

Continuum solvation models: Dissecting the free energy of solvation

F. Javier Luque,^{*a} C. Curutchet,^a J. Muñoz-Muriedas,^a A. Bidon-Chanal,^a I. Soteras,^a
A. Morreale,^b J. L. Gelpi^b and Modesto Orozco^{*b}

^a Departament de Fisicoquímica, Facultat de Farmàcia, Universitat de Barcelona, Av. Diagonal s/n, 08028 Barcelona, Spain. E-mail: javier@far1.far.ub.es

^b Departament de Bioquímica i Biologia Molecular, Facultat de Química, Universitat de Barcelona, c/. Martí i Franqués 1, 08028 Barcelona and Unitat de Modelització Molecular i Bioinformàtica, Institut de Recerca Biomèdica. Parc Científic de Barcelona, c/. Josep Samitier 1, 08028 Barcelona, Spain. E-mail: modesto@mmb.pcb.ub.es

Received 18th June 2003, Accepted 23rd July 2003

First published as an Advance Article on the web 4th August 2003

The most usual self-consistent reaction field (SCRF) continuum models for the description of solvation within the quantum mechanical (QM) framework are reviewed, trying to emphasize their common roots as well as the inherent approximations assumed in the calculation of the free energy of solvation. Particular attention is also paid to the specific features involved in the development of current state-of-the-art QM SCRF continuum models. This is used to discuss the need to maintain a close correspondence between each SCRF formalism and the specific details entailing its parametrization, as well as the need to be cautious in analyzing the balance between electrostatic and non-electrostatic contributions to the solvation free energy between different SCRF models. Finally, special emphasis is given to the post-processing of the free energy of solvation to derive parameters providing a compact picture of the ability of a molecule to interact with different solvents, which can be of particular interest in biopharmaceutical studies.

Introduction

An overview of theoretical studies over the last decades shows the extraordinary evolution experienced by quantum mechanical methods in their application to the study of chemical systems.¹ The research effort put into this field has crystallized in a series of elaborate methods, which have impelled quantum mechanical chemistry to approach the limit of “experimental” accuracy in the gas phase. The Nobel Prize awarded to Kohn and Pople in 1998 is a clear recognition of the impact of quantum theory in the chemical scenario. In the beginning of the 21st century there is no doubt that quantum chemistry constitutes an extremely powerful tool to understand the structural and reactive properties of molecules in the gas phase.

The study of chemical systems in condensed phases is, however, far more difficult.² The main limitation consists of the enormous number of molecules that must be considered in a dynamic way to represent the assembly of chemical (solute, solvent) entities which constitutes the solution state. Such a complexity has given rise to a wide variety of computational approaches,³ which include methods based on (i) the elaboration of physical functions; (ii) computer simulation of classical liquids, where any property of the system is obtained from an ensemble of configurations representative of the solute–solvent system; (iii) a supermolecule description of the solution, which provides limited, but detailed information about specific solute–solvent interactions, (iv) the combination of quantum mechanical treatments of the solute with statistically averaged descriptions of discrete solvent molecules, and (v) continuum models, where the attention is mainly focused on one component of the system, the solute, whereas the solvent is treated in a very simplified way as a polarizable medium.

In the last decades there has been an evolution towards more elaborate methods for the study of condensed phases. Combined strategies using the diverse methods mentioned above

for the solvent molecules in conjunction with classical or quantum mechanical treatments of the solute have given rise to a plethora of methods, which are under continuous progress. A comprehensive analysis of the evolution experienced by these methods has been given in several reviews,³ which provide a critical evaluation of their suitability for the study of chemical and biochemical systems.

This paper gives an overview of the current status and of the perspectives of theoretical treatments of solvent effects based on continuum solvation models where the solute is treated quantum mechanically. It is worth stressing that our aim is not to give a detailed description of the physical and mathematical formalisms that underlie the different continuum models examined here, since this issue has been covered in preceding reviews.⁴ Rather, our goal is to stress the features that have contributed to make continuum methods successful, to examine the factors that limit their reliability and to point out potential areas where those methods can be useful to our understanding of (bio)molecular systems in solution.

The basic continuum model

Continuum solvation models rely on the definition of an effective Hamiltonian for the solute M , \hat{H}_M (eqn. (1)), which can be expressed as the addition of the usual electronic Hamiltonian *in vacuo*, \hat{H}_M^0 , and an interaction potential, \hat{V}_{int} . Within the Born–Oppenheimer approximation, the Hamiltonian of the solute depends on the coordinates of the electrons, \mathbf{q} , and parametrically on the coordinates of nuclei, \mathbf{Q} . The interaction potential also depends on the solvent coordinates, collectively denoted by $\mathbf{\Omega}$, so that $\hat{V}_{\text{int}} = \hat{V}_{\text{int}}(\mathbf{q}, \mathbf{Q}, \mathbf{\Omega})$.

$$\hat{H}_M(\mathbf{q}, \mathbf{Q}, \mathbf{\Omega}) = \hat{H}_M^0(\mathbf{q}, \mathbf{Q}) + \hat{V}_{\text{int}} \quad (1)$$

Following Ben-Naim’s definition of a solvation process,⁵ the

embedding of a solute into a given solvent can be defined as the process in which a particle of the solute is transferred from a fixed position in the gas phase into a fixed position in solution at constant temperature, pressure, and solvent composition. Under these conditions, the Gibbs free energy of solvation, ΔG_{sol} , can be related to the reversible work necessary to build up the solute M in the solvent S at equal number densities in the gas phase and in solution. Such a work includes direct solute–solvent interactions as well as the contributions due to internal changes in the solute and solvent upon solvation (eqn. (2)).

$$\Delta G_{\text{sol}} = W(\text{M/S}) + RT \ln \left(\frac{(q_{\text{rot}} q_{\text{vib}})_{\text{gas}}}{(q_{\text{rot}} q_{\text{vib}})_{\text{son}}} \right) \quad (2)$$

where $W(\text{M/S})$ stands for the coupling work of the solute M in the solvent S, and q_{rot} , q_{vib} denote the partition function for rotation and vibration of M.

