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Implicit Solvation Models: Equilibria, Structure, Spectra, and Dynamics

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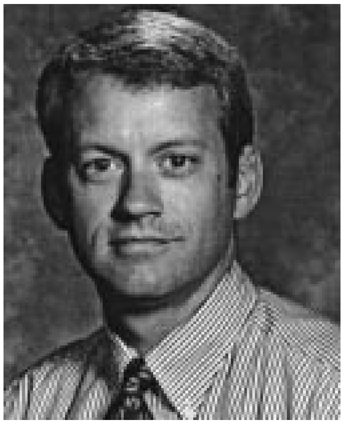
1. Introduction

The present review is concerned with continuum and other implicit models of solvation effects. We will concentrate on the elements required to make such models successful and on the factors that limit their accuracy. We will discuss explicit solvent models only to the extent that they provide a complementary picture or a context, since physical models of solvation, e.g., nonequilibrium solvent coordinates, can often be achieved using either a continuum treatment of solvent or one that recognizes individual solvent molecules.

There are two principal advantages of continuum models. The first is a reduction in the system's number of degrees of freedom. If we treat 200 molecules of a solvent explicitly, this adds 1800 degrees of freedom for water, 9000 degrees of freedom for ethyl ether, and 16 200 degrees of freedom for 1-octanol. Observable structural and dynamical properties of a solute must be averaged over these degrees of freedom, typically by Monte Carlo or molecular dynamics techniques. If, however, we can treat the solvent as a continuous medium bathing the solute, the averaging becomes implicit in the properties



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attributed to the bath. Although approximate models are seldom perfect, we may be able to make the errors small enough that our attention can be focused elsewhere, e.g., on a better quantitative treatment of the solute or the dynamics, rather than on further improving the description of solvent effects.

The second advantage is appreciated when one realizes that complementary methods based on explicit solvent are also imperfect. Only when such models are considerably refined do they model the solvent electric polarization as well as a continuum model based on the experimental dielectric constant. Thus, the second advantage of continuum solvent models is that they provide a very accurate way to treat the strong, long-range electrostatic forces that dominate many solvation phenomena. There is a third advantage in practice. Most explicit-solvent simulations still neglect solute electronic polarization due to cost (a notable exception being an extensive body of work of Gao and co-workers[1,2]), whereas there is over 20 years worth of experience with polarizable solutes using continuum theory.

2. Previous Reviews

Before proceeding to discuss implicit models of solvation, we note that the present review is but one in a steady stream of reviews of this subject in recent years. This high review activity stems, of course, from a large number of original papers on the subject and a concomitant steep rate of research progress. For example, the 1994 review of continuum solvation theories and calculations by Tomasi and Persico[3] has 838 references, with over 300 of them from 1988 or later. Furthermore, the subject continues to be in an exponential growth stage with no end in sight. Thus, not only will our review of the literature be selective, even our review of reviews (i.e., the following paragraphs) will be selective. We note the following reviews that particularly complement the one presented here (with a brief description of each).

The 1994 review of Tomasi and Persico,[3] entitled “Molecular Interactions in Solution: An Overview of Methods Based on Continuous Distributions of the Solvent”, provides a particularly complete discussion of the historical development of various continuum approximations for computing the electrostatic component of the solvation free energy. It describes how early research on idealized systems having analytic solutions to Poisson’s equation led to more general approaches for realistic cavities and, moreover, provides a thorough analysis of the relative utility of different numerical recipes for solving Poisson’s equation recast as a surface integral over apparent surface charges. Finally, this review provides comparisons of different approaches for including the solvation free energy in the one-electron Fock or Kohn−Sham operator needed for various quantum chemical calculations, i.e., so-called self-consistent-reaction-field (SCRF) computations. A less detailed but still edifying summary of accounting for nonelectrostatic components of the solvation free energy is also provided. A 1997 review by Tomasi et al.[4] presents an updated analysis of quantum mechanical continuum solvation models, a comparison of alternative methods, and a summary of selected applications.

Rivail and Rinaldi[5] reviewed this field in a book chapter entitled “Liquid State Quantum Chemistry: Computational Applications of the Polarizable Continuum Models”. This review pays particular attention not only to the nature of the solute−solvent interface (e.g., ideal vs nonideal cavities, size of the cavities, etc.), but also to the means by which the solute charge distribution is represented. The Nancy group has carefully examined the degree to which the continuous solute charge distribution can be realistically represented as a truncated multipolar expansion at one or more positions within the solute cavity. This is an alternative approach to the solution of Poisson’s equation in terms of apparent surface charges. They also review the use of analytic gradients for geometry optimization to study solvent influences on molecular geometries and reaction dynamics.

At about the same time, the present authors reviewed the field in two book chapters,[6,7] both entitled “Continuum Solvation Models”. The former review was particularly complete on the generalized-Born-plus-atomic-surface-tensions approach and contained extensive comparisons of the results of different approaches applied to the same systems. The latter review provided a fairly complete recapitulation of SCRF theory and the derivation of the appropriate one-electron operator for inclusion of solvent effects in molecular orbital theory within the context of linear response theory. A systematic classification scheme for different continuum models was proposed, and a complete enumeration of extant models to that point was attempted. In addition, the subject of dynamical processes within the context of continuum solvation was discussed. Finally, a thorough review of continuum calculations of solvent effects on tautomeric equilibria, particularly those of heterocycles, was presented.

Richards[8] has provided the most recent review of continuum solvation models as part of a larger work focusing on the application of semiempirical quantum mechanical methods to biological systems. Detailed derivations and descriptions of popular models are provided. We also mention the 1994 review of Rashin and Bukatin[9] which discussed additional thermodynamic quantities beyond the free energy of solvation where continuum models of hydration can be compared to experiment.

Five other reviews are mentioned because of their discussion of solvation modeling in general, including both continuum and discrete methods. In particular, the reviews of Tapia[10] in 1992, Warshel[11] and Smith and Pettitt[12] in 1994, Orozco et al.[13] in 1996, and Hummer et al.[14] in 1998 provide useful comparisons of the underlying assumptions of continuum vs discrete models (including lattice dipole models) and of their relative performance for different classes of problems. The Warshel and Orozco-Luque groups have been particularly active in comparing different theoretical models against one another in a variety of systems; for the general practitioner, such comparisons can be very helpful in analyzing how first to attack a specific problem.

Finally the reader is referred to two recent monographs[15,16] that contain a large number of chapters on solvation topics,[17−23] including in each case at least one review on continuum approaches to solvation modeling.

3. Elements of Continuum Solvation Theory

Traditionally, continuum models of solvent were focused on dielectric models of electrostatic effects. In a dielectric model the solvent is modeled as a continuous medium, usually assumed homogeneous and isotropic, characterized solely by a scalar, static dielectric constant ϵ. This model of the solvent assumes linear response of the solvent to a perturbing electric field. The model was developed and exploited by Born,[24] Onsager,[25] and Kirkwood[26] 60−80 years ago. However, it was soon recognized that the quantitative applicability of their results was limited by the specific interactions of the solute with solvent molecules in the region close to the solute where the solvent has properties different from the bulk; this is the so-called cybotactic[27] region. These effects are dominated by the first solvation shell, and we call them first-solvation-shell effects.

A variety of approaches to "correct" continuum models for first-solvation-shell effects were proposed. For example, the assumption of linear response of a solvent to a local electric field may break down in the first solvation shell if the local electric fields in the vicinity of the solute are high. Typically one expects the dielectric response to be overestimated by continuum theory in such a case. This leads to the concept of dielectric saturation or more generally to the notion of a microscopic permittivity field whose value at any point in space is a local effective dielectric constant and whose value near the solute differs from the bulk value. Another way to think about this is to recognize that the properties of even individual solvent molecules in the first solvation shell differ from the properties of bulk solvent molecules, just as the latter differ from the properties of gas-phase molecules of the solvent. There is an even more basic ambiguity surrounding the continuum treatment of the solvent, namely, where does the solute stop and the continuum begin?[28−33] One can postulate that the boundary coincides with the surface of a space filling model of the solute, but that still leaves open the question of the atomic radii to be used in constructing the space filling model. Consider a monatomic solute of radius ρ at the origin and consider a point in space with coordinates r, θ, ϕ. Ideally we can set the dielectric constant equal to unity (corresponding to no solvent, which is appropriate if solute polarization is treated explicitly) if $r \le \rho$ and to its bulk value (corresponding to implicit solvent) if $r > \rho$. Clearly this is an oversimplification, and it illustrates the connection of the radius question to the nonhomogeneous permittivity field. The long history of various advocates of continuum models trying to "fix up" this problem by a clever choice of effective atomic radii, combined with the sensitivity of the calculated results to the resulting choice of radii, is probably the single most important contributor to the negative impression some researchers formed of continuum models. One goal of this review will be to show how this uncertainty need not be a fatal problem. In particular, the failures of the bulk-dielectric model to provide a satisfactory treatment of the first solvation shell can be addressed by adding first-solvation-shell effects to the theory in other ways, rather than simply by finding the "best" effective radii. Furthermore, this can be done by methods that still treat the solvent implicitly.

So far, we have emphasized the breakdown of a bulk-dielectric treatment of the solvent as a critical issue in the first solvation shell. There are also other first-solvent-shell issues, such as dispersion interactions and hydrogen bonding. But the one that has most stimulated the historical development of the theory is the hydrophobic effect. Modern understanding of the hydrophobic effect attributes it primarily to a decrease in the number of ways that favorable hydrogen bonding can be achieved by solvent water molecules when they are near to a non-hydrogen-bonding solute; this decreases the solvent's entropy.

Another effect that must be absorbed in the first-solvation-shell term is charge transfer to or from the solvent. In nonconducting solvents, this charge transfer must be dominated by the first solvation shell, and presumably it contributes to the solvent Lewis acidity or basicity, respectively.

The magnitude of the free energy effect associated with any first-solvation-shell phenomenon can, to a first approximation, be considered proportional to the number of solvent molecules in the first solvation shell. The key to a continuum treatment of these effects is to recognize that this number, after averaging over solvent configurations, is a noninteger continuous function of solute geometry that is characteristic for a given solute in a given solvent at a given temperature. Furthermore, it can be calculated as the area of a hypersurface that passes through the middle of the region occupied by the first shell of solvent when treated as a continuous medium. This is the essence of the concept of solvent-accessible surface area (SASA), introduced independently by Lee and Richards[34] and Hermann.[35] This area is calculated as the area traced out by the center of a ball rolling over the surface of a solute, where the radius of the ball is the effective half width of the first solvent shell (~1−2 Å for water). This is very reasonable for simple spherical solvent molecules; the question of the effective solvent radius for polar, hydrogen bonding, and long-chain solvents has been considered by Gogonea et al.[36]

The SASA approach is very general and has been widely applied, and our understanding of the concept of SASA has been refined over the years. For example, consider a small molecule dissolved in *n*-hexadecane and suppose we wish to make a continuum estimate of the solute−solvent dispersion-force interactions. For this purpose only part of a hexadecane molecule should be thought of as residing in the first solvation shell since dispersion interactions are too short ranged to extend to the part of the solvent molecule separated from the solute by several $-CH_2-$ groups. If we approximate the range of dispersion forces as, say, 1.5 Å, then an effective solvent radius of 1.5 Å is more appropriate for this calculation than the much larger radius one would estimate by considering the size of an actual hexadecane solvent molecule. However, if we wish to make a continuum calculation of the free energy effect of the solute perturbing the structure of the liquid solvent, the latter, larger radius is probably more relevant.[37] This example also illustrates that the "size" of the "first solvation shell" is a flexible concept, depending on which solvation property is under consideration. (An interesting corollary of this observation is that the effective cavity size for electrostatics may also be different for various components of the solvent's electric response; for example there may be distinct effective cavity sizes for the so-called inertial response due to polar solvent reorientation and the inertialess response due to electronic polarization of the solvent.[38,39])

As an item of particular interest, special techniques have been developed to study first hydration shells of proteins. Analysis[40] of the amount of water adsorbed on partially hydrated lysozyme powders as a function of the partial pressure of the surrounding water vapor indicates that the free energy of surface water differs from the bulk solvent by only about $\Delta G = -0.5$ kcal/mol with $\Delta H = -1.4$ kcal/mol and $T\Delta S = 0.9$ kcal/mol. The results are consistent with a monolayer interface.

In the SM*x* models,[41−44] the SASA is used with empirical atomic surface tensions and usually combined with an electrostatic term. It is useful here to explain how this combination "resolves" the ambiguity of the atomic radii in the continuum-dielectric approach to electrostatics. We will do this with a simple example. Consider a monatomic ion whose radius might equally likely be modeled as 1.5 or 1.6 Å and for which the effective dielectric constant of the solvent within 3 Å of the ionic nucleus might differ significantly from the bulk value. The region where the electrostatic treatment is uncertain is a shell extending from 1.5 to 3 Å from the center of the ion. But this whole shell is contained in the first solvation shell. Thus, if the handling of the first solvation shell takes the bulk-dielectric electrostatic treatment as a given and includes an estimation of the deviation of the true situation from the idealized one with a specific choice of atomic radius for the ion, the deficiencies of the bulk-dielectric model can be largely overcome. This is the foundation of the SM*x* solvation models.[41−44] By combining electrostatics with additional terms for first-solvation-shell effects, one retains the strength of the bulk-dielectric model, which is that it provides a very economical and very accurate estimation of the long-range electrostatic effects, which are quite large, without its weakness, which is its oversimplification of and ambiguity in the cybotactic region. A chief limitation in the current SM*x* methods is that the surface tensions do not depend explicitly on solute charges (although they do depend on some bond distances and thus indirectly correlate with charge), and thus, they cannot fully account for ambiguities in the radii, which are charge dependent.[31]

An alternative approach to eliminating the ambiguity of atomic radii was proposed by Bernhardsson et al.[45] and Serrano-Andrés et al.[46] These authors introduced a pseudopotential to mimic the steric exchange repulsion between solute and solvent and to help prevent solute electron penetration into the solvent. This transfers the uncertainty from the parametrized atomic surface tensions to the parameters in the pseudopotential.

Of course one need not limit oneself to the SASA in making continuum approximations of first-solvation-shell effects. Continuum models for specifically calculating first-solvation-shell dispersion[47−54] and repulsion[52−54] free energies have been developed by the Nancy, Extremadura, and Pisa groups. These are typically added to the cavitation free energy as calculated by the method of Pierotti,[55,56] or Claverie's[57,58] generalization of Pierotti's equation, to compute the full first-solvation-shell contribution. The alternative approach of using the SASA and parametrized atomic surface tensions, as practiced by the Minnesota and Barcelona groups for the SM*x*[19,37,41−44,59−77] and MST-ST[13,78−85] models, respectively, does not attempt to quantitate the relative contributions of these different first-solvation-shell interactions; it aims rather to account for their sum and also, by virtue of being semiempirically fitted, to correct for any systematic inaccuracies in the electrostatic treatment. In the case of the SM*x* models, organic solvents are treated generally, with surface tensions for a given level of theory being a function of certain macroscopic solvent parameters, like surface tension, index of refraction, a free-energy-based solvent-acidity parameter, etc. In the PCM-ST models, separate parametrizations have been performed for each choice of solvent and level of theory—presently, parametrizations for chloroform and carbon tetrachloride are available in addition to water. Marten et al. have also become converts to the need for empirical surface tensions to augment electrostatics.[86] Although most attempts to use atomic surface tensions employ cavities of arbitrary (molecular) shape for computation of both the electrostatics and the SASAs, Tuñon et al.[87] have parametrized atomic surface tensions on a small training set for use with ellipsoidal cavities; this combination is expected to be less reliable.

Having introduced the elements of implicit-solvent modeling, we now outline the rest of this review. First we consider various implicit models for the electrostatic and first-solvation-shell effects at equilibrium. After that we consider equilibrium properties of solutes, especially dipole moments and equilibrium constants. Then we turn to the two most important dynamical processes in condensed-phase chemistry: absorption of electromagnetic radiation and chemical reactions. For both of these dynamical problems we must consider not only the equilibrium properties of the solvent but also the speed of its response to a perturbation.

4. Models for Equilibrium Solvation

4.1. Widely Used Models

The electrostatic interaction of a solute with the solvent depends sensitively upon the charge distribution and polarizability of the solute. The latter is important because the solute and solvent relax self-consistently to each other's presence. In continuum models the ability of the solvent to polarize under equilibrium conditions is encapsulated by its dielectric constant (a single number), but solutes, being the primary systems of interest, are allowed to have more components to their personality. Ultimately, the charge distribution of a solute is determined by quantum mechanics. Thus, we can classify solute treatments as follows: (i) quantum mechanical, flexible (QM-F), including electronic and geometric relaxation (distortion) in the presence of solvent; (ii) quantum mechanical, rigid (QM-R), by which we mean that electronic but not geometric relaxation is included; (iii) quantum mechanical, nonpolarizable (QM-NP), in which electronic relaxation is also neglected; (iv) polarizable molecular mechanics (PMM), by which we mean classical and electronically polarizable; (v) molecular mechanics (MM), by which we mean classical and nonpolarizable. So far, most work with implicit-solvent models has involved QM-F and QM-R approaches. Since modern theories tend to be complicated (a fact of life bemoaned by a referee of one of our recent papers) one can usually find some method that is imperfectly classified by just about any scheme one devises (those become "hybrid" methods), but the above classification serves reasonably well to classify existing approaches.

The critical physical concept for treating solute polarization in solution is the reaction field. The reaction field is the electric field exerted on the solute by the solvent that it has polarized. Including this in the solute Hamiltonian predicts a new ("distorted") solute electronic structure, which further alters the polarization of the solvent. Iterating to self-consistency is called the self-consistent reaction field (SCRF) method. SCRF theory may be employed in QM-F, QM-R, and PMM approaches. In fact the original work of Onsager[25] used the PMM approach.

The perturbational viewpoint on SCRF theory, the basic symmetry properties of the reaction potential response function due to the linear response approximation, and the relationship between the solute distortion energy and the polarization energy have been elucidated by Constanciel, Ángyán, Surján, Fortunelli, and Luque et al.[88−95] These papers assist not only in uncovering formal inconsistencies in some treatments, but also in developing less expensive computational schemes that may be useful for large solutes and ascertaining the conditions of validity of the various approximations.

The history of and theory behind continuum solvation models have been laid out exhaustively in various places,[3−11,13,18,27,90,96] so we do not consider it necessary to repeat it here. We do, however, begin with a review primarily of those models which have gained wide acceptance and are in use by multiple research groups around the world.

Finite Difference Solutions of the Poisson Equation. Most currently available continuum solvation models compute the electrostatic component of the solvation free energy by solution of the Poisson equation. In the case of nonzero ionic strength,[97−115] solution of the Poisson−Boltzmann equation is more appropriate, but we will not explicitly consider salt effects in this review. Methods that discretize the Poisson differential operator over finite differences or finite elements have long been in use for biopolymers having classical charge distributions.[12,102,104,105,109−113,116−136]

Sitkoff et al.[125] have proposed one such Poisson-equation model specifically for aqueous solvation. The model, called PARSE, treats the solute classically and includes accounting for the hydrophobic effect based on the total molecular solvent-accessible surface area. They optimized atomic charges and radii plus an empirical surface tension by fitting to experimental solvation energies. Simonson and Brünger[137] have described a very similar model using OPLS charges and radii and a single molecular surface tension fitted to cyclohexane/water transfer free energies for amino acid side chains.

