Solvent Effects in Quantum Chemistry

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Abstract

The properties of a molecule may change quite substantially when passing from the isolated state to a solution, and computational chemistry requires the possibility of taking into account the effects of a solvent on molecular properties. These changes are mainly due to long range interactions, and electrostatics involving a large number of solvent molecules play the major role in the phenomenon and free energy changes have to be evaluated. Statistical calculations by means of usual Monte Carlo or molecular dynamics coupled with a full quantum chemical description of a sample representative of the solution is still out of reach for standard molecular modeling computations nowadays. Nevertheless, several simplified approaches are available to evaluate the free energy changes which appear when an isolated molecule, as described by standard quantum computations, undergoes the influence of a solvent and to predict the changes in

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J. Leszczynski et al. (eds.), *Handbook of Computational Chemistry*,
DOI 10.1007/978-3-319-27282-5_15

the molecular properties which are the consequences of solvation. In this chapter, we develop the principles of the most usual methods that a computational chemist can find in standard codes or can implement more or less easily to approach the solvent effects in quantum chemistry investigations.

Introduction: Importance of Solvent Effects in Chemistry

Most of the chemical reactions as well as experimental structure determinations are performed in solutions. On the contrary, usual quantum chemical computations usually deal with isolated chemical species. This may lead to erroneous conclusions. For instance, the addition of bromine to an ethylenic hydrocarbon is known for having a different mechanism in the gas phase and in solution. In this example, the velocity constant vary by a factor of 10^{10} when going from carbon tetrachloride to water as a solvent (Reichardt 1979), although the mechanism is the same. These features are confirmed by appropriate quantum chemical computations which show that the transition state of ethylene-bromine would be dissymmetric and 55 kcal/mol above the van der Waals complex in the case of the isolated species (Yamabe et al. 1988), while with a simple simulation of the solvent effect one finds a symmetric transition state lying 30.79 kcal/mol above the van der Waals complex in a non dipolar solvent and 0.02 kcal/mol in water (Assfeld 1994).

A full quantum mechanical treatment of a sample containing the solute and a number of solvent molecules large enough to simulate the solution is still out of reach of usual quantum chemical computations not only because the system of interest should be pretty large but also because the free energy computations would require a statistical treatment on millions of configurations of this system. One is therefore led, in general, to use model systems, simplified expressions of interatomic interactions allowing either statistical simulations or the derivation of molecular distribution functions or some semi-empirical approaches. In this vade mecum, we summarized different ways of modeling solvent effects in quantum chemistry. This includes the supermolecule model, the continuum and semi-macroscopic models, the full quantum description of liquids, the QM/MM methods (see Fig. 1), and the use of analytical molecular distribution functions (Hirata 2003). All these approaches have their limits, and one is led to choose one or the other according to the kind of problem being addressed.

The Supermolecule Model

In some cases, in particular that of aqueous solutions, the specific interactions may be modeled by means of a supermolecule made of an aggregate of the solute and a limited number of solvent molecules treated as an isolated single molecular system at the desired quantum chemical level. This approach may give useful information on strong intermolecular interactions (Catak et al. 2009; Harb et al. 2004) but cannot model correctly the effect of the solvent because the long-range electrostatic

