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Methodological Aspects of the Solvation Models Based on Continuous Solvent Distributions

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Some general aspects of the solvation models based on an effective Hamiltonian and a continuous solvent distribution are presented and discussed. The emphasis is placed on the versatility of the approach. The computational procedures may range from very sophisticated quantum-mechanical formulations to simple classical expressions based on the use of rigid atomic charges. The model may be applied to the study of very different phenomena, by introducing minor changes in it. The necessity of complementing this approach with others of a different nature, to get an efficient progress in our understanding of the chemical behaviour of systems in solution, is also stressed.

Examples are drawn by applications of our model, but the discussion is valid also for other computational models.

1. INTRODUCTION. THEORETICAL MODELS FOR SOLUTIONS: FROM PHYSICS TO CHEMISTRY

In the recent evolution of theoretical methods addressed to the study of matter in the fluid state, it is easy to detect a progressive tendency of the models towards »molecularization«, *i.e.* a tendency to pay more attention to a realistic description of the molecular aspects of the model. In other words, these methods are acquiring a more evident chemical flavor.

Chemistry has a complex relationship with physics. Methodological and conceptual tools of theoretical chemistry are derived from physics, as it is well known, but theoretical chemistry has been able to preserve and to develop the essential aspects of the chemical approach to the study of matter. The chemists understand quite well the meaning of the expression »chemical approach«, a concept not easy to reduce to a short and comprehensive definition, but in which we may identify, for our present scopes, the close scrutiny of the differences in behaviour of portions of matter exhibiting small differences in composition and/or in other analogous parameters.

The quantum mechanical model for molecules, elaborated by physics, was recast several decades ago into formulations more appropriate to the specific needs of chemistry and gradually developed into a new branch of chemistry, molecular quantum chemistry.

In these last years, there has been a similar appropriation by chemists of the physical models for liquids. This appropriation is made easier by the natural evolution of models and methods towards a description of finer aspects of the problems under examination. Finer descriptions also pay more attention to the molecular details of the constituting elements. At a given moment, the evolution assumes the aspect of a qualitative change: from that moment any further progress of the model is no more ruled by considerations on the physical relevance of the modification but it is addressed to a better study of chemistry in solution.

Computer simulation may be taken as an example. A very large amount of information on fluid systems has been obtained by applying simulation methods to very simple material models (*e.g.* hard spheres). The evolution of the research has lead to consideration of more complex material models (*e.g.* disks, soft spheres, spheres with a dipole, *etc.*) and eventually to models including detailed descriptions of the geometries and properties of the molecular components of the fluid. At this point of its evolution, the approach is ripe for chemical use. However, this evolution has not been a mere deterministic effect of the laws of increasing complexity operating in all human activities: it has been purposefully guided with foresight and determination by a limited number of persons. In the case of computer simulations, the leading man has undoubtedly been E. Clementi;[1] his stimulus has excited innovative contributions by others,[2] and nowadays computer simulation is the main road to theoretical and computational studies of chemistry in solution.

2. THE CONTINUUM MODELS

In the process of chemical reformulation of theoretical models for fluids which, in our opinion, is still in the initial stage, the approaches based on the continuum description will presumably play an important role.

The continuum models, in their original definitions formulated two generations ago,[3-5] were excellent exemplifications of what is a physical model. The molecular structure of the solvent was completely neglected, the structure of the solute reduced to the minimum (a point charge, a dipole), the interactions extremely simplified. These models have been of extremely high importance for the progress of our understanding of matter in condensed phases, and are still instrumental in elaborating preliminary formulations for new interpretative models. There has been, however, a parallel evolution of the continuum approach towards realism, with more attention paid to the molecular aspects of the model, and ultimately towards chemistry.

The beginning of the »chemical« evolution of the continuum approach is quite recent. In the middle of the seventies, the efforts addressed to this scope were cultivated by a handful of men, a few of which, Claverie, Rivail, Tapia[6-8] have largely contributed to the evolution of the model in the eighties. At present, the computational procedures operational or proposed are of the order of one or two dozens, and the number has rapidly increased in the recent years. In addition, methods derived from the Kirkwood-Onsager continuum model have merged with methods having their origin in the supermolecular approach. So, the number of available computational methods that look similar is large and it is not easy for a potential user to select among them the variant that best satisfies his needs of accuracy, generality, computational cost, *etc.*

A classification of the various methods could be of some help. Recently, we made an attempt to classify the continuum-derived methods in ref. [9]. The classification was based

a) on the distinction between the classical and quantum-mechanics methods, the latter making explicit use of a Hamiltonian and then of a Schrödinger equation
b) on the distinction between the methods limited to the use of a isotropic infinite continuum medium and the methods allowing the use of structured media, of other kinds of molecular interactions *etc.* In both cases, classical and quantum versions are possible.

Even more recently,[10] we have suggested a further particularization of the main heading under which various methods could be collected and compared. This heading is identified by the abbreviation EHCD which stays for Effective Hamiltonian methods using a Continuous Distribution. This concept was already present in our preceding classification,[9] but it seems convenient to use this last abbreviation. The category of the EHCD methods is, in fact, larger than that of the continuum methods and if used as a non-rigid taxonomic criterion, it may permit to unify and to appreciate the differences of many methods. Emphasis may be placed on the Effective Hamiltonian, leaving in the shade the Continuous Distribution, thus permitting grouping of methods like the solvaton one[11-12] or the more recent revised versions.[13-16] Emphasis may be placed on the quantum description of the Effective Hamiltonian, or, in contrast, on its classical reddition, with quantum mechanics in the background, as a justification of the properties of the molecular quantum description (we call them »classical« methods).[17-26] Mixed methods, in which »quantum motifs« are defined as interacting with »classical motifs« and continuous distributions supplement the discontinuous ones,[27-30] also belong to EHCD. Methods which recover concepts of the continuum approach *via* discrete models[31] may represent an interesting link between EHCD and other approaches.

This listing could be further expanded by adding new methodological variants that may be regrouped under the heading EHCD, but what has been said is sufficient to transmit to the reader that the number and the variety of methods is really large.

3. THE POLARIZABLE CONTINUUM MODEL (PCM)

To continue our discussion, we shall refer now to the EHCD method developed in Pisa (or better, the set of methods) often indicated by the abbreviation PCM.

The passage from general considerations about the need of a classification of a number of related but considerably different methods, expressed in the preceding section, to the examination of a single method could seem to be a too abrupt jump, requiring at least the presentation of the classification as an intermediate step.

There are at least two reasons to pass from general considerations on EHCD methods to the examination of the PCM one. First, an attempt at motivated classification, with bibliography, has already been made in ref. [9] for the continuum methods, and an enlargement to other EHCD approaches would exhaust all the space available. Second, the examination of a single specific method may add something to our general and methodological considerations, and the PCM method seems to us quite appropriate for this scope.

The first PCM version was published in 1981[32] and was expressed in the *ab initio* SCF formalism, using an isotropic description of the medium characterized as a continuous dielectric.

We may consider this as the basic (or primitive) version of the model from which to start in different directions. We may consider, in fact, the basic version as a small region in a many-dimensional space put at the centre of a reference frame where each axis corresponds to a different aspect of the whole problem: exploration of a set of physical phenomena and contemporary elaboration of the appropriate models.

The level of the description of the system is one of the most important methodological aspects. We propose here introduction of two »axes« regarding the levels of description 1) of the molecular Hamiltonian $H_M{}^0$, 2) of the effective interaction operator V_{int}.

Another aspect regards the complexity of the phenomena under examination: we shall not enter in a detailed description, but at least a few distinct »axes« must be mentioned 1) the complexity of the solute, *i.e.* of the part M of the liquid to which the Hamiltonian $H_M{}^0$ refers; 2) the nature of the phenomena occurring in M under different but specific conditions (*e.g.* chemical interactions, interactions with the light, interactions with the medium, *etc.*); 3) the complexity of the whole system, reflected in the introduction of boundary conditions (*e.g.* the occurrence of a surface limiting the liquid phase, *etc.*).

Coming back to the first couple of »axes«, regarding the level of description of $H_M{}^0$ and V_{int}, we remark that the primitive model is rather sophisticated, at least when compared to physical models. The Hamiltonian is treated at the *ab initio* SCF level, as already said, and V_{int} is described in terms of the apparent charge distribution σ spread on the surface S_M of a cavity C_M accurately modelled on the shape of M. Simpler versions of the continuum electrostatic model are, of course, possible.