A number of groups have now described SCRF approaches that couple a grid-based numerical solution of the Poisson equation to the quantum mechanical SCF process.[138−141] An accounting for aqueous first-solvation-shell hydrogen-bonding and hydrophobic effects using atomic surface tensions has also been described for one such model.[86]

PCM. An alternative to the use of finite differences or finite elements to discretize the differential operator is to use boundary element methods. The most popular of these is the polarized continuum model (PCM), developed primarily by the Pisa group of Tomasi and co-workers,[3,142−145] which casts the quantum mechanical SCRF equations into a boundary element problem with apparent surface charges (ASCs) on the solute cavity surface. There are currently three different approaches for carrying out PCM calculations. The original method, called dielectric PCM[142,143] (D-PCM), an alternative model in which the surrounding medium is modeled as a conductor instead of a dielectric[146] (C-PCM, cf. the COSMO model below), and an implementation whereby the PCM equations are recast in an integral equation formalism[147,148] (IEF-PCM). The latter method has lent itself to the calculation of various molecular gradient and response properties, as detailed in section 4.2.

Nonelectrostatic effects have been treated differently by different users, or ignored, but they can be included by uniform continuum calculations of cavity, dispersion, and repulsion effects[51−56,149] or by an approach[13,58,78−83,85,150] that involves SASAs and empirical atomic surface tensions parametrized against experimental solvation free energies along the lines introduced first in the SM*x* models. The latter combination is usually called Miertus−Scrocco−Tomasi-plus-surface-tensions (MST-ST, the MST portion of the acronym after the authors of the reference[142] describing the original PCM formulation). Amovilli and Mennucci[151] have recently described an approach whereby Pauli repulsion and dispersion contributions are computed self-consistently as part of the reaction field operator.

The PCM and MST-ST models are typically used with a solute cavity defined as a union of overlapping spheres having radii determined empirically; the most popular choice for most atoms is typically[145] 1.2 times the atomic van der Waals radius of Bondi.[152] A modification of the original PCM formalism has been proposed in which the solute cavity is determined instead by a specific value of the electronic isodensity surface.[144,153−162] That isodensity surface can either be from a gas-phase calculation (IPCM) or can be determined self-consistently, i.e., taking account of the effect of solvation on the isodensity contours (SCI-PCM). Ours and others'[144] experience with these modifications is that they can lead to considerable instability in the SCRF procedure and that they are less reliable than the original PCM. Another approach, pursued by Barone and Cossi,[146] is to bury H atoms in the heavy atoms to which they are attached and assign heavy atom radii based on hybridization and bonding pattern; a very similar approach is employed in the SM2 and SM3 models.[42−44]

Other PCM Variations. Other groups have implemented the original PCM equations at various levels of electronic structure theory. Wang and Ford described an implementation at the semiempirical neglect of diatomic differential overlap (NDDO) level,[163] but their reaction field operator included an extra factor of 1/2, so their solvated wave functions do not minimize the free energy in solution.[7,90,91,164] Sakurai and co-workers[165−167] have also described NDDO PCM implementations and examined sensitivity to atomic radii. Kölle and Jug[158] developed a method for using scaled charges in PCM calculations based on SINDO1 semiempirical molecular orbital theory. Semiempirical models designed to solvate both ground and excited states (cf. section 7.1) have been described by Rauhut et al.[168] and Chudinov et al.[169] at the NDDO level and by Fox et al.[170,171] at the INDO level. Rashin et al.[172] have described a PCM model implemented at the density functional level of theory.

Alagona and Tomasi and co-workers[173,174] have introduced a series of approximations in which the SCRF charge distribution and reaction field are produced by sums of polarizable or nonpolarizable contributions from chemical group fragments. Purisima and Nilar[175,176] have also examined simplified methods for efficiently computing the apparent surface charge density that determines the reaction field. Nilar[177] has introduced a simplified PCM model in which the quantum mechanical treatment of the solute is replaced by a set of polarizable charged spheres, i.e., a PMM charge distribution. Horvath et al.[178] have described a classical PCM model including atomic surface tensions for modeling cavitation and hydrophobic effects.

COSMO. A method that is very similar to PCM (although it was developed independently and preceded the description of the still more similar C-PCM[146] variation) is the *co*nductor-like *s*creening *mo*del (COSMO) developed by Klamt and coworkers[179−182] and used later by Truong and coworkers.[156,183−187] This model assumes that the surrounding medium is well modeled as a conductor, which simplifies the electrostatics computations, and corrections are made a posteriori for dielectric behavior. Accounting for nonelectrostatic effects with the original formulation tends to be ad hoc, but now Klamt has proposed a novel statistical scheme, called COSMO for real solvents (COSMO-RS), to compute the full solvation free energy for neutral solutes.[181,188] The COSMO model has also recently been parameterized with SM5-type atomic surface tensions (Dolney, D. M.; Hawkins, G. D.; Winget, P.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G. To be published).

Multipole Expansions. Alternative QM-F and QM-R methods for solving the Poisson equation are to represent the solute and the reaction field by single-center multipole expansions, as first pioneered by the Nancy group of Rivail and co-workers.[189−191] Originally, this formalism was adopted because it simplified computation of solvation free energies and analytic derivatives for solute cavities having certain ideal shapes, e.g., spheres or ellipsoids.[153,157,192−205] The formalism has been extended to arbitrary cavity shapes and multipole expansions at multiple centers.[5,206−209] (An analogous methodology for distributed multipole representations was developed for the implementation of the COSMO method into the GAMESS computer package.[210]) Different research groups using this model have tended to treat first-solvation-shell effects on an ad hoc basis, although more recently a systematic approach has been proposed.[207]

The convergence of the single-center multipole expansion method deserves additional comments. This expansion is usually truncated after only a few terms, and this can be dangerous. The original Onsager model involved a classical (although potentially polarizable) charge distribution represented by a multipole expansion in a spherical cavity, and in early work employing SCRF methods, the distribution was truncated at the dipole moment[197,204,211,212] (maximum value of the spherical harmonic order $l_{\max}$ equal to 1). When a spherical cavity and a truncation at the dipole moment is used for an SCRF calculation, this has come to be called an "Onsager model" calculation. Modern calculations typically include more multipoles but are nevertheless usually limited to $l_{\max} < 10$. Experience shows, however, that the single-center expansion of the electrostatic potential is slowly convergent, especially the part from the nuclei; for example, it was shown that electron scattering by acetylene requires $l_{\max} = 44$ for good convergence.[213] Convergence appears to be faster for free energies of solvation; e.g., a recent calculation[205] of the electrostatic part of the solvation free energy of *trans*-1,2-dichloroethane in acetonitrile is presented as an example in Table 1. For this small molecule, the results are converged within 7% at $l_{\max} = 8$. For larger molecules it is easily shown that $l_{\max}$ should increase linearly within the distance from the center of the expansion to the farthest nucleus from that center.

Table 1. Electrostatic Polarization Contribution to the Solvation Free Energy (kcal/mol) of 1,2-Dichloroethane as a Function of the Highest-Order Spherical Harmonic in the Spherical Harmonic Expansion.[a]

l_{max}	ΔG_{EP}
1	0.00
2	−0.93
5	−1.14
8	−1.70
10	−1.79
12	−1.81
15	−1.82
20	−1.82

[a] Reference 205.

Generalized Born. The idea of a distributed multipole expansion to represent the charge distribution is also employed by the so-called generalized Born (GB) approach to continuum solvation. In this instance, however, only monopoles (i.e., atomic partial charges) are employed and instead of solving the Poisson equation with this charge distribution, one uses the generalized Born approximation,[41,44,88,96,211,214−226] which—when used with the dielectric descreening algorithm of Still et al.[224]—has been demonstrated to give results very close to those obtained from solution of the Poisson equation[227−232] or from explicit molecular simulations.[233] The dielectric descreening algorithm of Still et al.[224] is based on integrating the solvent free energy density over the volume occupied by the solvent, an old idea[24,234] cleverly and powerfully adapted to a new context. The most widely used solvation models adopting this procedure are the original generalized Born/surface area (GBSA) approach of Still and co-workers,[224,235,236] including the subsequent extensions and adaptations of several groups,[227,237−241] in which the generalized Born electrostatics are combined with a classical MM treatment of the solute, and the SM*x* models of Cramer, Truhlar, and co-workers,[17,19,37,41−44,59−61,64−66,68−71,73−77,242] in which generalized Born electrostatics are employed in a quantum mechanical treatment of the solute. In both of these approaches, semiempirical atomic surface tensions are used to account for nonelectrostatic solvation effects. Kikuchi and co-workers[225,243−245] and Harada et al.[226] have also described QM GB models that employ slightly different GB equations than that used by the GBSA and SM*x* models; they differ primarily in the functional forms used for the GB Coulomb integrals. A consistent treatment of first-solvation-shell effects has not been described for either model.

For the SM*x* models, the value of *x* ranges from 1 to 5.42, corresponding to successively improved versions of the prescriptions for atomic charges and radii, the dielectric descreening algorithm, and the functional forms for the atomic surface tensions. A characteristic of the SM*x* models is that the value of the surface tension depends on the atom, and surface tension parameter values are optimized semiempirically against a large body of experimental data. A special characteristic of the surface tensions in SM5-type models (i.e., SM*x* models with $x = 5.0-5.42$) is that they depend on the local geometry of the solute. Thus, the geometry-dependent surface tensions serve to assign molecular mechanics "types" to the individual atoms. As in molecular mechanics, the types depend only on local geometry. Unlike molecular mechanics though, they are assigned automatically by the computer (eliminating tedious and sometimes ambiguous human typing) and are continuous and differentiable functions of molecular geometry that automatically vary smoothly along reaction paths. The surface tension approach has been shown to perform better than explicit solvent models for amines, and it also captures the difference between *n*-hexane and cyclohexane.[77] A particular strong point of SM5.4 and SM5.42 models[64−66,68−71,73−77] is the selfconsistent incorporation of Class IV atomic partial charges in the solute.

The generalized Born approximation lends itself to a particularly efficient computational approximation called pairwise descreening,[62,63,227,235,246,247] and successful general aqueous solvation models (called SM*x* PD) have been developed based on this idea.[63] Qiu et al.[235] have described an alternative algorithm for improving the efficiency of calculating descreening effects at the MM level that involves using the atom−atom connectivity whose definition is required by the force field. Approaches similar in spirit, although not originally derived from generalized Born theory, have been described by Gilson and Honig,[247] Schaefer et al.,[230,248] and Horvath et al.[227]

Shoichet et al. have recently emphasized the efficiency of the generalized-Born-with atomic-surface-tensions approach when used to compute desolvation energies for ligand−receptor binding.[249] Ghosh et al. have reformulated the generalized-Born equations using a surface integral formalism (in a fashion analogous to finite element vs boundary element approaches to solving the Poisson equation) and suggested empirical corrections to their model designed to improve agreement with accurate solutions of the Poisson equation.[250]

Other Methods. Several MM solvation models relating the entire solvation free energy to the exposed surface area (and the atomic nature of that surface area) have been proposed.[67,72−74,251−258] Such models are particularly efficient for very large molecules, where only a small fraction of the atoms have exposed surface area; Weiser et al.[259,260] have recently described methods for the rapid detection of solvent-inaccessible atoms and for the rapid calculation of the surface area of those atoms that are exposed.

Although the pure-surface-tension approach does not account for long-range electrostatics in a physically realistic way, such models do represent the solvent as an equilibrium-averaged continuum insofar as solvent is absent. Atomic surface tensions are assigned to individual atoms, and the free energy of solvation is determined from the exposed surface areas of all the atomic types; we will call this kind of model a pure-ST one. Although early pure-ST models were limited to peptides in water, the most recent one is defined for all neutral molecules composed of H, C, N, O, F, S, Cl, Br, and I in water or any organic solvent, and an extension to certain kinds of ions commonly found in proteins has been described.[72]

Fukunishi and Suzuki[261,262] have extended the surface area model by including an energetic penalty for creating void volumes. Combining this approach with a force field describing Coulombic and van der Waals interactions, they have computed potentials of mean force for host−guest interactions in solution.[262] Stouten et al.[263] have proposed a solvation model that, like an earlier solvent model of Kang et al.,[264] is based exclusively on the solvent-accessible volumes around atoms. The choice of volume rather than surface area was motivated[263] by algorithmic simplicity. Two further studies have explored this model;[264,265] in the latter study the new solvation model failed to improve the dynamical properties of a protein.

The large number of pure-ST models developed for proteins has motivated comparison for protein-specific problems; Juffer et al.[255] found wide variations in predictions from different models and suggest that contradictions between models require that they be employed cautiously. Klepeis and Floudas[266] came to similar conclusions based on an analogous study that included comparison of solvent-accessible-surface-area models and one solvent-accessible-volume model.

An alternative method for computing solvation energies based on properties of the solute molecular surface, in particular of the electrostatic potential on that surface, has been described by Murray et al.[267] This approach combines quantum mechanical calculations with regression analysis, and in that sense it is a quantitative structure−activity relationship (QSAR) taking computed properties as variables.[268−270] A complete discussion of the vast literature describing different QSAR approaches to computing solvation free energies and/or partition coefficients is outside the scope of this review.

4.2. Recent Methodological Extensions

Much work has gone into developing algorithms for molecular orbital and density functional calculations that scale linearly in system size.[271−287] Rega et al.,[288] within the framework of the PCM model, have recently described new iterative procedures for determining solvation free energies and their gradients[289−291] that also exhibit linear scaling. Bharadwaj et al.[292] have presented a linear scaling boundary element method, and Kong and Ponder[293] have presented a linear-scaling method for reaction fields based on off-center multipole distributions.

The computation of analytical gradients of the free energy in solution with respect to nuclear coordinates is important for efficient geometry optimization and dynamics. Rivail and the Nancy group have recently extended their multipole-expansion SCRF formalism to permit the analytic computation of first and second derivatives of the solvation free energy for arbitrary cavity shapes, thereby facilitating the assignment of stationary points on a solvated potential energy surface.[153,208,294] Similar progress has been made for the COSMO model, with analytic first and second derivatives available for a number of levels of theory.[146,179,180,184,210,295] Analytic gradients[146,289,291,296−301] and second derivatives[299−301] have been developed for PCM models using several different approaches.[146,289,296−301] Analytic gradients for SM*x* models at ab initio levels of theory have been recently described;[302] analytic SM*x* gradients have been available longer at the semiempirical level.[303,304] Analytic gradients for finite difference solutions of the Poisson equation have been presented by Gilson et al.[305] and Im et al.[306] and for finite element solutions by Cortis et al.[141] Analytical gradients are also available for multiconfiguration self-consistent-field (MCSCF) treatments; in particular, Mikkelsen et al.[195] implemented analytic gradients for a complete-active-space self-consistent-field wave function with a multipole reaction field, and analytic gradients for a method coupling generalized valence bond theory with a finite element solution of the Poisson equation has been reported by Cortis et al.[141] While solvation effects on geometries are often rather subtle, an example of a large change in geometry upon dissolution is the $NH_3\cdots HBr$ complex, in which the H−Br distance changes by 0.59 Å.[307]

Kong and Ponder[293] presented two general methods for calculating the reaction field generated by a set of off-center point multipoles, and for one of these they also described methods for analytic gradients.

A topic of particular interest for molecular design is the extent to which solvation or transfer free energies can be decomposed into contributions from different portions of a molecule (e.g., atoms, functional groups, etc.). Because they compute free energies of solvation using atomic charges and surface tensions, GB−ST models have lent themselves, in particular, to this sort of analysis.[19,61,70,71,73,304,308−313] The transferability of chloroform/water partition coefficients for functional groups in a series of substituted purine and pyrimidine bases was evaluated using this approach (the transferability was predicted to be quite good).[310] Luque et al. have recently described a formalism for decomposing PCM-ST solvation free energies in an analogous fashion.[314]

Although almost all work to date has used a discontinuous model for the dielectric constant in which it changes from one value inside the solute (unity if solute polarization is explicit and some larger number (>2) if it is not) to the bulk value at the solute−solvent boundary. Im et al.[306] have recently suggested using a continuous function that depends on a volume exclusion function that describes the distribution of solvent particles around the solute. A nonzero ionic strength characterizes a different situation where the surrounding medium is not well characterized by a single dielectric constant. Mennucci et al.[148] have described an extension of IEF-PCM to account for such salt effects; Srinivasan et al.[115] have done the same for pairwise GB.

Several papers have recently appeared addressing a difficulty with QM methods that use apparent surface charges on the solute cavity surface (original COSMO, PCM, IPCM, and SCIPCM, but not multipole, distributed multipole (including the GAMESS/COSMO implementation) or GB methods). Since the solute wave function has tails that extend to infinity, some density is necessarily truncated by the construction of the cavity. This can lead to the (shockingly) incorrect result that the magnitude of the solvation free energy for an anion can go down as the cavity size is reduced, because the charge inside the cavity tends to zero instead of −1. This kind of effect can be corrected for either by including additional volume polarization terms,[162,315−317] by first fitting the continuous density to a multipolar expansion and then determining the surface charges,[210,318] or by charge renormalization.[3,143,145] DMOL/COSMO does not use any of these schemes but rather a double cavity to correct for outlying charge error.[182] It is worth mentioning that COSMO itself is intrinsically less sensitive to outlying charge effects than dielectric approaches such as PCM. Newton also corrected for the short-range interaction of the penetration tail with the medium and coupled this correction to the variational principle.[319] Despite these corrections and advances, outlying charge remains troublesome and is one of the reasons that we prefer the distributed-monopole approach of the generalized Born approximation to the PCM approach.

Karlstrom and Halle[320] have recently presented a method to calculate the “solvation of a polarizability” by low-frequency (classical) fluctuation modes of the solvent. This is the contribution to the dispersion interaction from the classical degrees of freedom of the fluid. Fortunelli has presented an alternative statistical mechanical perspective that distinguishes the response of acoustic/orientational solvent excited states from the response due to vibrational and electronic excitation.[321] He also considered the new effects that arise when the solute has a low-lying excited electronic state.[321,322]

Another area of recent methodological interest is the treatment of nonequilibrium solvation effects. This is primarily of interest for three fields: electronic spectroscopy, kinetics (including electron transfers and the sudden creation of charged species), and frequency-dependent molecular properties (including those important for nonlinear spectroscopy). The first two are in sections 7 and 8, respectively, and the third is beyond the scope of this review.

4.3. Electron Correlation

This section is concerned with intramolecular electron correlation in the solute. Intermolecular electron correlation between solute and solvent, which leads to solute−solvent dispersion forces, and the change in intramolecular and intermolecular solvent electron correlation upon insertion of the solute, which may be considered part of the cavity and solvent structure terms, are included in the terms discussed in section 4.5.