The preceding definition omits the contribution due to the so-called “liberation free energy” (eqn. (3)), which arises from the differences in momentum partition functions, A_{M} , of the solute in the gas phase and in solution.

$$\Delta G_{\text{lib}} = -RT \ln \left(\frac{A_{\text{M, gas}}}{A_{\text{M, son}}} \right) \quad (3)$$

The coupling work between M and S can be determined by the charging parameter method (eqn. (4)),⁶ where the transition from the states corresponding to the isolated solute + pure solvent to the solute immersed in the solvent (denoted by indexes 0 and 1, respectively) is performed by means of a charging parameter, λ , so that the interaction between solute and solvent is progressively turned on as λ varies from 0 to 1.

$$W(\text{M/S}) = \int_0^1 d\lambda \int d\Omega [\rho_{\text{S}}(\lambda) V_{\text{int}}(\mathbf{q}, \mathbf{Q}, \mathbf{\Omega}) g_{\text{S}}(\mathbf{\Omega}; \lambda)] \quad (4)$$

where $g_{\text{S}}(\mathbf{\Omega}; \lambda)$ denotes the thermally averaged distribution function of the infinite assembly of solvent molecules corresponding to the interaction potential $\lambda V_{\text{int}}(\mathbf{q}, \mathbf{Q}, \mathbf{\Omega})$.

The partition of the reversible work $W(\text{M/S})$ into several contributions,⁷ typically cavitation, dispersion, repulsion and electrostatic components, allows solving eqn. (4) from consecutive integrations that involve different charging parameters: (i) a length-dependent parameter for cavitation, a parameter related to (ii) the electron transition density for dispersion, or (iii) the electron overlap for repulsion, and a parameter associated to (iv) the electric charge for electrostatics. We should note that such partitioning is convenient from a practical point of view, but it is not strictly rigorous because it neglects the mutual coupling between the components of the solute–solvent interaction potential. In other words, due to its nature of state function, the free energy computed directly or in several independent integrations is the same, but this is not true for its components.

Since only the total free energy of solvation is experimentally measurable, to assess the magnitude of the coupling between the different terms is difficult. The development of theoretical formalisms that consider explicitly the mutual coupling between the different contributions appears to be the only valuable approach to determine the reliability of the partitioning scheme.^{8,9} Though the computational cost of the calculations still limits the range of applicability of these studies, it can be assumed that the most important fraction of the solvent reorganization effects arises from cavitation and electrostatics, especially for polar solvents. Since cavitation contains the largest portion of the repulsion term, the coupling between repulsion and electrostatics is expected to be small. It can also be considered that dispersion is weakly coupled to electrostatics, at least for neutral solutes and polar solvents. Under

these assumptions, the separate treatment of electrostatics and non-electrostatics terms in continuum models might be justified. Particularly, the basic continuum model involves a simplified form of the interaction potential, \hat{V}_{int} , which is reduced to the electrostatic component, whereas non-electrostatic terms are generally determined by using a variety of formalisms that mainly exploit geometrical parameters of the solute and general properties of solvent.

Based on the preceding discussion, eqn. (1) typically deals only with the electrostatic problem of the solvation of a solute in a given solvent, which is treated as a linear isotropic polarizable medium characterized by suitable macroscopic properties, such as the permittivity of the bulk solvent. Nevertheless, the perturbation created upon inclusion of the solute makes that the solvent molecules surrounding the solute exhibit properties clearly different from those of the bulk solvent. Since the accurate representation of the differential response of the solvent molecules located closer to the solute in a continuum model is not straightforward, most methods consider a simple *bulk-like* electrostatic component, correcting short-range effects in some effective way, either by modulating the location of the boundary between solute and solvent or by adjustment of the non-electrostatic contributions.

The non-electrostatic problem in continuum methods

Cavitation

This term accounts for the work spent in creating a cavity of appropriate volume and shape to accommodate the solute into the bulk solvent. Once the cavity is formed, the other terms—dispersion, repulsion and electrostatics—are switched on by means of the charging parameter method (see above).

Different formalisms have been proposed for the calculation of the cavitation free energy based on the shape and size of the solute and on solvent properties, such as the surface tension, the isothermal compressibility, or the molecular radius and number density.¹⁰ A specially elaborate formulation of the cavitation free energy is Pierotti’s scaled particle theory.¹¹ In this formalism, the molecules are assumed to behave as hard spheres and the cavitation free energy is expanded in powers of the radius of the sphere which excludes the centers of solvent molecules (eqn. (5)). The coefficients K are expressed in terms of properties of the solvent and of the solution (eqns. (6a)–(6d)), such as molecular radius (R_{S}) and number density of the solvent (n_{S}), pressure (P) and temperature (T).

$$\Delta G_{\text{cav}} = K_0 + K_1 R_{\text{MS}} + K_2 R_{\text{MS}}^2 + K_3 R_{\text{MS}}^3 \quad (5)$$

$$K_0 = RT \left[-\ln(1-y) + \frac{9}{2} \left(\frac{y}{1-y} \right)^2 \right] - \frac{4\pi R_{\text{S}}^3 P}{3} \quad (6a)$$

$$K_1 = -\frac{3RT}{R_{\text{S}}} \left[\frac{y}{1-y} + 3 \left(\frac{y}{1-y} \right)^2 \right] + 4\pi R_{\text{S}}^2 P \quad (6b)$$

$$K_2 = \frac{3RT}{R_{\text{S}}} \left[\frac{y}{1-y} + \frac{3}{2} \left(\frac{y}{1-y} \right)^2 \right] - 4\pi R_{\text{S}} P \quad (6c)$$

$$K_3 = \frac{4\pi P}{3} \quad (6d)$$

where $y = 4\pi R_{\text{S}}^3 n_{\text{S}}/3$, and R_{MS} is the sum of the radii of solvent and solute, *i.e.* $R_{\text{MS}} = R_{\text{M}} + R_{\text{S}}$.

Pierotti’s formalism is expected to work reasonably well for solvents and solutes of small, spherical size. However, the suitability of the method for solvents having nonspherical shape is more delicate, it being then necessary to define an effective radius for the solvent molecules. For instance, in the case of *n*-octanol an effective radius of 6.8 Å was derived from an

accurate parametrization based on solubility data of rare gases in this solvent.¹² The extension of Pierotti's formalism to solutes having complex shape can be done following Claverie's equation (see eqn. (7)),¹³ where the free energy of cavitation computed for each atom in the molecule is weighted by a factor proportional to the solvent-exposed surface of that atom.

$$\Delta G_{\text{cav}} = \sum_i \frac{S_i}{4\pi R_i^2} \Delta G_{\text{cav}}(R_i) \quad (7)$$

Dispersion–repulsion

In methods based on a discrete treatment of molecules these contributions are typically evaluated from pair potentials expressed as truncated expansions in powers of $1/r$ that relate suitable chemical fragments (atoms, bonds, chemical groups) of solute and solvent molecules. For a solute (M) surrounded by solvent (S) molecules, the average dispersion–repulsion energy can be determined from eqn. (8), where N_S is the number of fragments of type s in the solvent molecule, n_s is the macroscopic density of the solvent, and g_{ms} is a correlation function between chemical fragments m and s .

$$\langle E_{\text{dis-rep}} \rangle = n_S \sum_{s \in S} N_S \sum_{m \in M} \int U_{ms}(r_{ms}) g_{ms}(r_{ms}) dr_{ms}^3 \quad (8)$$

where

$$U_{ms} = \sum_k \alpha_{ms,k} r_{ms}^{-k} \quad (9)$$

with k denoting the different terms considered in the truncated expansion, and $\alpha_{ms,k}$ being the coefficients of the series expansion.

