

# Molecular Interactions in Solution: An Overview of Methods Based on Continuous Distributions of the Solvent

Jacopo Tomasi<sup>†</sup> and Maurizio Persico

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56126 Pisa, Italy

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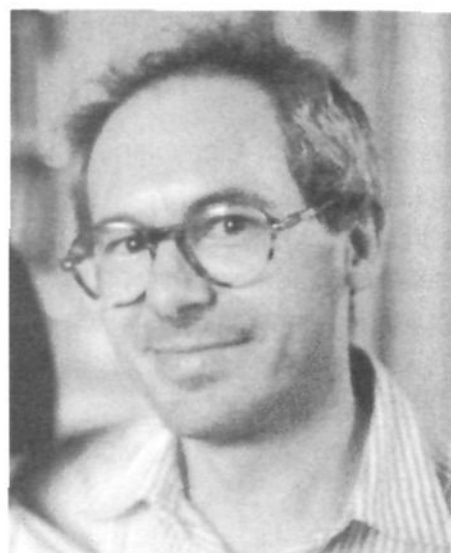
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## I. An Overview of Different Approaches to Studying Chemistry in Solution

This paper is a report on the state of the art and on the perspectives of the theoretical treatments of solvent effects, based on continuum models. We feel that such a review may represent a useful complement to an issue of *Chemical Reviews* devoted to the description and understanding of noncovalent molecular interactions. In fact, a solution may be considered, *prima facie*, as a large assembly of molecules held together by noncovalent interactions: under this point of view, an investigation of such interactions in physical systems of increasing complexity should start with dimers, continue through larger clusters, and end with solutions. The methods



Jacopo Tomasi was born in Diano Marina, Italy, in 1934. Student of the Scuola Normale Superiore di Pisa, he was awarded the degree of "Dottore in Chimica" at the University of Pisa, in 1958, discussing a thesis on the theoretical aspects of the overtone IR spectroscopy, under the supervision of professor E. Scrocco. In 1968 he received the title of "Libero Docente" in Theoretical Chemistry. He was Assistant Professor from 1960 to 1972 in the Faculty of Sciences of the University of Pisa, and he served as Research Director in the Institute of Quantum Chemistry and Molecular Energetics (C.N.R.) from 1972 to 1980. Since 1980 he has been Professor of Quantum Chemistry at the University of Pisa. His research interests cover several aspects of theoretical chemistry, namely structure and properties of isolated molecules, chemical reactivity, reaction mechanisms, intermolecular interactions, photophysical processes. In the last years his main interest has been the study of the solvent effects on molecular systems and processes. He has published more than 180 research papers, a book (in Italian) and 20 chapters in collective books.



Maurizio Persico was born in Genova, Italy, in 1952. In 1976, he was awarded the degree of "Dottore in Chimica" at the University of Pisa, discussing a thesis in theoretical chemistry, and the "Diploma di licenza" of the Scuola Normale Superiore di Pisa. He has held a postdoctoral fellowship in the Institut für Physikalische Chemie der Freie Universität Berlin. Since 1981 he has been a researcher in the Scuola Normale Superiore of Pisa, and since 1988 he has been an associate professor in the Department of Chemistry and Industrial Chemistry of the University of Pisa. He is teaching Photochemistry and Mathematical Methods in Chemical Physics. His research field is theoretical and computational chemistry, mainly the study of photochemical and photophysical processes. He has also contributed to the study of solvent effects in reaction dynamics and in ionic solutions. He has published about 50 research papers.

based on the explicit description of a subunit of the whole solution (the "solute" M), and representing the other components (the "solvent" S) with an interaction potential  $\hat{V}'_{int}$ , have the appropriate features to be inserted in this ideal line of studies. We shall focus our attention on such methods, without neglecting other approaches giving access to the same kind of information.

Actually, solutions are more complex than assemblies of weakly interacting molecules, and, in particular, the study of reactivity in the presence of a solvent cannot be reduced to that of noncovalent interactions. The approaches we shall consider are also addressed to the description of chemical reactions in solution. A proper understanding of such phenomena is the ultimate goal of theoretical chemistry in this field; models and computational techniques should allow the prediction of rates, mechanisms, and other features of specific processes occurring in solutions. These goals require the evaluation of many physicochemical properties, both of local and of macroscopic character. The continuum approach we shall consider here may give some contributions in this field, but it is evident that it cannot cover the whole range of properties and phenomena of interest. Its combination with other methods is necessary in many cases, and some promising results have already been obtained, as we shall see in the following pages. However, the elaboration of multiapproach strategies is still in its infancy, and we hope that the present review will provide a stimulus to proceed further in this direction.

The noticeable evolution of the continuum models in recent years parallels evolutions of comparable importance in other theoretical approaches for the study of liquid systems. This fact makes the traditional classification of these methods incomplete and partially misleading. It is however convenient to report a classification in the "old style" and to show where and why it should be revised.

The "old style" classification may be reduced to four groups of approaches: (a) methods based on the elaboration of physical functions, (b) methods based on computer simulations of liquids, (c) methods based on the continuum (electrostatic) model, and (d) methods based on a supermolecule description of the solution.

In the first group, we include the approaches based on the virial expansion of the equation of state<sup>1</sup> and on the corresponding expansion of the distribution functions of the molecules forming the condensed system. Also belonging to this group are the integral equation descriptions of correlation functions, and the methods based on perturbation theory applied to physically simple reference systems (Yvon,<sup>2</sup> Born-Green,<sup>3,4</sup> Percus-Yevick<sup>5</sup>) and related approaches, such as the scaled particle theory (Reiss<sup>6-8</sup>). Last comes the reference interaction-site model (RISM, Chandler and Andersen<sup>9</sup>), later extended for the treatment of polar and ionic systems (XRISM, Rossky and co-workers<sup>10</sup>). An excellent and authoritative review of these approaches has been done by Barker and Henderson.<sup>11</sup> The emphasis here is placed on the physical aspects of the problem, and for many years the evolution of these methods has been based on the use of drastically simplified expressions of the intermolecular interaction potentials. The chemical aspects of the problem have been relegated in the background.

In the second group, b, we collect the Monte Carlo<sup>12</sup> (Metropolis, 1953) and the molecular dynamics<sup>13,14</sup> (Alder and Wainwright, 1957; Rahman and Still-

inger, 1971) simulations. In both cases, the condensed system is represented by an assembly of interacting particles: the statistical distribution of any property, or its evolution in time, is obtained as a sum over all particles, with appropriate rules. Standard references for the early stages of these approaches are provided by the two books edited by Berne,<sup>15</sup> especially the reviews by Valleau and Whittington<sup>16</sup> and Valleau and Torrie<sup>17</sup> for MC, and by Kushick and Berne<sup>18</sup> for MD. In this field, the computational effort of performing reliable simulations has compelled for many years the use of very simple expressions for the potentials, with the effect of again giving more emphasis to physical problems and not exploiting the chemical potentialities of the approach.

The continuum models, group c, have their origin in simple physical considerations. The attention has been focused since the very beginning on a microscopic description of one component of the system (i.e. the "solute" M). The expressions given by Born<sup>19</sup> and Bell,<sup>20</sup> for the classical interaction energy of a simple M with a medium represented as a continuous dielectric, were formally extended by Kirkwood<sup>21</sup> in 1934 to quantum descriptions of M, without limits in the complexity of the system. The decisive contribution of Onsager<sup>22</sup> in 1936 was to provide an interpretative tool, used by chemists for many years: the simplicity of the formal expressions successively elaborated has stimulated application to various solvent effects (solvent shifts on vibrational and electronic spectra, molecular conformations, reactivity, etc.). The standard reference for the basic aspects of the dielectric continuum models are the two editions of Böttcher's book.<sup>23,24</sup> A similar approach has been developed for ionic solutions, starting from the original formulation of Debye and Hückel.<sup>25</sup> There is an extensive specialized literature on this subject; for many years the book by Harned and Owen<sup>26</sup> has been the standard reference. The continuum and physical functions approaches have been fruitfully combined also in the past decades.

Lastly, there is the supermolecule approach. Models considering the interaction of two or more molecules have been used in the early stages of the theoretical investigation of condensed phases, before the advent of quantum mechanics. The interaction potentials themselves have been checked or corroborated on the basis of these same models. Under item d of our classification we collect, however, the approaches developed after the implementation of efficient quantum molecular computing codes. One of the aims is to get limited, but detailed, information about solvation effects on the properties of M and on the characteristics of the solvation sites: the appropriate strategy was first applied by Alagona et al.,<sup>27</sup> and later systematically exploited by Pullman's group.<sup>28</sup> Another aim is the determination of the structure of inner and outer solvation shells, as done e.g. by Newton and Ehrenson.<sup>29</sup>

This is a schematic description of the situation around 1975–1980. We may recognize that there were many methods to treat physical aspects of solutions, with several interconnections (the feedback between groups a and b has always been active),

while the chemical or physicochemical aspects were dealt with by continuum models, supplemented by indirect evidence based on supermolecule studies.

The changes that have occurred subsequently may be ascribed to a tendency to pay more attention to the molecular aspects of the models; all methods are acquiring a more evident chemical flavor. Similar mechanisms of birth and development of other methods of theoretical chemistry have been active in the past. In fact, theoretical chemistry has derived its conceptual and methodological tools from theoretical physics, but it has been able to elaborate them within a chemical approach. Attention is focused on the dependence of the behavior of material systems on the composition and related parameters. Quantum mechanics for isolated systems is an outstanding example of this evolution. The model, elaborated by physicists, was recast, several decades ago, into formulations more appropriate to the needs of chemistry and gradually developed into a new branch of science, molecular quantum chemistry.