The reaction field is generated from a solute charge distribution. The more accurate the charge distribution, the more accurate the reaction field, which implies that charge distributions from wave functions computed with some accounting for electron correlation will provide higher accuracy. While this seems almost too obvious to merit discussion, issues do arise with respect to the computational approach adopted for SCRF procedures including electron correlation.

For example, there are two different alternatives with respect to including solvation effects at the level of second-order perturbation theory (MP2). One can carry out the SCRF procedure at the Hartree−Fock (HF) level and then perform a normal calculation of the MP2 energy using the solvated HF orbitals, i.e., the correlation energy is computed in the solvent reaction field obtained at the HF level.[5,91,92,323−326] Alternatively, one can further iterate so that the reaction field itself reflects the density computed from the first-order wave function.[5,91,92,197,323−327] These have been referred to in the literature as PTE and PTD[324,325] (PTD is sometimes called PTED[326] or PTDE[4]), respectively, reflecting their application to either the energy (E) or the density (D). Ángyan has shown that the approach which is most formally consistent in the sense of including only terms through second order in the perturbation theory is PTE.[91,92] We note, though, that formal consistency, although esthetically pleasing and useful for deriving analytical derivatives, does not necessarily provide the best route to practical accuracy. Olivares del Valle et al.[325] and Fortunelli[326] have compared results from the PTE and PTD approaches for MP2 calculations and other perturbative ansatzes for 20 small molecules, focusing primarily on changes in the molecular charge distributions. No clear preference arises for either choice; although the PTD approach includes certain terms to higher order, in practice the enhanced polarizability of the solute at the PTD level is offset by the reduced polarity of the solute (and thus of the self-consistent reaction field) so that there is a near cancellation in terms of net effect. Chipot et al. have also studied this level of theory with respect to its ability to predict the solution structure of the ammonia-HCl complex[328] and to describe proton transfer in the mono- and dihydrated complexes of HF and HCl.[329] The work of Fortunelli[326] extends this analysis of PTE vs PTD to higher orders of perturbation theory, as well as to coupled cluster and quadratic configuration interaction approaches, and examines the convergence properties of each method.

A case where the inclusion of correlation energy is much more clear cut is density functional theory (DFT). Since correlation is part of the one-electron Fock−Kohn−Sham operator and since the reaction field is added directly to this operator in a manner analogous to HF theory, there are no ambiguities associated with consistently accounting for the reaction field in both HF and post-HF operators. Although this point has not been touted as a particular advantage, many methods have been developed for DFT SCRF calculations,[75,138−140,146,155,172,180,204,307,318,330−336] and these have become quite routine.

Other correlated levels of theory for which SCRF implementations have been described include configuration interaction (CI) theory[337−339] and multiconfiguration self-consistent field (MCSCF) theory,[45,195,203,337,340] including the special case of generalized valence bond (GVB) theory,[139] and also coupled cluster theory with single and double excitations (CCSD).[205]

4.4. Direct Reaction Field

A fundamental difficulty with partitioning systems into solute and solvent is that, unlike the Born−

Oppenheimer separation of electronic and nuclear motions, there is no clear separation of time scales between solute and solvent. For example, the appropriate time scales for orbital relaxation in the solute and noninertial electric polarization of the solvent are comparable. So far, we have emphasized the self-consistent reaction field (SCRF) (or more generally, self-consistent mean field) approach in which one defines a solvent electric polarization by averaging over the solvent distribution and the solvent equilibrates to the average solute electronic distribution. Thus, solute–solvent dispersion interactions, which require consideration of the instantaneous electron positions (i.e., consideration of solute charge fluctuations), are not included in the electrostatics. Since the solvent sees the average electronic distribution, this approach corresponds to the limit where motion of solute electrons is very fast. However, it is also possible to approach the situation from another limit, where the solvent interacts with the instantaneous distributions of the solute electrons. This approach, although computationally and conceptually less straightforward, has also received some attention.[341−361] It is variously called the direct reaction field (DRF) method, the Born–Oppenheimer (BO) method, or the polarization-correlated (PC) approach; the BO label is easily susceptible to misinterpretation, and the PC label has not become popular, so we will use the DRF label for this approach.

Originally[341,342] the DRF model was applied to the entire solvent response (inertial and inertialess). More recently a practical configuration interaction scheme for partitioning the solute electronic manifold into a DRF active space (where the model meaningfully applies) and a core was reported and applied.[353] A critical issue to be identified before carrying out applications is the role of the various time scales.[319,362,363] The correct equilibrium picture must lie somewhere between the SCRF and DRF extremes and not at either limit, and Ángyán and Jansen[363] presented an intermediate Hamiltonian interpolating between the direct and average reaction field limiting cases, an idea that has subsequently been used fruitfully by others.

In one interesting application to an S_N2 reaction, Basilevsky et al.[352] found insignificant differences between SCRF and DRF methods, whereas in a later study of S_N2 reactions, Mathis et al.[364] found very large differences. Furthermore, Kim and Hynes[349] pointed out that the DRF formalism may be required for calculating nonequilibrium solvation effects on slow (weak coupling) electron-transfer reactions. Bianco and Hynes[355] showed that as I_2^- is dissociated in acetonitrile, the DRF limit becomes more and more appropriate; furthermore, the extra electron begins to localize on one center when the I–I distance is stretched to 3.4 Å, as compared to an equilibrium distance of 3.2 Å, and localization is almost 100% by 5 Å. Interestingly, although the SCRF approach has been implicit in most of the quantum chemistry literature concerned with equilibrium solvation energies and solute properties, the DRF approach has been implicit in much of the electron-transfer literature, where nonequilibrium effects have received the greatest amount of study. The unification of these approaches[348−351,354,355,365] deserves further study, but in the rest of this chapter we will discuss only the SCRF approach.

4.5. Individual First-Solvation-Shell Effects

The first solvation shell has been defined in different ways by different workers. It could be defined, for example, as an integer number of solvent molecules on the basis of a predetermined distance or energy cutoff or it could be defined in terms of the atom–atom solute–solvent distribution functions. If the latter approach is based on the radial distribution function, it may be inadequate for solutes with irregular shape.[54] In the atomic surface tension approach,[6,7] the first-solvation-shell effects are identified as components of the free energy that correlate statistically with the solvent-accessible surface area or the exposed van der Waals area (which is the special case of solvent-accessible surface area for a solvent of zero effective radius). The definition in terms of exposed van der Waals area is similar to, but not identical to, defining the first solvation shell as those solvent molecules that make hard-sphere contact with the solute. More generally, the atomic surface tension approach corresponds to a noninteger average number of solvent molecules in the first solvation shell. The average may be either an ensemble average or a time average. For weak solute–solvent coupling, the average may be over a continuous distribution of solvent configurations of nearly equal energy; for stronger solute–solvent coupling, there may be fluctuations between configurations with different solvation numbers. For example, the Ca^{2+} ion appears to have two well-defined solvation structures with 8 or 9 water molecules and an average solvation number of 8.6.[366]

Given the statistical definition of the first solvation shell and the mixing of various effects due to solute–solvent antisymmetrization,[10,345] it is not possible to rigorously separate out the different physical effects contributing to the free energy, but one can ask whether it is still useful to do so for modeling purposes. One of the first attempts to discuss the individual solvation components in a systematic way was the work of Claverie.[367−370] He used an MM description of the solute with a cavity of interlocking spheres and discussed the electrostatic, dispersion, and repulsion contributions. Our own preference is to identify the latter two effects with the first solvation shell, which also contributes the dominant parts of the cavitation and solvent–structure terms. We do not usually single out solute–solvent repulsion as a named contributor but rather lump it with the cavitation and solvent–structure terms. Cavitation itself is an ambiguous phrase since creation of a physical cavity changes the solvent–solvent dispersion energy and the local solvent structure. When we say cavity, dispersion, and solvent structure, the cavity part includes changes in solvent–solvent dispersion due to missing solvent in the cavity but not necessarily the dominant contributions due to changes in local solvent structure, and dispersion refers to solute−solvent dispersion interactions, which is also the sense in which others use the term.

A difficulty with actually calculating the dispersion (D) and cavitation (C) terms separately is that they have opposite signs and partially cancel, a situation that requires high accuracy in the partly canceling terms. For example, Mineva et al.[335] made continuum calculations of G_C and G_D for 16 solutes and G_D averaged −89% of G_C. Dillet et al.[207] made continuum calculations of G_C and G_D for acetamide in water and found $G_C = +9.2$ kcal, $G_D = -4.2$ kcal, and $G_C + G_D = +5.0$ kcal. No estimate was made of a structural contribution, but one expects a significant hydrogen-bonding contribution from the amide functional group and a hydrophobic contribution from the methyl. Acetamide was recalculated by Mineva et al.,[335] who obtained $G_C = +12.1$ kcal, $G_D = -10.3$ kcal, and $G_C + G_D = +1.8$ kcal, to which they add a repulsive term of +1.6 kcal, for a total first-solvation-shell contribution of +3.4 kcal. The SM5.42R/BPW91/DZVP model[75] has G_{CDS} −3.3 kcal, which is quite different from either of the above treatments. The total free energy of solvation from these three calculations is −3.2,[207] −9.1,[335] and −10.5[75] kcal/mol, respectively, as compared to an experimental value of −9.7 kcal. Thus, the second and third calculations both agree well with experiment, despite quite different partitionings of electrostatic and first-solvation-shell contributions. (For nine neutral organic molecules plus water and ammonia, Mineva et al.[335] obtained a mean unsigned error of 0.65 kcal/mol, whereas SM5.42R/BPW91/DZVP yields a mean unsigned error of 0.5 kcal/mol for the same set of eleven molecules.) It is discouraging that the two G_D calculations[207,335] differ by a factor of 2.5.

Matyushov and Schmid[371] calculated the dispersion contribution to the free energy of solvation of nitromethane in eleven solvents at 298 K and found values ranging from −7.4 kcal/mol for DMSO to −9.9 kcal/mol for THF. For nine of the solvents, the cavity formation energy canceled 68−89% of the dispersion energy, and for the other two (DMF and DMSO) it exceeded the dispersion energy by 18% and 35%. Their model allowed them to estimate enthalpic and entropic contributions separately, and they found that the small size and low expansibility of water gives it a uniquely negative entropy of cavity formation.

Cavitation and dispersion are the most important first-solvation-shell effects for non-hydrogen-bonding solvents, but in the more general case, we must consider specific solute effects on the solvent structure; these effects can be either favorable or unfavorable. An example of the former would be hydrogen bonding interactions that orient a proton-donating solvent around a carbonyl group of a solute molecule. An example of the latter would be the loss of orientational freedom of water molecules around a nonpolar solute, resulting in a hydrophobic effect. The three dominant first-solvation-shell effects, cavity formation (C), dispersion interactions (D), and solvent−structure perturbation (S), are not completely separable and are sometimes grouped together as the cavity-dispersion−solvent-structure (CDS) component of the free energy of solvation. In the SM*x* models, these effects are treated by atomic surface tensions.

Using a method that treats the solvent as a polarizable continuum, Amovilli[149] calculated the dispersion energy contributions for CH_4 and NH_3 in water to be −4.6 and −4.3 kcal/mol, respectively, including a 10% correction for an expected systematic error in the solute polarizability. The dispersion free energy increased approximately linearly with surface area, in agreement with the surface tension approach to CDS terms. Amovilli and Mennucci[151] estimated dispersion, cavity, and repulsion, as well as electrostatic, contributions for 20 solutes in water. Dispersion and cavity contributions tended to be within 10−20% of each other and opposite in sign, with repulsion about a factor of 3−4 smaller in magnitude. The large amount of cancellation is not encouraging for the prospects of estimating the individual terms separately and adding the contributions. Amovilli and Mennucci[151] also estimated the individual contributions for eight solutes in *n*-hexane and 10 in 1-octanol. In these solvents, in 14 of 18 cases the negative dispersion term has a larger magnitude than the sum of the positive cavity and repulsion terms. Cancellation tends to be less complete in these systems with dispersion being more dominant.

One additional issue that must be dealt with carefully in general, but especially for mixed cluster/continuum calculations, involves the different kinds of energies involved in a given liquid−solution phase computation. For instance, the electronic energy associated with the gas-phase HF wave function has the status of a potential energy for nuclear motion. To calculate a solute's free energy, zero-point vibrational energies and energetic contributions from thermal populations of higher energy electronic, vibrational, and rotational states must be included. For a cluster, a proper accounting for free energy further requires sampling over all relevant cluster configurations, which contribute in a Boltzmann-weighted sense to the overall cluster free energy. Finally, the Poisson equation and various approximations provide electrostatic free energies of solvation, but different schemes for computing nonelectrostatic effects are sometimes less obviously defined.

4.6. Universal Solvation Models

An important development in the past few years has been the parametrization of atomic surface tensions not only in terms of properties of the atoms of the solute but also in terms of solvent properties.[60,65,68−77] By using widely available solvent descriptors, this has allowed the development of several SM*x* solvation models that are applicable not only to water but to any organic solvent. These models are specifically SM5.4,[65,68,70,71,73,74] SM5.2R,[69,73,74] SM5.0R,[72−74] and SM5.42R.[74−77]

The COSMO−RS extension of COSMO is designed to predict various thermodynamic quantities, including the free energy of solvation, for uncharged solutes in any organic solvent as well as solvent mixtures.[181,188]

Finally, Torrens et al.[372] have proposed a parametrized model for organic solvent−water partition coefficients based on associating a free energy with the solvation sphere[373−375] of each atom in the solute.

4.7. Explicit Solvent in the First Solvation Shell

In principle, one can model first-solvation-shell effects by including the first shell of solvent with the solute and then surrounding this "supermolecule" with continuum solvent. However, the addition of explicit waters, with or without further solvent treated as a continuum, has its own problems. First of all, it is not clear how to determine the number and orientation of nonbulk water molecules. For a complete first solvation shell of even a medium-sized solute, there must be a very large number of orientations that are local minima. The only satisfactory way to average over these orientations is to perform a full Monte Carlo or molecular dynamics simulation involving explicit waters in at least the second solvation shell as well. In such simulations one typically treats the solute as rigid and nonpolarizable, i.e., one includes solvent explicitly, but not quantum mechanically nor with all its degrees of freedom. Such treatments are usually called QM/MM since the solute is modeled by QM and the solvent by MM.[376] In QM/MM methods one can introduce solute polarizability but only at a computational cost much higher than a full continuum treatment.[1,2] Furthermore, such methods typically treat the solvent molecules as nonpolarizable as well, and this is unrealistic. At the present time it is unclear whether these deficiencies can be overcome realistically and efficiently enough for simulations with full explicit solvent to be reliable, and the supermolecule approach with only a few waters is even more questionable. Nevertheless, each of these methods may be the preferred compromise of efficiency and expected reliability for particular problems under particular circumstances.

When the explicit solvent molecules are treated quantum mechanically at the same level as the solute, the necessity to average over the many possible locations and conformations of the explicit solvent molecules makes the approach unwieldy with more than about two explicit solvent molecules. Nevertheless, one can often learn a lot from continuum calculations with one or two explicit solvent molecules. One can also learn a lot about the first solvation shell from calculations on microsolvated clusters without a surrounding continuum. We next summarize several results from such calculations that are particularly informative.

A classic calculation on hydrogen-bonded solvent molecules is the paper of Pullman et al. on adenine−thymine base pairs; it is predicted that adenine has four hydrogen-bonded water molecules in the first hydration shell, thymine has three, and the base pair has six.[377] Since hydrogen bonding is partly electrostatic, loss of solute−solvent hydrogen bonding on base-pair formation should show up partially in dielectric descreening as one base displaces the dielectric medium from the vicinity of the other. But since hydrogen bonding is not completely predictable from bulk electrostatics, one should see an additional effect that can be modeled either by loss of solvent-accessible surface area at a hydrogen bonding site or by explicit first-solvation-shell water. Claverie et al.[378] offered a similarly detailed early analysis of hydrogen bonding in the solvation of ammonia and ammonium ion.

Zeng et al.[379] have proposed a treatment in which the solute is surrounded by approximately 70 water molecules, and this supersystem is then surrounded by a dielectric continuum. Then, by reducing the radius at which the continuum boundary is enforced, they converted explicit water molecules to continuum and attempted to separate specific hydrogen bonding effects and gain insight into microscopic origins of environmental effects. The electrostatic component of hydrogen bonding was also elucidated in mixed discrete/continuum calculations by Sanchez Marcos et al.[380]

Tuñón et al.[381] attributed the major differences between discrete and discrete−continuum calculations on HO^- in water to the noninclusion of charge transfer beyond the cavity.

Recent papers by Alemán and Galembeck[382,383] investigated the combination of explicit solvent with three different SCRF treatments, namely, PCM, PCM with surface tensions, and SM2. They concluded that these approaches, which they (and others) call "combined discrete/SCRF models" (Rick and Berne[31] call them "semicontinuum methods"), constitute a very reasonable strategy. On the basis of comparison to experimental results, similar conclusions were reached by Bräuer et al.,[384] who combined DFT cluster calculations with SM*x* continuum solvation to study ground-state tautomerism and excited-state proton transfer processes in a functionalized imidazole. One difficulty with this strategy however, has, been recognized for a long time;[380] in particular, the attempt to directly introduce a hydrogen-bonded solvent molecule will not yield more accurate free energies if the quantum mechanical level used to treat the supermolecule (consisting of solute and explicit solvent) is not high enough. Since continuum models (especially those with semiempirical surface tensions) are often accurate to a fraction of a kcal/mol, even for hydrogen bonding solvents, at least that accuracy is required for an explicit quantum mechanical treatment of hydrogen bonding, if it is to improve the continuum descriptions.

Martínez and co-workers[385] calculated the energies of $Ag(H_2O)^{n+}$ clusters in the gas phase and in aqueous solution for $n = 1-12$; in the case of $n = 12$, two hydration shells (an inner of 4 waters and an outer of 8) were considered, and in this fashion they observed opposite effects on the Ag−O distances for specific and long-range (continuum) solvent interactions. Hecht et al.[386] showed that frequency and intensity shifts of solvating water molecules are correlated with the hydrophobicity of amino acid side chains in water; this was interpreted as a measure of hydrogen bonding in the first solvation shell. Fukunaga and Morokuma[387] compared the absorption spectrum of formaldehyde in $HCHO(H_2O)_n$ clusters and in water solution. Though the shift in transition energy is greater in bulk water, the bandwidth is nearly the same in the cluster and in bulk solution.

Gai et al.[388] performed quantum mechanical and classical mechanical simulations of the nuclear motions in $Cl^-(H_2O)_n$ clusters with $n = 1-6$ in order to determine the effect of quantum delocalization of the nuclei on binding enthalpies (ΔH) and radial distribution functions. At 300 K, the quantum effect makes ΔH less negative by about 0.8 kcal/mol per water molecule, due in part to zero point effects. The effect would be smaller for bulk liquids because solute–water hydrogen bonds replace water–water ones.