A methodological consideration is appropriate here. When one studies a *physical model* (*i.e.* a reduced and incomplete description of the actual physical effects active in the objective counterpart of the *material model*, see ref. [33] for more details), it is extremely convenient to be free from the limitations imposed by the mathematical formulation selected to build up the model. Even when the primary goal of the researcher is to obtain a cheap and rapid algorithm, it is convenient to start from descriptions in which the physical model acts at its best.

The literature of theoretical chemistry offers a large number of counter examples. Limiting ourselves to the case of molecular interactions, akin to the problem of solvent interactions considered here, many »conclusions«, reported in the past years about the limits *e.g.* of the electrostatic approximation, suffer from the use of an inadequate method for describing the molecular wavefunction (many semiempirical methods are not able, for example, to describe non-covalent interactions) or from the use of atomic charges, instead of the full charge distribution *via* the molecular electrostatic potential (MEP) or from the use of a poor basis set. Analogous considerations could be made for many other aspects of the interpretation of chemical phenomena in theoretical chemistry. We thus need a method able to treat the molecular problem on a large variety of models, from correlated wavefunctions to rigid atomic charges. The *ab initio* SCF method stays just in the middle.

The same holds for the expression of V_{int}. The primitive model avoids the use of multipolar expansions, which are in principle incomplete, in favor of a numerical integration over the cavity surface. The integration grid may be refined *ad libitum* in test calculations to ensure the degree of reliability of the numerical results. The number and location of points we have selected for routine calculations[34] give numerical errors within chemical accuracy. Other devices have been introduced to account properly for related phenomena of different kinds, like the effect of self-polarization on the polarization charge σ, the effects due to the finite size of the solvent molecules (solvent excluded volumes and solvent accessible surface). *etc.* Details may be found in the original papers[32,34,35] and have been mentioned here to emphasize that the mathematical elaboration of the model does not introduce additional approximations, hidden or evident, with respect to those stated at the beginning: a SCF treatment of M inserted in a cavity with well defined boundaries of a medium at constant permittivity.

We may shortly resume the main points of the primitive model. There is a Schrödinger equation to solve:

$$H_{\text{M}}\,\Psi^{\text{f}} = (H^{\circ}_{\text{M}} + V_{\sigma})\,\Psi^{\text{f}} = E^{\text{f}}\,\Psi^{\text{f}} \tag{1}$$

in which the effective interaction operator V_{σ} is actually a function of the solution Ψ^{f}. The implicit equation is solved iteratively with an algorithm which splits the calculation into two nested cycles. This splitting is the starting point for other versions of the model placed at lower levels on the axis of complexity.

V_{σ}, which replaces the more general operator V_{int}, is the electrostatic potential of the surface charge distribution $\sigma(s)$

$$V_{\sigma}(\text{r}) = \int_{S} \frac{\sigma(s)}{|\vec{r} - \vec{s}|}\, d\vec{s} \tag{2}$$

The surface charge distribution is, in turn, related to the difference in the normal component of the polarization vector on the cavity surface:

$$\sigma(s) = \mathbf{P}_{-}\cdot\mathbf{n} - \mathbf{P}_{+}\cdot\mathbf{n} \tag{3}$$

The polarization vector at the interior ($\mathbf{P}_{-}$) or at the exterior ($\mathbf{P}_{+}$) of the cavity is related to the gradient of the potential V

$$P_{\text{i}} = -\frac{1}{4\pi}(\varepsilon_{\text{i}} - 1)\,\nabla V_{\text{i}}(s) \tag{4}$$

V_{i} is composed of two parts

$$V_{\text{i}} = V_{\text{M}} + V_{\sigma} \tag{5}$$

the first component derives from the charge distribution of M, and it is its MEP function. If we solve the Schrödinger equation (1), dropping out the V_{σ} term

$$H^{\circ}_{\text{M}}\,\Psi^{\circ} = E^{\circ}\,\Psi^{\circ} \tag{6}$$

we obtain the solution for the system *in vacuo*, and then $V_M{}^o$, *i.e.* the MEP function is not affected by the solvent.

Using this constraint, $V_M{}^o$ fixed or, in other words, the solute charge distribution $\Gamma_M{}^o$ kept rigid as it is *in vacuo*, our problem is reduced to the classical electrostatic problem of solving the Poisson equation

$$\nabla^2 V(\mathrm{r}) = -4\pi\Gamma(\mathrm{r}) \tag{7}$$

with the usual boundary condition at the cavity surface

$$V_+(s) = V_-(s) \tag{8}$$

$$-\varepsilon_+ \frac{\partial}{\partial n}(V(s))_+ = -\varepsilon_- \frac{\partial}{\partial n}(V(s))_- \tag{9}$$

This is the inner cycle of our iterative procedure. Putting in (5) $V_\sigma = 0$, we obtain a first guess of $\sigma(s)$ as applied in eqs. (4) and (3); this value is called $\sigma^{oo}(s)$. Using now eq. (2), we obtain $V_\sigma{}^{oo}$ which may be placed now in eq. (5), *etc.* At the end of the cycle, we have a definition of surface polarization charge $\sigma^{of}(s)$, always referred to fixed $\Gamma_M{}^o$.

We are now in a position to start with the outer cycle. $V_\sigma{}^{of}$ is put in eq. (1), and a new wavefunction Ψ^1, and the corresponding charge distribution $\Gamma_M{}^1$ are obtained. The outer cycle, applied again, gives a new value σ^{1f}. The second cycle is applied until self-consistency, and the final value of the operator $V_\sigma{}^{ff}$ gives, *via* eq. (1), the answer we have asked for.

It is evident that no additional approximations have been introduced in this cycle. In actual calculations, the surface integral (eq. (2)) is replaced by a finite summation. The process converges quickly, generally in three iterations for the outer cycle and three iterations for each passage in the inner cycle.[35]

The quantities derived from this procedure, E^f, Ψ^f and V_σ, are the starting points for the theoretical analyses. The attention in theoretical studies on molecular solutes is usually directed to the differential effects produced by the solvent, tacitly considering the theoretical analyses of the corresponding systems *in vacuo* as already done. This is generally not true, and it will be less true in the future, when good quality EHCD methods will be routinely used; the *in vacuo* and in solution descriptions are obtained at the same time and both must be interpreted. Parallel interpretation of molecular properties *in vacuo* and in solution may lead to some innovations in the usual technique of analysis. New analytical tools may be drawn, for example, from V_σ. These tools may be also used to shed light on the intrinsic properties of *M in vacuo.*

4. THE »ENERGY« OF THE SYSTEM. FREE ENERGY AND ITS ELECTROSTATIC CONTRIBUTION

The mathematical elaboration for the primitive model has been guided and controlled by many checks. Some of these checks are of the internal nature, and it is not possible to discuss this matter here, others tend to the numerical evaluation of quantities for which there is an experimental value available. When this direct comparison is not possible, the judgment on the success of the check must rely on the physical plausibility of the results.

In quantum mechanics, the checks on a computational method start from the energy. We shall follow the same line, even if things in solution are not simple as *in vacuo*.

The energy E^f obtained as solution of eq. (1) does not play the principal role. It may be interpreted as the work spent in putting nuclei and electrons (in a quantum-mechanical description) of M into the cavity C_M of a dielectric already polarized to the right extent. The use of E^f is thus limited to a specific model intended to describe phenomena in which the change in energy of the surrounding medium is not important.

In general, the work spent on polarizing the dielectric must be accounted for. The quantity of direct use, provided with a clear physical meaning, is the following:

$$G_{el} = E^f - \frac{1}{2} \int \Gamma_M^f \, V_\sigma \, dr \tag{10}$$

E^f is the total energy, containing also nuclear repulsion terms, and $\Gamma_M{}^f$ is the total first order density matrix, containing also nuclear contributions. G_{el} has the status of free energy and corresponds to the free energy change from a system composed of non-interacting nuclei and electrons plus a non-polarized infinite dielectric with a cavity C_M of appropriate shape, to that of a system in which M is built in the cavity and solute-solvent reciprocal interaction energies are taken into account.