For each solute fragment m , an exclusion volume where no s solvent units exist can be defined. The union of all the exclusion areas around the solute defines a cavity with a surface σ , which allows the reformulation of eqn. (8) in terms of surface integrals (eqn. (10)) by means of auxiliary functions $A_{ms}(r_{ms})$ (eqn. (11)). Different approximations have been considered to solve eqn. (11), such as the replacement of the functions $g_{ms}(r_{ms})$ by factors calibrated for a given solute,^{14a} or the adoption of explicit, but simple forms for $g_{ms}(r_{ms})$, such as the so called “uniform approximation”,^{14b} where $g_{ms}(r_{ms})$ is 0 or 1 depending on whether the distance r_{ms} lies or not within the solute cavity.

$$\langle E_{\text{dis-rep}} \rangle = n_S \sum_{s \in S} N_S \sum_{m \in M} \int_{\sigma} A_{ms} n_{\sigma} d\sigma \quad (10)$$

where n_{σ} is the outer normal to the surface at position σ .

$$\vec{\nabla} A_{ms}(r_{ms}) = U_{ms} g_{ms}(r_{ms}) \quad (11)$$

Simpler expressions to the calculation of the dispersion–repulsion contribution rely on the assumption of a linear dependence with the molecular surface (eqn. (12)). In fact, previous studies have shown a linear relationship between the dispersion–repulsion values computed from eqn. (10) in the “uniform approximation” approach and the van der Waals surface (and volume) for hydrocarbons.^{15a} Moreover, linear relationships have also been found for the solvation free energy of hydrocarbons and the solvent-accessible surface^{15b}.

$$\Delta G_{\text{dis-rep}} = \sum_k \zeta_k A_k \quad (12)$$

where A_k denotes the contribution of a given atom to the surface of the cavity and ζ_k is the surface tension of atom k .

The simplified expression given by eqn. (12) takes advantage of the fact that dispersion forces decay as r^{-6} , which facilitates the contribution of a given atom to be less dependent on the nature and spatial distribution of nearby atoms. It must be

noted, nevertheless, that models based on a simple surface area dependence might not be totally adequate for large solutes, where buried atoms (*i.e.*, those not directly accessible to the solvent) can play a relevant contribution to the dispersion interaction. In these cases addition of a term related to the solvent excluded volume appears to be necessary.¹⁶

It is also worth to distinguish between the microscopic atomic surface tensions used in continuum models and the macroscopic surface tension of the solvent. The parameters ζ_k are typically derived by fitting to experimental free energies of solvation (see below). Therefore, besides dispersion–repulsion contacts between solute and solvent, they have to effectively account for any systematic inaccuracy in the electrostatic treatment as well as for other effects ascribed to the interaction of the solute with the solvent molecules in the first-solvation shell.

The electrostatic problem in continuum methods

Within the framework of the linear response approximation, the QM treatment of the solute embedded in a continuum is formally represented by the Schrödinger equation given in eqn. (13), where the perturbation operator added to the solute Hamiltonian, \hat{V}_{ele} , couples the electrostatic response of the solvent, characterized by the macroscopic dielectric constant ϵ , to the charge distribution of the solute, ρ_M , and E is the electronic energy of the solute plus the electrostatic contribution to the free energy of solvation. The factor $\frac{1}{2}$ in eqn. (13) accounts for the work spent in polarizing the solvent, which amounts to half the solute–solvent interaction energy.

$$\left[\hat{H}_M^0(\mathbf{q}, \mathbf{Q}) + \frac{1}{2} \hat{V}_{\text{ele}}(\mathbf{q}, \mathbf{Q}, \rho_M, \epsilon) \right] \Psi(\mathbf{q}, \mathbf{Q}) = E(\mathbf{Q}) \Psi(\mathbf{q}, \mathbf{Q}) \quad (13)$$

The electrostatic free energy can be determined by subtracting the energy of the solute *in vacuo*, E° , to the electrostatic free energy of the solute in solution, G_{ele} (eqn. (14a)), which can be obtained by a variational calculation of the functional given in eqn. (14b), where both the wavefunction of the solute and the reaction field, which are mutually dependent, are simultaneously optimized.

$$\Delta G_{\text{ele}} = G_{\text{ele}} - E^{\circ} \quad (14a)$$

with

$$G_{\text{ele}} = \left\langle \Psi(\mathbf{q}, \mathbf{Q}) \left| \hat{H}^0 + \frac{1}{2} \hat{V}_{\text{ele}}(\mathbf{q}, \mathbf{Q}, \rho_M, \epsilon) \right| \Psi(\mathbf{q}, \mathbf{Q}) \right\rangle \quad (14b)$$

At the Hartree–Fock level, this can be accomplished by a modified Fock matrix, whose elements are altered, in comparison to those appropriate for the solute *in vacuo*, by the addition of the \hat{V}_{ele} contribution to the mono-electronic term (eqn. (15)).

$$F_{\mu\nu} = F_{\mu\nu}^0 + \langle \mu | \hat{V}_{\text{ele}} | \nu \rangle \quad (15)$$

Different methods have been reported in the literature to describe the solvent reaction field, and therefore to solve the electrostatic problem. Here we limit ourselves to point out the most remarkable features of the underlying formalisms and address the reader to specialized reviews for an in-depth explanation of the methods.

Multipolar expansion methods (MPE)

In this approach both the solute charge distribution and the solvent reaction field are expressed as truncated multipolar expansions. This definition encompasses models originally proposed by Born, Kirkwood, Bell and Onsager.¹⁸ The Born model^{18a} involves a monopole in a spherical cavity, which was further elaborated by Kirkwood to account for ionic strength effects.^{18b} Bell's^{18c} model describes the solvation free energy of

a point dipole in a spherical cavity. Onsager's model is a refinement of Bell's treatment by adding to the system an isotropic dipolar polarizability term.^{18d} Further improvements to these methods come precisely from the inclusion of higher terms in the multipolar expansion and from the use of more realistic cavities. In the QM framework, MPE models were developed by Hall *et al.*,^{19a} Tapia and Goscinski,^{19b} Rivail and Rinaldi,^{19c,d} Yomosa,^{19e,f} Karelson and Zerner,^{19g} Mikkelsen and coworkers^{19h} and Wiberg *et al.*¹⁹ⁱ

The Nancy group has developed a very accurate and elegant self-consistent reaction field model based on multipole expansions. In the newest versions of the method multicentric multipolar expansions up to terms with $l = 12$ are used,²⁰ though acceptable convergence is achieved in most cases upon truncation at $l = 6$. Moreover, the spherical cavity was replaced by an ellipsoid^{21a} and subsequently adapted to molecules of general shape.^{21b} Typically the cavity is built up from superpositions of nuclear-centered spheres by using Bondi's atomic radii scaled by a factor of 1.3, which was derived to fit the experimental molecular volume of a set of reference liquids.