A recent study[389] of $N(CH_3)_4^+$ in water showed that water molecules in the first solvation shell are primarily oriented with the dipole moments tangent to a sphere centered at the nitrogen atom. This shows that methyl groups remain hydrophobic even in the ion, confirming an assumption inherent in parametrizing atomic surface tensions against experimental data for simple neutral compounds. Furthermore, the influence of the ion on the orientation of the water molecules was found to be almost negligible beyond the first hydration shell.

First solvation shell effects are especially large for doubly charged metal ions such as Ca^{2+} and Zn^{2+}. In fact, in these cases the second solvation shell is also very important both energetically and structurally.[390] Nevertheless, one can obtain quite accurate free energies of solvation by treating only the first shell explicitly.[391,392] The structure of doubly charged and multiply charged anions in water has also been studied recently, but including only bulk electrostatic effects.[393]

Gordon and co-workers have explored representing the solvent molecules in the first solvent shell with effective fragment potentials.[394–396] This approach permits a compromise between efficiency in sampling the relevant cluster phase space and accuracy in handling quantum effects such as charge transfer, dispersion, etc. Pearl and Zerner,[397] based on QM/MM studies of microsolvated amino ruthenium complexes, have emphasized the possible importance of charge transfer in solvent effects on electronic spectroscopy. Krauss and Webb[398] showed that all-electron and effective-fragment-potential calculations agree well for the electronic excitation spectrum of formamide.

Most studies of first-solvation-shell phenomena have focused upon water. However, first-solvation-shell structures have received some study in nonaqueous media, e.g., Soetens et al.[399] characterized the local structure around Li^+ and BF_4^- ions in ethylene carbonate and dimethyl carbonate.

Floris et al.[392,400,401] have calculated ion–water pair potentials in the gas phase and in the presence of continuum aqueous solvent. The former are strictly two-body potentials, whereas the latter are effective potentials that include multibody effects in an average way. Molecular dynamics simulations of ferrous and ferric ions in water yield better agreement with experimental hydration numbers when the effective potentials are employed.[400]

Comparison of explicit solvent models to continuum theory can be very informative if well designed. A particularly lucid analysis based on such a comparison was provided by Rick and Berne,[31] who studied the quantitative importance of electrostriction, in which the solvent molecules are attracted more strongly to the solute molecule as its polarity is increased, thereby decreasing the effective cavity radius as the magnitudes of partial atomic charges increase (this makes the free energy of solvation more negative). However, the Rick–Berne treatment does not take account of the fact that even in the gas phase the radius depends on charge, e.g., atomic cations are much smaller than atomic anions of the same nuclear charge.

Models with explicit solvent molecules can also provide insight into many fundamental issues where continuum models do not provide unique pictures. For example, the coupled dynamics of solute and solvent[366,402] could be used to study the SCRF and DRF limits. The surface-constrained soft sphere dipoles (SCSSD) model avoids the continuum approximation but at decreased cost compared to full explicit models, since it drastically simplifies the solvent molecules.[403] The surface-constrained all-atom solvent (SCAAS) model[404–406] demonstrated that the explicit shell should be surrounded by an explicit surface region (between the explicit shell and the bulk regions) in order to generate its proper polarization.

In an interesting approach for future study, Nina et al.[407] have used explicit-water simulations in a novel bootstrap way as a standard against which to parametrize atomic radii on systems (amino acids) for which experimental data are unavailable (see also ref 312). An alternative approach[408] for determining amino acid radii using a solvent interaction potential and quantum mechanically derived charges has been described by Smith,[409] who used these parameters to calculate the relative binding energies of six benzamidine inhibitors with trypsin.

Note that this review does not include the Langevin dipole model[11,220,406,410] (LD), which falls on the borderline of implicit and explicit solvation models. The hybrid character of this model is further strengthened in its latest version[411] that uses atomic charges fitted to HF/6-31G|PCM calculations of the electrostatic potential of the solute.

We also do not discuss integral equation methods such as the hypernetted chain equation, the Ornstein–Zernicke equation, or the reference interaction site model (RISM), but we here provide a few key references and brief comments. The RISM model[412–415] takes solvent electrostatic and van der Waals parameters for input and yields solute–solvent interactions in terms of site–site distribution functions. While this is a microscopic model and the parameters are typically taken from solvent models developed for explicit simulations, the RISM representation is not atomistic, making this method also something of an implicit/explicit hybrid. Promising developments in this area include the inclusion of polarizable media in RISM,[416,417] the coupling of the RISM equations to a quantum mechanical description of the solute,[418–421] including analytic derivatives for solute geometry optimization,[419] and the development of integral-equation methods to account for 3-dimensional anisotropy in solvent distributions about realistically shaped solutes.[416,417,422−424]

4.8. Effect of Solute Volume

We next consider a subject on which considerable ink has been expended in recent years—are there size-dependent or volume-dependent contributions to the Gibbs free energy of solvation that invalidate the usual relationships between partition coefficients or other equilibrium constants and free energies? Although several workers[425−428] challenged the initial claims[429,430] that the standard treatment[431] is incorrect, the claims continued to attract new adherents, as summarized by Ben-Naim and Mazo.[432] Nevertheless, in agreement with Ben-Naim and Mazo,[432] we see no reason to modify the standard theory, and we repeat our original recommendation[428] that experimental data do not need to be "corrected" for size-dependent entropy terms and that such size-dependent terms do not need to be added to the conventional free energies to predict experimental data. A related question is whether there is a nonnegligible entropic term in the free energy of solvation that is proportional to the solute molecule's volume. This question appears to have been answered most clearly by Shimizu et al.,[433] who conclude that there is not such a term. Finally, another question one may consider is whether it is worthwhile, for specific circumstances, to model the combinatorial entropic part of the free energy of solvation with terms depending explicitly on the size or volume of the solute. Although it was shown[428] that such modeling does not appear useful for the case for which it was originally proposed,[429] some progress has been made in delineating the conditions under which such models might or might not be useful[434−436] and how some of the volume-proportional terms that have been proposed have erroneously arisen.[433]

5. Dipole Moments and Charge and Spin Distributions

We now focus upon an area where there is considerable need for experimental advances to be made in order to further refine the theory. In quantum mechanical implementations of continuum solvent models, the nature of the model is such that the Fock operator is modified by addition of another operator, namely, the reaction field, as described above. The corresponding Schrödinger equation is then nonlinear because the reaction field depends on the solute charge distribution, and thus, the SCRF density matrix must render stationary the expectation value of the nonlinear free energy functional.[7,90,91,96,189,211,217,403,437] That being the case, unless the reaction field is very, very small, it is clear that the density matrix minimizing the energy of the solute in solution will differ from that which is stationary for the gas-phase Fock operator. Since the wave function generating the gas-phase density matrix is the one that minimizes the expectation value of the gas-phase Hamiltonian, it is equally clear that this "distortion" of the density matrix in solution must accrue an energetic penalty associated with the gas-phase portion of the solution Hamiltonian. Why then does the wave function distort? Because the solvent polarization field set up by the solute charge distribution acts like an externally applied field—it induces a polarization of the solute. What makes the SCRF procedure different from an external perturbation, though, is that the distortion itself affects the external field (which is generated from the solute charge distribution) and thus must be accounted for in a self-consistent manner. We have recapitulated these fundamental details because the degree to which the solute charge distribution distorts (or "relaxes", depending on which Hamiltonian, the gas-phase or solution, one chooses to focus upon) is a physical observable, and in principle, this observable can provide a critical test of the details of SCRF approaches.

As noted previously, one cannot separate the free energy of solvation (or indeed any free energy) into electrostatic and nonelectrostatic components in any rigorous way. (In a certain sense,[438,439] it is all electrostatic, but here we use the usual language by which "electrostatic" refers to the part associated with the bulk dielectric properties of the solvent.) Furthermore, we have emphasized that, while the electrostatic component of the solvation free energy from various continuum solvation models may be quite sensitive to cavity dimensions and/or the theoretical levels used to determine the wave function, it is possible to construct equally successful solvation models (as judged by their accuracy in prediction of gas-solvent transfer free energies) for quite different choices of protocol in the electrostatics calculations and quite different partitioning of effects between the electrostatic part and the nonelectrostatic part, because potential flaws in one part of the calculation can be counterbalanced in a semiempirical fashion in a different part of the calculation. However, solute properties such as the charge distribution or its dipole moment are sensitive to the partitioning of effects because the solute wave function is self-consistently relaxed in the SCRF procedure, whereas cavity, dispersion, and solvent−structure effects are usually treated non-self-consistently. Thus, to assess the physicality of a given model, it would be valuable to be able to test the degree to which the solvated charge distribution agrees with reality.

An example of a case where a solute dipole moment changes significantly on going from the gas phase to a condensed phase is water, where estimates of 2.6 D,[440] 2.45 D,[441] and 2.23−2.73 D[442] are available for water in ice (as compared to the gas-phase value of 1.85 D[443]). One might assume that a similar or larger increase would be found in liquid water, where one should carry out a time average or ensemble average over a distribution of dipole moments for individual water molecule snapshots. The width of the distribution in liquid water has been estimated[444] to be about 0.6 D (FWHM). The value of 2.6 D represents a significant induced moment of 41% in solution, and a number of different theoretical models support this value,[445−447] although the final word is not in. However, water is a small and rather special molecule (for example, Wei and Salahub[448] have noted that the

Table 2. CM2 Dipole Moments in the Gas Phase and Aqueous Solution for Selected Solutes

μ, D	aniline	benzaldehyde	1-iodopropane	methanol	phenol	pyridine	toluene
gas[a]	1.46 (1.53)[b]	2.82	2.30 (2.04)	1.63 (1.70)	1.16 (1.45)	1.85 (2.15)	0.49 (0.30)
water[c]	1.58	3.62	2.83	1.80	1.52	2.39	0.62

[a] HF/MIDI! [b] Where available, experimental moments[443,453,454] are provided in parentheses below the computed moments. [c] SM5.42R/HF/MIDI!

accurate computation of the solvent-induced moment for such a small molecule requires a particularly flexible basis set), so one hesitates to use this single data point to evaluate the physicality of different choices of electrostatic parameters. Unfortunately, other useful data do not appear to be unambiguously available.

The difficulty lies in the nature of the measurement—to ascertain the dipole moment of a solute molecule in solution it is critical that the molecules of the solvent have no dipole moment of their own. Thus, the most typically used solvents for liquid-solution-phase dipole moments are *n*-hexane, benzene, carbon tetrachloride, and 1,4-dioxane.[449] The range of dielectric constants spanned by these four solvents is $1.88 < \epsilon < 2.27$,[449] i.e., they are quite nonpolar. As a result, one does not expect to see much change in solute dipole moment on solvation. Indeed, Reichardt[449] has compiled dipole moments for 100 common organic solvents (measured as solutes in one of the four solvents listed above), and changes in dipole moment as compared to the gas phase are always very small. Sometimes the solvated dipole moment is smaller than the reported gas-phase dipole moment, suggesting that the error in the measurement may be nontrivial. Furthermore, the interpretation of liquid-phase dipole moment measurements is not unambiguous because one requires assailable theoretical assumptions to partition the observable polarization into a part associated with the solute (which is what we seek) and a part associated with the solvent (which is unavoidable).[450] As a result, the search for a molecule, other than water, whose liquid-phase dipole moment differs by a known amount from its gas-phase dipole moment (in either neat liquid or solution) is much like the search of Diogenes.

We offer further detail for two examples: the gas-phase dipole moments of ethanol and aniline have been measured as 1.69 and 1.53 D, respectively, while Reichardt[449] reports their nonpolar solution moments to be 1.74 and 1.50 D, respectively. At the HF/MIDI! level, by comparison, the CM2 gas-phase dipole moments are computed to be 1.51 and 1.46 D,[451] while in nonpolar solution (carbon tetrachloride as solvent for ethanol, benzene for aniline) the SM5.42R/HF/MIDI![76] CM2 dipole moments are 1.61 and 1.51 D. (The “!” in the MIDI! basis set denotes polarization functions on all atoms except H and C.) The quantitative agreement is gratifying, but the small changes involved (e.g., for ethanol, 0.05 D experimentally and 0.10 D computed) appear to be within the uncertainty of the value obtained for the solution measurement.

The dearth of liquid–solution-phase dipole moments in solvents having a high dielectric constant is really quite vexing, because dipole moment changes are naturally expected to be larger in such solvents. This is not based solely on the measurement for water. Fortunelli has computed significant changes in dipole moments for 20 neutral molecules in water at the HF, DFT, MP2, and QCISD levels.[326] Table 2 compiles predicted gas-phase and aqueous dipole moments as calculated at the HF/MIDI! and SM5.42R/HF/MIDI! levels, respectively, and one sees that changes in the dipole moment range from 8% (for aniline) to 31% (for phenol), with the upper end of the scale approaching the water-in-water change of 41%. Analogously, calculations[308] of the dipole moments of the five common nucleic acid bases at the AM1-SM2 level predict aqueous solvation to increase solute dipole moments at the gas-phase geometries by 41–49% (Gao[452] has made similar predictions using a solute-QM/solvent-MM aqueous solvation model with an AM1 wave function for these same solutes). This suggests that large changes in dipole moments are not restricted to small solutes such as water but are also common for large polarizable molecules such as substituted heterocycles. Furthermore, we note that the dipole moments of the nucleic acid bases were predicted to increase by up to 10% more upon relaxation of their geometries at the AM1-SM2 level.[308] Geometric relaxation is not an effect considered in Table 2.

It may be that theory can assist in identifying systems where large changes in dipole moment on solvation may make experimental studies more tractable. An interesting example is methylene peroxide (CH_2OO). Both Parrondo et al.[455] and Bernhardsson et al.,[45] using MCSCF continuum solvent models, have shown that solvation strongly stabilizes the zwitterionic configuration of this system compared to a diradical configuration having roughly equal weight in the gas phase—this causes the dipole moment to increase from 3.6 to 7.0 D. Other instances where solvation may strongly influence a dipole moment include cases where some solute geometrical coordinate couples strongly both with the solvent and the solute charge distribution. For example, Ruiz-López et al.[307] showed that the dipole of the $NH_3 \cdots HBr$ complex increases from 6.3 to 13.6 D when solvation increases the interfragment distance in the complex (cf. section 4.2). Merocyanine dyes and other push–pull systems also are known to undergo large changes in dipole moment on solvation, and some continuum solvation modeling has been done on these systems.[295,456–458] Many other especially sensitive systems could no doubt be found.

In summary, we consider comparison of distortion/relaxation behavior for different theoretical models to be an area that has been only cursorily explored, and a more in-depth look might reveal key insights into how this phenomenon varies with different choices of cavity definition and handling of the (quantum) electrostatics. The development of experimental techniques for measuring dipole moments in high-dielectric media would make such a comparison particularly valuable. Until such time, comparisons between different theoretical methods may prove useful in order to better understand how different approximations affect charge distribution. Gao et al.[459] determined that induced dipole moments from a PCM-type continuum model agree well with those from explicit solvent simulations involving a classical model for water and a quantum mechanical solute. To further quantify the degree of charge redistribution taking place on solvation, Mestres et al.[460] have proposed a scheme which they call "quantum molecular similarity" and applied their analysis to a series of small anionic, neutral, and cationic species. Their conclusion is that different regions within a molecule can show markedly different propensities to polarize (we also have observed this, e.g., in the nucleic acid bases where different nitrogen atoms polarize to a different extent[310]) and that further study is warranted. Germane to this point, MM models for condensed-phase biomolecules, that almost invariably use fixed atomic partial charges that attempt to account for polarization in an average way, have gone through several generations of empirical refinement over the years. In a recent comparison[461] we were encouraged to find that solution-phase partial charges of nucleic acid bases and dipeptides by SMx models agree quite well with those obtained from the most modern models used widely in biological simulations.

Interestingly, an alternative tool is available for analyzing solvent-induced changes in electronic structure when the solute is a radical. In such a case, while changes in the overall density are not any simpler to measure, electron spin resonance (ESR) techniques can provide useful information about changes in the spin density from analysis of nuclear hyperfine splittings. For example, Langgard and Spanget-Larsen[462] have predicted hyperfine couplings in benzosemiquinone radical anions to be quite sensitive to solvation. Barone and coworkers,[463−465] Takase et al.,[466,467] and Chipman and co-workers[161,162,315−317] have been particularly active in developing computational models to explore solvent effects on doublet ESR spectra, and it may be that closed-shell calculations will benefit from lessons learned in the open-shell systems. Barrows et al.[468] showed that solvation can have very large effects on spin localization in polynitroaromatic radical anions.

In principle, one might consider nuclear magnetic resonance (NMR) observables (e.g., either chemical shift or spin−spin coupling constants) to provide an analogous tool for understanding charge relaxation in closed-shell systems. Mikkelsen and co-workers[469] have recently described the theory for a MCSCF gauge invariant atomic orbital (GIAO) method for computing magnetic susceptibility and nuclear magnetic shielding tensors in solution using a multipolar expansion for the reaction field. Åstrand et al.[470] have extended the theory to permit computation of spin−spin coupling constants. Cammi and co-workers[471,472] have described very similar efforts at the HF and DFT levels within the context of the PCM solvation model using both the GIAO approach and a continuous set gauge transformation (CSGT) methodology. However, the coupling of these nuclear magnetic quantities to the electronic charge distribution is considerably more complex than is the case for hyperfine couplings, and moreover, the computational methods are considerably less straightforward for computing NMR observables compared to ESR,[473,474] so analysis of polarization based on NMR probably remains at best a long-range goal.

6. Solvent Effects on Equilibria

The broad applicability of implicit solvation models together with their increasing availability in user-friendly software packages has led to an explosion of applications, especially for predicting solvent effects on diverse equilibria. Table 3 categorizes a large number of such applications, primarily from 1996 on, indicating whether the goal was prediction of solvation effects on conformational, tautomeric, acid/base, or other equilibria or on partitioning of a solute between two phases. Several of the applications were chosen because they have been the subject of multiple investigations, and thus, they are particularly useful for comparing the relative merits of different models. In addition to the different solvent models employed (vide supra for acronyms), the source of the charge distribution, whether quantum or classical, is also listed: MM is molecular mechanics, MNDO,[475] MNDO/d,[476−478] AM1,[479] and PM3[480] are widely used semiempirical Hamiltonians, HF is ab initio Hartree−Fock theory,[481] B3LYP[482] and BH&HLYP[483] are hybrids of HF and density functional theory (DFT) along the lines proposed by Becke,[484] BPW91[485,486] is a pure DFT functional, VS + B is a combination of the Vosko−Wilks−Nusair and Stoll density functionals to obtain the wave function with a perturbative treatment of a Becke exchange functional,[487] MPn indicates perturbation theory[488] of order n applied to the HF wave function, and QCISD is quadratic configuration interaction including single and double excitations.[489]

In the table we list only the method used for solvation. For example, Wang and Boyd[490] used AM1 for the solvation part but added the solvation free energies to MP2 gas-phase energies.