The same appropriation of physical models by chemists is happening for the liquid state. Much of the recent evolution of models is not suggested on physical or mathematical grounds, but dictated by the need of studying chemical problems in solution. Computer simulations are an example of passage from a physical to a chemical leadership. Simulations started from very crude models (the molecules described as spheres). The consideration of more complex molecular shapes (dumbbells, spherocylinders, etc.) and of more complex interactions (interaction site models, soft potentials, etc.) paved the way to formulations clearly addressed to chemical problems. Nowadays, computer simulations are also able to describe complex chemical events, such as the evolution of free energy during a chemical reaction. These methods exploit information derived from detailed quantum mechanical descriptions of microscopic events, at a super- and submolecular level. This evolution is apparent when comparing the references quoted above,<sup>15–17</sup> with more recent reviews on this topic.<sup>30–35</sup> A more intimate merging of quantum and classical force field models is one of the most significant recent progresses.<sup>36–40</sup>

Also in the field of purely statistical approaches, such as RISM/XRISM, we have more chemically oriented applications in the recent years.<sup>41–46</sup> An interesting proposal combining the RISM and quantum chemical approaches has been put forward by Ten-no et al.<sup>47,48</sup> Partial charges representing the charge distribution of a solute molecule are computed at the SCF *ab initio* level; these charges enter the RISM integral equations and contribute to determining the solute–solvent pair correlation functions. In turn, the electrostatic potential computed from the solvent distribution is introduced in the solute Hamiltonian for a new SCF calculation. The *ab initio* and RISM problems are repeatedly solved until mutual consistency. We have spent a few words about this particular method because of its close analogy with the quantum continuum methods described in section IV.

A shift or evolution toward chemical models is active also for the continuum methods, and it will

be the subject of the following sections; we anticipate here some schematic remarks. The accurate description of  $M$ , given by quantum molecular methods, may now be exploited to its full extent, also including molecules in chemical interaction; the description of the medium is no longer limited to isotropic homogeneous dielectrics, nor to electrostatic interactions; nonequilibrium, or dynamical, effects may now be accounted for. Combined strategies using continuum models, supermolecule calculations, computer simulations, and the elaboration of physical functions are in continuous progress.

This evolution is not a mere deterministic trend of increasing complexity; it was purposefully guided by a limited number of scientists. In the case of computer simulations, a decisive contribution has been given by E. Clementi;<sup>49</sup> his stimulus has been accompanied by innovative contributions by other workers, so that nowadays this is the main road to theoretical and computational chemistry in solution. In the middle of the 1970s, a similar role was played, for the continuum models, by a restricted number of persons, among whom we quote in particular Claverie,<sup>50-52</sup> Rivail,<sup>53,54</sup> and Tapia.<sup>55,56</sup> All of them have contributed to the further evolution of the model in recent years. An important step toward a full exploitation of the *ab initio* quantum molecular methods came as well from our laboratory.<sup>57,58</sup> The number of computational procedures within this family has rapidly increased in recent years.

We now return to the problem of a renewed classification of the methods. However, this is a hard task, the outcome of which will soon be outdated because of the rapid evolution and admixture of the methods. It will be convenient to limit ourselves here to reconsidering the continuum models which are the subject of this review. We have recently advocated the introduction of the acronym EHCD (effective Hamiltonian methods which use a continuum distribution of the solvent). Under this heading we may collect: (c1) the new versions of the continuum model, based on a quantum description of the solute, and including the interaction with a medium via a continuum description of the latter (quantum mechanical continuum methods); (c2) other versions of the continuum approach, which describe the solute as a classical polarizable charge distribution, and combine it with a continuum description of the surrounding medium (classical continuum methods); (c3) approaches based on modifications of the solute  $M$ , such as to represent the interaction with the medium, without an explicit representation of the latter (solvatons, virtual charge models).

A unifying concept in all these methods is that of "reaction field", i.e. the electric field generated by the polarized solvent; the interaction mediated by the reaction field is included in the Hamiltonian of the solute.

This classification leaves out the methods relying on a discrete molecular description of the whole solution (we recall, however, that  $M$  in the continuum models may be a cluster including several solvent molecules). Some applications of discrete approaches (a combination of supermolecule and solvent simulations) may give pertinent information about typical

parameters of the continuum models, e.g. the reaction field.<sup>59-62</sup> Simplified descriptions of a portion of the solvent, based on the analysis of supermolecule studies, are often used with corrections arising from a continuum description of more distant regions of the solvent. An outstanding example is given by the use of Langevin dipoles to simulate water, adopted by Warshel in many papers.<sup>63,64</sup> These approaches will not be reviewed here. They are, however, an indication that the evolution of the methodology will lead to a merging of different approaches and to the proposal of new ones, making obsolete any classification.

Several preceding reviews have considered the three aspects of this reduced classification (Tapia,<sup>65</sup> Tomasi et al.<sup>66,67</sup>). The reviews specialized for the first section, c1, mainly report on the activity of a single research group.<sup>68-71</sup> The second kind of approach, c2, has many applications in the biological field: most reviews reflect this interest.<sup>72,76</sup> A balanced view and a detailed discussion have been presented by Davis and McCammon.<sup>77</sup> A critical review of the third group of methods, c3, has been given by Constanciel.<sup>78</sup> We note that this latter paper brings out several errors hidden in preceding formulations. A systematic derivation of the classical electrostatic formulas used in continuous dielectric models has been done by Blaive in his doctoral thesis.<sup>79</sup> Blaive has detected numerous inconsistencies and errors in previous work: his criticism has also been expressed in separate papers.<sup>80</sup>

In the present review we shall address the methodological aspects of this evolution. Applications to specific chemical problems, the number and variety of which is rapidly increasing, will not be surveyed systematically. The literature we are covering reaches the first months of 1994.

## II. The Basic Continuum Model

### A. The Effective Hamiltonian

Let us consider an infinite assembly of molecules which, at a given temperature and pressure, have the typical features of the liquid state. The system is in thermal and mechanical equilibrium, and chemical reactions may take place. This physical system is the starting point for the quantum mechanical formulation of a continuum model of solutions, assumed here as a reference point, with the view of introducing later more complex features, or of reducing it to simpler forms.

The formal derivation of the model is based on the use of partitioning and averaging techniques of general application in molecular mechanics. The reader may find detailed formal presentations in papers by Ángyán<sup>81</sup> and by Tapia;<sup>82</sup> the latter completes a series of preceding, less detailed, formulations,<sup>65,83,84</sup> more transparent to a nonspecialised reader. The final result of such formal manipulations is to justify the definition of an effective fixed-nuclei Hamiltonian  $\hat{\mathcal{H}}_M$  for the solute  $M$ .  $\hat{\mathcal{H}}_M$  depends on the coordinates of  $N_{el}$  electrons  $\mathbf{q} \equiv \mathbf{q}_1, \dots, \mathbf{q}_{N_{el}}$  and, parametrically, on the coordinates of  $N_{nuc}$  nuclei,  $\mathbf{Q} \equiv \mathbf{Q}_1, \dots, \mathbf{Q}_{N_{nuc}}$ .

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

Here  $\hat{\mathcal{H}}_M^{(0)}$  is the usual electronic Hamiltonian in vacuo, according to the Born–Oppenheimer approximation, and  $\hat{\mathcal{V}}$  is an interaction potential which will be defined subsequently. The related Schrödinger equation is

$$\hat{\mathcal{H}}_M(\mathbf{q}; \mathbf{Q}) \Psi^{(f)}(\mathbf{q}; \mathbf{Q}) = E^{(f)}(\mathbf{Q}) \Psi^{(f)}(\mathbf{q}; \mathbf{Q}) \quad (2)$$

All relevant information about the solvent effects on the solute M is contained in the eigenvalues  $E^{(f)}$  and in the wave functions  $\Psi^{(f)}$ . For most purposes, the molecular charge distribution  $\varrho_M$  is conveniently used in place of  $\Psi^{(f)}$ .  $\varrho_M$  is the sum of a discrete nuclear charge distribution  $\varrho_{\text{nuc}}$  and of the electron density function  $\varrho_{\text{el}}$ :

$$\varrho_M(\mathbf{r}; \mathbf{Q}) = \varrho_{\text{nuc}}(\mathbf{r}; \mathbf{Q}) + \varrho_{\text{el}}(\mathbf{r}; \mathbf{Q}) \quad (3)$$

$$\varrho_{\text{nuc}}(\mathbf{r}; \mathbf{Q}) = \sum_{\alpha} Z_{\alpha} \delta(\mathbf{r} - \mathbf{Q}_{\alpha}) \quad (4)$$

$$\varrho_{\text{el}}(\mathbf{q}_1; \mathbf{Q}) = - \int |\Psi^{(f)}(\mathbf{q}, \mathbf{Q})|^2 d\mathbf{q}_2 \dots d\mathbf{q}_{N_{\text{el}}} \quad (5)$$

Here  $Z_{\alpha}$  is a nuclear charge and the index  $\alpha$  runs over all the nuclei of M. The negative sign in  $\varrho_{\text{el}}$  accounts for the electronic charge ( $-1$  in atomic units).

$\hat{\mathcal{V}}_{\text{int}}$  itself carries additional information which can be used in the study of chemical problems. Its definition implies the knowledge of a thermally averaged distribution function of the solvent molecules,  $g_{\text{S}}$ , so that we may write

$$\hat{\mathcal{V}}_{\text{int}} = \hat{\mathcal{V}}_{\text{int}}(\mathbf{q}, \mathbf{Q}, g_{\text{S}}) \quad (6)$$

The origin and the extent of the average which defines  $g_{\text{S}}$  can be stated more precisely during the elaboration of the model. The EHCD models are based on eqs 1–6. The word “continuous” in this acronym and in related definitions refers to the fact that  $g_{\text{S}}$  has the form of a continuous distribution.