The physical meaning of G_{el} is clear, but this quantity is far from the quantities actual experiments may measure.

A quantity nearer to actually observable quantities is

$$\Delta G_{el} = G_{el} - E^o \tag{11}$$

E^o is the total energy of the system *in vacuo* (*i.e.* with $V_\sigma = 0$). ΔG_{el} is the electrostatic contribution to the solvation free energy $\Delta G_{sol}{}^o$, which is a quantity accessible by experimental measurements.

Several »errors« introduced in the calculation of G_{el} and E^o, due to the limitation of the basis set, to the neglection of electron correlation effects, *etc.*, are considerably compensated in the difference which defines ΔG_{el}.

ΔG_{el} is not accessible to experiments. We have to add other terms to get a better description of the solvation energy.

The standard state used to define G_{el} (eq. (10)) is rather unphysical because it contains a cavity in the medium with a predetermined shape. It is more satisfactory to start from a continuous medium and to consider the free energy necessary to form the cavity: G_{cav}.

Definitions (10) and (11) tacitly imply that the cavity is centred at an unspecified but fixed point within the solution. The selection of this point is immaterial because the medium in this model is infinite and isotropic but, anyway, the selection of a fixed point limits the possibility for M to wander inside the whole solution. This point has been carefully discussed by Ben Naim[36] and taken as the key point for his interpretation of transfer processes. It is sufficient to remark that the release of this constriction gives origin to an entropic contribution to the free energy, called »liberation free energy«, related to the changes in the momentum partition function of M in passing from the gaseous state to the solution.

Following the line of analysis exposed in the preceding page, we have shifted from purely molecular models – deterministic in the quantum mechanical meaning of the term – to statistical models. The last step to be added actually regards the partition function of M, which may be safely factorized out, in regular solutions, from those belonging to the other molecular components of the liquid system. The correct expression of $\Delta G_{\mathrm{sol}}{}^{0}$ must thus be supplemented by terms related to changes in the vibrational and rotational partition functions, q_{vib} and q_{rot}, due to the passage of M (at a given geometry) from the gaseous state to the solution. Also, changes in the vibrational zero point must be included, as well as the so called »cratic« term depending on the thermodynamical standard states one has selected.[37,38]

Even in this simple extension of the primitive model considered here, other factors must be taken into account. The interaction between M and the solvent has been assumed to be exclusively electrostatic in nature. We know from the study of two- or few-body interactions that dispersion and repulsion terms play a not negligible role in intermolecular interactions.

The basic primitive model is not equipped to treat these terms, and they may be added in some way. There are several ways to do it, and we have selected two different methods which preserve both the basic features of the PCM approach, *i.e.* the use of a detailed description of the molecular surface, an explicit expression for the solvent distribution (constant and isotropic in the basic formulation) and the use of surface integrations.[39] We shall not enter into details.

The final expression may be given in the following form

$$\begin{aligned}\Delta G^{0}_{\mathrm{sol}} = \Delta G_{\mathrm{el}} + G_{\mathrm{disp}} + G_{\mathrm{rep}} + G_{\mathrm{cav}} + \Delta(PV) - \\ -RT\,[\ln(V^{\mathrm{sol}}/V^{\mathrm{gas}}) + \ln(q^{\mathrm{sol}}_{\mathrm{rot}}/q^{\mathrm{gas}}_{\mathrm{rot}}) + \ln(q^{\mathrm{sol}}_{\mathrm{vib}}/q^{\mathrm{gas}}_{\mathrm{vib}})]\end{aligned} \tag{12}$$

The most direct comparison with experimental energies comes out from this expression. Derived quantities are, in our computational scheme, the enthalpy, computed *via* the Gibbs-Helmholtz theorem,[40] and by difference the entropy.

We will present some results below but before passing to numerical comparisons, we shall make a few comments.

We have selected the solvation free energy as the first test for the model because $\Delta G_{\mathrm{sol}}{}^{0}$ is the experimental quantity more directly related to the basic outputs of the EHCD methods. In spite of this, we have been obliged to resort to a quantum-mechanical statistical treatment and to introduce new concepts, and new energy contributions into the relatively simple original picture. An effort has been made, even if it is not manifest in this concise summary, to build up the new elements within the framework of the original theory. So, zero-point energy contributions are evaluated by a straightforward extension of *ab initio* Born-Oppenheimer SCF calculations at the PCM scheme; the same holds for the vibrational contributions, evaluated in the harmonic approximation except for low frequency motions for which a numerical evaluation of the population of the states has been performed and, except for X–H fragments of M, involved in hydrogen bonds with the solvent, for which the corrections suggested by our previous experience of these interactions have been introduced. It has been necessary, however, to include a further modellistic assumption to describe the hindered rotation of M (similar to those introduced by Nemethy and Scheraga[41]) and to resort to the

RSM theory[42,43] to evaluate G_{cav}. These two last points could be somewhat refined by new data derived from computer simulation or other methodological approaches.

We would like to stress this last remark: even for the simple problem of the evaluation of ΔG_{sol}^{o}, the combination of different approaches makes the study easier, or possible. In passing to more complex problems, the necessity of a coordinated use of different approaches becomes more and more compelling.

Let us consider now some methodological questions arising in the development of the method.

Eq. (11) regards a free energy change, and the two quantities on the right side should be physically comparable. E^{o} is actually free energy, corresponding to the work necessary to put together electrons and nuclei at 0 °K to form M *in vacuo* (clamped nuclei approximation); G_{el} is an analogous work in which, however, the temperature plays a role, being G_{el} parametrical dependent on ε which is a function of the temperature.

G_{el} and E^{o} parametrically depend on the nuclear geometry ($\mathbf{R}_M$). The dependence on the nuclear geometry is usually treated in the framework of the Born-Oppenheimer approximation: there are no questions, apart from the validity of the Born-Oppenheimer approximation, when the quantity in question is the internal energy. Here, we have to make a further step, and to introduce Potential Free Energy Surfaces, defined on the nuclear coordinate space. This extension has aroused some discussion, which seems to us definitively settled by the analysis and definition done by Laidler and Polanyi.[44] We shall need, as it will be shown later, further extensions of this definition.

We may pass now to some numerical comparisons. To save space, we do not report ΔG_{sol}^{o} values computed with basis sets of increasing complexity. Some data have been reported in preceding papers[45,46] and it is sufficient to state that the influence of the basis set is remarkable, but that with 6-31G* or better basis sets the result seem to be stable (at least for solutes of small and medium complexity).

The first line of Table I reports the linear correlation expression between the experimental and computed ΔG_{sol}^{o} values (gas → water, T = 298 K) for a set of esters, ranging from methyl formate to propyl propanate.

The correlation is quite good, the computed values are a little more negative than the experimental ones, and this systematic trend seems to be almost completely corrected by correlation energy contributions (*vide infra*).

It is not easy to select many other sets of related chemical systems for which ΔG_{sol}^{o} is known with good precision for a significant number of components. The results available refer to collections of systems with a lower statistical impact, or to solvent transfer energies, for which the number of data – even if often at a lower precision – is large. The *ab initio* calculation of solvent transfer free energies is an easier job, and it will not be considered here. The results, on the whole, are of the same quality as those reported in the first column of Table I.[47,48]

Quite interesting, for our modellistic interests, is the comparison between the experimental ΔG_{sol}^{o} and computed ΔG_{el} values reported in the second line of Table I and referred to the same set of compounds as in the first line. The correlation is almost as good as in the first comparison. In other words, the non-electrostatic components, numerically important and depending, to some extent, on the nature of the solute, are almost constant in the set. This characteristic has been confirmed by the other checks we have performed.

TABLE I

Linear correlation equations $y = a + bx$ for some selected examples. R: regression coefficient; n: number of solutes. Values in kcal/mol

Solute	Solvent	y	x	a	b	R	n
esters	water	ΔG_{sol}(calc)	ΔG_{sol}(exp)	–0.328	1.028	0.998	16
esters	water	ΔG_{el}	ΔG_{sol}(exp)	–4.790	1.089	0.995	16
esters	water	ΔG_{el}	ΔG_{sol}(calc)	–4.442	1.060	0.996	16
amides	water	ΔG_{el}	ΔG_{sol}(calc)	–10.408	0.900	0.989	7
heterocyclics	water	ΔG_{el}	ΔG_{sol}(calc)	–4.416	4.287	0.994	15

Line 3 of Table I compares $\Delta G_{sol}{}^{o}$(calc) and ΔG_{el} for the same set of molecules again, line 4 reports the same comparison for a set of amides and line 5 for a set of two-ring heterocyclic systems. In these last cases, a few comparisons are possible with experimental ΔG_{sol} values: the agreement is similar to that shown in lines 1 and 2.