By denoting with I, J the centers of the multipolar expansion, the electrostatic component of the solvation free energy is obtained by introducing in the Fock matrix elements, $F_{\mu\nu}$, a term due to the solvent reaction field, as noted in eqns. (16).

$$F_{\mu\nu} = F_{\mu\nu}^0 + \sum_I \sum_J \sum_{l,l'} \sum_{m,m'} \langle \mu | \hat{M}_l^m(I) | \nu \rangle \times f_{ll'}^{m,m'}(I, J) M_{l'}^{m'}(J) \quad (16a)$$

with

$$M_{l'}^{m'}(J) = \sum_{\lambda} \sum_{\eta} \langle \lambda | \hat{M}_{l'}^{m'}(J) | \eta \rangle \quad (16b)$$

where $F_{\mu\nu}^0$ represents the Fock matrix element for the isolated solute, \hat{M}_l^m denotes the operator for the multipolar expansion of the solute charge distribution, and $f_{ll'}^{m,m'}$ are the reaction field factors, which only depend on the dielectric constant of the solvent and on the shape of the cavity.

Extension of the method to account for electron correlation effects has also been considered at the Møller–Plesset perturbation theory or at the density functional theory.²² Moreover, analytical expressions for the first and second derivatives of the free energy have been derived.²³

Generalized Born model (GB)

The GB model can be considered to be a special case of the MPE methods, as it is a multicenter generalization of the one-center Born equation for monoatomic ions. In the GB model the charge distribution is represented by a set of point charges centered at nuclei. The electrostatic component of the solvation free energy is determined from the individual Born solvation of each atom (charge), corrected by the perturbing effect of the other atoms (charges).

Besides preliminary efforts made in the development of GB or related models,²⁴ the most elaborate QM GB method corresponds to the series of SMx models developed by Cramer and Truhlar,^{4f} which were originally implemented in semiempirical AM1 and PM3 methods. Here the elements of the Fock matrix adopt the form indicated by eqn. (17), where only the diagonal elements of the Fock matrix are modified as a consequence of the Kronecker delta function, $\delta_{\mu\nu}$.

$$F_{\mu\nu} = F_{\mu\nu}^0 + \delta_{\mu\nu} \frac{\epsilon - 1}{\epsilon} \sum_{k'} q_{k'} \gamma_{kk'} \quad \text{with } \mu \in k \quad (17a)$$

where

$$q_k = Z_k - \sum_{\mu \in k} P_{\mu\mu} \quad (17b)$$

where k, k' denote atomic indices, Z_k is the nuclear charge of atom k , P is the first-order density matrix, q_k denotes the atomic charge, and $\gamma_{kk'}$ is the Coulomb integral.

The original versions of the solvation model have been refined in a number of ways leading to the latest SM5 model.²⁵ The first remarkable feature is the refinement of the monopole distribution. Earlier versions of the GB model used Mulliken population analysis²⁶ to obtain the atomic charges, but the SM5 model adopts the class IV charges,²⁷ which are based on a mapping procedure aimed at reproducing charge-dependent observables. Particularly, the SM5.42 models rely on the Charge Model 2 (CM2) mapping,²⁸ where atomic charges are determined by first computing Löwdin charges,²⁹ and then by applying the charge mapping indicated in eqn. (18).

$$q_k^{\text{CM2}} = q_k^{\text{Löwdin}} + \sum_{k \neq k'} B_{kk'} (D_{Z_k Z_{k'}} + C_{Z_k Z_{k'}} B_{kk'}) \quad (18)$$

where $B_{kk'}$ is the Mayer bond order between atoms k and k' , and the matrix elements of C and D , which dictate how charge is redistributed between atoms having different atomic numbers, are fitted to reproduce the agreement between experimental gas-phase dipole moments and those computed from CM2 point charges.

Another critical aspect of the GB method is the determination of the effective Born radii for the different atoms, which in turn depends on the intrinsic Coulomb radii and on the geometry of the molecule. In earlier versions of the GB model the intrinsic Coulomb radii were determined as a function of the atomic charge.³⁰ In the SM5 formalism, nevertheless, they are constant for all atoms but hydrogen, which is assigned different values depending on the atom it is attached to. A complementary refinement concerns the treatment of the dielectric descreening, where a number of approximate methods have been examined to estimate the descreening of one part of the solute by the presence of another part of the solute.³¹ The simplest approximation is the use of pairwise descreening function,^{31b} an approach which largely enhances the computational efficiency of the method, and that after some calibration reproduce well more accurate approaches. Moreover, it also facilitates the evaluation of analytic gradients into solvation calculations.

Apparent surface charge (ASC)

A different solution to the electrostatic component of the solvation free energy comes from the apparent surface charge model. Particularly, the original formulation of the polarizable continuum model (PCM) was developed by Miertus, Scrocco and Tomasi.³²

The method relies on the calculation of an apparent surface charge that simulates the solvent response to the perturbing effect generated by the solute's charge distribution. To this end, the solute cavity is tessellated into a number of surface elements small enough as to assume that the solvent's charge density is constant. Then, the apparent charge can be determined from the component of the electric field normal to the surface (eqn. (19)).

$$q_j = -\frac{\epsilon - 1}{\epsilon} S_j \left(\frac{\partial V_T}{\partial n} \right)_j \quad (19)$$

where V_T is the total electrostatic potential, which includes both solute and solvent contributions, n is the unit vector normal to the surface element j , S_j is the area of the surface element j , and ϵ is the solvent dielectric constant.

The electrostatic component of the solvation free energy is obtained by adding a term that account for the electrostatic interaction with those apparent charges to the Fock matrix

elements, $F_{\mu\nu}$ (eqn. (20)).

$$F_{\mu\nu} = F_{\mu\nu}^0 + \left\langle \mu \left| \sum_k \frac{q_k}{|r - r_k|} \right| \nu \right\rangle \quad (20)$$

where the summation runs over the total number of surface elements in which the solute cavity is divided and $\{q_k\}$ is the set of charges (located at r_k) that represents the solvent response.