The basic continuum model involves a simplified form of the interaction potential;  $\hat{\mathcal{V}}_{\text{int}}$  is reduced to its classical electrostatic component, and  $g_{\text{S}}$  describes a linear isotropic continuum, characterized by the static dielectric constant  $\epsilon$  of the bulk solvent, which depends, in turn, on the temperature  $T$ . We shall use the symbol  $\hat{\mathcal{V}}'_{\sigma}$  in place of  $\hat{\mathcal{V}}_{\text{int}}$ , when only electrostatic polarization effects will be considered:

$$\hat{\mathcal{V}}_{\text{int}} = \hat{\mathcal{V}}'_{\sigma}(\mathbf{q}, \mathbf{Q}, \varrho_M, \epsilon) = \sum_{\alpha} Z_{\alpha} \Phi_{\sigma}(\mathbf{Q}_{\alpha}) - \sum_i \Phi_{\sigma}(\mathbf{q}_i) \quad (7)$$

Here  $\Phi_{\sigma}(\mathbf{r})$  is the value of the electrostatic field generated by the polarized dielectric at the position  $\mathbf{r}$ . The solute–solvent interaction contribution to the total energy  $E^{(f)}$  is given by the integral

$$W_{\text{MS}} = \int_{\text{all space}} \Psi^{(f)*} \hat{\mathcal{V}}'_{\sigma} \Psi^{(f)} d\mathbf{q}_1 \dots d\mathbf{q}_{N_{\text{el}}} = \int_{\text{all space}} \varrho_M(\mathbf{r}) \Phi_{\sigma}(\mathbf{r}) d\mathbf{r}^3 \quad (8)$$

$\hat{\mathcal{V}}'_{\sigma}$  is a mono-electronic operator, and the evaluation  $W_{\text{MS}}$  is not, usually, a time-consuming step in the calculation. The quantum problem is treated with

more or less standard techniques. The most frequently used is the Hartree–Fock method; in this case  $\hat{\mathcal{V}}'_{\sigma}$  is simply added to the Fock operator.

Let us summarize what we have done up to now. We have set up a formalism that allows the full exploitation of the potentialities of quantum chemistry; in fact, the perturbed Hamiltonian  $\hat{\mathcal{H}}_M$  has the same structure as  $\hat{\mathcal{H}}_M^{(0)}$  and involves the same integrals. At the same time we have given an implicit rule to determine  $\hat{\mathcal{V}}'_{\sigma}$ . In fact, this operator depends on the total charge distribution  $\varrho_M$  (modified by solvent effects), on the assumed geometry of M (the  $\mathbf{Q}$  coordinates) and on the value of the dielectric constant,  $\epsilon$ .

## B. Quantum and Classical Definitions of $\varrho_M$ and $\Phi_{\sigma}$

The quantum formulation of the basic electrostatic and continuum model requires the simultaneous definition of two problems, namely: (1) the quantum mechanical problem of computing the electron distribution  $\varrho_M$ , with fixed nuclei, in the presence of  $\Phi_{\sigma}$ ; (2) the electrostatic problem of determining the solvent reaction potential  $\Phi_{\sigma}$  and its interaction energy with the charge distribution  $\varrho_M$ .

This is a typical nonlinear problem, because  $\Phi_{\sigma}$  and  $\hat{\mathcal{V}}'_{\sigma}$  depend in turn on  $\varrho_M$ . Its solution requires the elaboration of an appropriate strategy. The most intuitive approach will consist in performing a self-consistent iterative procedure, by solving alternately the quantum problem to determine  $\varrho_M$  and the classical electrostatic problem to determine  $\Phi_{\sigma}$ . Of course one needs a reasonable initial guess for  $\Phi_{\sigma}$  or  $\varrho_M$ . There are however other approaches, which will be examined at the appropriate time.

The classical formulation faces an apparently simpler problem. There are no quantum equations, but the electrostatic problem is similar. The solute charge distribution  $\varrho_M$  is considered a classical entity (even if in the most refined versions of the method it derives from quantum calculations). A complete solution of the electrostatic problem would include polarization effects on  $\varrho_M$ , due to the solvent reaction field: in this case, an iterative procedure would be necessary. The classical methods presented so far adopt one of the following options: (1) The solute polarization effect is discarded and  $\varrho_M$  is not modified (rigid models,  $\varrho_M = \varrho_M^{(0)}$ ) or (2) the solute polarization is included at the first order, giving a  $\varrho_M^{(1)}$  distribution function, without further feedback on  $\Phi_{\sigma}$  (polarization models,  $\varrho_M = \varrho_M^{(1)}$ ). We shall reserve the name “extended Born models” to the versions of the rigid models in which  $\varrho_M$  is reduced to a set of point charges.

Both quantum and classical models have different options to describe  $\Phi_{\sigma}$  and the electrostatic interaction energy between  $\varrho_M$  and  $\Phi_{\sigma}$ . The approaches of widest use are (1) multipole expansion, (2) apparent surface charge, (3) image charge, (4) finite differences, and (5) finite elements. The first three approaches have been implemented for quantum versions of the model, all five approaches are used in classical models.

### C. The Solute Cavity

In all the five approaches mentioned above, one defines an empty cavity in the dielectric medium, in which the solute  $M$  resides. The introduction of a cavity is a necessary step for methods based on the explicit use of  $\hat{\mathcal{H}}_M$  and is also advisable for classical continuum methods. Methods belonging to group c3 (polaron and virtual charge models) do not make explicit use of a cavity.

The shape and size of the cavity are critical factors in the elaboration of a method. An ideal cavity should reproduce the shape of the solute  $M$ , with the inclusion of the whole charge distribution  $\rho_M$  and with the exclusion of empty spaces which can be filled by the solvent continuous distribution. If the cavity is too large the solvation effects are damped; if it is too small serious errors may arise in the evaluation of the interaction energy for the portions of  $\rho_M$  (atoms or bonds) near the boundaries. A cavity with a wrong shape introduces distortions in the description of the reaction field and of the related solvent effects. The cavity shapes actually employed are the following ones: (1) regular shapes, namely (a) spheres, (b) ellipsoids, and (c) cylinders; or (2) molecular shapes, namely (a) unions of overlapping spheres centered on the nuclei of  $M$ , (b) unions of overlapping spheres centered on some chemical groups of  $M$ , (c) unions of overlapping spheres, some of which are not centered on nuclei, located so as to fill all the space not accessible to the solvent, and (d) unions of overlapping spheres and cylinders, connected with portions of concave solids, to fill the space not accessible to the solvent.

The cavities of type 1 simplify the use of multipolar one-center expansions of  $\Phi_\sigma$  and  $\rho_M$ . The use of image charge methods is also simplified when the cavity has a regular shape. The other representations of  $\Phi_\sigma$  are not critically dependent on a simple geometrical definition of the cavity.

A cavity is also characterized by its size, i.e. volume and surface area. The problem of the most convenient definition of molecular volumes and surfaces in condensed phases has attracted the attention of many researchers and aroused discussions. Its relationship with the solution of the continuum electrostatic models is only one of the relevant aspects of the general question. A complete discussion about this topic is beyond the scope of this review. We limit ourselves to quote two surveys on this subject.<sup>85,86</sup>

As we shall see later, in passing from the basic model to other continuum models containing non-electrostatic terms (e.g. dispersion, repulsion, cavitation), it will be necessary to reconsider the problem of the cavity. In fact, these additional terms require cavities of different size, usually larger than those used for the electrostatics: typically, the excluded volume is related to the sum of the solute and solvent radii (see section V).

In the original version of the polarizable continuum model (PCM), put forward by Miertüs, Scrocco, and Tomasi,<sup>57</sup> we defined the cavity in terms of spheres with radii  $R_\alpha$ , proportional to the van der Waals radii:

$$R_\alpha = fR_\alpha^{(\text{vdW})} \quad (9)$$

The most popular set of reference atomic radii is probably that of Bondi, obtained from crystallographic data:<sup>87</sup> see for instance the works of Cramer and Truhlar; Luque and Orozco; Miertüs; Olivares del Valle and Aguilar; Silla and Pascual-Ahuir; Sakurai; Tomasi; Wang and Ford, and their co-workers, cited in the following. The initially proposed factor, for the evaluation of the electrostatic term with neutral solutes, was  $f = 1.2$ . There was clear numerical evidence, in the different steps of the computational procedure, that the van der Waals radius should be a lower limit for the cavity radius: the factor  $f$  must be slightly larger than 1. The value of  $f = 1.2$  was obtained by considering the results of Kitaura and Morokuma's energy decomposition<sup>88</sup> for a few  $M \cdot S_n$  clusters ( $M = \text{H}_2\text{O}, \text{CH}_3\text{OH}, \text{H}_2\text{CO}, \text{NH}_3, \text{CH}_3\text{NH}_2, \text{S} = \text{H}_2\text{O}, \text{CH}_3\text{OH}, \text{NH}_3, \text{CH}_3\text{NH}_2, \text{CH}_4, \text{Ar}$ ). Later we confirmed this choice by comparing the  $\Phi_\sigma$  values inside the cavity, obtained with PCM and with Monte Carlo calculations for different solvents ( $\text{H}_2\text{O}, \text{CH}_3\text{OH}, \text{CH}_3\text{NH}_2$ ). These tests have not been published, because only a rough estimate of the  $f$  factor was needed for our purposes.

Probably today, with better interaction potentials and more efficient computer simulation programs, the choice  $f = 1.2$  could be refined or supported with more confidence. There are a few independent tests based on the study of radial distributions derived from molecular dynamics and on the analysis of the hydration free energy of neutral molecules,<sup>89,90</sup> indicating that the choice  $f = 1.20$ – $1.25$  is reasonable; in fact, atomic bond or lone pair charge centers of the solvent molecules are normally located a bit further from the solute atoms than a van der Waals radius.<sup>89</sup> Only for hydrogens bonded to heteroatoms, have smaller radii been found convenient:<sup>90</sup> notice that this is a common practice also in force field methods. Another test has been performed in our group, with results only partially published,<sup>91</sup> using a more complete expression of the solvation free energy (including dispersion, repulsion, and cavitation contributions, each computed with cavities based on the van der Waals radii), we have varied the factors  $f_1$  and  $f_2$  so as to reproduce the solvent transfer free energies, or partition coefficients, between two solvents,  $S_1$  and  $S_2$ . Given a number of neutral solutes  $M$  and solvents  $S$  (water, 1-octanol, chloroform, benzene, toluene, cyclohexane), we have determined the set of  $f_1, f_2$  values which reproduce the experimental data relative to each system  $M$ – $S_1$ – $S_2$ . The most consistent choice, based on a statistical analysis, is  $f = 1.2$  for water and  $f = 1.1$ – $1.2$  for the other solvents.