To conclude, it seems that with a computational time not exceedingly larger than that necessary to get E^{o} values *in vacuo* (for rigid molecules the computational time is larger by a factor near 3), the PCM method gives estimates of $\Delta G_{sol}{}^{o}$ of appreciable quality, and for most of the chemical applications the computed value of $\Delta G_{sol}{}^{o}$ may be replaced by the ΔG_{el} value with a computational cost comparable with that of a single-geometry calculation of E^{o} *in vacuo* (time larger by a factor 2–3).

5. MORE CHECKS ON THE PRIMITIVE MODEL?

The long exposition reported in the preceding pages concerning the control of just one of the primary quantities coming out from the calculations shows the complexity of systematic implementation of a computational procedure.

Even the conclusions reached at the end of the preceding section are of limited validity. We have not considered, for example, charged systems, molecules subjected to important structural changes when passing in solution, complex systems with many local conformational minima, *etc.* The analysis must then be extended to other energetic quantities (enthalpy, entropy), to the energy of excitations to other electronic states, to a representative set of physical observables, still remaining at the level of the primitive approach. It is a hard and somewhat tedious task that we have performed in the past ten years (to be frank, without much alacrity). For some of the questions mentioned above, we have sufficient material to support almost definitive conclusions, but we prefer to be less systematic here and to pass to a different, though related subject.

The point we shall consider here has been selected by its methodological relevance. It shows that even in fields that seem completely assessed, there is always the possibility of »surprises«. Good models should always provide some »surprises« in their applications. Models, in fact, are intended to bring in evidence something not so evident to the user before the application of the model. Models without surprises are dull confirmations of the foresight – or of the limitations – of the model builder.

As said in section 2, the physical model is clearly set. Actually, there is a quantity which could be considered as a free parameter, the geometrical definition of the cavity. There are strict limitations on this parameter. The most accurate definition is given in terms of spheres centred on the solute nuclei, even if several tests have shown that for simple groups (*e.g.* CH_2, CH_3) a single sphere is sufficient. The radii of such spheres should be near to the van der Waals radii. This indication is not dictated by considerations based on the definition of the van der Waals radii, but rather on the analysis of the decomposition of the interaction energy in molecular clusters, a work done before the implementation of the PCM, showing that the evaluation of the rigid electrostatic, ES, and polarization terms, PL (we refer here to the interaction energy decomposition schemes[49,50]) at a distance near to the van der Waals radius or a little larger were able to reproduce the whole electrostatic contribution, and that this distance was not too sensitive to the geometry or size of the cluster. These considerations, of course affected by the poor basis sets used at that time, were used by us as starting points and, after a few additional controls, performed on the comparison of the reaction field at the nuclei obtained with the PCM and with Monte Carlo snapshots, recast into a recipe saying that the cavity is formed by the van der Waals spheres multiplied by a factor $f = 1.2$.

The calculations presented in Table I were performed using this factor. We have later had other indirect indications that $f = 1.2–1.1$ is a fair value, but other people interested in the PCM (Miertus[51], Olivares[52]) have developed more refined techniques. The general idea in both cases is of relating f_k to the electron distribution of atom k in the molecule. We shall not enter into details here, suffice it to say that the values of ΔG_{el} are not greatly affected by this change of the definition of the cavity.

Recently, during a joint research with Olivares del Valle, we experienced one of the »surprises« mentioned above. The research project involved the implementation of the PCM at a higher level, including electron correlation *via* perturbation theory.[53] To do it, it was convenient to divide ΔG_{sol} into separate contributions according to the order of the perturbation and to the number of bodies. This partition was tested for a small number of molecules using cavity radii defined according to the rules elaborated in the two groups: the two cavities for the water molecule are superimposed in Figure 1. In the general agreement of the values obtained for the two cases, a striking difference in the zero-body and one-body zeroth order contributions came out.

Let us resume the formalism of the decomposition of ΔG_{el} into orders (lower index) and bodies (upper index). The SCF expression contains only the zeroth order and first order contributions

$$\Delta G(\mathrm{SCF}) = \Delta G_o + \Delta G_1 \tag{13}$$

The zeroth order contribution may be split into zero- and one-body contributions. In total, one has

$$\Delta G(\mathrm{SCF}) = \Delta G_o^o + \Delta G_o^1 + \Delta G_1 \tag{14}$$

From a more detailed study involving a systematic variation of the two radii, R_H and R_O, defining the cavity for water (a more complete report will be published by Olivares del Valle and Aguilar[54]) we have drawn the results reported in Figures 2 (a,b,c,d).

Figure 2a shows the SCF values of ΔG_{el} (calculations with a 6-31G** basis set): point A corresponds to Pisa's definition of the cavity (*i.e.* with $f = 1.2$) point B to Badajoz definition ($fo = 1.41$ $f_H = 0.76$). As anticipated, ΔG_{el} is almost the same for points A and B.

Figure 2b reports the zeroth order zero-body contribution, $\Delta G_o{}^o$, Figure 2c the zeroth order one-body contribution $\Delta G_o{}^1$ and, finally, Figure 2d the first order contri-

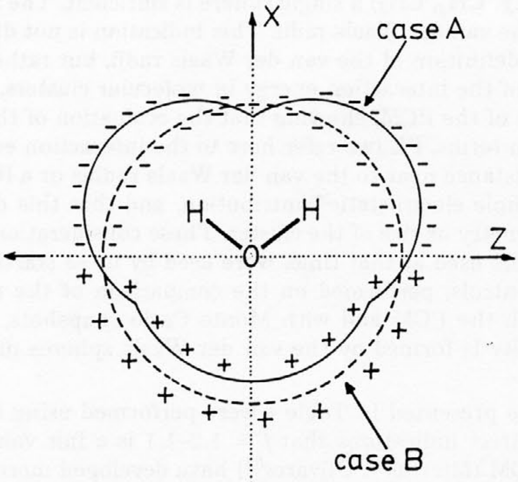

Figure 1. Superimposition of the sections of two definitions of the molecular cavity for H_2O. A: cavity based on van der Waals radii, multiplied by a factor $f = 1.2$; B: cavity based on the rules presented in ref. [52].

bution ΔG_1. The trend of ΔG_1 (as well as that of $\Delta G_o = \Delta G_o{}^o + \Delta G_o{}^1$, not reported here) is similar to that of ΔG(SCF), while for $\Delta G_o{}^o$ and $\Delta G_o{}^1$ the values at A and B are completely different. $\Delta G_o{}^1$ (Figure 2c) is strictly related to the solvent-shift of the orbitalic energies; $\Delta\varepsilon_i = (\varepsilon_{sol} - \varepsilon_{vac})_i$

$$\Delta G_o^1 = \sum 2\Delta\varepsilon_i - \frac{1}{2}\int \rho_M V_\sigma \, d\tau \qquad (14)$$

(note that only the electronic contribution to integral $\frac{1}{2}\int \Gamma'_M V_\sigma \, dr$, see eq. (10), is considered here). Actually, with the two cavities we found very different estimates of the $\Delta\varepsilon$ values (Table II). Solvent effects on the orbital energies have been often invoked in qualitative discussions on the solvent effects on the reactivity, and more quantitative estimates (see *e.g.* refs. [55,56]) have given quite reasonable results. On our part, we have recently published fairly good correlations between $\Delta\varepsilon_i$ values and V_σ or F_σ (solvent reaction potential and solvent reaction field, respectively).[46] The sensitivity of $\Delta\varepsilon_i$, to the cavity shape was not detected before, and so now the problem must be considered again from this point of view. As a first step in this new set of analyses, in a domain already considered as settled, we publish here the maps of V_σ of water within the cavity for the two cases A and B (Figure 3). The changes are numerically important and evidence the importance of the shape of the cavity (cases A and B correspond to two cavities of almost equal volume). We have, of course, hypotheses for the explanation of this finding, but the subject will be treated with appropriate care on another occasion. Suffice it to conclude here that this is an additional reason for continuing checks on the primitive model.