Space limitations do not permit a detailed discussion of all the table entries. We content ourselves with a few general observations. Conformational equilibria of most interest tend to be those involving oligopeptides, sugars, or drug molecules. Quantitative accuracy inevitably requires some accounting for first-solvation shell effects, but continuum electrostatics are often sufficient to predict qualitative trends in systems where the dominant component of differential solvation is the electrostatic term (this is true for other applications in the table as well).

The large number of data available[600,601] for solvent effects on tautomeric equilibria makes them particularly attractive for study, as earlier reviews have also indicated.[7,549,602] One system which has attracted considerable attention is 5-hydroxyisoxazole,[547−549] where results from explicit solvent models are also available for comparison.[547,549] Taken as a whole, one key message which may be gleaned from studies on tautomeric equilibria is the importance of using a realistic solute cavity in the continuum electrostatics calculation—early results using spherical or ellipsoidal cavities (most not shown in Table 3) tended to be unreliable. In the case of azidoazomethine–tetrazole tautomerism, Cubero et al.[541] have examined a simple scheme for separating the electrostatic part of the free energy of solvation into its enthalpic and entropic components and observed good agreement with experiment for these quantities. Careful analyses of such separations for well described tautomeric equilibria may be a useful tool in further refinement of continuum solvation models.

With respect to acid/base equilibria, the prediction of an absolute pK_a by any first-principles theory remains extraordinarily hard, in part because of the difficulty in computing accurate gas-phase deprotonation free energies and also because of the large magnitude of solvation effects for charged species.[140,334,411,559,560,568,569,603–606] Typical accuracies in the computed quantities are rarely better than 2–5 kcal/mol, which results in absolute errors of possibly several log units in pK_a—a disappointing result given the accuracy possible from experimental measurement (when such measurements can be made). Fortunately, trends in pK_as across similar compounds tend to be much more accurately predicted,[334,560,566,568,569,603–607] although rationalizing differences in some simple series, e.g., the methylated amines, continues to be challenging.[77,140,607–616] A long-term goal in this area is the successful prediction of the pK_as for all ionizable groups in a given protein.[123,563,617–624]

Selected other equilibria are also provided in Table 3. These are primarily associated with molecular recognition and other bimolecular "binding" events. As these events necessarily involve removal of some portion of each solute's first solvation shell, it is again critically important to account for first-shell effects.[625] We note that, looking to the future, refining continuum solvent models to improve potentials of mean force along binding coordinates is a particularly ripe area for study, as has also been noted by other authors.[133,231,239,626,627] A related issue is the presence of a contact minimum in the potential of mean force between interacting partners even when they do not bind chemically. Pitarch et al.[628] showed that such a minimum is obtained in PCM-plus-surface tensions calculations of the methane–methane potential of mean force when the hydrophobic surface tension is multiplied by the solvent-excluding surface area but not when it is multiplied by the solvent-accessible surface area. This, however, is a rather specialized case on which to found general surface-area methodology.

Prediction of the partitioning behavior of a solute between two liquid phases has motivated extensive parametrization efforts for different solvent models. The most complete such parametrizations are the SM5 suite of universal solvation models which have been parametrized on over 2000 pieces of free energy data in 91 solvents.[64–77] Additional work has been motivated primarily by the relationship between bioavailability of drugs and their partitioning behavior between aqueous and nonpolar phases, where the latter may be either a model solvent or an actual biomembrane.[71,73,599,629,630]

Modifications required to extend continuum models to describe solvation in nonisotropic or nonhomogeneous media, such as liquid crystals,[148,631,632] or at interfacial phase boundaries are of considerable interest.[71,167,633–635] The Pisa group suggested a simple model for liquid/liquid interfaces several years ago;[634,636] a more recent development is the extension of the COSMO formalism to a solid/liquid interface as proposed by Stefanovich and Truong.[635] In addition, Chambers et al.[71] have successfully reproduced the partitioning of organic solutes across a water/phospholipid bilayer phase boundary by modeling each as a homogeneous medium, suggesting that such simple approaches may still be powerful tools in predicting properties of key relevance to drug design.

One unmet challenge for continuum solvation theories is to predict the temperature dependence of free energies of solvation. For those cases where there are experimental data, it is clear that the temperature dependence is not well predicted by a purely electrostatic treatment with temperature-independent solute radii. Thus, we need a theory of first-solvation-shell effects that includes temperature. However, the only qualitatively successful continuum models at the present time are semiempirical ones, and there do not appear to be enough experimental data available to extend these to predict the temperature dependence of free energies of solvation. One might at first think that this presents a situation where explicit-solvent models have a clear advantage. But there has been relatively little work on predicting the temperature dependence of $\Delta G_S°$ by explicit-solvent models so this hypothesis is unproven. Furthermore, these methods may have the same kinds of difficulty as continuum models because they are based on semiempirical force fields. As emphasized especially by Jorgensen,[637] the most successful force fields are specifically optimized for liquid simulations, and it is not clear that they can predict the temperature dependence of solvation free energies with temperature-independent parameters. The subject of temperature dependence of solvation effects is an important area for future work.

7. Solvent Effects on Spectra

7.1. Electronic Spectra

Solvatochromic effects on electronic spectra may be classified as positive or negative, depending on whether they promote a red shift or a blue shift, respectively. Red shifts are called positive solvatochromic effects because they are more common.[449] Red shifts are also called bathochromic shifts, and blue shifts are also called hypsochromic shifts.

The starting point for modeling solvent effects on electronic spectra is to recognize that just as for equilibrium properties, there are long-range dielectric

Table 3. Selected Applications of Continuum Solvation Models to Conformational, Tautomeric, Acid/Base, and Other Equilibria, and to Partitioning between Solvents—Organization Is Alphabetical by Most Critical Keyword Associated with the Molecule(s) Studied

subject of study	electronic structure model^a|solvation model^b	ref
Conformational Equilibria		
acetylcarnitine in water	AM1, HF|COSMO, PCM	491
β-alanine and related compounds in water	HF|Poisson	492
alanine dipeptide in water	MM|Poisson	493,494
	HF, DFT|PCM	336
alanine zwitterion in water	HF|multipole expansion, PCM	495,496
	HF|GB	225,497
alkanes and idealized amphiphiles in water	MM|Poisson	498
anomerism in various heterocycles in water	HF|PCM	499
asparagine dipeptide, water and chloroform	AM1|MST-ST	500
bilirubin in water	HF|PCM	501
carbonyl oxide and derivatives	B3LYP|SCIPCM	502
cocaine, transition-state analogue for the hydrolysis of, in water	PM3|SM*x*	503,504
cyclic 3′,5′-adenosine monophosphate, syn/anti isomerism in water	AM1, PM3|SM*x*	505
1,2-dihaloethanes	MP2, B3LYP|IPCM	155
dimethoxymethane and dimethoxyethane in water	HF|multipole expansion	457
N,*N*-dimethylaminoacrylonitrile in water	HF|IPCM	506
4,6-dimethyl-2-methoxytetrahydropyran, anomerism in water	AM1|SM*x*	70
	AM1, HF, B3LYP|SM*x*, PCM, cluster	507
1,3-dimethylthiourea	AM1, PM3|SM*x*	508
1,3-dithianes, 5-substituted	PM3|multipole expansion	509
diuron (herbicide, urea) in water	HF|Onsager, IPCM, cluster	510
dopamine in water	HF|PCM	511
ecgonine methyl esters (inhibitors of cocaine binding)	AM1|SM*x*	512
fluoroglycine in water	HF|PCM, multipole expansion	513
glucose, exo-anomerism in water	AM1|SM*x*	514
anomerism and hydroxymethyl rotation in water	AM1|SM*x*	311
glycinyl radical in water	B3LYP|PCM	464
glyoxal, neutral and protonated, rotational isomers in water	MP2|PCM, cluster	515
guanidine and guanidinium ions, *N*-methylated, water and CHCl$_3$	HF, MP2|PCM	516
hexoses, aldo and keto, in water	HF|IPCM	517
Hoechst 33258 (drug, DNA minor groove binder) in water	HF|PCM	518
	AM1|SM*x*	519
bis-iminonitroxide in water	B3LYP|PCM	520
isoxazoline and oxime derivatives from 7-ketolignans in water	AM1|SM*x*	521
4-methyl-3-thiosemicarbazide in various solvents	AM1, PM3|SM*x*	522
nitroaromatics, radical anions of, in water	AM1|SM*x*	468
oxocarbenium ions, cyclic, in water	HF, MP2, B3LYP|SCIPCM	523
2-phenethylamines, neutral and protonated, in water	AM1|SM*x*	524
phosphate, phosphonate, and phosphorothioate esters in water	HF|PCM, LD	525
piperazines, aryl, protonated and not, serotoninergic ligands in water	AM1|SM*x*	526
polyamine transport inhibitors	AM1|SM*x*	527
polynucleic acid and phosphoramidate helixes in water	MM|Poisson, GB	229
polypeptides (ala, gly, aib), helical preferences in CCl$_4$ and water	AM1|MST-ST	528
polypeptides APGD, APGN, and AYPYD in water	MM|Poisson	529,530
polypeptides, *N*-methylated and *N*-hydroxylated, in water	MM|GBSA	531
polypeptides, conformational issues in water	MM|Poisson	532
	MM|Poisson, GBSA, pure-ST, others	228
succinic acid and its monoanion in water	AM1, PM3|SM*x*	533
sulfoxide-Lewis acid complexes, α,β-unsaturated, in CH$_2$Cl$_2$	B3LYP|SCIPCM	534
tartaric acid, diester, diamide, fluorine-substituted analog in water	AM1, PM3, HF, MP2|SM*x*	535
titanium-based constrained-geometry catalyst in benzene	HF|SCIPCM	536
Tautomeric Equilibria		
acid/enol equilibrium for acetic acid in ethanol and water	B3LYP|SCIPCM	537
2-azaadenine and 2-azahypoxanthine in water	AM1, HF|SM*x*, MST-ST	538
8-azapurine in water	AM1|SM*x*	539
azidomethine/tetrazole in CCl$_4$, CHCl$_3$, and water	HF|MST-ST	540
also separation of enthalpic and entropic effects	HF|MST-ST	541
cytosine, protonated, in water	HF, MP2|PCM	542
cytosine and guanine, neutral and protonated, in water	AM1, HF|MST-ST	543
2,4-diamino-5-phenylthiazole, neutral and protonated, in water	PM3, HF|PCM, cluster	544
dicopper—dioxo compounds in various solutions	HF|GB	545
4,5-dimethyl-2-(2′-hydroxyphenyl)imidazole in water	AM1|SM*x*	384
formohydroxamic acid in water	AM1, PM3|SM*x*	546
hexoses, aldo and keto, furanose vs pyranose in water	HF|IPCM	517
5-hydroxyisoxazole in water	HF|Onsager, PCM	547
	AM1|SM*x*	548
	HF|MST-ST	549
hypoxanthine and allopurinol in water	AM1, HF|SM*x*, MST-ST	550
maleimide and phthalimide derivatives in water	AM1, HF|SM*x*, PCM	551
4-methylimidazole and 3-hydroxypyrazole in water	HF|MST-ST	549
purine and several derivatives in water	B3LYP|Onsager, PCM	552
thymine, uracil, and bromouracil in water	HF|MST-ST	553
xanthine/alloxanthine in water	AM1, HF|SM*x*, MST-ST	554
xanthine oxidase substrates and inhibitors, 12 molecules, in water	AM1|SM*x*	555

Table 3. Continued

subject of study	electronic structure model[a]|solvation model[b]	ref
Acid/Base Equilibria		
acetaldehyde-BF$_3$ complex in THF, CH$_2$Cl$_2$, and water	B3LYP|GB	556
carboline isomers in water	HF|multipole expansion	557
carbonyl derivatives (esters, ureas, etc.) in water	B3LYP|PCM	558
carboxylic acids in water	AM1|COSMO, SM*x*	559
	AM1, BPW91|PCM, COSMO, SM*x*	560
dimethyl sulfide and BF$_3$ complexation in various solvents	MP2|Onsager	561
guanine and thymine bases, methylated, in water	AM1|SM*x*	562
HIV protease and other pK_as, conformational dependence in water	MM|GB	563
	MM|Poisson	564
9*N*-[(1′*R*,3′*R*)-*trans*-3′-Hydroxycyclopentanyl]adenine in water	AM1|SM*x*	565
imidazole and substituted imidazoles in water	B3LYP|Poisson	566
indole and pyrrole carboxylic acids in water	B3LYP|multipole expansion	567
nitriles in water and chloroform	HF|PCM, SCIPCM, MST-ST	568
phenol and chlorinated phenols in water	AM1|COSMO, SM*x*	559
	HF, MP2|PCM	569
2- and 4-[(2,4,6-trinitrophenyl)amino]benzoic acid in water	AM1, HF|Onsager, SM*x*	570
Other Equilibria		
carbene−ether ylide equilibrium in diethyl ether	BPW91|SM*x*	571
[2]catenanes, translational equilibria in water	MM|GBSA	572
cyclodextrin complexation of various guests in water	AM1|SM*x*	573,574
cytochrome P450, binding of phenylimidazole inhibitors, in water	MM, AM1|Poisson, SM*x*	575
dimerization of carboxylic acids in CHCl$_3$ and water	AM1, HF|SM*x*, MST-ST	576
dimers of formamide and water, isomers, in water	MP2|PCM	577
heterolysis of MgF$_n$ ions	B3LYP|COSMO	393
ion pairing between arginine and lysine and phosphorylated amino acids	PM3|SM*x*	578,579
ion pairing between ions of like and unlike charge in water	HF|PCM	580
	MM|Poisson	21,581
ionic vs neutral pairing of Me$_3$N and formic acid in water	HF|SCIPCM, cluster	582
nucleic acid base pairing	HF|PCM, LD	583,584
nucleic acid base stacking in water	MM|Poisson	585
nucleic acid oligomer duplexes, stability in water	MM|GB−ST	229
	MM|Poisson, pairwise GB−ST	586
nucleic acid oligomers, stability in water	MM|Poisson, pairwise GB−ST	235
oxidation potentials for polycyclic aromatic hydrocarbons in CH$_3$CN	PM3|GB	226
peptide inhibitors binding to HIV-1 protease in water	MM|Poisson	587
proton transfers of heterocycles in water	AM1|SM*x*	490
redox potentials, iron−sulfur clusters in CH$_3$CN and water	VS + B|Poisson	487
ribonucleic acid oligomers, hairpin stability, in water	MM|Poisson, GB−ST	588
singlet−triplet equilibria of nitrenium ions in various solvents	DFT|SM*x*	242,589
	B3LYP, QCISD|IPCM	590
singlet−triplet equilibria of non-Kekulé molecules in water	AM1|SM*x*	591
VX-478 and analogues binding to HIV-1 protease in water	AM1, PM3|SM*x*	592
Two-Phase Partitioning		
amino acids, octanol and water	MM|Poisson	593
drug molecules, crystalline solids and water	AM1|SM*x*	594
fuel system icing inhibitors, alkanes and water	AM1|SM*x*	595
nucleic acid bases, chloroform and water	AM1, HF|MST-ST	596
	AM1|SM*x*	70,310
	AM1, HF, BPW91|SM*x*	597
organic solutes, alkanes and water	MM|Poisson	598
organic solutes, blood and brain	AM1|SM*x*	599
organic solutes, CCl$_4$ and water	MNDO, AM1, PM3, HF|MST-ST	83
organic solutes, CHCl$_3$ and water	MM|GBSA	237
	MNDO, AM1, PM3, HF|MST-ST	84
	AM1, PM3|SM*x*	66
organic solutes, multiple organic solvents and water	MNDO, MNDO/d, AM1, PM3|SM*x*	65,68−71, 73,74,77
	HF, DFT, B3LYP|SM*x*	75−77
	|pure-ST	72−74
organic solutes, octanol and water	MM|GBSA	238,241
organic solutes, phosphatidylcholine bilayers, and water	AM1|SM*x*	71

[a] See text for explanation of acronyms for electronic structure levels. [b] See text for explanation of acronyms for solvation models.

polarization effects and short-range effects. For electronic spectra, the short-range effects were traditionally assumed to be dominated by dispersion interactions, which are expected to be positive when the excited state is more polarizable than the ground state, which is usually the case. In recent years, many theoretical studies have demonstrated that specific hydrogen bonding effects must also be considered.

The cavity component (but not necessarily the dispersion or solvent structure component) should be less important for spectroscopy than it is for equilibrium properties, because the solute size and shape do not change much upon excitation. However, the solute's electrical properties, and hence its van der Waals radius, do change, and this effect should in general be negative (i.e., should cause a blue shift), since one expects excited states with their more loosely held electrons to be larger than corresponding ground states and thus experience greater repulsion with the surrounding solvent. This analysis relies on the reasonable assumption that the solvent geometry remains essentially fixed on the time scale of an electronic excitation.

Consider, as an example, the implication of frozen solvent for a hydrogen bond to the carbonyl group of benzylacetone in methanol. For a $\pi \rightarrow \pi^*$ excitation in the ring, the hydrogen bonding should be largely unaffected, except for small indirect effects, whereas one would expect an $n \rightarrow \pi^*$ excitation on the carbonyl to decrease the favorable energetic interaction of the solvent with the lone pairs. To the extent that this energetic interaction is stronger than one would predict from bulk electrostatics, it leads to a negative solvatochromic effect that should be modeled by including a first-solvation-shell hydrogen-bond term or an explicit first-solvation-shell methanol molecule along with continuum electrostatics and dispersion. Karelson and Zerner[638,639] have pointed out that the shifts that occur in hydrogen-bonding solvents are complex and may be in either direction, but the take-home message is that specific first-solvation-shell effects cannot be ignored. For three nitrogen heterocycles in water, Karelson and Zerner found that including two explicit solvent molecules and a surrounding continuum solvent gave an $n \rightarrow \pi^*$ transition energy 1500−2900 cm^{-1} farther to the blue then just including continuum solvent.[638] (Earlier calculations[640] had also given a blue shift, but of magnitude 300−400 cm^{-1}, in less quantitative agreement with experiment.) Fox and Rösch made similar calculations for acetone in water but obtained different directions for the effect of explicit water when they reference the shift to the gas phase and when they reference it to nonpolar cyclohexane.[170] Karelson and Zerner have shown for several examples that inclusion of both a few explicit water molecules and a continuum performs better than including either environmental effect by itself.[638,639] Some recent papers on explicit-solvent treatments of electronic spectra are also very useful in sorting out the physical effects that need to be included in SCRF−CI calculations.[641,642]

Induction forces and the interaction of permanent moments contribute to hydrogen bonds, but they are also important more generally. Induction forces and the interaction of permanent charges or multipole moments of the solute with permanent multipole moments of the solvent molecules are included in the electrostatic term, but the response of the first solvation shell can differ from the bulk to a different extent in the ground and first excited states, and this can lead to another first-solvation-shell contribution to the solvatochromic effect. In section 3 of this review, we mentioned the charge-transfer contribution to the free energy of solvation, and since solute−solvent charge transfer can be more or less facile in the excited state than in the ground state, it too can contribute to the solvatochromic shift.