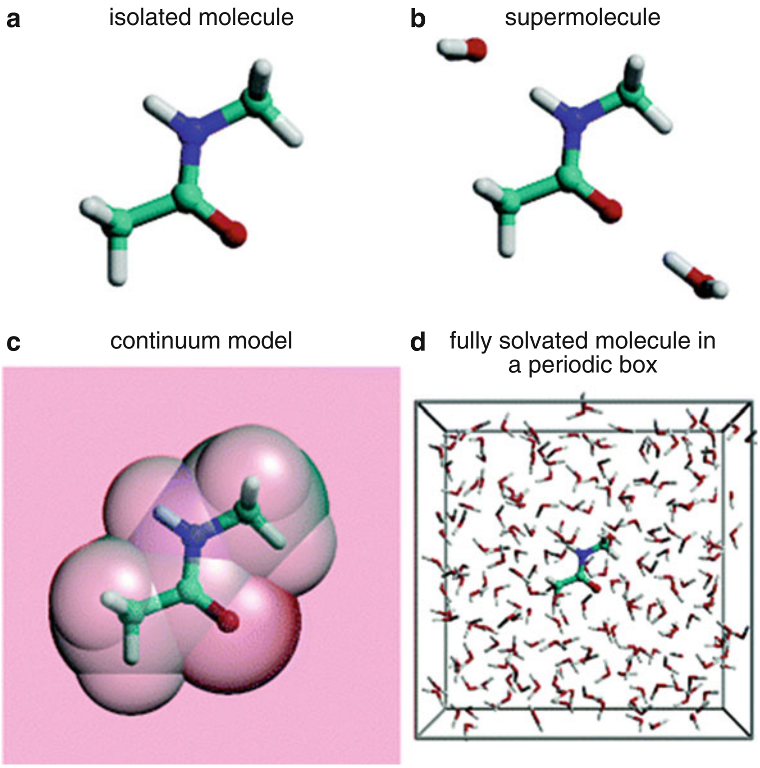

Fig. 1 The different approaches for modeling a solute molecule in a solvent. From *top left* to *bottom right*: (**a**) the isolated molecule (gas phase); (**b**) the supermolecule (solute with a few solvent molecules); (**c**) the continuum approach (the molecule is inserted in a cavity surrounded by a dielectric continuum); (**d**) the fully solvated system (the solute is inserted in a periodic box filled with solvent molecules)

interactions, which play an important role in a liquid (Buckingham 1967, 1978), are not taken into account. An efficient way to model these long-range electrostatic interactions is to use a continuum model.

Continuum Models

These models are by far the most widely used in current computational chemistry nowadays, and several review articles give an overview of them (Rivail and Rinaldi 1996; Tomasi 2004; Tomasi et al. 2005). They are based upon the consideration of the solvent as a continuous medium characterized by its macroscopic properties: bulk dielectric permittivity, possibly surface tension. The solute is assumed to occupy a cavity surrounded by this continuum. The free energy of interaction between this molecule and its surrounding may be analyzed as the sum of three contributions:

- The free energy variation of the system when the cavity is created in the bulk of the liquid. This can be considered as an increase of its free area and is a positive free energy variation.
- The dispersion-repulsion energy arising between a polarizable solute and the solvent molecules of finite size, which is always a negative contribution.
- The electrostatic free energy arising from the polarization of the solvent by the charge distribution of the solute. The result of this polarization is a non zero electrostatic potential within the cavity which perturbs the charge distribution of the solute, leading to changes in the solute's structure, compared with the isolated molecule (Luque et al. 2003).

The earlier attempt to approach the electrostatic contribution to the free energy of solvation is due to Kirkwood (1934). This model is based on a multipole expansion of the charge distribution of the solute at the center of a spherical cavity surrounded by a continuum represented by the dielectric permittivity of the solvent. When this expansion is limited to rank 1 which corresponds to a pure dipole μ, one finds the Onsager model (Onsager 1936) in which the electrostatic contribution to the free energy of solvation by a solvent of dielectric constant ε of a molecule having a dipole moment μ in a cavity of radius a takes the expression:

$$\Delta G = -\frac{1}{2a^3}\frac{2(\varepsilon - 1)}{2\varepsilon + 1}\mu^2. \tag{1}$$

Onsager has shown, in the case of a pure liquid made of dipolar, polarizable molecules, that the dielectric constant of the liquid is fairly well predicted when the volume of the cavity is equal to the apparent molecular volume in the liquid. This finding gives a hint to the estimate of the volume of the cavity which is a parameter in the Kirkwood model. In the case of a non neutral solute, the charge q corresponds to the multipole of rank 0 and the corresponding term in the multipole expansion is the well-known Born formula (Born 1920) giving the free energy of solvation of charged solutes:

$$\Delta G = -\frac{1}{a}\frac{\varepsilon - 1}{\varepsilon}q^2. \tag{2}$$

This approach which has the advantage of giving an analytical formula of the free energy of solvation has been extended to ellipsoidal (Rinaldi and Rivail 1973) and spheroidal cavities (Rivail and Terryn 1982) and has been applied long ago to quantum chemical computations, at various levels of approximation (Rinaldi et al. 1983). As the perturbation to the wavefunction depends on the charge distribution of the solute which is defined by the wavefunction to be computed, the computational scheme requires self consistency combined with the usual self consistent computational algorithms for quantum chemistry. This is frequently referred as the Self Consistent Reaction Field (SCRF) where the solute is polarized by the solvent which is, in return, polarized by the solute. Nowadays, this model has been extended to cavities of any shape using a multicentric multipole expansion on all the atoms of the solute (Rinaldi et al. 2004). In all these approaches, the first and second derivatives of energy are computed allowing a full geometry optimization and the determination of the stationary points in the potential energy surface and the computation of the harmonic vibrational frequencies (Rinaldi et al. 2006).

A closely related approach, using the same kind of molecular cavity has been developed by Tomasi et al. (1981). In this model, the multipole expansion is replaced by a numerical computation of the electrostatic potential inside the cavity, due to the polarization of the boundary by the solute. This model also has been improved along the years. It has various versions all known under the acronym of PCM (Cancès et al. 1997) which are implemented in the Gaussian suites of programs, and a closely related model is available in the Jaguar package (Marten et al. 1996; Tannor et al. 1994).

Rather, different approaches are based on the so-called generalized Born model in which the charge distribution of the solute is represented by point charges on all atoms and the solute–solvent interaction is defined by a sum of the Born contributions of each atom in which the reciprocal of the sphere radius in Eq. 2 is replaced by a parameterized empirical formula. The most elaborated applications of this model is found in the series of SM x models of Cramer and Truhlar ($x = 1$ to 8 nowadays, corresponding to successive improvements) (Cramer and Truhlar 1991, 2008).

Finally, to simplify the electrostatic algorithm some methods start with a dielectric permittivity $\varepsilon = \infty$ corresponding to a conductor like solvent and then correct the result either by the ratio $2(\varepsilon - 1) / (2\varepsilon + 1)$ of the Onsager factor of the actual dielectric permittivity of the solvent to the limiting value when $\varepsilon = \infty$, or by the ratio of the Born factors: $(\varepsilon - 1) / \varepsilon$. It is noteworthy that the difference may not be negligible for low dielectric constants. This approximation has first been introduced in the COSMO model (Klamt and Schüürmann 1993). A version of the PCM model, known as C-PCM (Barone and Cossi 1998) uses the same approximation to evaluate the electrostatic solvation term.

The importance of any kind of solvents, including the non polar ones has to be emphasized because some people claim that the properties in a non polar solvent should be close to the gas state. The experimental results mentioned in (Reichardt 1979) show that it is not true, and this can also be seen in the case of the Born or Onsager models. If one considers a solvent such as cyclohexane with a dielectric permittivity close to 2, one sees that the electrostatic free energy of solvation is for the former and the latter model respectively 50 % and 40 % of the limiting value at infinite permittivity. Similarly, one also notices that for high dielectric permittivities, these terms do not vary noticeably when this constant varies, justifying the COSMO-type models in particular in the case of water and highly polar solvents.

The quantitative use of continuum models requires care. The absolute values of free energies of solvation depend on many parameters. The electrostatic contribution mainly depends on the shape and volume of the cavity. The most widely used shapes are defined by the “molecular surface” (Pascual-Ahuir and Silla 1990; Silla et al. 1991) defined after the atomic radii (Bondi 1964) multiplied by a factor of the order of 1.3. A test for the choice of this parameter can be the comparison of the volume of the cavity with the apparent molecular volume of the solute (when known) in the liquid state or in the solution like in the Onsager’s theory of the dielectric permittivity of pure polar liquids.

The non electrostatic contributions are far more difficult to model. Usually, they are evaluated by empirical formulae which, in the most favorable cases, introduce some error bars. The models parameterized on a large number of experimental data, such as SM8 (Cramer and Truhlar 1991, 2008), are probably rather reliable although one may deal with a case which is an exception. Conversely, variations of solvation energy for systems in which the non electrostatic terms are assumed not to vary significantly, such as conformational equilibria, may be approached rather safely by means of these computational efficient models.