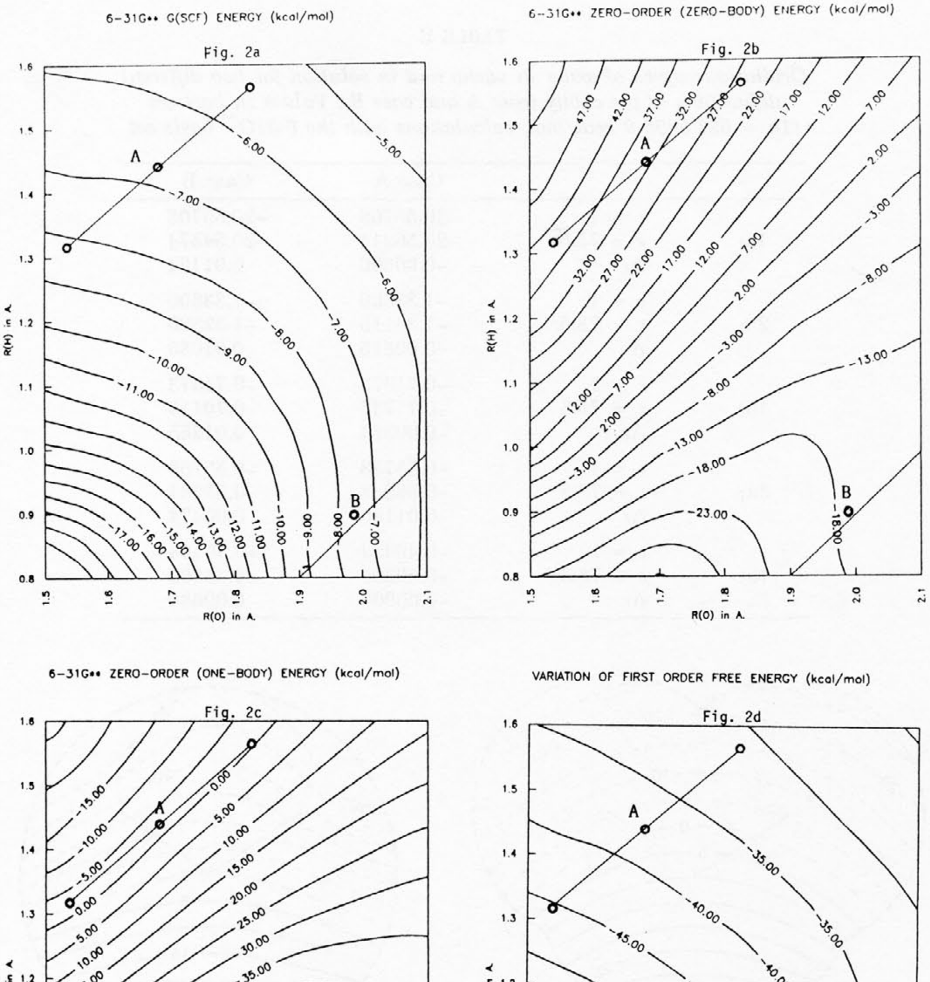

Figure 2. Maps of some energetic quantities related to the solvation of H_2O (in water) in function of the radii of the spheres centred on the nuclei of O and of H. a) ΔG_{el}(SCF) values; b) zeroth order zero-body contribution $\Delta G_0{}^0$; c) zeroth order one-body contribution $\Delta G_o{}^1$; d) first order contribution $\Delta G_1{}^1$. Calculations performed with the 6-31G** basis set. Distances in Å, values in kcal/mol. From ref. [54], with permission of the Authors.

TABLE II

Orbitalic energies of water in vacuo and in solution for two different definitions of the cavity (case A and case B). Values in hartrees (1h = 627.5095 9 kcal/mol; calculations with the 6-31G** basis set

		Case A	Case B
$1a_1$	$\varepsilon = 1$	−20.55708	−20.55708
	$\varepsilon = 78.5$	−20.56214	−20.54574
	$\Delta\varepsilon$	−0.00506	0.01134
$2a_1$	$\varepsilon = 1$	−1.33600	−1.33600
	$\varepsilon = 78.5$	−1.34115	−1.32520
	$\Delta\varepsilon$	−0.00515	0.01080
$1b_2$	$\varepsilon = 1$	−0.71373	−0.71373
	$\varepsilon = 78.5$	−0.71747	−0.70118
	$\Delta\varepsilon$	−0.00374	0.01255
$3a_1$	$\varepsilon = 1$	−0.55758	−0.55758
	$\varepsilon = 78.5$	−0.56938	−0.55284
	$\Delta\varepsilon$	−0.01180	0.00474
$1b_1$	$\varepsilon = 1$	−0.49484	−0.49484
	$\varepsilon = 78.5$	−0.50390	−0.48800
	$\Delta\varepsilon$	−0.00906	0.00684

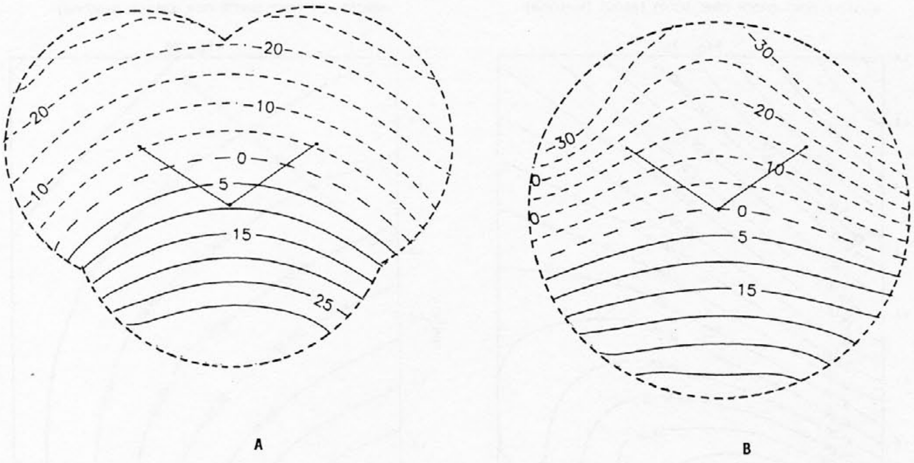

Figure 3. Maps of V_σ for H_2O in water computed: a) with cavity A of Figure 1;. b) with cavity B of Figure 1. Values in kcal/mol.

6. UP AND DOWN THE AXIS OF THE MOLECULAR LEVEL

While checks on the primitive version are continuing, an extension of the approach along the several axes mentioned above is in progress. The methodological approach to implementing a new model cannot be too methodical and cautious. A correct compromise must be found, and there are no general rules to suggest for doing so: each type of model has its own characteristics, and the strategy elaborated, *e.g.* for EHCD models, is surely of little value for models addressed to other problems *e.g.* superconductivity. However, a bold and hurried extension of a model with frail bases quite easily leads to disastrous errors, and a correct appreciation of the weak points of a model comes out when it is stressed and extended.

Up

We have already mentioned in passing some extension of the PCM model up the axis of the methodological level. The set of papers of the electron correlation in the PCM model[53] is not yet finished, and we think that going on with our analysis we will eventually arrive at a more detailed and satisfactory comprehension – and prediction – of the mechanism of mutual interaction between correlation and solvent effects. Both have their origin in the molecular structure of the solvent and we have tried to develop a formalism able to decouple these non-linear effects.

In the past years, theoretical chemistry has been engaged in elaborating more efficient methods to describe the properties of a molecule, including electron correlation. It is our impression that the time is ripe now to extend this activity including also the simultaneous effect of the solvent. The main road followed by theoretical chemistry in its evolution, *i.e.* describing with care a significative element, considering other elements or factors and looking at the effect they have on the original description, may be further pursued, taking the solvent as an additional element introduced in the analysis.