Different aspects of the physical and mathematical features of the original PCM have been refined over the years. First, owing to the mutual dependence between solute and solvent charge distributions (eqns. (19) and (20)), an iterative procedure was initially proposed to obtain self-consistency between the solute wavefunction and the apparent charges spread on the cavity surface. This iterative procedure was reformulated using other procedures, such as the closure approach^{33a} or the matrix-inversion method.^{33b,c} Within this latter formalism, the development of analytical expressions for the first and second free energy derivatives has allowed the implementation of algorithms for geometry optimization in solution.³⁴

Another issue that has deserved particular attention has been the treatment of the charge compensation, which stems from (i) the tails of the solute charge density that escape from the solute cavity, and (ii) numerical errors due to tessellation of the cavity surface. Originally this effect was corrected by defining a factor, f^X , that satisfies the relation given by eqn. (21), where X denotes the net charge of the solute.

$$f^X \sum_k q_k = -\frac{\epsilon - 1}{\epsilon} Q_M^X \quad (21)$$

where Q_M denotes the total charge of the solute.

The most elaborate treatment of the charge compensation relies on two features.³⁵ First, the introduction of separate factors for the apparent charges induced by the nuclei and the electrons. In this case Q_M^X (see eqn. (21)) accounts for the total nuclear charge ($X = N$) and for the total number of electrons ($X = e$). Second, the explicit treatment of the escaped charge density as a source of an effective apparent charge. This is achieved by computing the escaped solute charge, Q_{tot} , from the difference between the total number of electrons, N_{el} , and the solute charge really inside the cavity, Q_{in} , which is determined by resorting to the Gauss theorem (eqn. (22)). It is worth noting that by calculating with sufficient accuracy the outer solute charge, Q_{out} , and by taking into account its effect through an extra set of apparent charges, the solvent response induced by the nuclei and the solute charge density inside the cavity are then only affected by the same numerical errors.

$$Q_{\text{out}} = -(N_{\text{el}} - Q_{\text{in}}) = -\left(N_{\text{el}} + \frac{1}{4\pi} \int_S \mathbf{E}_M(s) \cdot \hat{\mathbf{n}}_s \cdot d\mathbf{s} \right) \quad (22)$$

Another aspect that has deserved particular research effort has been the refinement of the procedure used to build up the solute/solvent interface, which has been reformulated to obtain a finer description of the cavity as well as to deal with medium-to-large size solutes.³⁶ Finally, while the original PCM model was developed to treat an isotropic homogeneous medium, the Pisa group has also made efforts to deal with more complex systems, including anisotropic dielectrics and ionic solutions, within the so-called integral equation formalism,³⁷ which represents a significant improvement with regard to the original formulation.

Inclusion of correlation effects within the PCM method has also been performed at different levels,³⁸ using CI, MC-SCF, MBPT and density functional theories. Particular attention has been paid to the inclusion of solvent effects only at the energetic level or both at the energetic and density matrix levels simultaneously.

A closely related ASC method is the conductor-like screening model (COSMO) developed by Klamt and Schüürman.³⁹

The main feature of COSMO is that the solvent response is treated by assuming an ideally screening state corresponding to a conductor instead of a dielectric. The main practical benefit of this approach arises from the simplification of the electrostatic problem, which facilitates the calculation of analytic gradients. The transition from a conductor to a high polar solvent is not difficult, but such a transition is less evident for a low polar solvent. To this end, the authors introduced an empirical factor, $f(\epsilon)$ (see eqn. (23)), to correct the electrostatic free energy, where the parameter δ was chosen to be $\frac{1}{2}$ as a compromise between the optimal values for a net charge and for a dipole embedded in a cavity. Finally, the problem of the escaping charge density was corrected by using an auxiliary cavity lying approximately 1 Å further outside the main cavity.^{39b}

$$f(\epsilon) = (\epsilon - 1)/(\epsilon + \delta) \quad (23)$$

Other methods based on a conductor-like description of the solvent have been reported in the last years.⁴⁰ Compared to the Klamt–Schüürmann COSMO model, the main differences concern the definition of the cavity and the treatment of the charge outlying effects. Moreover, the choice of different values for the parameter δ (eqn. (23)) depending on the solute charge, specially in apolar solvents, has also been investigated.

An extension of the model is the so-called COSMO-RS (real solvent) method.⁴¹ In this approach both solute and solvent molecules are initially described by means of COSMO calculations, which provide ideally screened (free) energies and apparent charge densities. The intermolecular interactions then described as pairwise interactions of surface segments. Accordingly, the deviations from ideal screening are described as pairwise misfit interactions (eqn. (24)) of the ideal apparent charges on contacting parts of the solute and solvent molecules.

$$E_{\text{misfit}}(\sigma, \sigma') = \frac{\alpha'}{2} (\sigma + \sigma')^2 \quad (24)$$

where σ, σ' are the local screening charge densities of the interacting pieces of surface, and α' is an adjustable parameter that accounts for corrections in effective contact area and the reduction in the misfit energy due to electronic polarization of the interacting surface segments.

The solute cavity: parametrization of continuum models

A key issue in any continuum model is the definition of the solute–solvent interface, since it largely modulates the electrostatic contribution to the solvation free energy. Generally cavities are built up from the intersection of atom-centered spheres whose size is determined from fixed standard atomic radii.⁴² However, other strategies have been proposed, such as the use of variable atomic radii, whose value depends on the molecular environment or the charge distribution of the solute,⁴³ the analysis of radial distribution functions obtained from discrete simulations of diluted systems⁴⁴ or the choice of a given isodensity contour.⁴⁵ Finally, though most SCRF methods use the same cavity for all the solvents, solvent-adapted cavities have also been considered.⁴⁶

The development of any continuum model unavoidably implies certain degree of arbitrariness, which mainly involves the choice of the solute cavity and the treatment of non-electrostatic contributions to the solvation free energy. In turn, this requires a certain parametrization effort, mostly accomplished by fitting experimental and predicted free energies of solvation, but also extended to properties such as solvatochromic effects, solvent-induced shifts in chemical equilibria, or specific properties of solutes in solution.^{2,3d,g,4} Though the limited

size of this manuscript precludes a detailed description, it is worth to point out here the main features underlying the parametrization of the most commonly used continuum models.

The MPE model

This model was parametrized by Tuñón *et al.* to treat solvation in water.⁴⁷ The electrostatic term was determined at the Hartree–Fock level with the 6-31G(d) basis using a mono-centric multipolar expansion up to $l = 6$ and an ellipsoidal cavity, whose size was related to the axes of inertia of a solid of uniform density limited by a van der Waals surface and whose volume was constrained to be equal to the average molecular volume in the liquid.