The Full Quantum Approaches of Liquids

A reliable computation of free energies in a molecular system requires the use of statistical mechanics on a sample which can be considered as macroscopically representative. In the case of solutions, this requires more than one hundred solvent molecules and the computation of an enormous number of different configurations. Full quantum chemical studies are now possible thanks to some specific algorithms but they are still lengthy. An efficient approach uses a standard semi-empirical code, reparameterized to account properly for intermolecular energies (Bernal-Uruchurtu and Ruiz-López 2000; Bernal-Uruchurtu et al. 2000), coupled with a linear scaling divide and conquer algorithm (Dixon and Merz 1996, 1997), which allows the simulation of a set of 216 water molecules in a quite affordable computer time (Monard et al. 2005). The use of fast DFT methods can now replace the semi-empirical ones (Hu et al. 2007) and one may anticipate that in the near future, the theoretical and algorithmic improvements will make possible the use of non empirical treatments. The use of plane wave basis sets (Todorova et al. 2006; VandeVondele et al. 2005) is another attempt to improve the efficiency of the codes.

In contrast with the previous approaches in which the energy and the forces calculated at each configuration of the system are computed within the usual Born-Oppenheimer approximation (BOMD), the Car-Parrinello unified approach for molecular dynamics and DFT (Car and Parrinello 1985) is an efficient alternative to the simulation of macroscopic samples although it requires rather large computational facilities and time. The CPMD package is available for such computations which require some expertise to be ran safely (Marx and Hutter 2000). A comparison of CPMD and BOMD simulations may be useful to determine the best computational procedures (Kuo et al. 2006). Car-Parrinello computations are widely applied to the simulation of liquids, mainly water (Izvekov and Voth 2002) but other liquids are also considered (Bakó et al. 2006). All these full QM approaches are, for the time being, mainly limited to the understanding of the structural properties of pure liquids.

The Quantum Mechanical/Molecular Mechanical (QM/MM) Models

Chemical studies usually deal with a solute which can be a single molecule or a molecular complex or transition state in a chemical reaction. In such systems, the role of the solvent is mainly a physical perturbation which can be simulated at a lower theoretical level than that required for the study of the subsystem of chemical interest. The success of continuum models confirms this statement. In order to describe the solution at the molecular level and to perform full statistical mechanics computations on a model of macroscopic sample, one may set up some computationally efficient approaches by limiting the quantum chemical study to the solute and using one of the usual classical force-fields to represent the solvent molecules. The computation of the statistical averages can be done by means of either Monte Carlo or molecular dynamics algorithms. The so-called QM/MM models are now widely used in such chemical studies.

The Hamiltonian is a sum of three terms: H_{QM}, the usual quantum Hamiltonian of the solute, H_{MM}, the classical Hamiltonian corresponding to the configuration of the solvent $H_{QM/MM}$, which corresponds to the interaction energy between the classical solvent molecules and the quantum solute (Monard et al. 2003). The first two Hamiltonians are well defined by the choice of the quantum methodology and the classical force field chosen to model the liquid. The definition of the interaction Hamiltonian is far more difficult. It is usually made of a sum of van der Waals interaction energies between the classical atoms of the solvent and the quantum atoms of the solute, the long-range electrostatic interactions between the classical solvent molecules and the electron distribution and the nuclei of the solute and the possible specific interactions (hydrogen bonds). This is the most delicate part of the methodology, which requires specific parameterizations for each kind of quantum chemical method used as well as each classical force field. A large number of papers have been published on this problem (Freindorf and Gao 1996; Freindorf et al. 2005; Giese and York 2007; Luque et al. 2000; Riccardi et al. 2004). For specific problems, useful methodologies have been set up to determine the most appropriate parameters (Martín et al. 2002).

Once the methodology has been defined, running a computation requires the usual molecular dynamics or Monte Carlo codes, but the necessity of taking into account a large number of configurations makes any improvements which accelerate the process very valuable. One of the time consuming step is the computation of the long-range electrostatic interactions for which some algorithms, such as the use of Ewald sum (Nam et al. 2005) or periodic boundary conditions (Laino et al. 2006), may become very efficient to compute accurate free energies (Gao et al. 2005).

Various methods and levels of approximation can be used for the QM part of the studies, from semi-empirical (Cummins and Gready 1997; Geerke et al. 2008), empirical Valence Bond (Sumner and Iyengar 2008) to correlated levels (Kongsted et al. 2003; Woods et al. 2008). QM/MM simulations also work with the Car-Parrinello methodology (Laio et al. 2002).