For charged solutes (ions, zwitterions, ion pairs) the factor  $f$  may need to be reconsidered, because of nonlinear effects in the polarization of the dielectric with high fields; we may have negative deviations from linearity, due to saturation, or positive deviations, due to charge migration in the field gradient (electrostriction).<sup>24</sup> These two physical effects suggest changes of the  $f$  factor in opposite directions.<sup>92</sup> A modification based on the analysis of some supermolecule calculations has been used by Bonaccorsi et al.<sup>93</sup> for the solvation of the zwitterionic form of glycine. A recent comparison<sup>94</sup> with Monte Carlo

simulations of aqueous solutions of charged molecules (with  $\pm 1$  charges) suggests a value of  $f = 1.10$ – $1.15$ . An attempt of defining a unique factor  $f$  for cations, and another one for anions, so as to reproduce experimental solvation free energies, enthalpies, and entropies in a representative set of eight solvents, was not successful;<sup>95</sup> the use of a unique factor leads to errors larger than the chemical accuracy. This is probably due to the strong dependence of the first solvation shell structure on the size and polarity of the solvent molecules, and on the charge and radius of the ion. Better results have been obtained with a layered cavity model that will be examined later. Similar conclusions were drawn from the recent determination of the best cavity for Br in various oxidation states and in different solvents.<sup>96</sup> In this work  $R_{\text{vdw}}$  is assumed to depend linearly on the atomic charge, and the  $f$  factor ranges from 1.20–1.25, when the solvent is water, methanol, ethanol, or chloroform, to 1.40 in dichloromethane and dichloroethane. Rashin and Namboodiri<sup>97</sup> suggest the use of the ionic radius for anions and of the covalent radius for cations (water as solvent).

General rules for the definition of  $f$  factors as functions of the atomic charges within the molecule  $M$  have been proposed by Miertuš<sup>98</sup> and, more systematically by Olivares del Valle et al.<sup>99–101</sup> Miertuš et al.<sup>98</sup> modify the Stokes rules to get ionic radii and elaborate a functional dependence of  $R_{\text{vdw}}$  on the Mulliken charge, based on the values of  $R_{\text{vdw}}$  at three different oxidation states. Olivares del Valle et al.<sup>99–101</sup> define the radii  $\langle R_k \rangle$  for neutral and ionic states of the atom  $k$  in terms of the square root of the expectation value of the second moment of the electronic density. The authors then determined an appropriate functional relationship connecting  $\langle R_k \rangle$  to the atomic charges  $Q_k$ . The numerical parameters to be employed for a large number of basis sets are reported.

### III. The Classical Electrostatic Problem

#### A. Boundary Conditions

Once the shape and size of the cavity are defined, one may pass to the solution of the electrostatic problem.

The dielectric constant assumes one of two values:

$$\epsilon(\mathbf{r}) = 1 \quad \mathbf{r} \in V_{\text{in}} \quad (10)$$

$$\epsilon(\mathbf{r}) = \epsilon \quad \mathbf{r} \in V_{\text{out}}$$

$V_{\text{in}}$  and  $V_{\text{out}}$  are the volumes inside and outside the cavity, respectively.  $V_{\text{out}}$  extends to infinity. The charge distribution  $q_M$  is supposed to be confined inside the cavity:

$$q_M(\mathbf{r}) = 0 \quad \mathbf{r} \in V_{\text{out}} \quad (11)$$

With these assumptions we may derive the basic Poisson and Laplace equations defining the total electrostatic potential  $\Phi$ :

$$\nabla^2 \Phi(\mathbf{r}) = -4\pi q_M(\mathbf{r}) \quad \mathbf{r} \in V_{\text{in}} \quad (12)$$

$$\nabla^2 \Phi(\mathbf{r}) = 0 \quad \mathbf{r} \in V_{\text{out}}$$

For the asymptotic region, very far from  $M$ , we have the boundary conditions:

$$\lim_{r \rightarrow \infty} r\Phi(\mathbf{r}) = \alpha \quad (13)$$

$$\lim_{r \rightarrow \infty} r^2 \nabla \Phi(\mathbf{r}) = \beta$$

with finite values for  $\alpha$  and  $\beta$ . For points very close to the cavity surface:

$$\Phi_{\text{in}} = \Phi_{\text{out}} \quad (14)$$

$$\frac{\partial \Phi_{\text{in}}}{\partial \mathbf{n}} = \epsilon \frac{\partial \Phi_{\text{out}}}{\partial \mathbf{n}}$$

Here  $\Phi_{\text{in}}$  and  $\Phi_{\text{out}}$  are the values of the electrostatic potential at neighboring points just inside and outside the cavity;  $\partial/\partial \mathbf{n}$  is the derivative in a direction perpendicular to the cavity surface; the  $\mathbf{n}$  vector points outward.

For a given charge distribution  $q_M$ , the electrostatic potential  $\Phi$  differs from that calculated in vacuo, because it contains also the reaction field generated by the solvent charge distribution. Moreover, in the polarizable models,  $q_M$  is modified by the reaction field itself; only in the rigid models is  $q_M$  the same in solvent and in vacuo.

In a classical model, the solute–solvent interaction integral, eq 8, is limited to the volume inside the cavity, because  $q_M = 0$  outside:

$$W_{\text{MS}} = \int_{V_{\text{in}}} q_M(\mathbf{r}) \Phi_{\sigma}(\mathbf{r}) d\mathbf{r}^3 \quad (15)$$

We recall here that a quantity more pertinent to the study of thermodynamic properties is the work necessary to bring the charge  $q_M$  into the cavity (Böttcher,<sup>24</sup> p 143). For a rigid model we have

$$\Delta G_{\text{el}}^{(0)} = \frac{W_{\text{MS}}}{2} \quad (16)$$

This quantity has the status of a free energy, the electrostatic contribution to the solvation free energy change. The index  $i$  in  $\Delta G_{\text{el}}^{(i)}$  denotes the level of approximation in the description of the mutual solute–solvent polarization effects ( $i = 0$ , rigid charge;  $i = 1$ , solute polarization in response to the reaction field;  $i = f$ , fully relaxed description).

We shall examine now the five approaches to the solution of the electrostatic problem, listed in section II.B.

#### B. The Multipole Expansion (MPE) Approach

##### 1. Spherical Cavities

The simplest case is that of a charge distribution embedded in a spherical cavity with radius  $R$ . According to the standard elaboration (see for instance Böttcher,<sup>23</sup> p 194), the electrostatic potential  $\Phi$  may be written in terms of Legendre polynomials (spherical harmonics). In principle one needs four sets of expansion coefficients: for negative and positive

powers of  $r$ , and for points inside and outside the cavity. Under the conditions introduced in section III.A, the general formulas can be simplified in the following way:

inside the cavity

$$\Phi(\mathbf{r}) = \sum_{l=0}^{\infty} \frac{1}{r^{l+1}} \sum_{m=-l}^l B_{lm} Y_l^m(\theta, \phi) + \sum_{l=0}^{\infty} -\frac{(l+1)(\epsilon-1)}{l+(l+1)\epsilon} \frac{r^{l+1}}{a^{2l+1}} \sum_{m=-l}^l B_{lm} Y_l^m(\theta, \phi) = \Phi_M + \Phi_\sigma \quad (17)$$

outside the cavity

$$\Phi(\mathbf{r}) = \sum_{l=0}^{\infty} \frac{2l+1}{l+(l+1)\epsilon} \frac{1}{r^{l+1}} \sum_{m=-l}^l B_{lm} Y_l^m(\theta, \phi) \quad (18)$$

Here  $Y_l^m(\theta, \phi)$  is the spherical harmonic with total angular momentum  $l$  and projection  $m$  along the  $z$  axis.  $B_{lm}$  are constant coefficients and  $a$  is the cavity radius. Of the two terms contributing to  $\Phi$  inside the cavity,  $\Phi_M$  may be identified with the potential generated by  $\varrho_M$ , and  $\Phi_\sigma$  with the solvent reaction field.

Readers acquainted with multipolar expansions of molecular charge distributions and interaction potentials are well aware of the disappointing properties of one-center multipole expansions; the problems of convergency and asymptotic behavior within and outside the sphere containing all the charge distribution have been analyzed many times (see for instance Claverie<sup>102</sup>). However, the treatment of the interaction with a continuum within a classical model is simpler, under some respect, than that of intermolecular forces; one only needs to evaluate  $W_{MS}$  through the integral 15. The problem of the asymptotic behavior in the  $l$  summations, eqs 17 and 18, remains open, however. Romano,<sup>103</sup> for example, examined the effect of including high terms in the  $2^l$ -pole expansion, for a solute  $M$  composed of an amino acid and a sizeable number of water molecules (250). He extended his study of the effect on  $W_{MS}$  up to  $l = 100$  and concluded that  $l = 25$  was the lowest acceptable limit. Things are surely better for molecules of smaller size, but it is clear that old methods, relying on the experimental values of a few  $B_{lm}$  coefficients, may give indications of trends and little more. In fact experimental dipole moments ( $l = 1$ ) are available for many molecules, quadrupole moments ( $l = 2$ ) are less abundant, and octopole moments ( $l = 3$ ) are a rarity.  $B_{lm}$  coefficients may be derived from the wave functions, through the expectation value of the corresponding variable (dipole, quadrupole, etc.), or by resorting to a decomposition of  $\varrho_M$  into local contributions (such as atomic charges, atomic or bond dipoles), which are expanded over the set of Legendre polynomials with the origin in the center of the sphere. This is the approach used, for instance, in the quoted work by Romano, who represented each water molecule with a set of point charges.

Multipolar expansions based on many centers, e.g. the chemical groups of  $M$ , with a set of Legendre

polynomials for each expansion center, are of course feasible, but the expressions of  $\Phi$  are far more complex, and there are problems of overcompleteness in the Legendre basis set, which may produce computational troubles.<sup>51</sup>

It is worthwhile to remark here that the expansions 17 and 18, as well as other expansions, multicenter or using cavities of different shape, may be split into an electronic and a nuclear contribution. The latter is inherently related to a point charge distribution; we shall later exploit this remark.