The nonelectrostatic terms were treated by using a linear relationship with the atomic contribution to the surface area (eqn. (25)). Accessible surface areas were calculated adding the radii of a water molecule (1.4 Å) to the van der Waals radii of the solute atoms. Each atomic surface tension is constant for a specific atom type (C, N and O; different atom types were considered for hydrogens depending on whether they are bonded to C, N or O atoms) and was obtained by fitting to the experimental free energies of hydration for a series of 35 small and medium-size neutral organic molecules, with a root-mean square deviation between calculated and experimental values of 0.75 kcal mol⁻¹.

$$G_{n\text{-ele}} = \sum_k \gamma_k A_k \quad (25)$$

The SM5 model

It has been subjected to a thorough parameterization by the Minnesota group. Besides the semiempirical AM1 and PM3 Hamiltonians, the SM5.42R method⁴⁸ has been parameterized at the *ab initio* Hartree–Fock (HF/MIDI!6D;²⁵ HF/MIDI!, HF/6-31G(d), HF/6-31 + G(d), HF/cc-pVDZ)^{49b} and density functional (BPW91 with MIDI!6D, DZVP and 6-31G(d) basis;^{49a} BPW91 and B3LYP with MIDI! basis)^{48b} levels of theory.

The nonelectrostatic terms (typically denoted by CDS for “cavitation–dispersion–solvent structure” effects) were determined by using a functional form related to the solvent-accessible surface area of the atoms (H, C, N, O, F, P, S, Cl, Br, I) in the solute [eqn. (26)]. The atomic surface tension, σ_k , was defined as a multilinear function of semiempirical surface tension coefficients, $\tilde{\sigma}_{km}$ (eqn. (27)). The first-solvation-shell functional forms, T_m , depend on interatomic distances of atoms within bonding distance and sometimes within the range of distances characteristic of geminal interactions.²⁵ Moreover, within the so-called universal solvation model⁵⁰ they also depend on a small number of solvent descriptors.

$$G_{\text{CDS}} = \sum_k \sigma_k A_k \quad (26)$$

$$\sigma_k = \sum_m \tilde{\sigma}_{km} T_m \quad (27)$$

A large number of solvents were considered (including water, alkanes, cycloalkanes, arenes, alcohols, ketones, esters, ethers, amines, pyridines, nitriles, nitro compounds and amides) in the universal SM5 model. The parametrization was performed by considering 2135 free energies of solvation for 275 neutral solutes and for 91 solvents, and for 49 ions in water. Mean unsigned errors between calculated and experimental free energies of solvation are typically 0.4–0.5 kcal mol⁻¹ for neutral solutes, and around 4 kcal mol⁻¹ for ions in water.

The UAHF PCM model

This model was parametrized by Tomasi and coworkers at the HF/6-31G(d) level for neutral molecules and cations, and at the HF/6-31 + G(d) level for anions.⁵¹

The nonelectrostatic terms included cavitation and van der Waals terms. The former was determined by using the Claverie–Pierotti equation (eqns. (5)–(7)), and the latter was calculated by using eqn. (10) and the uniform approximation to the solvent^{14b,c} (contributions to the dispersion arising from $k = 6, 8, 10$ terms in eqn. (9) and an exponential repulsion term were considered). These terms were determined by using a van der Waals-like surface obtained by using atomic radii augmented with the solvent radius. For the electrostatic term, a solvent-excluded surface obtained by scaling the atomic radii by a factor $f > 1$ (1.2 for aqueous solutions) was used.

The UAHF parametrization is characterized by three main features. First, hydrogens do not have individual spheres (united atom approach), but they are included in the spheres of the heavy atoms to which they are bonded. Second, the elements of each periodic table row have the same “basic” radius, which is modified by the molecular environment. Third, a series of rules have been defined to estimate the “effective” atomic radius by taking into account the molecular environment where the atom is inserted to. To this end, properties such as the hybridization state, the number of linked hydrogens and the nature of the vicinal heavy atoms, among other, are explicitly considered in those rules.

The UAHF procedure was applied to compute the hydration free energies for molecules containing H, C, N, O, F, P, S, Cl, Br and I. The optimized radii reduced the mean error with respect to the experimental hydration free energies below 0.2 kcal mol⁻¹ for a set of 43 neutral solutes and around 1 kcal mol⁻¹ for 27 ions.

The MST model

This model also uses the PCM³² approach for the calculation of the electrostatic component of the solvation free energy. It has been parametrized by the Barcelona group at the HF/6-31G(d) and semiempirical AM1 and PM3 methods.⁵² The method has been parametrized to describe solvation in water, dimethylsulfoxide, octanol, chloroform and carbon tetrachloride.

The MST method computes the nonelectrostatic contributions from the addition of cavitation and van der Waals contributions. The cavitation component was computed using the Claverie–Pierotti expression (see eqns. (5)–(7)), and the van der Waals term was calculated using a linear relationship with the atomic surface (eqn. (12)) by defining surface tensions for atoms H, C, N, O, S, F, Cl and Br. Molecular-shaped GEPOLE cavities⁵³ were used. In the last parametrization of the model a dual-cavity strategy⁵⁴ was used, so that nonelectrostatic contributions are determined by using a van der Waals surface built up mainly from Pauling radii, whereas the electrostatic term is determined by using a solvent-exposed surface created by scaling the atomic radii by a solvent-dependent factor. The use of solvent-dependent cavities was justified by the need to account for the different placement of the first solvation shell in different solvents,⁵² as determined from the comparison of MST results with those obtained from discrete simulations of the solute in solution using classical force fields and mixed quantum mechanics/molecular mechanics calculations. For ions, a reduction of the cavity by a factor of ~ 0.9 has been found to be necessary⁵⁵ to reproduce the fact that solvent molecules approach more to charged than to neutral solutes.

The latest parametrization of the MST method was performed by considering 228 small to medium-sized neutral molecules containing prototypical organic functional groups,^{52d} 75 octanol/water partition coefficients^{52d} and 47 ionic compounds.^{55b} Generally, root-mean square deviations less than 0.6 kcal mol⁻¹ have been reported for neutral solutes in the different solvents, 0.4 (in log P units) for the

octanol/water partition coefficients, around 3–4 kcal mol⁻¹ for the hydration of ionic compounds.

The COSMO-RS model

The parametrization of this method has been performed at the DFT level with the BPW91 functional.⁵⁶ The solute cavity was built up by using a set of radii chosen so that the volume of the cavity approximated the molar volume of the compound. The COSMO radii are about 1.17 times the Bondi van der Waals radii. The DFT/COSMO calculations for each of the individual molecules of the system affords the screening charge density (SCD) for each piece of the molecular surface. To account for hydrogen-bonding effects, additional SCDs for hydrogen-bond donor and acceptor capabilities, which are determined upon parametrization, are considered. A dispersion term proportional to the exposed surface area, with the atomic surface tensions being determined by fitting experimental data, is also included. Finally, other adjustable parameters are also exploited.