QM/MM methods have now reached a good level of achievement and have opened the way to refined studies of molecular structure and reactivity in the liquid state (Hu and Yang 2009). However, may be one of the last remaining challenges for QM/MM methods is to correctly and efficiently handle reactivity problems where one or more solvent molecules are directly implied in the chemical mechanism. The usual solution found in literature is to choose among all solvent molecules the unique molecule which will react with the solute. Some solutions which take into account the dynamical nature of the first solvation shell have been suggested so far (Kerdcharoen and Morokuma 2002, 2003; Tongraar et al. 1998; Tongraar and Rode 2004), but they have not been applied to reactivity problems yet.

Other Statistical Approaches of the Solvent

Reference Interaction Site Model (RISM)

Integral equations of the liquid state provide us, in principle, with a rigorous statistical description of the liquid, although, to solve them, one is forced to use several approximations, in particular various closure conditions to get pair correlation functions (Hansen and McDonald 1976). These approaches have been successfully used to describe simple liquids. In the case of polyatomic molecules, the difficulty increases rapidly with the number of sites and the nature of the interatomic potential. Nonetheless, a Reference Interaction Site Model (RISM) has been proposed to extend the treatment to polyatomic liquids (Chandler and Andersen 1972) and has been successfully applied to several problems dealing with molecular solutions (Hirata and Rossky 1982). Some routines are now available to solve the RISM equations. These equations have also been coupled with a quantum computation of the solute (Ten-no et al. 1993). The interatomic potentials have the standard Lennard-Jones expression in which the electrostatic interactions are developed on a basis of point charges. Therefore, the electronic distribution of the solute is limited to effective partial charges $q\lambda$ located on the atoms (denoted by a greek index here λ). The Hartree-Fock equations are modified by introducing a perturbative potential on each atom λ of the solute:

$$V_\lambda = \rho \sum_{j \in S} qi \int_0^\infty r^{-1} g_{\lambda j}\,(r, q_\lambda)\, 4\pi r^2\, dr, \tag{3}$$

where ρ is the solvent density and $g_{\lambda j}(r, q_\lambda)$ is the radial distribution function of the jth site of solvent molecules S relative to the λth site of the solute molecule. This function is given by the RISM equations. The RISM-SCF cycle simultaneously optimizes the pair correlation functions and the electronic wavefuctions. This approach has been successfully applied to the study of solvent effects on the electronic spectra of carbonyl compounds (Ten-no et al. 1994).

Langevin Dipole Model (LD)

Between a macroscopic description of the solvent represented by the continuum models and a microscopic approach where all solvent atoms are explicitly represented, there exists an alternative semi-macroscopic approach: the Langevin Dipole model. This model treats the solvent (usually water) explicitly but in a simplified way. It represents the time average polarization of the solvent molecules by a cubic grid of polarizable dipoles (Warshel 1991; Warshel and Russel 1984). According to the Langevin equation (Langevin 1905), the electrostatic field of the solute reorientes and polarizes the grid point dipoles. While this method has been successfully applied to the computation of the free energy of solvation of small neutral and ionic molecular solutes at a quantum level (Florián and Warshel 1997, 1999; Kongsted et al. 2009), the Langevin Dipole model has been mostly used to represent the electrostatic interactions between water as a solvent and proteins through the Protein Dipoles/Langevin Dipoles (PDLD) method (Roca et al. 2007; Warshel et al. 2006).

The Future of Studies in the Liquid State

The number of selected papers dealing with various approaches of the liquid state and solutions clearly indicate that taking into account the influence of the solvent in quantum chemical studies will soon become quite usual. The large variety of methods allows us to adapt the level of modeling to the accuracy required to get useful chemical information. The methodology is still expected to improve in the near future. In particular, the full quantum treatment of a solution which takes advantage of the advances in quantum modeling of pure liquids seems to be at hand, especially when one can use different quantum levels for the solute and for the solvent. Like in the case of QM/MM the key feature is the proper treatment of the interaction between both subsystems but one can be confident to the quantum chemists to find the proper solutions to this problem.

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