Obviously, this study requires dissection of the effects and the analysis of the various components of the electron correlation is the solution. Other studies require this level of description of the system as the starting point without component analysis, the investigation being addressed to other scopes. We mention as an example the mechanistic studies of reactions which often cannot be properly performed at the SCF level. In Pisa, as well as in other Laboratories, there are working versions of the PCM algorithms or of other EHCD methods, able to give MCSCF, MRCI or MBPT results without much analysis of the intermediate effects. The progress of the research requires both approaches.

Down

In the past years, we paid more attention to the extension of the basic model down the axis of sophistication in the description of the solute rather than up. This has also been the main trend for other groups involved in similar activities. EHCD methods are in fact approximate in nature and their primary task is that of providing chemists with computational models able to satisfy their needs with reasonable accuracy. Chemical problems of actual interest are too complex for sophisticated theories and so the primary goal is that of exploiting the information and the confidence gained with the basic *ab initio* SCF model to develop simpler models.

The effect of motivations related to the preceding history of our research group has been even more important. The decision to try a new version of the continuum solvation model was prompted by our studies on the semiclassical model, and on the role played in chemistry by the classical molecular electrostatic potential and related physical quantities.[57,58] The continuum approach makes it possible to use quantities and concepts quite familiar to us in a different field. Among these concepts, there were the simplified description of the first order density matrix of a molecule and the effect of these approximations on some observables, like the molecular electrostatic potential and field (MEP and MEF), which play a prominent role in the continuum solvation theories (see Section 3).

We shall summarize now a set of approximations, starting from the basic version of the PCM, looking at the total charge distribution Γ_M to the two auxiliary quantities V_M and V_σ, which all have an explicit and well defined role in the PCM, and finally to the solvation free energy. In the following discussion we shall neglect changes in the internal geometry of M: a feature which complicates the analysis, but which will be, anyway, satisfactorily dealt with, and which gives, in appropriate cases, a remarkable contribution to our knowledge of the system.

A1) The basic SCF version of the PCM gives us a first order density function of M modified by the solvent effect:

$$\Gamma_M^f(r_1) = \int dr_2 \ldots dr_n \, \Psi'^f(r_1 \ldots r_n) \, \Psi'^{f*}(r_1 \ldots r_n) + \sum Z_\alpha \delta(r_1 - r_\alpha) \tag{15}$$

and the corresponding MEP

$$V_M^f(r_1) = \int \Gamma_M^f(r_1)(|r - r_1|)^{-1} \, dr \tag{16}$$

The solvent reaction potential is an implicit function of $\Gamma_M{}^f$ and $V_M{}^f$, as detailed in the section, as well as from other parameters (dielectric constant, cavity, shape, *etc.*)

$$V_\sigma^{pf} = V_\sigma^{pf}(\Gamma_M^p, V_M^p) \tag{17}$$

We have used a two-index notation as reminder that the final result comes out at the end of a two-cycle iteration process. The first index indicates the outer cycle (*i.e.* the SCF cycle on Ψ'_M), the second index the inner cycle (*i.e.* the polarization of σ at fixed $\Gamma_M(r)$). The solvation free energy is given by eq. (11), and it is here rewritten, for convenience, with the following notation

$$\Delta G(\mathrm{A1}) = \Delta G_{\mathrm{el}} = G_{\mathrm{el}} - E^{\circ} \tag{18}$$

A2) The level theory is the same of A1. The only difference is in the expression of the solvation free energy

$$\Delta G(\mathrm{A2}) = \frac{1}{2} \int \Gamma_M^f V_\sigma^{ff} \, dr \tag{19}$$

This formula, simpler than eq. (18), is based on neglection of the differences in the mean kinetic energy *in vacuo* and in solution.

A3) Neglection of the solute polarization induced by the solvent corresponds to the use of the molecular density and MEP computed *in vacuo*. The quantities of interest are:

$$\Gamma_M^{\circ}(r_1) = \int \Psi^{\circ} (r_1 r_2 \ldots r_n) \Psi'^{\circ *}(r_1', r_2' \ldots r_n') dr_2 \ldots dr_n + \sum_\alpha Z_\alpha \delta(r_1 - r_\alpha) \tag{20}$$

$$V_M^{\circ}(r_1) = \int \Gamma_m^{\circ}(r_1)(|r - r_1|)^{-1} \, dr \tag{21}$$

$$V^{of}_{\sigma}(\mathrm{A3}) = V^{of}_{\sigma}(\mathrm{A3})\,dr \tag{22}$$

The outer cycle is no more necessary. The solvation free energy (eq.11) is directly done by the expression:

$$\Delta G(\mathrm{A3}) = \Delta G^{o}_{el} = \frac{1}{2}\int \Gamma^{o}_{\mathrm{M}} V^{of}_{\sigma}(\mathrm{A3})\,dr \tag{23}$$

A4) It is well known that the electronic wavefunction may be subjected to arbitrary non singular linear transformations, leaving the electronic change distribution unchanged. We are interested in transformations giving origin to localized subunits. The different criteria in use produce almost equivalent descriptions.[59] A simple formal partition of the atomic charges allow us to define charge distributions for chemical groups g within M, the sum of which is exactly equivalent to the original Γ_{M} function. This procedure may be applied both to the $\Gamma_{\mathrm{M}}{}^{f}$ and $\Gamma_{\mathrm{M}}{}^{o}$ functions defined at points A1 and A3, but we shall make use of the quantities defined *in vacuo*:

$$\Gamma^{o}_{\mathrm{M}}(\mathrm{r}) = \sum_{g\in \mathrm{M}} \gamma^{o}(g,M) \tag{24}$$

The notation emphasizes the fact that the quantities on the right side of eq. (24) refer to the description of the g groups *inside M.*

The electronic contributions of the group description have relatively small »tails« on the other groups of M, which make the dependence of the $\gamma(g,)$ distributions on M more explicit.

A »deletion of the tails« means replacing the $\gamma(g,M)$ functions with the $\overline{\gamma}(g,M)$ ones (note the bar put on the function). $\gamma(g,M)$ is described in terms of the basis set AOs spanning the whole molecule M (basis set χ_M while $\overline{\gamma}(g,M)$ is described in terms of the AO subset spanning the atoms of g ($\chi_g \in \chi_M$).

There is no more complete equivalence between the original functions $\Gamma_{\mathrm{M}}{}^{o}$ and $V_{\mathrm{M}}{}^{o}$ and their counterpart written in terms of *strictly localized* group distributions

$$\overline{\Gamma}^{o}_{\mathrm{M}} = \sum_{g} \overline{\gamma}^{o}(g,M) \tag{25}$$

$$\overline{V}^{o}_{\mathrm{M}} = \sum_{g} \overline{V}^{o(\mathrm{M})}_{g} \tag{26}$$

It is still convenient to perform the inner optimization cycle in the definition of V_σ

$$V^{of}_{\sigma}(\mathrm{A4}) = \overline{V}^{of}_{\sigma}(\Gamma^{o}_{\mathrm{M}}, \overline{V}\,\mathrm{vm}^{o}) \tag{27}$$

$$\Delta G(\mathrm{A4}) = \frac{1}{2}\int \overline{\Gamma}^{o}_{\mathrm{M}}\, \overline{V}^{of}_{\sigma}(\mathrm{A4})\,dr \tag{28}$$

This step in the sequence of approximations is not computationally convenient but it is the starting point for other approximations.

A5) $\overline{\gamma}(g,M)$ differs from the description of the charge distributions of the same functional group g in a different molecule or in the same molecule at a different non-equivalent position. The differences between the various descriptions are not large (the concept of chemical group has a well established empirical evidence) and it seems reasonable to introduce a reference description (a paradigm, or an archetype, for persons loving words of Greek origin) $\bar{\gamma}(g,0)$ defined as the mean of several $\bar{\gamma}(g,M)$ descriptions.

Thus, we may build up a library of $\bar{\gamma}(g,0)$ functions not connected to specific molecules but related to a well defined basis set. The $\bar{\gamma}(g,0)$ functions are subjected to changes due: to a) their insertion in the molecule M, b) the solvent effect acting on M.