Two problems with most of the earlier literature (prior to about 1990) on the electrostatic component of solvatochromic shifts were (i) an almost exclusive focus on dipole moments and dipole polarization and (ii) the assumption of a spherical cavity. The dipole moment is simply the first term (l=1) in the multipole series, and vanishingly few solute molecules are anywhere close to being spherical. We know that there can be large electric polarization effects even in molecules without dipole moments (e.g., 2 kcal/mol in the aqueous free energy of solvation of *p*-dichlorobenzene or *p*-dibromobenzene[77]), and the quantitative treatment of molecules with nonzero dipole moments requires inclusion of higher moments (l up to 4−8 for small molecules or even larger l for large molecules). Thus, modern treatments that do not truncate the multipole series or do not even introduce it (using distributed charge instead) and that use realistically shaped cavities allow one to make a new quantitative attack on solvatochromic shifts. To do this, however, requires careful consideration of time scales and effective Hamiltonians.

An SCRF−CI procedure assuming proportionality of every state to $(1 - 1/\epsilon)$ generates equilibrium-solvated excited states (recall that ϵ is the solvent bulk dielectric constant). These may be useful for dynamical processes if the process is slow compared to the time scale for relaxation of the solvation. If one carries out geometry optimization on these excited states, one obtains the so-called adiabatic spectrum.

In many cases, though, one is interested in the vertical spectrum. According to the Franck−Condon principle,[643] the vertical spectrum should be calculated without allowing nuclear motions. In particular, absorption spectra correspond to transitions between equilibrated ground electronic states and vertical electronically excited states, and fluorescence spectra correspond to transitions between an equilibrated excited electronic state and a vertically related ground electronic state. In some cases, the post-absorption (dark) transition between a vertically excited state and a relaxed excited state can be studied experimentally by subnanosecond fluorescent spectroscopy, measuring the time-dependent Stokes shift of the fluorescence.[644−647] In many cases, this has been studied as a function of solvent. Non-time-resolved fluorescence spectra, however, are dominated by the contributions that occur after solute−solvent relaxation.

Thus, for calculating absorption spectra, the solute and solvent geometry should be frozen at their optimum values for the ground state and the electronic wave function for the excited states should be determined using a reaction field in which the atomic and reorientation parts (usually grouped together and somewhat confusingly called just the reorientation part) are equilibrated to the ground state, but in which the electronic structure of the solute and solvent are optimized for the excited state. Note that the atomic relaxation is the same as the part sometimes called vibrational or packing relaxation. It has an intermediate time scale between the electronic and orientational parts. The atomic and orientational parts together constitute what is called here the inertial part, sometimes called the nuclear part or the slow part, whereas the fast part is called noninertial, inertialess, or electronic. None of these labels is perfectly suitable—for example, the relaxation of “inertial” polarization is partly inertial and partly diffusive; nevertheless, we use the inertial/noninertial language because it is conventional and well understood.

A similar situation applies to calculations of downward vertical transitions, i.e., the fluorescence spectrum. Here the excited state should be fully relaxed, but the ground state of solute and solvent should be optimized only for the electronic degrees of freedom. In this chapter we will specifically discuss absorption and simply note here that similar considerations apply to fluorescence.

That the noninertial and inertial polarization fields must be treated along these lines due to the vertical nature of optical transitions (the Franck−Condon principle) was originally pointed out by Ooshika[648] and by Bayliss and McRae.[649,650] Considerable experimental data are available on such effects.[3,449,450,651−655] Three early reviews laid out the critical elements of solvation effects on electronic spectra in a particularly clear fashion.[652,656,657]

As an example of how to incorporate these elements into SCRF models, we will consider the absorption spectrum in the generalized Born approximation. To calculate the *equilibrated* excited-state the Hamiltonian is

$$H^{\text{eff,eq}} = H^{\text{g}} - \left(1 - \frac{1}{\epsilon}\right)\sum_k q_k \sum_{k'} \gamma_{kk'}\, \hat{q}_{k'} \qquad (1)$$

where H^{g} is the gas-phase Hamiltonian, ϵ is the dielectric constant, $\gamma_{kk'}$ is a Coulomb integral[41−44,223,224] between the charge distributions represented by q_k and $q_{k'}$, q_k denotes the “current” partial charge on solute atom k, i.e., the partial charge calculated from the current electronic wave function and nuclear geometry of the solute, and $\hat{q}_{k'}$ is a one-electron operator. Notice that the factor of 1/2 to account for the free energy cost of reorganizing the solvent is missing in the nonlinear Hamiltonian, just as discussed elsewhere for ground states.[7] Note also that in eq 1, the various q_k generate the polarization field and they must be determined iteratively since they also are affected by the polarization field. For further development it will be convenient to note that $\hat{q}_k$ is the operator that generates the partial charges, i.e., if ψ is some electronic wave function, the associated partial charges are $\langle\psi|\hat{q}_k|\psi\rangle$. Furthermore, it will be convenient to write the effective Hamiltonian in general as

$$H^{\text{eff}} = H^{\text{g}} + H^{\text{N}}(\{q_k^{\text{N}}\}) + H^{\text{I}}(\{q_k^{\text{I}}\}) \qquad (2)$$

where $\{q_k^{\text{N}}\}$ denotes the set of partial charges with which the noninertial polarization of the solvent is in equilibrium and $\{q_k^{\text{I}}\}$ denotes the set of partial charges with which the inertial (i.e., atomic and reorientational) polarization is in equilibrium. Furthermore, we have the definitions

$$H^{\text{N}}(\{q_k^{\text{N}}\}) = -\left(1 - \frac{1}{\epsilon_{\text{opt}}}\right)\sum_k q_k^{\text{N}} \sum_{k'} \gamma_{kk'} q_{k'} \qquad (3)$$

and

$$H^{\text{I}}(\{q_k^{\text{I}}\}) = -\left(\frac{1}{\epsilon_{\text{opt}}} - \frac{1}{\epsilon}\right)\sum_k q_k^{\text{I}} \sum_{k'} \gamma_{kk'}\, q_{k'} \qquad (4)$$

where ϵ_{opt} is the so-called optical dielectric constant given in terms of the optical refractive index n by[658]

$$\epsilon_{\text{opt}} = n^2 \qquad (5)$$

Then eq 1 becomes

$$H^{\text{eff,eq}} = H^{\text{g}} + H^{\text{N}}(\{q_k\}) + H^{\text{I}}(\{q_k\}) \qquad (6)$$

I.e., the same self-consistent charge controls both polarization fields.

In contrast, to calculate the vertical excited states the Hamiltonian is

$$H^{\text{eff,vert}} = H^{\text{g}} + H^{\text{N}}(\{q_k\}) + H^{\text{I}}(\{q_k^0\}) \qquad (7)$$

where $\{q_k^0\}$ denotes the set of “prior” charges, i.e., those with which the inertial polarization field is still in equilibrium. Note that each q_k (as opposed to q_k^0) is still determined iteratively with $H^{\text{eff,vert}}$ and, just as for $H^{\text{eff,eq}}$, this can be accomplished by the SCRF−HF or SCRF−CI methods. Since eq 7 does not correspond to equilibrium solvation, it provides a simple example of nonequilibrium solvation.

The separation of the two polarization fields as in eq 7 was first introduced into quantal SCRF theory by Bonaccorsi et al.,[659] and it has been used by many later workers as well,[45,46,168,170,171,195,337,638,639,660−674] combining the basic treatment with various methods for treating the electrostatics. The treatment here generalizes this idea to the generalized Born approximation for the electrostatics. The time scale issues leading to eq 7 have been discussed by many previous workers not only in the context of vertical transitions in spectroscopy[45,46,168,170,171,337,638,639,648−650,659−665,667−678] but also in the context of vertical transitions in electron-transfer reactions[7,667,679,680] and ionization.[195,337,668,681−683] (Electron transfer, like radiation-induced electronic transitions, may sometimes be assumed to occur rapidly on the nuclear time scale; this assumption is valid in the so-called limit of nonadiabatic electron transfer, which occurs when the splitting between the two diabatic charge transfer states is small.)

As an alternative, Kim has considered the application of a direct reaction field method to electronic spectra.[357]

Note that if the CDS terms (see section 4.5) are assumed to depend only on geometry, i.e., not directly on aspects of electronic structure (like bond orders and partial charges), then they do not change upon vertical excitation. If, however, the CDS terms depend on solute electronic structure, then their effect on excitation is hard to estimate (since the electronic structure changes, but the nuclear structural part of the first solvation shell does not have time to adjust, and empirical surface tensions based on ground-state equilibrium free energies have the electronic and nuclear parts of the first solvation shell effects mixed together).

The next question concerns the evaluation of the vertical excitation energy itself. The effective Hamiltonian (eq 2), like eq 1, is nonlinear, and it is well-known that even for equilibrium states the energy or free energy is not simply the eigenvalue of the Hamiltonian when it is nonlinear.[7,437] The difference has a simple physical interpretation—work must be done on the solvent to polarize it; the free energy cost of this work cancels one-half of the solute−solvent interaction energy. The free energy cost can be calculated by electrostatic theory[337,669] or by assuming linear response of both the inertial and noninertial fields.[684] Notice that since the nascent vertically excited state is not an equilibrium situation, its free energy is not a true free energy (strictly speaking, free energy is only defined for equilibrium systems), but it is still a nonequilibrium free energy (because the entropy and volume do not change[685]); the solvatochromic shift on the vertical excitation energy therefore involves the difference of an equilibrium and a nonequilibrium free energy.

Although the physical ideas behind the application of linear response theory[7] are straightforward, a wide variety of equations and procedures appear in the literature, even for the electrostatic part. However, the linear response assumption is fully consistent with the vertical energy expression obtained by Aguilar, Olivares del Valle, Sánchez, and Tomasi,[337,669] based on Marcus' theory of the free energy of states with nonequilibrium electric polarization.[337,686−688] Their derivation includes the interaction between the preexisting slow reaction field in the excited state and the change in the fast reaction field.[337,669] The question of how to calculate the vertical excitation energy had been discussed earlier by Bonaccorsi et al.[660,661] and Sheyket et al.,[689] but Bonaccorsi et al. do not take into account that no work is done on the internal energy of the solvent nuclear degrees of freedom by a vertical excitation, and the result of Sheyket et al. (their eq 17) involves a calculation (the first term of that equation) on the vertically excited state in which the polarization field is controlled by the equilibrated charge distribution of the excited state, but the latter quantity appears no place in the correct result. Karelson and Zerner[639] discussed these issues at length, but they explicitly add in the inertial polarization cost for absorption, which is incorrect since the nuclear coordinates of the solvent do not change during absorption. Fox et al.[664] and Serrano-Andrés et al.[46] noted that the fraction of the reaction field which is due to slow relaxation processes must be held fixed, but they nevertheless included the cost for that term. The problems are compounded by the fact that some workers have used the wrong Hamiltonian (i.e., they incorrectly included the cost term in the Hamiltonian itself) for finding both the ground-state and excited-state charge distributions.

Note that in water, where $\epsilon = 78.4$ and $\epsilon_{\text{opt}} = 1.8$, we have

$$1 - \frac{1}{\epsilon} = 0.987 \tag{8}$$

$$1 - \frac{1}{\epsilon_{\text{opt}}} = 0.444 \text{ (45\% of (9))} \tag{9}$$

$$\frac{1}{\epsilon_{\text{opt}}} - \frac{1}{\epsilon} = 0.543 \text{ (55\% of (9))} \tag{10}$$

With this treatment about 55% of the solvent polarization field is frozen upon vertical excitation in water. The quantity in eq 10 is called the Pekar[690] factor, and it occurs in many discussions of this type.[416,648,650,691−693] The contributions of eqs 9 and 10 are what we have been calling noninertial and inertial, respectively. Note that the partition of eqs 8−10, which is a direct consequence of the partition of eqs 3 and 4, has been challenged by some workers, who argue that the noninertial contribution should become smaller as ϵ increases because the magnitude of the noninertial dipole field is decreased by the inertial polarization.[694] The separation of inertial polarization in PCM-type theories is nontrivial.[337,671,695]

The above discussion of nonequilibrium free energies could be repeated from the point of view of the reaction field. Thus, we could define the generalized Born reaction field at atom k' due to polarization of the solvent by charges $\{q_k\}$ as

$$\phi_{k'}^{\text{RF}} = \left(1 - \frac{1}{\epsilon}\right) \sum_k q_k \gamma_{kk'} \tag{11}$$

We could then rewrite the entire development above in terms of ϕ^{RF} rather than H^S. This would make $\gamma_{kk'}$ an effective coulomb interaction potential, depending on coulomb radii, that governs interactions between point charges $\{q_k\}$, but we prefer to consider $\gamma_{kk'}$ as an effective coulomb integral governing interactions between atomic charge distributions characterized by the point charges $\{q_k\}$ and by the coulomb radii.

Instructive examples of the effect of the dispersion interaction on electronic excitation spectra are given by the work of Sánchez et al.,[669] Bader and Berne,[696] and Naka et al.,[697] who all studied the $n \rightarrow \pi^*$ excitation of formaldehyde in water. Sánchez et al.,[669] using a continuum model of the solvent for both electrostatics and dispersion, calculated a (blue) shift of −1.2 kcal/mol, of which −1.5 kcal/mol comes from electrostatics and +0.3 kcal/mol comes from dispersion. However, if the excitation is treated at the configuration interaction with single substitutions (CIS) level instead of by more accurate configuration interaction with single and double substitutions (CISD), then the dispersion contribution is incorrectly calculated to be negative (the usual sign convention is used here, which is opposite to theirs). The calculation of Bader and Berne[696] cannot be accepted as a literal model of formaldehyde because their charge model is too polar. Nevertheless, we can think of it as a model system, and for that polar model system they found by an explicit solvent model that dispersion contributes only 3% of the shift. In a following paper[698] they improved the solute charge distribution and compared polarizable explicit solvent, nonpolarizable explicit solvent, and continuum solvent; they found that the continuum solvent gave a solvatochromic shift ranging from 62% to 128% of the explicit water result, depending slightly on the explicit water model and significantly on the solute charges and the choice of radii. Naka et al.[697] used the RISM-SCF method and considered formaldehyde. They found a blue shift of 6 kcal/mol, in good agreement with the experimental result for acetone solvent. A very recent study of the $n \rightarrow \pi^*$ excitation of acetone in nine solvents, based on a GB extension of Aguilar et al.[337] and Class IV charges for excited states, yields excellent agreement with experiment when electrostatics, dispersion, and hydrogen bonding are all accounted for (Li, J.; Cramer, C. J.; Truhlar, D. G. *Int. J. Quantum Chem.*, in press).

Chabalowski et al.[699] studied the effect of solvent on the spectrum of indole and found that solvent can invert the order of the excitation energies. Besley and Hirst[700] studied the several electronic transitions of formamide and *N*-methylacetamide in cyclohexane and water, and their studies elucidate the solvent effects on Rydberg states and show good agreement with experiment.

Cacelli and Feretti[701] applied the PCM method to calculate the solvent effect on a much bigger molecule, $[(NH_3)_5Ru{-}pyrazine]^{2+}$, and were able to account for the experimentally observed solvatochromic red shift of the metal-to-ligand charge-transfer band.

Rösch and Zerner[702] discussed perturbation theory methods for calculating solute−solvent dispersion effects on electronic spectra. They especially noted the difficulty of balancing the correlation energy and dispersion interaction in the ground and excited states so that the shift is meaningful. Nevertheless, by using the Thomas−Reiche−Kuhn sum rule twice, they were able to make some progress on using a continuum model to calculate solvent shifts of nonpolar molecules or polar molecules in nonpolar solvents that are dominated by dispersion.

Time-dependent extensions of dielectric continuum theory have been reported recently and used to calculate multiexponential solvation time correlation functions for benzophenone anion in acetonitrile and dimethyl formamide, solvation relaxation functions for coumarin dyes in water, methanol, and acetonitrile, and time-resolved fluorescence anisotropy and the dynamical Stokes shift of polar solutes.[703−705]

7.2. Solvent Effects on Vibrational Spectra

Solvent effects on vibrational spectra are also important. A summary of the early, pioneering work on solvent effects on vibrational spectra, including successful applications of continuum models, is available in the review of Rao et al.[657] Linder has proposed a refined continuum model building in part on this work.[706] Now such effects are beginning to receive quantitative attention with methods based on full electronic structure calculations. The earliest work in this direction was a series of preliminary studies reported by Olivares del Valle and co-workers.[707−709]

Wang et al.[710] tested an SCRF calculation based on a spherical cavity at the HF/6-31G(d,p) level for the vibrational spectrum of methanol in methanol. They do not say whether they limited attention to only the dipole term, but since they do not mention the number of multipole moments, one assumes they included only the dipole. First-solvation-shell effects were neglected. The experimental solvent shifts range from -353 to $+ 50$ cm^{-1} in this case. The crude SCRF model got the sign correct in only one-half the cases and did not predict the trends correctly even for the larger shifts. It appears that it is necessary to include higher multipole moments and/or first-solvation shell effects to explain these trends.

Stefanovich and Truong[711] used the COSMO continuum model to calculate vibrational shifts of five molecules in water. The experimental solvent shifts range from -67 to $+175$ cm^{-1} in these cases. COSMO uses the continuous electron probability density, so effectively all multipole moments are included, and it treats the cavity realistically as a superposition of atom-centered spheres. The mean unsigned error, averaged over the five molecules, was 24 cm^{-1}, and this decreased to 15 cm^{-1} when one water molecule was represented explicitly in each case. The improvement in the average on adding an explicit water comes primarily from formic and acetic acid, both of which make strong hydrogen bonds with water. Except for the explicit water molecule, no attempt was made to model first-solvation-shell effects. The trends were reasonably well represented with one explicit water molecule. These studies indicate the importance of both long-range polarization effects and first-shell hydrogen bonding.

A new algorithm for analytic second derivatives was used by Assfeld and Rinaldi[294] to calculate the solvent-induced frequency shifts of H_2O and HCN and of the CO stretches of H_2CO, CH_3CHO, and $CH_3C(O)CH_3$. The results were compared to experiment for nine cases. In all nine cases the sign of the shift was computed correctly (seven positive and two negative). Furthermore, the mean unsigned error in the shifts was 10 cm^{-1}, as compared to a mean unsigned value of 19 cm^{-1} for the shifts themselves.

The equilibrium solvation approach is questionable for high-frequency solute modes where the solvent motions may be too slow to track the solute motion. Rivail et al.[712] examined this question for the solvent-induced frequency shift of the 1746 cm^{-1} vibration of formaldehyde in cyclohexane. The charge distribution was represented by a multipole expansion, and the cavity boundary was at the molecular surface. The noninertial solvent polarization field was assumed to follow the vibration, but—unlike the other treatments of vibrational frequencies discussed here—the inertial polarization field was frozen at a value corresponding to the vibrational average; however, this freezing had only a small effect for formaldehyde in cyclohexane. First-solvation-shell effects were neglected. The calculated shift of -11 cm^{-1} at the scaled Hartree−Fock level agrees with experiment, but adding electron correlation decreased the magnitude of the calculated shift. In their discussion they raised the question of whether the orientational polarization can respond rapidly enough to the molecular vibrations to be treated as equilibrated at each molecular geometry, as is often assumed.