The method was parametrized by considering 217 small to medium-sized neutral molecules including a variety of chemical functionalities of the elements H, C, N, O and Cl using a variety of properties. An overall accuracy around 0.4 kcal mol⁻¹ for free energies of hydration (neutral molecules) and 0.8 log units for the octanol/water partition coefficients has been achieved.

Comparison of different SCRF formalisms

The preceding discussion suffices to state that parametrizations of current state-of-the-art QM-SCRF methods allow to estimate solvation free energies for a large variety of solutes with an error below 1 kcal mol⁻¹. Furthermore, in our experience similar accuracy is generally obtained for molecules not considered in the fitting databases. Such an agreement, nevertheless, does not warrant that all the methods provide similar values of the electrostatic and nonelectrostatic components of the solvation free energy. Accordingly, it is *a priori* necessary to maintain a close correspondence between each SCRF formalism and the specific details entailing its parametrization. Moreover, caution is needed in interpreting the various contributions to the free energy of solvation provided by different SCRF formalisms. Under these circumstances, whether or not different SCRF methods are equivalent in describing the solvation process of a given solute is unclear. At this point, comparison of the electrostatic term is particularly worth, since generally it is the only term affecting the solute wavefunction in solution (see above). Accordingly, a correct representation of the electrostatic component of the solvation free energy is necessary for a suitable representation of the solvent-induced changes in the solute properties.

Very recently a systematic analysis of the electrostatic response given by three different formalisms -the GB model as implemented in the SM5.42R model, the MPE (multicentric expansion up to $l = 12$ terms) model, and the MST version of the PCM model- has been reported.²⁰ For a set of 18 neutral molecules containing typical organic groups, calculations were performed at the HF/6-31G(d) level using the same geometries, solute cavities and solvent permittivities for all the continuum methods. The results clearly point out that the three SCRF formalisms behave similarly in capturing the changes in the electrostatic free energy as the dielectric permittivity is varied. Regarding the absolute value of the electrostatic term, both MPE and MST methods give rise to a similar electrostatic response (for the same cavity). On the contrary, the SM5.42R method yields electrostatic free energies smaller in magnitude than those derived from MPE and MST calculations when identical cavities are employed, which suggests that for this

method smaller cavities should be used (as already done in the current SM5.42 method).

The same study²⁰ also compared the induced dipole moment originated upon solvation. At this point, the results point out that this property is less sensitive to the specific details of the SCRF electrostatic formalism than the electrostatic component of the solvation free energy, since all the methods leads to a similar dipole moment enhancement. It must be noted, nevertheless, that not all the properties might exhibit the same sensitivity to the influence exerted by the solvent.

As noted above, the models could be further refined if not only solvation free energies, but also solvent-induced changes in solute properties were considered in the parametrization process. Owing to the limited length this article must have, we do not review here these aspects. Nevertheless, we want to address the reader to the excellent review by Cramer and Truhlar,^{4f} where a comprehensive compilation of studies devoted to the solvent effects on dipole moments, charge and spin distributions, and electronic and vibrational spectra is made. We also want to remark a couple of recent reviews by Tomasi *et al.*,⁵⁷ which examines properties such as hyperpolarizabilities, infrared and Raman spectra, circular dichroism and nuclear magnetic shieldings, among other topics.

Towards fractional solvation models

Partitioning of the solvation free energy into fragmental (atoms or groups) contributions has been the subject of large research effort due to two major reasons. First, it allows us to gain deeper insight into the physicochemical basis of the solute–solvent interaction, which can be valuable to analyze processes such as the “hydrophobic effect”.⁵⁸ Second, it allows a compact description of the solvation properties of molecules for structure-activity relationships.⁵⁹

Fractional contributions to the solvation free energy can be qualitatively estimated by using simple methods, such as the calculation of hydrophobic and hydrophilic surfaces⁶⁰ or the use of empirical group contributions.⁶¹ In particular, this latter approach has given rise to a plethora of methods to predict relevant physicochemical properties such as the octanol/water partition coefficient.⁶² Typically, these methods exploit databases of contributions assigned to specific atoms or groups in conjunction with a diverse set of combination rules, which correct the implicit assumption of the additive nature of fragment contributions. In this context, the development of fractional partitioning methods based on physical models can be extremely useful to refine those empirical methods, because (i) the contributions are computed considering explicitly the molecular environment, conformation, ionic and tautomeric states, and (ii) the fragmental contributions are directly extracted from real physical properties. In the context of continuum solvation methods, fractional methods have been developed within the GB framework by Cramer and Truhlar⁶³ and by our own group within the MST model.⁶⁴

Partitioning of the nonelectrostatic terms is straightforward, since they are typically related to the solvent accessible surface of atoms (see eqns. (7), (12) and (26)). The partition of the electrostatic term is more difficult due to the problems related to partitioning of the solute charge distribution. However, this problem can be alleviated by using perturbation theory, which permits the rewriting of the electrostatic component of the solvation free energy as shown in eqn. (28).⁶⁵

$$\Delta G_{\text{ele}} = \left\langle \Psi^0 \left| \frac{1}{2} \hat{V}^{\text{sol}} \right| \Psi^0 \right\rangle \quad (28)$$

where V^{sol} is the solvent reaction field generated by the fully polarized solute in solution, whose wavefunction is denoted by Ψ^{sol} .

Eqn. (28) allows us to determine the electrostatic component from the addition of fractional contributions (see eqn. (29)). We should note that within this partitioning scheme, the contribution of atom i ($\Delta G_{\text{ele},i}$) really accounts for the interaction of the entire molecule with the surface elements j which can be ascribed to the solvent-exposed surface of atom i .

$$\Delta G_{\text{ele}} = \sum_{i=1}^N \Delta G_{\text{ele},i} = \sum_{i=1}^N \sum_{\substack{j=1 \\ j \in i}}^N \left\langle \Psi^0 \left| \frac{1}{2} \frac{q_j^{\text{sol}}}{|r_j - r|} \right| \Psi^0 \right\rangle \quad (29)$$

The use of NDDO-based semiempirical methods permits further partition the contribution of atom i into *self* and *cross* components (see eqns. (30)–(32)).⁶⁶ The *self* term involves the electrostatic interaction of the core charge (Z_i) and the elements $\phi_\mu \phi_\nu$ of the electron charge distribution of atom i with the solvent reaction charges located at the surface of atom i (eqn. (31)). The *cross* term accounts for the interaction of the core charges (Z_k) and the elements $\phi_\mu \phi_\nu$ of the electron charge distribution of the rest of atoms with the solvent apparent charges at the surface of atom i (eqn. (32)).

$$\Delta G_{\text{ele},i} = \Delta G_{\text{ele},i}^{\text{self}} + \Delta G_{\text{ele},i}^{\text{cross}} \quad (30)$$

$$\Delta G_{\text{ele},i}^{\text{self}} = \frac{1}{2} \sum_{\substack{j=1 \\ j \in i}} \left[\left(\sum_{\mu \in i} \sum_{\nu \in i} P_{\mu\nu} \left\langle \chi_\mu \left| \frac{q_j}{|r_j - r|} \right| \chi_\nu \right\rangle \right) + Z_i \frac{q_j}{|r_j - r|} \right] \quad (31)$$

$$\Delta G_{\text{ele},i}^{\text{cross}} = \frac{1}{2} \sum_{\substack{j=1 \\ j \in i}} \sum_{k \neq i} \left[\left(\sum_{\mu \in k} \sum_{\nu \in k} P_{\mu\nu} \left\langle \chi_\mu \left| \frac{q_j}{|r_j - r|} \right| \chi_\nu \right\rangle \right) + Z_k \frac{q_j}{|r_j - r|} \right] \quad (32)$$

where χ stands for the basis of atomic orbitals, and P is the one-electron density matrix.