The semiclassical model reduces both changes to the classical polarization changes, under the influence of $F(M/g)$ and F_σ, *i.e.* the field of the groups of M other than g, and the solvent reaction field. We have developed a technique in order to take into account these polarization effects without resorting to polarizability functions, which seem to us harder to manipulate. The details may be found *e.g.* in ref. [60]. When both effects a) and b) are in action, symbolically we have:

$$\bar{\gamma}(g,0) \xrightarrow{F(M/g)+F_\sigma} \bar{\gamma}^{**}(g,M,\sigma) \tag{29}$$

The double asterisk indicates that there are two polarization processes in action. In this approximation, the *sum* of the two fields is used. In analogy with the preceding approximations, we may write:

$$\bar{\Gamma}^{**}_{\mathrm{M}} = \sum_{\mathrm{g}} \bar{\gamma}^{**}(g,M,\sigma) \tag{30}$$

$$\bar{V}^{**}_{\mathrm{M}} = \sum_{\mathrm{g}} \bar{V}^{**}(g,M,\sigma) \tag{31}$$

$$V^{\mathrm{of}}_\sigma(\mathrm{A5}) = V^{\mathrm{of}}_\sigma(\bar{\Gamma}^{**}_{\mathrm{M}}, \bar{V}^{**}_{\mathrm{M}}) \tag{32}$$

$$\Delta G\,(\mathrm{A5}) = \frac{1}{2}\int \bar{\Gamma}^{**}_{\mathrm{M}} \bar{V}^{**}_\sigma(\mathrm{A5})\,dr \tag{33}$$

A6) Using again the library of $\bar{\gamma}(g,0)$ functions, but discarding now the solvent polarization effect, we have:

$$\bar{\gamma}(g,0) \xrightarrow{F(M/g)} \bar{\gamma}^{*}(g,M,0) \tag{34}$$

$$\bar{\Gamma}^{*}_{\mathrm{M}} = \sum \bar{\gamma}^{*}(g,M,0) \tag{35}$$

$$\bar{V}^{*}_{\mathrm{M}} = \sum_{\mathrm{g}} \bar{V}^{*}(g,M,0) \tag{36}$$

$$V^{\mathrm{of}}_\sigma(\mathrm{A6}) = V^{\mathrm{of}}_\sigma(\bar{\Gamma}^{*}_{\mathrm{M}}, \bar{V}^{*}_{\mathrm{M}}) \tag{37}$$

$$\Delta G\,(\mathrm{A6}) = \frac{1}{2}\int \bar{\Gamma}^{*}_{\mathrm{M}} \bar{V}^{*}_\sigma(\mathrm{A6})\,dr \tag{38}$$

This approximation is an equivalent to approximation 3 in the sense that the solute is not polarized by the solvent, but instead of a SCF calculation of the density function of M, we have a by far computationally simpler juxtaposition of library functions modified by the molecular field.

A7) A still simpler use of the group function library consists of the summing up of $\gamma(g,0)$ functions without any other manipulation

$$\overline{\Gamma}_{\mathrm{M}}(0) = \sum_{\mathrm{g}} \overline{\gamma}(g, 0) \tag{39}$$

$$\overline{V}_{\mathrm{M}}(0) = \sum_{\mathrm{g}} \overline{V}(g, 0) \tag{40}$$

$$V_\sigma^{\mathrm{of}}(\mathrm{A7}) = V_\sigma^{\mathrm{of}}(\overline{\Gamma}_{\mathrm{M}}(0), \overline{V}_{\mathrm{m}}(0)) \tag{41}$$

$$\Delta G(\mathrm{A7}) = \frac{1}{2} \int \overline{\Gamma}_{\mathrm{M}}(0)\, V_\sigma^{\mathrm{of}}(\mathrm{A7})\, dr \tag{42}$$

This approximation, apparently quite crude, works surprisingly well not only for the solvation energy but also for the description of the details of the form of V_σ into the solvent cavity. This quantity may be used for the interpretation of several solvent effects;[61] a detailed example is given in ref. [46] and the corresponding approximation A7 in ref. [62].

A8) We have thus far used descriptions of the various portions of the molecule based on the expansion of the density function over a LCAO basis. These descriptions are more accurate, in short range, than multipolar expansions but are also more costly in computation time. We shall extend now the sequence of approximations leaving out the LCAO expansion. Several years ago,[57,63] we found that a fairly good description of the MEP originated by $\gamma(g,M)$, $\overline{\gamma}(g,M)$ and $\overline{\gamma}(g,0)$ distribution functions is done by an expansion in terms of a limited number m of unit point charges, placed at appropriate positions (the number m is lower that the total number of electrons). The $\overline{\gamma}(g,0)$ distributions could thus be replaced by the corresponding charge distribution. We may dispense with writing here expressions formally analogous to those reported above (eqs. 41–44). Expansions based on limited multipole multicentre expansions have been extensively employed to get approximate values of the MEP (for a recent view see ref. [64] and, potentially, are of interest for the calculations of solvent effects at the A8 level of approximation.

A9) As the last step in the reduction of the quality of the solute description, we pass to the description in terms of atomic charges. There are many definitions of atomic charges[65] and probably one more definition may be added. The best results we obtained refer to the »potential derived« atomic charges (PDAC) in the version given by Kollman *et al.*, but the quality of the results is far from being exceptional.[67] Another least square fit, based on the reproduction of the value of $\nabla V_M \cdot \boldsymbol{n}$ on the cavity surface (see eq. 4) could perhaps give better results.

At the end of this description, the reader surely expects some numerical result as illustration. Instead of doing so, we refer the interested reader to a recent review[60] and to the papers quote therein for numerical examples. The reason for our decision of avoiding a display of numerical results is the excessive space required by a sufficiently detailed exposition. The second reason is that we have no new unpublished material in a quantity sufficient to document all the approximations mentioned above.

It is preferable to use the space so spared for some comments. We have exposed one of the many possible sequences of approximations, the only one we have employed. Other researchers have developed other techniques and other different approximations of similar nature. The number of approximate methods will probably increase in the near future because there is a large experience in the field of bimolecular non covalent interactions to exploit.

Our sequence of approximations contains some intermediate steps of little, if any, practical use. Their importance relies on the documentation they give on the effect of the various approximations. It is advisable to supplement the approximate method one has selected for routine applications with the possibility of looking at intermediate levels. The controls should be performed in case of necessity, *i.e.* when there is a suspicion that something does not work properly. To do this for every case would be a waste of time and energy.

7. UP AND DOWN THE AXIS OF THE SOLVENT DESCRIPTION

Up

This is a delicate and crucial point in our objective of studying real chemistry in solution by using EHCD methods.

The number of problems for which the basic approach seems sufficient is surprisingly large and it is still increasing. Our initial objective was that of finding the limits of the continuum approximation and then proceeding further; we are still exploring new fields in which the continuum models give reasonable or quite good results. This finding may be classified under the category »surprise« that we have introduced earlier.

It is not our scope, however, to emphasize here the merits of the primitive model. Some improvements, or steps »upwards« along the axis concerning the description of the solvent involve inclusion of non-electrostatic terms in V_{int}. The most important contribution is the dispersion term. We have selected an empirical formulation which uses again a surface integration and a continuous distribution. The dispersion energy is expressed in the form of atom-atom contributions (the repulsion contributions to the free energy are treated in the same way).[39] Other methods of computing G_{dis} contributions have been added to the basic PCM computational framework by other Laboratories, Badajoz[68] and Bratislava.[69] We cannot analyze here the merits and limitations of the various approaches: it is sufficient to say that for this subject, as well as for many others, there is no unique valid solution, and that it is convenient to explore in parallel different approaches. The functional form selected in Pisa makes it easier to define quicker approximate algorithms (and this is, to be frank, a step down on the solvent description axis). It also facilitates the use of continuous non isotropic solvent distributions (cybotactic region), obtained from computer simulations, by RISM calculations or by experiment.[70] Cybotactic effects are also present in the electrostatic contribution: these effects are collected under the headings of dielectric saturation and electrostriction. The research work we are doing in this area has not yet produced definitive results, but the progress is steady and the publication of some new protocols dealing with saturation and electrostriction in the PCM should be not too far in time. A computational model able to treat also cybotactic features was elaborated several

TABLE III

Studies on material models involving a liquid separation surface

- Surface proximity effects on the solvation free-energy
  - a) at a liquid-air interface (planar)
  - b) at a liquid-liquid interface
  - c) at a liquid-solid interface
  - d) at the surface of a drop (spherical)
- Solute crossing of a planar, liquid-liquid interface
- Partial desolvation of a solute in proximity of a biologically active site

years ago[71] and recast in a slightly different and more efficient form by a Japanese group.[72] In this model, the dielectric is divided into non-overlapping portions, each having different physicochemical properties (in particular, different dielectric constants) and separated by sharp boundaries.

