently, the method has been extended to non-aqueous solvents [6b,58]. For carbon tetrachloride and chloroform the average RMS error in the free energy of solvation is found to be less than 0.5 kcal/mol.

The combination of fast semiempirical calculations with accurate solvation calculations makes the semiempirical MST very powerful in scientific areas like biochemistry, where the size of the molecules prevents the use of *ab initio* methods. An example is shown in Figure 5, where AM1/MST calculations are used to study the NADH->FAD electron transfer process in aqueous solution. The agreement between calculations and experiment is reasonable considering the noise in the calculation, the intrinsic shortcomings of semiempirical calculations, and the uncertainties in the experimental measurements. It is clear that semiempirical SCRF calculations cannot provide quantitatively accurate estimates for these processes. However, the results suggest that these calculations

can be used as a powerful tool to gain qualitative insight into complex biochemical processes.

COSMO introduces a novel approach to the study of a system in solution. In this method, Klamt and Schüürman developed a formalism based on the replacement of the dielectric continuum medium by a conductor, which facilitates the treatment of screening effects. The exact solution of the screening problem for the conductor is then corrected by a factor (eq. 24) for the application to a dielectric medium. Eq. 25 gives the total energy of the screened system. In this equation, Q is the generalized charge vector containing the point charges of the nuclei and of the electron densities elements, whereas the matrix A collects the interactions between the charges of the solute with the apparent charges spread over the cavity, and B the interactions between the different apparent charges. A molecular shape surface is defined for the solute cavity. COSMO has been recently implemented in the MOPAC-93 [57] package.

$$f(\epsilon) = \frac{\epsilon - 1}{\epsilon + 1/2} \quad (27)$$

$$\Delta E = -\frac{1}{2} \mathbf{Q} \mathbf{B} \mathbf{A}^{-1} \mathbf{B} \mathbf{Q} \quad (28)$$

Recently, a new approach based on COSMO for incorporating solvent effect for solutes of arbitrary shape has been reported. This approach is called GCOSMO [59] and has been

implemented in both *ab initio* and nonlocal Density Functional levels of theory by modifying the GAUSSIAN 92/DFT [60] program. In GCOSMO the solvent reaction field is included directly in the SCF procedure, and hence both the solute electron distribution and the solvent reaction field are converged simultaneously.

All these methods work in the framework of quantum mechanical codes ranging from semiempirical to post-Hartree-Fock levels. Because of the lack of a microscopic treatment of the solvent, which is represented by a continuum medium, the computational requirements for the study of solvation phenomena do not differ substantially from those required for an isolated molecule. Indeed, most of these codes are easily available, specially when they are distributed in standard computational programs of widespread use. For instance, Gaussian-94 [61] includes different SCRF methods, like a simple one based on the Onsager model, and different versions of the high level MST algorithm, which differ in the definition of the solute cavity. Undoubtedly, this facilitates the study of a broad range of processes in solution by non-expert users, and it can lead to a significant improvement in our level of knowledge of chemical processes in solution.

Conclusion

The theoretical representation of condensed phases can now be achieved by a large variety of techniques, which are at the disposal of computational chemists. Continuum or discrete representations of the solvent can be combined with quantum or classical treatments of the solute. Each technique has its strengths and shortcomings, and the proper selection of the appropriate method to be used in the study of a particular system is probably the most important decision for the study of a chemical process in solution.

Acknowledgments This work was supported by the Direcció general de Investigació Científica y Técnica (DGICYT; PB93-0779 and PB94-0940) and by the Centre de Supercomputació de Catalunya (CESCA, Mol. Recog. Project-95). We are indebted to Prof. G. Shields for assistance in the preparation of the manuscript. We thank Prof. J. Tomasi and Prof. J.-L. Rivail for sending us preprints of their research work. We thank also the help of many colleagues and coworkers whose names are in the reference section.

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