Ilich et al.[713] applied continuum methods to the vibrational spectra of solvated uracil. The calculations correctly reproduced a red shift of C═O vibrations and a blue shift of most of the out-of-plane modes. Solvent effects on carbonyl vibrations have also been studied by Rivail et al.[714] Ramírez et al.[715] calculated the vibrational frequencies and intensities of the solvated glutamine zwitterion with multipole moments up to $l = 6$ and an ellipsoidal cavity and with no account of first-solvation-shell effects. The results (after scaling) are in satisfactory agreement with experiment.

Wiberg et al. studied the effect of solvent on the ratio of infrared intensities for *gauche*- and *trans*-1,2-dichloroethane and found a 10% change in acetone.[155]

8. Dynamics

8.1. Equilibrium Solvation

8.1.1. Theory

Where might continuum models be most inadequate? One important area is nonreactive dynamics. Consider, for example, the vibrational relaxation of a low-frequency dipolar diatomic molecule in acetonitrile. For this problem, Ladanyi and Stratt[716] found that the onset of solute vibrational relaxation is controlled by binary interaction of the solute with a specific solvent molecule. The independent binary collision model in fact has a long history of successful applications to vibrational energy relaxation in solution.[717,718] However, longer-range collective motions that are well treated by continuum models may well be dominant in other cases.[719]

Reactive dynamics is probably the most complicated problem in all of solvation theory. Our discussion of solvation effects on kinetics will be presented in the language of transition state theory.[720−723] In phenomenological transition state theory, a rate constant is given by

$$k = \frac{\tilde{k}T}{h(C^0)^{n-1}} \exp[-\Delta_{\mathrm{act}}G_T^0/RT] \tag{13}$$

where $\tilde{k}$ is Boltzmann's constant, T is temperature, h is Planck's constant, C^0 is the concentration corresponding to the standard state (typically 1 M for liquid-phase solutions), n is the molecularity of the reaction (2 for bimolecular reactions, 1 for unimolecular reactions), R is the gas constant, and $\Delta_{\mathrm{act}}G_T^0$ is the phenomenological molar free energy of activation at temperature T. Thus, transition state theory provides a means whereby a reacting system can be treated as involving a quasiequilibrium between reactant(s) and an activated complex. Therefore, in principle, solvation effects on kinetics may be addressed by considering the different solvation free energies of these stationary points; corrections for solvation effects on the reaction coordinate motion and nonequilibrium solvation can be added to further refine the model.

Conventional transition state theory is predicated on a quasiequilibrium between reactants and conventional transition states, which are hypothetical species located at a saddle point of a potential energy surface and missing one degree of freedom (the reaction coordinate). Normal-mode analysis at the saddle point (which is possible because the gradient of the potential energy surface vanishes at a saddle point) is used to separate the reaction coordinate for gas-phase reactions.[720,721,723] There are a number of conceptual difficulties in extending this molecular model to reactions in the liquid phase (such as the existence of a myriad of saddle points with very similar solute properties differing mainly in the conformations of the solvent, the fact that the values of solute coordinates for a gas-phase saddle point are unlikely to be identical to values of solute coordinates for saddle points of the full system, the inseparability of solute rotation and the conversion of gas-phase solute rotations into low-frequency librations strongly coupled to the solvent, and the intrinsic necessity to include collective entropic effects for any discussion of liquids), and these have traditionally been “swept under the rug” by the artifice of using a quasithermodynamic formulation.[724,725] Dynamical effects can be incorporated in conventional transition state theory by multiplying the right-hand side of eq 13 by a transmission coefficient κ.[721,723] When $\Delta_{\mathrm{act}}G_T^0$ is determined empirically by comparing eq 13 to experiment, it implicitly includes a contribution of $-RT \ln \kappa$ from the transmission coefficient.[726]

To make progress beyond conventional transition state theory, it is useful to reformulate transition state theory in terms of the flux through a phase-space hypersurface separating reactants from products.[727−731] With this formulation one recognizes that $\Delta_{\mathrm{act}}G_T^0$ arises from the statistical probability of being in the hypersurface (which has one degree of freedom less than the full phase space) and $\tilde{k}T/h$ arises from kinematic factors in the flux calculation. This formulation leads naturally to variational transition state theory where the location of the hypersurface is varied to minimize the calculated rate constant, which is strictly justified for classical mechanical systems,[727−729,731−733] and it also leads to insight into incorporating quantum mechanical effects.[733,734] For the present purposes, though, the critical issue is that it allows progress toward understanding solute−solvent separability, the meaning of nonequilibrium solvation,[735−737] and the requirements for a molecular-level derivation (as opposed to a quasithermodynamic formulation) of transition state theory in solution.[738−742]

Transition states are identified with phase-space hypersurfaces, and we can express their free energy in terms of well-defined statistical mechanical procedures. A transition state defined by making a normal-mode analysis of the solute Hamiltonian at a saddle point and eliminating the imaginary-frequency normal mode is a conventional transition state. Any other hypersurface for which we calculate the free energy is a generalized transition state, and varying the definition of the generalized transition state to maximize its free energy of activation or to minimize the calculated rate constant yields a variational transition state.

In discussing reaction rates in solution and especially their dependence on free energies of solvation, it is important to keep in mind the dependence of such quantities on the choice of standard state. We illustrate this by a simple calculation.

The upper limit for the rate constant of bimolecular reactions in solution is the diffusion-controlled limit, a typical value of which is 4×10^{9} M^{-1} s^{-1}.[743] For reactions of monocharged ions in water at room temperature, this may be increased or decreased by about a factor of 2. In transition state theory, the rate constant of a bimolecular reaction is given by eq 13. For $C^{0} = 1$ M and $T = 298$ K, eq 1 becomes

$$k = 6.2 \times 10^{12} e^{-\Delta_{\mathrm{act}} G_T{}^{0}/(0.592\,\mathrm{kcal})}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1} \qquad (14)$$

Equating this to 4×10^{9} M^{-1} s^{-1} shows that reactions with $\Delta_{\mathrm{act}}G^{0}_{298} \lesssim 12$ kcal proceed at or close to the diffusion limit. This value clearly depends on the standard state, so one must be careful about attributing any special meaning to $\Delta_{\mathrm{act}}G^{0}_{298}$ independent of the standard-state convention. It is also worth noting that the rate constant depends on the standard-state free energy of activation and is independent of the concentration-dependent free energy of reactants. Thus, for example, the rate of a reaction involving OH^{-} is accelerated by increasing [OH^{-}], but the rate constant is unchanged except for ionic strength and nonideal-solution effects.

Unimolecular rate constants present a different story. The free energy of activation for a unimolecular reaction is independent of the standard state. Unimolecular dissociation reactions though are the reverse of bimolecular reactions, and again, there is a maximum rate constant because the reaction cannot occur faster than the products can diffuse away.[743] Using the same typical parameters as those used for the bimolecular diffusion rate constant, the maximum upper limit is about 10^{10} s^{-1}. Dissociation reactions with $\Delta_{\mathrm{act}}G^{0}_{298} \lesssim 4$ kcal/mol are limited by this diffusion step.

To calculate $\Delta_{\mathrm{act}}G^{0}_{T}$ for reactions in solution, one can take a variety of approaches. We think it is useful to organize these in the following hierarchy: (i) treatments based on the gas-phase reaction path (or just the gas-phase saddle point) and the equilibrium free energy of solvation of a point or points along that path; (ii) treatments based on a solution reaction path computed under the assumption of equilibrium solvation of points on that path; (iii) treatments including nonequilibrium solvation effects. These kinds of treatments will be denoted separable equilibrium solvent (SES), equilibrium solvation path (ESP), and nonequilibrium solvation (NES), respectively.

If the Hamiltonian were separable into solute terms and solvation terms, one could simply add solvation free energies to solute free energies. For weak solute–solvent coupling, this may sometimes be a good approximation. At the level of conventional transition state theory, the SES approximation corresponds to

$$\Delta_{\mathrm{act}}G^{0}(\mathrm{liq}) = \Delta_{\mathrm{act}}G^{0}(\mathrm{gas}) + \Delta G^{0}_{\mathrm{S}}(\mathrm{S.P.}) - \Delta G^{0}_{\mathrm{S}}(\mathrm{R}) \qquad (15)$$

where S.P. and R denote saddle point and reactants. All quantities in eq 15 are understood to be evaluated at the same temperature T, which is now suppressed in the notation.

Variational transition state theory (VTST) provides a more general framework for discussing chemical reactions in solution.[186,304,723,731,742,744−747] In VTST we first define a reaction path (RP), and the signed distance along the reaction path is called the reaction coordinate (RC), s, with $s = 0$ at the saddle point, s negative on the reactants' side of the saddle point, and s positive on the products' side. (For reactions without a saddle point, the origin of s is arbitrary.) Then we define the sequence of generalized transition states intersecting the RP at various points s. The local orientation of the dividing surface (i.e., its orientation in the vicinity of the RP) is called R. In conventional transition state theory the transition state is located at $s = 0$ and the orientation R is such that the transition state is locally orthogonal to the imaginary frequency normal mode of the saddle point. In VTST, s and R are to be optimized. Thus, in VTST the rate constant of a chemical reaction at temperature T is written

$$k = \kappa \frac{\tilde{k}T}{h} K^{\ddagger,0} \min_{s,\mathsf{R}} \exp[-\Delta_{\mathrm{act}}G^{\mathrm{GT},0}(s,\mathsf{R})/RT] \qquad (16)$$

$$= \kappa \frac{\tilde{k}T}{h} K^{\ddagger,0} \exp[-\max_{s,\mathsf{R}} \Delta_{\mathrm{act}}G^{\mathrm{GT},0}(s,\mathsf{R})/RT] \qquad (17)$$

where κ is the transmission coefficient, $\tilde{k}$ is Boltzmann's constant, h is Planck's constant, $K^{\ddagger,0}$ is the reciprocal of the standard-state concentration for bimolecular reactions and unity for unimolecular reactions, $\Delta G^{\mathrm{GT},0}(s,\mathsf{R})$ is the standard-state molar free energy of activation for temperature T and generalized transition-state (GT) location s and orientation R, and R is the gas constant. In most cases R is not numerically optimized but rather the GT is fixed locally perpendicular to the RC; thus, when it is not mentioned, one should assume that the R degree of freedom is fixed (by some prescription) in the sequence of GTs, and the generalized free energy of activation function will be written $\Delta_{\mathrm{act}}G^{\mathrm{GT},0}(s)$. Considered as a function of s this quantity is often called the free energy profile. Notice that the location of the minimum of eq 16 and maximum in eq 17 depends on T.

The free energy of activation may be written

$$\Delta_{\mathrm{act}}G^{\mathrm{GT},0}(s) = G^{\mathrm{GT},0}(s) - G^{\mathrm{R},0} \qquad (18)$$

where the quantities on the right-hand side are the standard-state free energies of the GT and the reactants (R), respectively. The GT, like conventional transition states, has one degree of freedom less than the full system because the reaction coordinate is missing.

The physical meaning of eq 16 with $\kappa = 1$ is that it represents the one-way classical flux in the direction of products through the variational transition state. Although the motion through the GT is intrinsically classical in this theory, the motion of reactants and the motion in the GT (in which the RC is missing) may be quantized if desired (and in fact, high-frequency modes *should be* treated as quantized).

The role of fluctuations is sometimes discussed in a confusing fashion in the treatment of reaction rates in solution. Fluctuations are already included in transition state theory, and they do not need to be added as an extra element. The instantaneous barrier to reaction (however it may be defined) fluctuates due to thermal motions of all the atoms, and various systems react by passing over the barrier ridge at different values of the coordinates transverse to the reaction coordinate. The correct statistical average of the one-way flux toward products through a transition state dividing surface, including these fluctuations, is embodied in the transition-state-theory free energy of activation. Of course, it may sometimes be stimulating to think about the fluctuations, but one should not assume that anything is missing in the theory if one does not use the fluctuation language. The situation has been summarized succinctly by Warshel: "All reactions involve dynamical fluctuations of the reacting atoms. The chance that the fluctuations will take the system to the transition state, however, is determined mainly by the relevant energy of activation".[748]

As the above summary of the theory should make clear, there are two possible roles for the transmission coefficient: (i) It can account for the quantum effects on the RC motion, the most important of which is tunneling. (ii) It can account for the fact that even for classical RC motion, the net flux of systems from the reactants to products may be greater than the local one-way flux. This latter effect is usually called recrossing. For reactions in solution, recrossing effects may be classified into two types: those associated primarily with intrinsic solute dynamics (such recrossing effects can also occur in the gas phase) and those due primarily to solute–solvent interactions. The latter are often characterized as friction and caging, where friction refers to solute–solvent interactions close to the GT and caging refers to events that turn around potentially reactive trajectories at some point farther down the path. One sometimes refers to nonequilibrium solvation of the transition state. This is really just another way of looking at frictional recrossing effects; sometimes this is the preferred language because it may lead to a physically intuitive picture of the origin of the recrossing effect, especially for frictional recrossing.

Frictional effects are sometimes classified as dielectric friction and hydrodynamic (or mechanical) friction. It would be tempting to identify these effects with nonequilibrium solvent polarization and nonequilibrium CDS terms, respectively, but—just as for equilibrium free energies—the effects cannot be uniquely separated.

We can illustrate the connection between the frictional and nonequilibrium perspectives by an example. For simplicity assume that classical mechanics is valid and assume that the solute has n degrees of freedom. The gas-phase potential energy of the solute may be denoted $V(\mathbf{x})$ where $\mathbf{x}$ is n-dimensional. If solvent structure equilibrates instantly to any change in solute coordinates, i.e., if solvent adjusts adiabatically to solute, then the solute motion is governed by the potential of mean force, which is

$$W(\mathbf{x}) = V(\mathbf{x}) + \Delta G_S^0(\mathbf{x}) \tag{19}$$

where $\Delta G_S^0(\mathbf{x})$ is the equilibrium free energy of solvation that we have discussed above. The mean force, ∇W, on the solute coordinates is independent of standard state because the constant that must be added to $\Delta G_S^0(\mathbf{x})$ to change the standard state is independent of $\mathbf{x}$. Now the same algorithm that when applied to $V(\mathbf{x})$ yields the gas-phase RP can be applied to $W(\mathbf{x})$; the resulting RP is called the equilibrium solvation path (ESP). Applying variational transition state theory to $W(\mathbf{x})$ instead of $V(\mathbf{x})$ yields the ESP approximation to the liquid-phase rate constant. Suppose that one can find a perfect variational transition state on the $W(\mathbf{x})$ hypersurface; then $\kappa = 1$. However, we now recognize that the solvent does not equilibrate instantaneously. When the solute coordinates change at a finite rate from $\mathbf{x}$ to $\mathbf{x}'$, the solvent structure is not the same as if the solute were frozen at $\mathbf{x}'$ long enough for the solvent to equilibrate. Thus, the force differs from λ; sometimes this will cause a system to recross the ESP variational transition state. Thus κ may be 1. In a continuum description of the solvent, this may be likened to a frictional drag on the solute motion and may be associated with solvent viscosity. In other words, the solute coordinates are modeled as executing a diffusional motion through the solvent,[723,735,736,739,749–753] where the diffusion concept is broadened to refer to diffusion in momentum, not just spatially overdamped motion, i.e., one is referring to frictional drag. Part of the frictional drag comes from forces due to the long-range solvent order, and this part of the friction constant might be modeled by the bulk dielectric relaxation time, which describes the relaxation of a bulk collective mode. This is analogous to the electrostatic component of equilibrium free energies. But another part of the frictional drag is due to interactions between solute atoms moving along the reaction coordinate with their nearest-neighbor solvent atoms. This first-solvation-shell contribution can be treated by microscopic viscosities, diffusion constants, and relaxation times that differ[739,753–757] from their bulk values, analogously to the microscopic surface tensions used for equilibrium free energies of solvation—an implicit treatment of first-solvation-shell effects—or they may be treated by explicit solvent molecules. For example, if one includes two explicit water molecules, then the reaction path and transition state calculations involve $n + 18$ dimensions. If the six new coordinates adjust in the same way as in an ESP calculation in which these 18 coordinates are assumed to equilibrate to each position of the n solute coordinates, then there is no nonequilibrium effect.

Thus, nonequilibrium solvation may be identified by analyzing the participation of solvent coordinates in the reaction path.

The treatment of nonequilibrium solvation in terms of bulk collective modes or microscopic friction (using microscopic viscosities, diffusion constants, and relaxation times) may be reformulated, if desired, in terms of effective solvent coordinates. For example, one may add a single coordinate to the Hamiltonian to represent the coupling to a collective mode of the solvent.[352,402,735,736,741,742,744,752,758−765] Alternatively, the friction can be represented by a collection of oscillators and converged with respect to the number included.[761,762]

For typical solvents, the solvation relaxation time depends mainly on the solvent dipole density (number density times the square of the dipole moment); solvents with larger dipole density relax faster because a smaller motion is required to relax a fluctuation.[766] This observation is the basis for a simple formula that can be used to estimate the solvation relaxation frequency of a solvent from its number density, dipole moment, and moments of inertia.[766] For example, one obtains $\omega \cong 100$ ps^{-1} for water; this corresponds to a solvation time of 10 fs.

We now return to the classification of various approaches to theoretical reaction kinetics in solution. First we distinguish conventional transition state theory (TST), variational transition state theory (VTST), transition state theory corrected for solvent-mediated recrossing, and full molecular dynamics (MD) without mention of transition states. For reasons discussed above, a generic name for transition state theory corrected for solvent-mediated recrossing of the ESP variational transition state is nonequilibrium transition state theory (NETST). We will not be concerned with full MD in this chapter but we simply mention that with presently available techniques, this method, although instructive, is, as a general method, quantitatively inadequate due to neglect of quantum effects such as zero point energy and tunneling. Conventional TST is the special case of the above theory in which $s = 0$ and κ includes at most a tunneling correction based on an effective barrier assumed to have its maximum at $s = 0$. VTST includes a search for the maximum of $\Delta G^{\mathrm{GT},0}(s)$ and/or a tunneling correction based on an effective barrier with a maximum that is allowed to be at $s \neq 0$; the deviation of either the maximum of $\Delta G^{\mathrm{GT},0}(s)$ or effective barrier for tunneling from $s = 0$ is sometimes called a “variational effect.” NETST includes a correction for recrossing, which may be included by rotating R into solvent degrees of freedom (either the actual degrees of freedom of the solvent or the effective solvent degrees of freedom representing one or more collective modes) or—equivalently—by including friction in κ, and NETST may or may not include tunneling or variational effects. This classification is complementary to the one discussed above of separable equilibrium solvation (SES), equilibrium solvation path (ESP), and nonequilibrium solvation (NES). In principle, one can combine either conventional TST or VTST with SES or ESP. Thus, one obtains five general approaches: SES−TST, SES−VTST, ESP−TST, ESP−VTST, and NES−NETST.