A second point deserving attention is the relationship between the expansion coefficients of  $\Phi_M$  and  $\Phi_\sigma$  inside the cavity. It is clear from eq 17 that there is a simple relationship connecting each  $(lm)$  term in the two sums. Passing now to the notation employed by Rivail and co-workers,<sup>54,104,105</sup> who have largely exploited this feature, we may rewrite the interaction energy in the following form:

$$W_{MS} = \sum_{l=0}^{\infty} \sum_{m=-l}^l M_l^m R_l^m \quad (19)$$

where  $M_l^m$  are the components of the charge distribution and  $R_l^m$  are the components of the reaction field. The linear relationship between  $M_l^m$  and  $R_l^m$  permits one to rewrite the latter in the form:

$$R_l^m = f_l^m M_l^m \quad (20)$$

The coefficients  $f_l^m$ , called reaction field factors, have analytical expressions not depending on the actual values of the expansion coefficients ( $M_l^m$  or  $B_l^m$ ), but only on the shape of the cavity (sphere,<sup>54</sup> spheroid,<sup>106,107</sup> ellipsoid<sup>104,105</sup>). This simplification has been exploited to get fast geometry optimization of  $M$  (see section IV.E).

The reaction field factors may be introduced also in multicenter expansions,<sup>108</sup> yielding a more complex expression of  $W_{MS}$ :

$$W_{MS} = \sum_{l=0}^{\infty} \sum_{m=-l}^l \sum_{l'=0}^{\infty} \sum_{m'=-l'}^{l'} M_l^m f_{ll'}^{mm'} M_{l'}^{m'} \quad (21)$$

So far, we have considered general expressions for one-center multipolar expansions. The simplest terms are of widespread use. We report here the expression of the solvation energy for a few rigid models.

(1) Born model.<sup>19</sup> A point charge at the center of the sphere. Only the term with  $l = 0$  survives:

$$\Delta G_{el}^{(0)}(\text{Born}) = -\frac{\epsilon-1}{2\epsilon} \frac{q^2}{R} \quad (22)$$

(2) Bell model.<sup>20</sup> A point dipole  $\mu$  at the center of the sphere. Only  $l = 1$  survives:

$$\Delta G_{el}^{(0)}(\text{Bell}) = -\frac{\epsilon-1}{2\epsilon+1} \frac{\mu^2}{R^3} \quad (23)$$

(3) Abraham model.<sup>109</sup> A quadrupole at the center of the sphere:



$$\Delta G_{\text{el}}^{(0)}(\text{Abraham}) = -\frac{\epsilon - 1}{3\epsilon + 2} \frac{3}{4R^5} \sum_{i \neq j=1}^3 [4\theta_{ii}^2 + 3(\theta_{ij} + \theta_{ji}) - 4\theta_{ii}\theta_{jj}] \quad (24)$$

where  $\theta$  is a tensor related to the quadrupole moment, defined as a sum over bond dipoles  $\mu_k$  located at positions  $\mathbf{r}_k$ :  $\theta_{ij} = \sum_k r_{ki} \mu_{kj}$ .

Several other expressions using charges or dipoles out-of-center have been employed in the past. To these expressions based on fixed charge distributions we may relate analogous expressions taking into account the polarization of the solvent at the first order. The first and most widely used is that introduced by Onsager.

(1) Onsager model.<sup>22</sup> A polarizable dipole, with polarizability  $\alpha$ , at the center of the sphere:

$$\Delta G_{\text{el}}^{(1)}(\text{Onsager}) = -\frac{\epsilon - 1}{2\epsilon + 1} \frac{\mu^2}{R^3} \left[ 1 - \frac{\epsilon - 1}{2\epsilon + 1} \frac{2\alpha}{R^3} \right]^{-1} \quad (25)$$

(2) Thiebaut–Rivail model.<sup>110,111</sup> A polarizable dipole at the center of the sphere. We do not report here the explicit expressions, given in the original papers.

The last two examples are the simplest cases of classical polarizable models. A general expression for any charge distribution in a sphere has been given by Bonnor.<sup>112</sup> Bonnor made use of a power series expansion of the applied electric field, i.e.  $-\nabla\Phi_\sigma$ , and introduced the dipole, quadrupole, ...,  $n$ -pole (hyper)polarizabilities. The latter molecular quantities can be obtained by standard perturbation theory, following several formulations which differ in the mathematical details.<sup>113–116</sup> The mathematical expressions look quite formidable, and most applications rely on the use of induction terms for a set of dipole moments distributed in the molecule.<sup>117–137</sup>

Recently Sharp et al.<sup>138</sup> have proposed a different way of describing local dipole polarizabilities. The induced point dipole, located at a nuclear position, is simulated by adjusting the value of the local dielectric constant (LDC) in the portion of the cavity belonging to that atom. There is a complete electrostatic equivalence in the two models (inducible dipoles and LDC representation): in fact, polarizability and dielectric constant are two ways of describing the same effect. The LDC model may be applied to a spherical cavity (using an average LDC over the whole molecule) or better to cavities of complex shape. There is, of course, some arbitrariness in the choice of the atomic partition of the cavity.

A representative list of quotations of papers making use of spherical cavities in the different formulations would be almost meaningless, given the huge number of papers published in the past, but also in recent years.

## 2. Ellipsoidal Cavities

A sphere may be considered an appropriate cavity shape for a limited number of molecules. Spheroids and ellipsoids (oblate, prolate, or with three different axes) maintain analogous advantages of mathemati-

**Table 1. Multipole Contributions to  $\Delta G_{\text{el}}^{(0)}$  (kcal/mol) for  $n$ -Propylamine in Water<sup>104</sup> ( $\epsilon = 78$ )**

spherical cavity		ellipsoidal cavity	
	$\Delta G_{\text{el}}^{(0)}$		$\Delta G_{\text{el}}^{(0)}$
$l = 1$	-0.874	$l = 1$	-1.159
2	-1.075	2	-0.724
3	-0.915	3	-0.107
4	-0.592		
5	-0.378		
6	-0.188		
7	-0.129		
total	-4.152	total	-1.990

cal simplicity and are appropriate shapes for a larger number of molecules.

The use of ellipsoidal cavities in continuum solvent models dates back to the early stages of the model. Westheimer and Kirkwood<sup>139</sup> reported the formal expression for the case of a molecule described as a set of point charges located on the main axis of a prolate cavity. They expanded  $\Phi(\mathbf{r})$  on a basis of Legendre functions, expressed in terms of confocal elliptic coordinates (several signs are wrong in the formulas in this original paper). Applications to cases with point charges in the foci were reported in the same paper. This model has been later extended by Ehrenson,<sup>140</sup> Harrison et al.,<sup>106</sup> and then by Felder.<sup>107</sup>

Central expansions limited to the dipole term have been considered by Scholte<sup>141</sup> and by Abbott and Bolton<sup>142</sup> (with critical remarks by Buckingham<sup>143</sup>). The case of two dipoles located at the foci of an ellipsoid has been treated by Wade.<sup>144</sup>

We report here a representative list of applications, a few of which imply some modification of the model.<sup>145–155</sup>

The most decisive and consistent effort to implementing approaches based on the expansion of the reaction field in ellipsoidal cavities has been done by Rivail's group, with the view of applying it to quantum methods. The general expressions for the multipole expansion of a general charge distribution in a three-axis ellipsoid, and for the related quantities  $\Phi_\sigma$  and  $\Delta G_{\text{el}}^{(0)}$ , have been given by Rivail and Terryn,<sup>104</sup> in terms of ellipsoidal harmonics. This set of expansion functions presents some advantages over the usual spherical harmonics. For the definition and properties of the ellipsoidal harmonics and of the related Lamé polynomials see Hobson,<sup>156</sup> Perram and Stiles,<sup>157</sup> Stiles,<sup>158</sup> Rivail and Terryn,<sup>104</sup> and Rinaldi.<sup>159</sup> The last reference also describes a computer code available through QCPE (Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN). We do not report the formal expressions for the electrostatic potential and for the interaction energy, which are similar to those already reported for a spherical cavity.

More interesting is to compare the rate of convergence of  $\Delta G_{\text{el}}^{(0)}$  for a given molecule, in spherical and ellipsoidal cavities with the same volume. The data shown in Table 1 refer to  $n$ -propylamine in the extended conformation and are taken from Rivail and Terryn.<sup>104</sup> The multipole moments have been computed with the GEOMOS program<sup>160</sup> at the CNDO/2 level. The rate of convergence in the spherical cavity

is rather poor, while it is much better in the ellipsoidal one; moreover, the  $\Delta G_{\text{el}}^{(0)}$  obtained with a spherical cavity is much larger; both effects can be explained considering that the solute charge distribution approaches too closely some regions of the spherical surface, giving rise to nonphysical effects. The computer programs of Rivail's group presently manage ellipsoidal harmonics up to  $l = 6$ , by expansion into spherical harmonics.