Despite the arbitrariness implicit to any partitioning method of the solvation free energy, the surface-based partitioning scheme outlined above has recently been shown to yield consistently similar results to those obtained from alternative partitioning schemes defined in the context of classical continuum or discrete methods.⁶⁷ This gives us confidence in the fractional contributions derived in this way and makes this procedure useful to derive parameters to be used in structure–activity relationship studies.

The partitioning scheme outlined above has been recently used to explore the transferability of fragmental contributions to the octanol/water partition coefficient, $\log P_{\text{ow}}$.⁶⁶ The results obtained demonstrated the dependence of the fragmental contributions to the $\log P_{\text{ow}}$ on the electronic and steric properties of the substituents attached to the core of the molecule, as well as the variation in the fragmental contributions due to conformational, tautomerism and hydrogen effects. From a practical point of view, this opens the way to quantify the magnitude of these effects, which can in turn be used to refine the atom/group contributions in simple additive-based empirical schemes.

The graphical display of fractional contributions to the solvation free energy provides a 3D picture of the solvation properties of molecules,⁶⁴ which facilitates to compare compounds based on their distribution of hydrophobic/hydrophilic regions. For example, we found very useful for structure–activity relationships studies the use of the “solvation dipole” [64b,68; see eqn. (33)] as a simplified descriptor of the solvation profile of a molecule.

$$\mu_{\text{sol}} = \sum_i^N \Delta G_{\text{sol},i}(r_i - r_0) - \frac{\Delta G_{\text{sol}}}{N} \sum_{i=1}^N (r_i - r_0) \quad (33)$$

where r_0 is an arbitrary origin (typically the centre of mass of the molecule)

Comparison of two solvation dipoles can be easily done using the dot product of the unitary vectors (eqn. (34)), which affords a very compact similarity index ranging from 1 to -1 .

$$\vartheta_{\text{WZ}} = \frac{\mu_{\text{sol}}^{\text{W}}}{|\mu_{\text{sol}}^{\text{W}}|} \cdot \frac{\mu_{\text{sol}}^{\text{Z}}}{|\mu_{\text{sol}}^{\text{Z}}|} \quad (34)$$

where W and Z denote two molecules.

A more detailed comparison between the fractional distribution of two molecules (W with N_{W} atoms, and Z with N_{Z} atoms) can be obtained from similarity functions like that shown in eqn. (35).^{64d} Since the function A_{WZ} , depends on the mutual orientation of W and Z, the optimum orientation can be obtained by maximizing A_{WZ} using gradient optimization routines or simulated annealing procedures coupled to Monte Carlo simulations.

$$A_{\text{WZ}}(R_{\text{wz}}) = \sum_{i=1}^N \sum_{l=1}^{N_{\text{Z}}} \frac{\Delta G_{\text{sol},i} \Delta G_{\text{sol},l}}{(r_{il}^n + \delta)} \quad (35)$$

where n is an adjustable parameter that controls the shape of the similarity function and δ is a constant that avoids the occurrence of singularities in the similarity function.

The similarity index can then be determined by using, for example, a Carbó-like index,⁶⁹ as noted in eqn. (36), where A_{WW} and A_{ZZ} denote self-similarity indexes determined from eqn. (35) when $W = Z$ and $R_{\text{WW}} = R_{\text{ZZ}} = 0$.

$$\gamma_{\text{wz}} = \frac{A_{\text{wz}}}{\sqrt{A_{\text{ww}} A_{\text{zz}}}} \quad (36)$$

The usefulness of the hydrophobic similarity index in the context of structure–activity relationships, drug bioavailability and molecular recognition has been recently investigated.^{64b–d} The results suggest that his technique appears to be a powerful tool for the rational design of bioactive molecules.

Final remarks

During the last decade theoretical chemistry has started an irreversible journey from gas phase chemistry to chemical processes in solution, which is widening the range of phenomena that can be studied by theoretical methods. The development and popularization of continuum models have contributed decisively to this drastic change. Several SCRF methods are now finely parametrized and incorporated in the most popular computer programs, allowing solvation free energies of neutral molecules to be routinely calculated with an accuracy clearly below 1 kcal mol⁻¹. These calculations, which ten years ago could be made only by a handful of groups, are now possible for all the chemical community. Such a fast popularization has nevertheless some risks, particularly due to the use of these methods as a “black box” without knowing the implicit approximations inherent to their development. This review, mainly oriented toward non-expert readers, tries to give a concise description of the most popular solvation models, emphasizing the specific features of their underlying formalisms and the details of their parametrization.

The simplicity of continuum models and their accuracy guarantees an progressive extension in their application to different areas of chemistry. From a formal point of view, we cannot expect a massive development of new methods, but current methodologies will be probably refined to deal with new problems. To this end, comparison of results derived from SCRF models and discrete QM/MM methods, as well as calibration of solvent-induced changes in solute properties with suitable experimental data,^{4f,57} appear to be very promising. Developments for treatment of non-dynamic solvation effects are also expected.^{4a,f} Solvation in mixed solvents is another challenge

that will focus methodological developments in a near future. Finally, a large field for development exists in exploiting all the information provided by continuum models in biopharmaceutical studies.^{63,64} Perhaps in the near future, continuum solvation methods will be as popular in a pharmacological or biochemical laboratory as they are nowadays in a chemical one.

Acknowledgements

We are indebted to Profs. J. Bertrán, C. J. Cramer, J. L. Rivail and J. Tomasi for valuable suggestions. We thank the Ministerio de Ciencia y Tecnología for financial support (Grant Nos. SAF2002-04282, PM99-0046 and GEN2001-4758). C. C., I. S. and A. M. have fellowships from the Ministerio de Ciencia y Tecnología. J. M.-M. thanks the Departament d'Universitat, Recerca i Societat de la Informació for a fellowship.

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