8.1.2. SES and ESP Applications

The SES approximation has served as the basis of a number of previous investigations[19,186,223,242,309,312,339,767−810] of solvation effects on barriers using conventional or variational transition state theory. Some recent examples employing implicit-solvent methods are given in Table 4, which uses the same conventions as Table 3. Emphasis has been primarily on biologically relevant reactions, cycloadditions (partly because of questions about the possible role of hydrophobic forces in condensation reactions and partly because the large polarizability of the cycloaddition transition state can lead to interesting solvent effects), and reactions involving large changes in charge distribution so that solvent effects are profound. Good examples from the latter category are S_N1 reactions or the S_N2 Menschutkin reaction, the latter involving nucleophilic attack of a neutral amine on a neutral halohydrocarbon to create a cationic ammonium salt and an anionic halide ion—such charge separation is highly unfavorable in the gas phase but strongly stabilized in polar solvents. Key issues remaining for study in many systems include the degree to which solvation influences movement of the transition state along or orthogonal to the gas-phase reaction coordinate and the degree to which solvent motions couple with the reaction coordinate.

The ESP−TST and ESP−VTST approximations[304,742] have been less widely used due to their greater computational demands. Only recently have we begun to see transition state geometries optimized in solution,[22,87,186,304,456,745−747,789,811,816,824−829] which is the first step in any ESP calculation.

For example, Tunõn et al.[87] studied the Diels−Alder reaction of acrolein with s-*cis*-butadiene in water at the ESP−TST level with electrostatics treated by an HF/6-31G* SCRF calculation with six multipole moments and an ellipsoidal cavity and with first-solvation-shell effects treated by atomic surface tensions. They found a gas-phase barrier of 41.4 kcal that decreased to 38.4 kcal when the electrostatics of solvation were considered and to 36.8 kcal when first-solvation-shell effects were included.

Use of the potential of mean force to calculate a full minimum energy path and vibrational frequencies along this path, as required for ESP−VTST, is also now possible. Chuang et al.[304] carried out full ESP−VTST + tunneling calculations for the Menschutkin reaction and the transfer of a proton between ammonia molecules, both in aqueous solution. At the highest dynamical level, the differences between the SES−VTST and ESP−VTST results was about a factor of 2 in both cases. However, the final results differ from SES−TST calculations by 11 and 3 orders of magnitude, respectively.

A more complete application of ESP−VTST + tunneling calculations has been made recently to the free radical abstraction reactions $H + CH_3OH \rightarrow H_2 + CH_2OH$[313] and $H + C_2H_5OH \rightarrow H_2 + C_2H_4OH$[830] in aqueous solution. These calculations successfully

Table 4. Selected Applications of Continuum Solvation Models to Chemical Reactions—Organization Is Alphabetical by Most Critical Keyword Associated with the Reaction(s) Studied

subject of study	electronic structure model|solvation model	ref
acyloxy shift for acyloxyethyl radicals in water	AM1, B3LYP|SM*x*, SCIPCM	790
aldol condensation of HCHO	HF|PCM	339
aminolysis of phenylquinolinecarboxylates in water	AM1, HF|SM*x*, Poisson, SCIPCM	783
anhydride formation, cyclic, in water	AM1, HF, B3LYP|SM*x*, SCIPCM	791
Beckmann rearrangement of formaldehyde oxime in water	HF|Onsager, PCM, cluster	
benzil rearrangement, base catalyzed, in water	AM1|SM*x*	785
catechol *o*-methyl transferase model reaction in water	AM1, HF|SM*x*, PCM	792
Claisen rearrangement in water and some other solvents	AM1|SM*x*	19,811
	HF|multipole expansion, PCM	780,781
Claisen rearrangement, alkoxy substituted, in diethyl ether	HF|Onsager	795
cycloaddition, SO_3 with alkenes, [2+2] and [3+2] in CH_2Cl_2	B3LYP|SCIPCM	807
cycloaddition, ketene/carbonyl, [2+2]	AM1|COSMO	796
cycloaddition, ketene/imine, [2+2]	MP*n*|COSMO	747
	HF|multipole expansion	774
cytosine methylation in water	HF|IPCM	605
decarboxylation of 2-oxetanones in *o*-dichlorobenzene	HF, MP2, B3LYP|Onsager, multipole expansion, PCM, IPCM, SCIPCM	798
dechlorination of environmental contaminants by Fe(0), correlation of rate constants with solvated orbital energies	PM3|COSMO	810
dehalogenation of 4-chlorobenzoyl CoA in water	PM3|SM*x*	799
Diels—Alder reactions in water	HF|multipole expansion	87,812
epoxidation of allyl alcohol by dioxiranes in acetone	B3LYP|PCM	808
Favorskii rearrangement of α-chlorocyclobutanone	HF|multipole expansion	800
formamide, amide bond rotation, in water	HF|PCM	786
formate dehydrogenase, hydrogen transfer in acetonitrile and water	PM3, HF|SM*x*, SCIPCM	801
Friedel—Crafts reaction in water	HF|multipole expansion	776
halogenation of alkenes, electrophilic, in different solvents	HF|multipole expansion	782
Horner—Wadsworth—Emmons reaction	B3LYP|PCM	809
1,2-hydrogen shifts, methylphenylcarbene, -nitrenium, -borenide, various solvents	AM1|SM*x*	242
hydrolysis of ferric ion in water	B3LYP|Poisson	813
hydrolysis of *β*-lactams in water	PM3|SM*x*	793,802
	HF|multipole expansion	789
hydrolysis of mustard gas	AM1|SM*x*	784
	HF|GB	814
hydrolysis of phosphate esters in water	HF|PCM	803
	MM, HF|Poisson	804
	HF|Poisson	777
	PM3|SM*x*	309
	MP2|PCM, LD	803,815
internal rotation in *N*,*N*-dimethylamides	MP2|IPCM	154
internal rotation in 1,3-dimethylthiourea	AM1, PM3|SM*x*	508
internal rotation in furfural	MP2|Onsager and IPCM	160
Menschutkin reactions (e.g., S_N2 reaction of CH_3Cl with NH_3) in various solvents	HF|PCM	771
	HF|multipole expansion	208
	MP2, BH&HLYP|COSMO	186
	MCSCF|PCM	816
	PM3|SM*x*	304
	B3LYP|SCIPCM	817
	SINDO1|PCM	818
metalation of methane by $(CH_3Li)_2$ in THF	HF, B3LYP|PCM	819
nucleophilic substitution of 1-phenylethyl chlorides in water	AM1|SM*x*	794
polysiloxane from ring-opening polymerization of oligosiloxanes	HF|Poisson	820
	HF|PCM	821
proton transfer between H_2O or NH_3 and H_3O^+ in water	MP2|PCM	788
proton transfer between NH_3 and NH_4^+ in water	PM3|SM*x*	304
racemization of amino acids in water	B3LYP|IPCM, SCIPCM	787
ribonucleotide reductase, catalytic mechanism in (continuum) protein	B3LYP|SCIPCM	805
trihalide ion formation in various solvents	HF|GB	822,823
VX nerve agent, detoxification of, in water	AM1, HF|GB, PCM	806
zirconocene-catalyzed polymerization of ethylene in toluene	MNDO/d, BPW91|SM*x*	312
zwittazido cleavage of 4-azido-2-pyrrolinones in benzene and toluene	MP2|multipole expansion	797

reproduced and explained the experimental results for the gas-phase-to-aqueous speedup, the methyl-to-ethyl enhancement of the speedup, and several kinetic isotope effects. These calculations are important for illustrating the general applicability of the POLYRATE computer program[831,832] for VTST + tunneling calculations to reactions in liquid solutions including all degrees of the solute.

8.2. Nonequilibrium Solvation

Marcus' nonequilibrium continuum electric polarization theory,[38,39,337,686,688,692,759,833,834] mentioned above in conjunction with electronic spectroscopy, has also been used for chemical reaction dynamics.[352,687,741,759,764,765,835] Applications to date have made a number of nonsystematic approximations which must be removed if this treatment is to develop into a generally applicable method. A critical issue is whether one can incorporate realistic microscopic relaxation times and solute–solvent couplings into this theory.[836]

A nonequilibrium formulation that addresses the microscopic solute–solvent couplings and relaxation times more directly is the generalized Langevin approach to defining effective solvent coordinates.[352,687,741,742,744,752,758–765,837] In principle, calculations by this formulation can be systematically converged (within the assumption[838] of linear solute–solvent coupling), and all the microscopic parameters of this theory can be obtained from solute-constrained force–force correlation functions. The latter can be calculated from classical molecular dynamics simulations with explicit solvent, provided that the solute and solvent are sufficiently classical and the force fields used for the simulations are reliable. The latter is still far from assured in the present early days of polarizable force fields.

The generalized Langevin approach can be related to the nonequilibrium electric polarization field methods in various ways, and discussions of frequency-dependent friction,[839,840] frequency-dependent dielectric functions,[841–846] a distribution of relaxation times due to a spatially nonhomogeneous polarization field,[847] wave-vector-dependent dielectric functions,[848,849] and the contribution of specific solvent motions to the early time response[850] are particularly relevant. One possible approach to unifying these themes for nonequilibrium effects would be to use the same partition that has been successful for equilibrium properties, namely, bulk electrostatics and first-solvation-shell effects. Electrostatics can be treated with macroscopic solvent parameters, full SCRF calculations, and Marcus' nonequilibrium electric polarization theory or its various extensions. One would then recognize that first-solvation-shell effects must also be added by explicit solvent molecules or by one or more fictitious solvent modes with microscopic coupling constants and relaxation times. Just as for equilibrium quantities, the challenges are (i) make the first-solvation-shell terms consistent with the bulk electrostatic treatment, e.g., consistent with the choice of dielectric boundary, and (ii) make the partition into bulk electrostatics and first solvation shell as "physical" as possible for interpretive purposes, to obtain meaningful solute properties and to promote transferability of parameters.

A physically appealing method for defining nonequilibrium polarization fields for chemical reactions is to use the equilibrium polarization field at a nearby value of the reaction coordinate as a nonequilibrium polarization field at the present value of the reaction coordinate.[352,741] This reduces the infinite number of degrees of freedom of the polarization field to a manageable subset of electric polarization modes—in fact to a subset of one if the differences between nearby values and the current value are assumed proportional to the first derivative of the polarization field with respect to the reaction coordinate.[741] This kind of approach was first applied to the $Cl^- + CH_3Cl$ reaction.[352,741] More recently, Tomasi and co-workers[851,852] and Ruiz-López et al.[765] have calculated nonequilibrium solvent effects on the $F^- + CH_3F$ reaction in water. Tomasi and co-workers assumed that the inertial polarization of the solvent is frozen on the time scale of reaction coordinate motion. They found nonequilibrium effects of 2–11 kcal, which appear unrealistically large, at least at the high end. Ruiz-López et al. also began with the frozen solvent formulation but using the Marcus nonequilibrium polarization theory. They found that the nonequilibrium free energy of activation is 0.6 kcal higher than the equilibrium one; this would contribute a factor of 0.4 to the transmission coefficient. However, this is probably overly restrictive. Allowing fluctuations in an effective solvent coordinate eliminates this restriction and raised their estimate of κ to 0.6–0.9. Assfeld et al.[782] applied the same continuum method as used by Ruiz-López et al. to estimate the nonequilibrium solvation effect in the reaction $Br_2 + C_2H_2 \rightarrow CH_2BrCH_2Br$. They obtained $\kappa = 0.6$. Models employing explicit solvent can be used to gain insight into the assumption that solvent is sometimes frozen on the time scale of fast nuclear displacements in chemical reactions.[853,854]

Timoneda and Hynes[855] presented a theory for nonequilibrium free energy surfaces for proton transfer from phenol to an amide in chloroform or acetone. In this reaction two charged species are created which would not be created in the gas phase or in a nonpolar solvent like cyclohexane. The authors used valence bond theory and a solvent coordinate representing the orientational polarization of the solvent. Li et al.[856] studied proton donation by imidazole to formate in water. They assumed an equilibrium solvation treatment of the electronic polarization of the solvent but a frozen-solvent treatment of the inertial polarization of the solvent. Nonequilibrium effects on proton-transfer reactions have also been considered by Ruiz-López et al.[835]

Garrett and Schenter[744] evaluated the nonequilibrium effect on a solution-phase reaction, $H + C_6H_6$, for which they included tunneling contributions with a multidimensional semiclassical transmission coefficient based on three solute coordinates and one effective solvent coordinate. They found that nonequilibrium effects decreased the rate constant by a factor of 0.7 when tunneling was not included and a factor of 0.6 when it was. The correctness of the theory was validated by applying it to muon $+ C_6H_6$, where tunneling and nonequilibrium effects are much larger. This kind of treatment was generalized to include all the degrees of freedom of the solute and to include large-curvature tunneling, and as an example, it has been applied to the reaction of H with CH_3OH in water.[857]

Warshel and co-workers have also modeled nonequilibrium free energies and transmission factors in polar solvents, primarily by using an energy-gap coordinate to represent solvent polarization.[402,740,836,854,858,859] These authors have paid particular attention to the consistent treatment of solute–solvent coupling at the molecular level,[402] and they have advocated the use of an energy gap autocorrelation function rather than the force–force correlation function.

The ne plus ultra of nonequilibrium reaction types is the electron-transfer reaction.[347–349,353,359,360,667,687,693,834,839,841,847,860–881] In this kind of reaction the charge distribution of a molecule can change so suddenly that the nonequilibrium effects are similar to those found for electronic excitation by photon absorption.[693,882] Furthermore, the solvent participation in the reaction coordinate often becomes ~100%, i.e., the zero-order picture changes from solvent and other solute modes coupled to a solute-dominated reaction coordinate to solute and other solvent modes transverse to a solvent collective motion as reaction path. This subject has an extensive literature and has received many separate reviews. One can anticipate that electron-transfer reactions will continue to provide the most severe test of nonequilibrium solvation theories and the stimulus for new ideas.

A prototype problem that brings one of the central issues of electron transfer kinetics into sharp focus is the formation of I_2^- and its vibrational relaxation in polar solvents. In electron transfer from I_A^- to I_B, where A and B simply label the two iodine atoms, the initial state consists of the electron localized on I_A and the final state consists of the electron localized on I_B. At a given I–I separation in the gas phase, this electron would be symmetrically delocalized in a σ_u orbital. Thus, the condensed phase situation is an example of solvent-induced localization. However, for small I–I separations, the electron is delocalized even in liquid solutions. Stretching I_2^- far enough in a liquid solvent will cause the delocalized electron to localize on one or another center. Modeling the competition between covalency-induced exchange delocalization and solvent-induced localization goes to the very heart of solvation modeling. Hynes and coworkers[355,883,884] modeled this competition very successfully with valence bond theory and implicit solvent and showed that the transition between a symmetrical and asymmetrical charge distribution occurs at an I–I separation r of about 4 Å. For large amounts of vibrational excitation, i.e., when I_2^- samples the region with $r \approx 5-6$ Å, the frictional drag on the moving charge accelerates the vibrational relaxation rate. Related examples of solvent-induced symmetry breaking or charge transfer occur in I_3^- ion[885] and in the problem of twisted intramolecular charge transfer (TICT) states.[837,886,887]

Kim and Hynes[837] calculated the unimolecular reaction rate constant k_S of the TICT reaction of photoexcited *p*-(*N*,*N*-dimethylamino)benzonitrile, which involves a twisting motion of the dimethylamino group, for three solvents S. Experimentally $k_{\text{acetonitrile}}:k_{\text{methanol}}:k_{\text{ethanol}} = 2:1.5:1$. Kim and Hynes calculated 1.3:1.2:1 with equilibrium solvation, 1.15:1.3:1 with nonequilibrium solvation without dissipative friction, and 1.7:1.4:1 with dissipative friction.

Mathis and Hynes[888] provided a detailed analysis of the S_N1 ionization of *tert*-C_4H_9I in several solvents from two different perspectives. The first approach[888–890] used the "chemical reaction perspective" of a solute reaction coordinate coupled to a collective solvent coordinate. In this approach, large nonequilibrium solvation effects (1–4 kcal) were found. The second approach[888] used electron transfer theory where the reaction coordinate is treated as a solvent coordinate and the rate constant is evaluated as a function of nuclear geometry and then averaged over a distribution function of such geometries. In this approach it was necessary to include the dependence of solvent barrier on solute geometry (mathematically this means that not only is the orientation of R optimized, but the dividing surface is curved[891]). With this modification the two approaches give similar results for the rate constant, with the first, more general approach being slightly better. Marcus[892] has also discussed nucleophilic substitution reactions in the context of electron transfer theory, and he presented a unified expression for the reorganization energy.

8.3. Nonhomogeneous Media

An interesting application area for continuum models is reactivity in supercritical fluids, and there have been applications by three groups.[23,893–901] Both compressible and incompressible fluid models have been employed. Nonequilibrium effects have been considered as well.[897] A point of common interest where the reader can compare the various treatments is the $Cl^- + CH_3Cl$ reaction in supercritical water, which has been treated by all three groups. As a caveat, however, Cossi et al.[829] pointed out that the electrostatic component of the solvation energy of the $Cl^- + CH_3Cl$ transition state even in normal water depends strongly on atomic radii, and no doubt other workers have noticed such dependencies too. We still need more experience to know how reliable the solvation calculations are for transition states.

Another example of reactions in a nonhomogeneous medium is reaction near a lipid–water interface or reactions of guest molecules bound to macrocyclic hosts which are treated as a low-dielectric environment. Sakurai and co-workers[633,902] studied the transition state for decarboxylation of phenylcyanoacetate at a high dielectric constant/low dielectric constant interface. The reaction center of the transition state was shown to be more electron rich at the interface than in pure aqueous media. The electrostatic contributions to biomembrane processes have also been studied by Honig and co-workers.[903–906]

The Pisa group has extended the PCM model with dispersion interactions to treat systems in which there are two domains, each with a different dielectric constant.[634,636,907,908]

Stefanovich and Truong[635,909] have combined continuum dielectric theory and the COSMO model[179] with the embedded cluster approach[910–917] to treat systems at a liquid–crystal interface.

9. Conclusion

Continuum solvation models, especially when augmented by microscopic parameters implicitly describing the first solvation shell, can provide qualitative insight into a wide variety of solvation phenomena. In many cases, such implicit models are also the most effective choice enabling quantitative calculations to be undertaken. Future prospects are very bright for useful applications to partitioning and equilibria and solvent effects on molecular properties, including spectra, binding, and reactivity. The quantitative accuracy of such calculations for small solutes will improve as continuum solvation models including solute electron correlation become better developed. The applicability of these methods to large solutes will improve as we develop more experience with multilevel methods and methods that combine quantum mechanics with classical mechanics.

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