Cavities of regular shape, spheres and ellipsoids, present the additional problem of locating the center of the cavity with respect to M and, in the case of the ellipsoids, the orientation of the three axes. For the sphere, an old choice was the center of mass of the molecule. In the models elaborated by Rivail's group, the center of gravity of the nuclear charges is chosen; notice that the two centers of gravity, of the nuclear and of the electronic charge distributions, are coincident if the dipole of M vanishes and are normally not far apart also for polar molecules. The volume of the cavity has been usually assumed equal to the average molecular volume of M in the liquid state, following Onsager.<sup>22</sup> Alternatively, it has been related to the molecular polarizability and refractive index of M, through the Clausius–Mossotti equation:<sup>54,161</sup>

$$V_{\text{in}} = \frac{n^2 + 2}{n^2 - 1} \alpha_{\text{M}} \quad (26)$$

The axes of the ellipsoids have been taken colinear with the axes of the dipole polarizability tensor, and their lengths proportional to the eigenvalues.<sup>105</sup> In a more recent paper by the same group, the ellipsoid has been analogously defined with reference to the inertia tensor of the van der Waals solid, i.e. a solid of uniform density composed of interlocking van der Waals spheres.<sup>162</sup> Yet another option has been tested by Rivail's group:<sup>163,164</sup> the ellipsoidal surface is defined in terms of a best fitting of a given isopotential surface, i.e. a surface at a selected constant value of the molecular electrostatic potential, MEP.<sup>165,166</sup>

The results obviously depend on these choices. All the above definitions may lead to surfaces which are too close to one, or more, atoms of M. If the surface falls shorter than 90% of the van der Waals radius (corresponding to a factor  $f = 0.9$  as defined in section II.C), the multipole expansions may exhibit convergence problems. Another approach to define ellipsoidal cavities has been recently proposed by Ford and Wang.<sup>167</sup> They employ a simplified (spherically averaged) water molecule as a probe and compute the interaction energy  $V_{\text{MP}}$  between M and the probe, using molecular mechanics parameters.  $V_{\text{MP}}$  is averaged over all possible locations of the probe on the ellipsoidal surface, and the ellipsoid parameters are determined by minimizing the average  $\bar{V}_{\text{MP}}$ . The dimensions of the cavity are then increased by a constant empirical amount  $\Delta\varrho$  (the surface of the optimized ellipsoid in some cases lies too close to some of the nuclei of M). We report in Table 2 the  $\Delta G_{\text{el}}^{(0)}$  results for guanine, with three values of  $\Delta\varrho$ , and the dissection into  $2^l$ -pole contributions. For this molecule, if one defines the cavity axes through the

**Table 2. Multipole Contributions to  $\Delta G_{\text{el}}^{(0)}$  (kcal/mol) for Guanine in Water<sup>a</sup>**

$l$	$\Delta\varrho = 0$	0.43	0.85
1	-6.5	-4.3	-2.9
2	-9.1	-4.8	-2.9
3	-1.4	-0.5	0
4	-3.3	-1.4	-1.0
5	-1.9	-0.7	-0.2
6	-1.7	-0.5	-0.2
total	-23.9	-12.2	-7.2

<sup>a</sup> Optimized ellipsoidal cavity, with increment  $\Delta\varrho$  of the linear dimensions.

polarizability tensor, with a volume corresponding to  $\Delta\varrho = 0$ , the expansion diverges. It is evident that the  $\Delta\varrho$  value plays a decisive role. The convergence of the multipolar expansion is faster if the cavity is larger; however, too large a cavity underestimates  $\Delta G_{\text{el}}$ .

### 3. Molecular Cavities

Expansions in spherical harmonics may also be applied to cavities of irregular shape (our set 2 in section II.C). In fact, it is sufficient that the surface be piecewise differentiable, and the unions of spheres, ellipsoids, and other geometrical solids have this property.

The mathematical problem is rather formidable, but has been solved by Huron and Claverie,<sup>51</sup> in one of a set of papers which represent a cornerstone in the evolution of modern continuum methods. Huron and Claverie select a single set of harmonic functions  $r^l Y_l^m(\theta, \phi)$  for the expansion of  $\Phi_\sigma$  inside the cavity, and a multicentered basis set outside the cavity. The reasons for this choice are expressed in the original paper.<sup>51</sup> We do not report here the detail of the mathematical manipulation of the model, for which several approximations are worked out. In the most general cases a numerical quadrature over Koberov grids is employed.

### C. The Image Charge (IC) Approximation

The use of fictitious charges with appropriate positions and values, such as to directly describe the reaction potential generated by a dielectric on a given charge distribution, is an old device in classical electrostatics. The name of image charge method comes from the simplest example, that of a point charge  $q$  placed in the vacuum at a distance  $d$  from the plane surface of a semi-infinite grounded conductor. The single fictitious charge having the requested properties is a charge  $q' = -q$ , placed at a distance  $-d$  (i.e., inside the conductor). The conductor surface acts as a mirror.

Things are a bit more complicated when the semi-infinite conductor is replaced by a dielectric. We need in fact two image charges, the first,  $q'$ , to compute the potential  $\Phi$  outside the dielectric, and the second,  $q''$ , to compute  $\Phi$  inside (see eqs 17 and 18). One finds easily  $q' = -q(\epsilon - 1)/(\epsilon + 1)$ , located at  $d' = -d$ , and  $q'' = 2q/(\epsilon + 1)$ , at  $d'' = d$ .

This approach is of wide use for electrolytes or other fluids bearing localized systems of charges near a hard wall, or confined between parallel walls. We shall not review here such applications.

The case of a charge distribution within a spherical cavity of an isotropic linear dielectric has been treated by Friedman.<sup>168</sup> The treatment is restricted to a finite number of point charges and dipoles with arbitrary location inside the cavity. This type of charge distribution is sufficiently realistic for most practical applications. The expansion of  $\Phi_\sigma$  in terms of image charges is truncated to the first term (the presence of a spherical surface requires in fact an infinite set of image charges, each mirroring itself). The neglected terms are successively smaller by a factor  $(\epsilon + 1)^{-1}$ . This notwithstanding, their effect is not negligible. It is sufficient to compare Friedman's expressions of  $\Delta G_{\text{el}}^{(0)}$ , for the cases of a charge or a dipole  $\mu$  at the center of the sphere, with the exact solutions of the Born or Bell models, eqs 22 and 23. Within this formulation of the image charge approach we have

$$\text{charge } q \quad \Delta G_{\text{el}}^{(0)} = -\frac{\epsilon - 1}{\epsilon + 1} \frac{q^2}{2R} \quad (27)$$

$$\text{dipole } \mu \quad \Delta G_{\text{el}}^{(0)} = -\frac{\epsilon - 1}{\epsilon + 1} \frac{\mu^2}{2R^3} \quad (28)$$

These formulas differ from the exact ones by factors  $\epsilon/(\epsilon + 1)$  and  $(2\epsilon + 1)/(2\epsilon + 2)$ , respectively.

An extension of this approach has been given by Shaw.<sup>169,170</sup> Two main improvements are introduced: (i) the use of cavities defined in terms of piecewise regular surfaces (i.e., with local separation of coordinates), and (ii) the inclusion of the missing terms in the image expansion of  $\Phi_\sigma$ . To reach these goals Shaw makes use of the second Green identity (i.e., he reduces the potential to the integration of a polarization surface charge density  $\sigma$ , defined over the cavity surface). Then, by iteration, he derives a converged "multiple induction expansion" as a generalization of the set of image charges. An alternative to the multiple expansion is given by the use of direct numerical methods. Put in these terms, Shaw's approach resembles that of the apparent surface charge we shall consider in the next section.

A mixed method has been proposed by Rullman and van Duijnen.<sup>171</sup> The "solute" charge distribution is described by a set of point charges  $q_k$  and Friedman's IC approximation is applied for the reaction field. The polarization free energy of the solvent, however, is computed by means of Onsager's theory. As "solute" these authors consider the true solute molecule, supplemented by a generous amount of water molecules (two or three solvation layers). The method has not been extensively used, and other formulations coming from van Duijnen's group will be summarized later.

Coming back to the simplest versions of the image approach, these have been employed in a number of cases, their application being quite simple if the number of source charges is limited.<sup>172-174</sup> Of particular interest, as Friedman pointed out, is the use of this method in MC and MD computer simulations to take into account the boundary conditions for the finite sample of molecules explicitly treated.<sup>31,175</sup>

## D. The Apparent Surface Charge (ASC) Approach

According to classical electrostatics, the reaction potential  $\Phi_\sigma$  may be described, everywhere in the space, in terms of an apparent charge distribution  $\sigma$  spread on the cavity surface (ASC approach).

This method appears to be the most versatile and powerful for applications going beyond the classical model we are considering here.

The general formulation is dictated by the boundary conditions introduced in section III.A. A  $\sigma$ -charge distribution appears at each surface of discontinuity between different regions of the dielectric medium and can be expressed in terms of the difference of the respective polarization vectors  $\mathbf{P}_1$  and  $\mathbf{P}_2$ :

$$\sigma_{12} = -(\mathbf{P}_2 - \mathbf{P}_1) \cdot \mathbf{n}_{12} \quad (29)$$

where  $\mathbf{n}_{12}$  is the normal from region 1 to region 2.  $\mathbf{P}_1$  is related to the gradient of the potential:

$$\mathbf{P}_i = -\frac{\epsilon_i - 1}{4\pi} \vec{\nabla} \Phi \quad (30)$$

In our case we have only two regions, inside the cavity ( $\epsilon_1 = 1$ ;  $\mathbf{P}_1 = 0$ ) and outside ( $\epsilon_2 = \epsilon$ ;  $\mathbf{P}_2 = \mathbf{P}$ ), therefore

$$\sigma = -\mathbf{P} \cdot \mathbf{n} = \frac{\epsilon - 1}{4\pi} \vec{\nabla} \Phi_{\text{out}} \cdot \mathbf{n} = \frac{\epsilon - 1}{4\pi\epsilon} \vec{\nabla} \Phi_{\text{in}} \cdot \mathbf{n} \quad (31)$$

It is advisable to compute  $\sigma$  from the electric field inside the cavity, using the last member of the equation, because this formula gives a better approximation at the zero order (no self-polarization of the dielectric).

The potential  $\Phi$  is composed of two contributions,  $\Phi = \Phi_M + \Phi_\sigma$ , as shown before. We have the implicit relation

$$\sigma = \frac{\epsilon - 1}{4\pi\epsilon} \frac{\partial(\Phi_{M,\text{in}} - \Phi_{\sigma,\text{in}})}{\partial \mathbf{n}} \quad (32)$$

with

$$\Phi_\sigma(\mathbf{r}) = \int_\Sigma \frac{\sigma(\mathbf{s})}{|\mathbf{r} - \mathbf{s}|} d^2s \quad (33)$$

$\Sigma$  is the cavity surface and the  $\mathbf{s}$  vector defines a point on  $\Sigma$ .

An advantage of the ASC formulation of the electrostatic problem is that of clearly expressing an additional condition, derivable from the Gauss theorem:

$$\int_\Sigma \sigma(\mathbf{s}) d^2s = -\frac{\epsilon - 1}{\epsilon} Q_M \quad (34)$$

where  $Q_M$  is the total charge of M. The violation of this normalization condition generally occurs in quantum mechanical calculations and is mainly due to a portion of  $Q_M$  spreading out of the cavity<sup>57</sup> (but any source of inaccuracy in the solution of the electrostatic problem can also affect the normalization of  $\sigma$ ). A  $\sigma$  not correctly normalized may lead to significant numerical errors, and it is not easy to perform a renormalization when a multipole expan-

sion is employed. (This is the reason of several artifacts pointed out in preceding sections.)