The liquid systems with limiting boundaries are of wide occurrence and present interesting problems, in which chemistry may be related to biology, physics, engineering. Some specific problems that we have recently studied, or for which we have performed the first steps, are collected in Table III, to show the importance we attach to this subject.

More refined descriptions of the solvent distribution, like those considered in the last sentences, and others of almost equal importance not yet considered by our group, cannot rely on the EHCD method alone for the definition of some features of the model. We may stress here a concept valid for all the problems of doing theoretical chemistry in solution, namely that a complementary use of different approaches is necessary. A simple example may clarify the point. The EHCD approach alone is unable to describe the features of a liquid/liquid separation surface. In some cases, this surface is sharp and almost flat, in other cases the separation between the two liquids is good but there is formation of filaments of one liquid protruding in the body of the second (a phenomenon sometimes called »fingering«), in other cases the separation is diffuse and without a sharp boundary. Computer simulation, or experiment, may indicate the appropriate model for the case under consideration. The EHCD models, and the PCM in particular, are, in contrast, by far more efficient than simulation to evaluate the dependence of the free energy in function on the position and orientation of a solute near the separation surface.[73]

Down

Dispersion and repulsion free energy contributions act at a decidedly shorter radius than the electrostatic term. Thus, it has been a relatively easy task to define cutoff values for the local contributions to G_{dis} and G_{rep}.[74] The calculation of these contributions may be noticeably accelerated without detriment to the quality of the results: the computational time increases linearly with the solvent exposed surface.

Things are more complex with the electrostatic contributions present in the basic model. Reduction to a local effect as in the preceding case, and as it is implicitly assumed in the solvaton[12-15] or related models,[11] is not correct. The evaluation of the reaction potential, and of the electrostatic solute-solvent interaction energy, requires two sets of basic calculations (see Section 3). The first correspond to the calculation of the molecular potential at all positions of the cavity surface selected for the numerical integration, the second to the calculation of the V_σ potential at the same points on the cavity surface. Let us suppose, for the sake of clarity, that the solvent charge distribution is described by a set of M distinct point charge distributions, and that the number of points of the cavity surface is N.

In approximate methods, M may be considered roughly proportional to the number of atoms m (formally, and in exact expansions, it is equal to the number of distinct elementary charge distributions $\chi_r\chi_s$ over the molecular basis set[75]). It is just $M = m$ if only atomic charges are considered and, in general, it will be $M = km$ with $k \geq 1$. N is related to the number of atoms lying on the solvent accessible surface; in small molecules this number will be almost equal to m, but it decreases for larger and compact solutes. Let us call n the number of atoms lying on the surface. In the current version of PCM, the number of points on the surface will be quite near $N = n \cdot f \cdot 60$, where f is the fraction of the surface exposed to the solvent ($0 \geq f \geq 1$). Each atomic sphere is in fact divided into 60 equivalent portions, or tesseras, a part of which will contribute to forming the outer molecular surface.

We have, thus, to compute $2N$ values of solute MEP (two values are sufficient to evaluate $\nabla V_M \cdot \boldsymbol{n}$) *i.e.* $2N \cdot M$ distances, if the charge is expressed in terms of point charge. This quantity is proportional to m^2 for solutes of small size.

The second set of basic computations regards the calculations of $2 \cdot \frac{N(N-1)}{2}$ distances, a number again proportional to n^2. More than 90% of the computer time for the calculation solvation energies resides in these two sets of calculations.[76] In Section 6, we have considered some ways of reducing the computation times for the first set of calculations, and now we shall consider the second.

The largest contribution to the self-polarization contributions to V_σ came, for each portion of the surface, from the charge σ distributed on that portion. This quantity must be computed accurately, even when the surface of each portion is reduced (and then the number of equivalent tesseras is larger than 60). The iterative expression makes it possible to write the contributions from the other tesseras in a closed form. Moreover, the quantity to be computed, $\nabla V_\sigma \cdot \boldsymbol{n}$, makes unimportant surface charges unable to give a sizable contribution to the perpendicular component of V_σ at the site under consideration. Portions of surface almost parallel to that under consideration could be neglected.

These are simple considerations about possible reductions of the computational times which we have not yet tested. Another possibility of reducing the number of points on the surface has been suggested by Miertus and coworkers.[77] We have so far felt no necessity of reducing computation times. These considerations make us confident that it will be possible to make PCM calculations at short computational times, even for very large molecules. Other computational methods, derived from the PCM, introduce more compact formalism for this part of the program.[23,72,24,78] Some among them also introduce further approximations which help in reducing computation times.

8. APPLICATION TO CHEMICAL AND PHYSICO-CHEMICAL PROBLEMS

We have centred our exposition on problems of methodology. In the application, and extension of the approach to specific problems, other problems of methods arise.

The elaboration of methodological questions is more gratifying to the researcher when addressed to specific applications rather than to the set-up of the basic method, since every progress is felt as a real improvement in the description and understanding of the behavior of molecular systems. We guess that, for the same reasons, it is more interesting to read a relation concerning the difficulties found in the different applications, the devices developed to overcome them, the future prospects based on the experience gained in such a way, than an exposition of the set-up of general purpose methods.

Our exposition of the general part has been quite long and, therefore, we feel obliged to stop here.

The variety of problems treated with the PCM approach in Pisa or in other laboratories begins to be considerable. See *e.g.* Table III in ref. [9] and ref. [51b] The progress of the research and the refinement of the approach increase the number of cases in which there is a surprisingly good agreement with the description given by computer simulations, and with the experimental data. The exposition of these cases

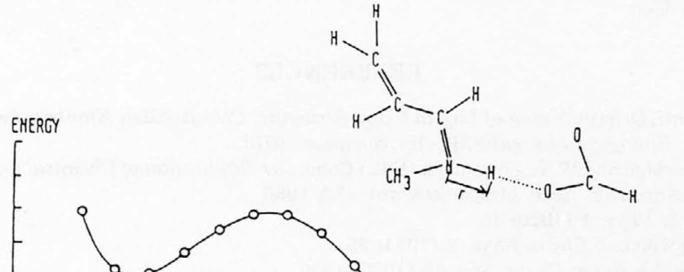

Figure 4. Proton transfer free energy profiles *in vacuo* and in two solvents at different permittivity. From ref. [79], with permission of Elsevier Science Publishers BV.

could support the assertion made in the introduction that there is a shift of solution models towards chemistry.

The only exception we made to our decision of cutting short the examples is to honor prof. Hadži, to whom this paper is dedicated. Prof. Hadži realized very early the potentialities of the PCM approach, for applications of large chemical and biochemical interest. He was the first, to our knowledge, to publish convincing examples of the reversal in the minimum positions in A···H···B systems produced by the solvent. An example is reproduced in Figure 4 taken from ref. [80].

More studies on proton transfer will surely follow, using more refined techniques and considering finer aspects of the problem as the dynamical ones. We are curious to see up to which point the EHCD methods will be of real use in this field, as well as in the many other fields of interest to chemistry. What now seems certain is that the EHCD methods have already demonstrated their utility, in specific cases and we may add that we have not yet found their intrinsic limits.

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SAŽETAK

Metodološki aspekti solvatacijskih modela utemeljenih na kontinuiranoj raspodjeli otapala

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Prikazani su i raspravljeni solvatacijski modeli utemeljeni na efektivnom hamiltonijanu i kontinuiranoj raspodjeli otapala. Naglasak je na fleksibilnosti pristupa. Računski postupci sežu od vrlo sofisticiranih kvatno-mehaničkih formulacija do jednostavnih klasičnih izraza utemeljenih na upotrebi krutih atomskih naboja. Model se može usmjeriti na studij vrlo raznolikih fenomena uz uvođenje neznatnih promjena. Naglašava se i potreba za nadopunom ovoga pristupa s drugima, koji su različite naravi, kako bi se postigao napredak u razumijevanju kemijskog ponašanja sustava u otopini. Navedeni su primjeri primjena opisanog modela, ali rasprava vrijedi i za druge računske modele.