The solutions of the implicit equations involved in the  $\sigma$ -based formulation of the electrostatic problem may be found by resorting to an expansion over an appropriate basis, e.g. spherical harmonics,<sup>24,51,169</sup> however, such a multipole expansion would suffer from the same problems of convergency and limitations on the shape of the cavity, which we have already discussed.

The fact that the novel source of electrostatic potential,  $\sigma$ , is confined to a surface makes simpler the numerical solution of the problem. The  $\Sigma$  surface is divided into an appropriate number of tesserae, each with an area  $\Delta S_k$  and containing a charge  $q_k$  in the internal point  $\mathbf{s}_k$ :

$$q_k = \Delta S_k \sigma(\mathbf{s}_k) \quad (35)$$

so that

$$\Phi_\sigma(\mathbf{r}) = \sum_k \frac{q_k}{|\mathbf{r} - \mathbf{s}_k|} \quad (36)$$

This approach may be called the boundary element method (BEM), this being the name reserved for analogous techniques in the fields of physics and engineering.<sup>176,177</sup> The application of the BEM to the electrostatic problem of a molecular charge distribution within a dielectric requires special care, in order to have a good representation of  $\Phi_\sigma$  everywhere and to reduce the computational costs. Important options in this respect are the geometrical partitioning of the  $\Sigma$  surface and the exact location of the  $q_k$  charges. Before discussing these topics, we outline the three available methods to solve the BEM problem, i.e. to determine the values of the  $q_k$  charges: (a) iterative solution, (b) closure solution, and (c) matrix inversion.

### 1. Iterative Solution

We may start from a first guess of  $\sigma$  given by eq 32 where we put  $\Phi_\sigma = 0$ . We call  $q_k^{00}$  the surface charges corresponding to this approximation; the first 0 index stands for a rigid charge model, i.e. fixed  $\Phi_M$  (this index will change when discussing quantum mechanical models); the second 0 index indicates that we neglect  $\Phi_{\sigma,\text{in}}$  in eq 32. We put

$$q_k^{00} = \frac{\epsilon - 1}{4\pi\epsilon} \Delta S_k \bar{\nabla} \Phi_{M,\text{in}}(\mathbf{s}_k) \cdot \mathbf{n}_k \quad (37)$$

Here  $\mathbf{n}_k$  is a unit vector, normal to the  $\Sigma$  surface in the point  $\mathbf{s}_k$  and pointing outward. The corresponding potential  $\Phi_\sigma^{00}$ , from eq 36, is inserted into eq 32 to get a better approximation,  $q_k^{01}$ , and so on; at convergence, one obtains the final self-polarized charges  $q_k^{\text{of}}$ . In our formulation of the ASC approach, the polarisable continuum method (PCM), we have implemented the iterative solution of the problem. In the first version of PCM,<sup>57,58</sup> as well as in the most recent ones,<sup>178,179</sup> three or four cycles are usually sufficient to reach convergence.

Equations 38–40 represent a compact formulation of the PCM iterative procedure for the self-polarization of the  $\sigma$  charge, including a correction for the

**Table 3. Convergence of the Iterative Process for the Calculation of the Apparent Charge,  $\sigma^a$**

cycle	C <sub>2</sub> H <sub>4</sub>	H <sub>2</sub> O	[Mg(H <sub>2</sub> O) <sub>6</sub> ] <sup>2+</sup>	Br <sub>3</sub> <sup>-</sup>
1	-1.068	-5.757	-180.300	-48.695
2	-1.176	-6.150	-180.631	-48.719
3	-1.218	-6.269	-180.372	-48.725
4	-1.234	-6.305	-180.375	-48.727
5	-1.240	-6.317	-180.376	
6	-1.243	-6.320		
7	-1.244	-6.321		

<sup>a</sup>  $\Delta G_{\text{el}}$  (kcal/mol) is tabulated for four different solute molecules M (ethylene, water, Mg<sup>2+</sup>-water octahedral complex, tribromide anion) in water, in the rigid  $q^{(0)}$  approximation.

finite size of the convex surface element  $\Delta S_k$ . In the PCM, the  $\Sigma$  surface is composed of interlocking spheres. The curvature radius  $R_k$  of the surface element  $\Delta S_k$  is then the radius of the sphere to which it belongs. At the  $m$ th iteration, we have

$$q_k^{0m} = q_k^{00} [1 + A_k + \dots A_k^m] - \sum_{i=0}^{m-1} A_k^i \sum_{l(i \neq k)} q_l^{0,m-i-1} B_{kl} \quad (38)$$

with

$$A_k = \frac{\epsilon - 1}{2\epsilon} \left( 1 - \sqrt{\frac{\Delta S_k}{4\pi R_k^2}} \right) \quad (39)$$

$$B_{kl} = \frac{\epsilon - 1}{4\pi\epsilon} \Delta S_k \frac{(\mathbf{s}_k - \mathbf{s}_l) \cdot \mathbf{n}_k}{|\mathbf{s}_k - \mathbf{s}_l|^3} \quad (40)$$

The  $A_k$  factor takes into account the self-repulsion of the  $q_k$  charge, by considering that it is uniformly spread on the  $\Delta S_k$  surface element, rather than being a point charge. Miertuš et al.<sup>57</sup> have shown that the expression derived from Gauss' theorem:

$$\lim_{\Delta S_k \rightarrow 0} -\bar{\nabla} \Phi_\sigma = -2\pi\sigma(s_k) \quad (41)$$

must be corrected for finite  $\Delta S_k$  for two reasons: first, the curvature of the surface element; second, the local inhomogeneity of the potential inside  $\Delta S_k$ . The local curvature introduces the correction term proportional to  $\eta_k^{1/2}$  in  $A_k$ ; notice that the negative sign of this term in eq 39 implies that  $\Delta S_k$  is convex. The expression of  $A_k$  was given by Miertuš et al.<sup>57</sup> without a formal derivation, which can be found in successive papers by Hoshi et al.<sup>180,181</sup> and by Wang and Ford<sup>182</sup> (in a shorter version). The second factor gives origin to corrections of the order of  $\eta_k^3/32$  ( $\eta_k = \Delta S_k/R_k^2$  is the solid angle subtending  $\Delta S_k$ ): thus far, it has been neglected by all authors. The formal derivation of the correction for the inhomogeneity factor, and of higher order corrections, has not yet been published.

The  $B_{kl}$  factor, eq 40, is related to the contribution to  $\bar{\nabla} \Phi_{\sigma,\text{in}}$ , due to the charge  $q_l$  (computed with a finite difference expression).

We report in Table 3 an example of the convergency of expression 38.

### 2. Closure Solution

The expression of a charge element at the  $m$ th cycle of the self-polarization procedure,  $q_k^{0m}$ , given in eq 38,

can be easily recast into a combination of series. The expression is particularly simple for  $q_k^{0f}$ , the final charge obtained at convergency. We have recently exploited this feature in a new algorithm which avoids iterations.<sup>183</sup> At a first level of approximation we have:

$$q_k^{0f} = [1 - A_k]^{-1} [q_k^{00} - \sum_l B_{kl} q_l^{00} (1 - A_l)^{-1}] \quad (42)$$

This expression is sufficient for the rigid charge model. It may be further improved by adding a correction in  $B_{kl} B_{k'l'}$ , without appreciable increase in computer time. Equation 42 or its simpler improvements remarkably reduce the computational effort, with respect to a converged iterative calculation.<sup>183</sup>

### 3. Matrix Inversion Procedures

The expressions which determine the set of  $q_k$  charges may be put in the form of a set of linear equations. It is convenient to adopt a matrix form:

$$\mathbf{D} \mathbf{q}^{0f} = \mathbf{E}_{in} \quad (43)$$

$\mathbf{D}$  is a square nonsymmetric and nonsingular matrix, of dimension equal to the number of surface elements:

$$D_{kk} = \frac{4\pi\epsilon}{\epsilon - 1} (1 - A_k) \quad (44)$$

$$D_{kl} = \frac{4\pi\epsilon}{\epsilon - 1} B_{kl} \quad (45)$$

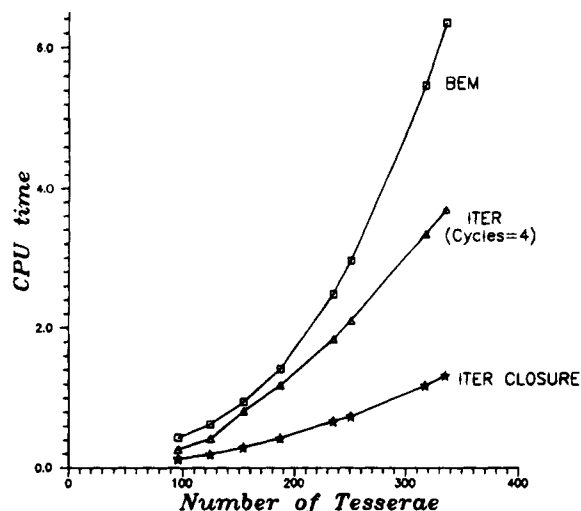
$\mathbf{q}^{0f}$  is a column vector, containing the unknown charges  $q_1^{0f}, \dots, q_t^{0f}$ .  $\mathbf{E}_{in}$  is also a column vector, collecting the effective components of the solute electric field multiplied by the surface elements:

$$E_{in,k}^0 = -\Delta S_k \vec{\nabla} \Phi_{M,in}(s_k) \cdot \mathbf{n}_k \quad (46)$$

Notice that the  $\mathbf{D}$  matrix only depends on the definition and partition of the cavity and on the dielectric constant. Therefore, when the linear system 43 has to be solved several times with different  $\mathbf{E}_{in}$ , as in the case of polarizable M, it may be convenient to invert  $\mathbf{D}$  and to store  $\mathbf{D}^{-1}$ . Then

$$\mathbf{q}^{0f} = \mathbf{D}^{-1} \mathbf{E}_{in} \quad (47)$$

There are several formulations of this method, differing in some details.<sup>180-190</sup> The paper by Hoshi et al.<sup>181</sup> may be considered the standard reference. Drummond<sup>184,185</sup> developed an iterative method to avoid the inversion of  $\mathbf{D}$ . Zauhar and co-workers<sup>186-189</sup> have presented a set of models of increasing complexity and accuracy, based on the  $\mathbf{D}$  matrix approach; some features of their method will be discussed later. Grant et al.<sup>190</sup> avoid the use of the curvature factor by dividing the tessera  $S_k$  in a larger number of elements, to compute  $D_{kk}$ . Also Rashin and Nambodiri<sup>97</sup> avoid the use of a curvature correction, and prefer to define two sets of charges, the larger one to account for curvature effects. Rashin and Nambodiri consider the importance of the proper nor-



**Figure 1.** Comparison of the CPU times required for the surface charge self-polarization, with the three procedures: iterative, matrix inversion (BEM), closure approximation.

malization of the  $\sigma$  charge, and they apply the same correction as in the original PCM.<sup>57</sup>

We report in Figure 1 the computing times for a representative set of examples, obtained with the three procedures outlined above, using the same computer. Notice that an explicit matrix inversion is not necessary, when classical models are considered; the solution of the linear equations in eq 43 may be obtained, by triangularization methods, with a computational effort about three times smaller than required for the complete matrix inversion. This is the procedure applied to get the results of Figure 1. The computing times increase with the number of tesserae  $M$ , according to different laws for the three methods: (a) iteration,  $time \approx N_{it} M^2$  ( $N_{it} \equiv$  number of cycles); (b) closure,  $time \approx M^2$ ; and (c) inversion,  $time \approx M^3$ .

The matrix inversion procedure should not be recommended for rigid classical models. Timings change when quantum mechanical models are considered.

The self-polarization iterations for  $\sigma$  must be nested in a self-consistent cycle for the polarization of M. The matrix inversion method, in contrast, offers the possibility of a direct solution. The matrix inversion requires more memory space than the other methods: this was a decisive factor in favor of the iterative solution in the first version of the PCM,<sup>57</sup> when core memory was relatively limited. Today there is more freedom of choice; however, as the number of tesserae increases with the size of the solute, a careful examination of the strategy to follow is needed. In applications of the latest ab initio version of the PCM program<sup>191</sup> to small molecules with fairly large basis sets, we found comparable computing times using the iterative and the matrix inversion procedures. When increasing the dimensions of the problem, the approximate closure solution may be preferred.

The matrix-inversion BEM procedure has been recently adopted by Klamt and Schüürman,<sup>192</sup> using a novel approach to the electrostatic solvation energy problem. They replace the dielectric outside the cavity with a conductor. Electrostatic formulas are simpler for a conductor. By introducing some ad-

ditional approximations, the set of apparent charges  $\mathbf{q}$  is defined as

$$\mathbf{q} = -\mathbf{A}^{-1}\mathbf{BQ} \quad (48)$$

and the energy is

$$\Delta E = -1/2\mathbf{Q}^\dagger\mathbf{B}^\dagger\mathbf{A}^{-1}\mathbf{BQ} \quad (49)$$

$\mathbf{Q}$  is a column vector collecting the  $N$  charges representing the solute  $\mathbf{M}$ ;  $\mathbf{q}$  is the analogous vector collecting the surface charges,  $\mathbf{A}$  is a square  $t \times t$  matrix with elements  $A_{\mu\nu}$ , representing the interaction between each couple of  $q_\mu - q_\nu$  unit charges;  $\mathbf{B}$  is a rectangular  $N \times t$  matrix, where  $B_{i\mu}$  describes the interaction between two unit charges placed respectively at the position of the solute charge  $Q_i$  and of the apparent charge  $q_\mu$ .

To pass from the conductor to the dielectric, Klamt and Schürman introduce an empirical factor  $f(\epsilon) = 2(\epsilon - 1)/(2\epsilon + 1)$  which multiplies  $\Delta E$ . The authors estimate that the error should not exceed  $1/(2\epsilon)$ . The definition of the surface elements derives from a complex procedure, not fully documented, starting from a very large number of elements, then reduced to a few hundreds. This approach, called COSMO (conductor-like screening model), has been quite recently implemented in the MOPAC package.<sup>193</sup>

#### 4. The Tessellation (Triangulation) of the Surface

Quite important, in assessing the performance of the various ASC methods and programs available, is the level of description of the  $\Sigma$  surface and of its tessellation. As we have already said, it is possible to model the cavity surface in different ways. We shall consider here four different definitions of  $\Sigma$ , all derived from the union of van der Waals spheres centered on the solute atoms.

The simplest definition, i.e. the mere union of spheres ( $\Sigma_{vdW}$ ), is sufficient to describe the continuum for molecules of small size; as already explained, the van der Waals radii should be multiplied by a factor  $f \approx 1.2$ .

When the complexity of the molecules increases, there may be regions of the outer space where the solvent cannot enter, being composed of molecules with a finite size. The molecular surface  $\Sigma_{MS}$  defined by Richards<sup>194</sup> is the closed envelope obtained by rolling a spherical probe of adequate diameter on the  $\Sigma_{vdW}$  surface. For completeness, we recall here a third definition, that of solvent accessible surface ( $\Sigma_{SA}$ ), defined by Lee and Richards<sup>195</sup> as the surface corresponding to the position of the center of the above mentioned spherical probe. The use of the  $\Sigma_{SA}$  surface has been advocated many times in the past, and reconsidered recently,<sup>196,197</sup> but the larger volume associated to  $\Sigma_{SA}$  leads to an underestimation of the solvation effects. The  $\Sigma_{MS}$  surface is everywhere differentiable, even in its concave or saddle-shaped portions. The analytical properties of such surfaces have been investigated by Connolly<sup>198-200</sup> and later by Gibson and Scheraga,<sup>201,202</sup> Kundrot et al.,<sup>203</sup> and Perrot et al.<sup>204</sup> The presence of reentrant (concave) portions of the cavity surface depends on the conformation of the solute: quite often a reentrant region appears or disappears as a consequence of a small

conformational change. The triangulation of this kind of surfaces for the calculation of the  $\sigma$  charge has been elaborated by Zauhar and Morgan<sup>187</sup> and it will be discussed later. The computational approach is different for convex and concave regions and this fact introduces additional difficulties in the treatment, because of the sharp dependence on the conformation.

These and other considerations have prompted us to develop an ASC treatment based on a fourth kind of surface, composed only of interlocking spheres.<sup>178</sup> Starting from  $\Sigma_{vdW}$ , the algorithm adds more spheres, not centered on the nuclei, to include in the cavity any region which cannot be occupied by the solvent. Later on, the same definition of  $\Sigma$  has been found useful to compute the surface and volume of the cavity, with a better accuracy and at a lower cost than achieved by means of Connolly's algorithm. The use of this method to define  $\Sigma_{MS}$ , as well as  $\Sigma_{SA}$  and other surfaces and the associated volumes, is pursued by Silla and co-workers.<sup>205-208</sup>

An advantage of this definition of  $\Sigma$  for the ASC calculation is that the same tessellation can be applied in all cases. There are several ways to produce a tessellation, that is, to define the surface elements  $S_k$ , the representative points  $\mathbf{s}_k$ , and the curvature correction (when applied). The partition of each sphere of the cavity into elements defined by parallels and meridians (spherical coordinates, with  $\Delta\theta$  and  $\Delta\phi$  increments) has been employed in the earlier versions of our PCM algorithm<sup>57,58</sup> and is still in use.<sup>209-211</sup> Since 1986 we have introduced in the PCM algorithm a new partition of the surface; in each sphere is inscribed a pentakis-dodecahedron, i.e. a polyhedron derived from the dodecahedron by replacing each pentagonal face with five triangles. This solid has 60 faces, all of equal area. The pentakis-dodecahedron belongs to a family of polyhedra with triangular faces, with geodesic formula<sup>212</sup>  $\{3,5\}_{1,1}$ . The surface of the sphere is correspondingly partitioned into 60 equivalent curvilinear triangles, almost equilateral. Higher order polytopes,  $\{3,5\}_{k,k}$ , with  $1 < k \leq 6$ , are used to describe the areas and centers of irregular tesserae deriving from the intersection of two spheres. Of course, hidden tesserae contained in the volume of the cavity, are not considered. The density of  $\mathbf{s}_k$  points, i.e. of the surface charges  $q_k$ , is about  $1.5 \text{ \AA}^{-2}$ . The GEPOL program for the construction of polyhedral surfaces is distributed by QCPE.<sup>213</sup>

Wang and Ford<sup>182</sup> start from the pentakis-dodecahedron, using the 32 vertices, in addition to the 60 centers of the faces, to define a set of 92 polygonal elements, 80 of which are hexagonal and 12 pentagonal.

Zauhar and Morgan<sup>187</sup> define a set of points (nodes) on  $\Sigma$ . The nodes are connected by segments (edges), which define a polyhedron with triangular faces (surface elements). Each element is specified by a triple of interconnected nodes. Making use of the normal to the surface at each node and of a ten-point Lagrangian interpolation polynomial, the authors also define curvilinear edges to take into account the curvature of the surface. The consistency of the triangulation is checked by computing the Euler

characteristic of the mesh (to avoid the occurrence of "holes" or "intersecting triangles"). The density of points Zauhar and Morgan found necessary is 2–4 Å<sup>-2</sup>, for neutral solutes.

Grant et al.<sup>190</sup> apply Connolly's numerical dot algorithm<sup>198–200</sup> with a density of points  $\approx 10$  Å<sup>-2</sup> (high density covering) and  $\approx 2$  Å<sup>-2</sup> (low density covering). Apparently, Rashin and Namboodiri<sup>97</sup> apply the same procedure, without giving much detail. Connolly's algorithm generates dots on  $\Sigma_{MS}$  by placing a sphere tangent to  $\Sigma_{vdw}$  at a finite number of locations. The latter are chosen along isolatitude circles for convex portions of  $\Sigma_{MS}$ , i.e. where the probe sphere is tangent to a single atom sphere. Saddle-shaped portions of  $\Sigma_{MS}$  are obtained when the probe is tangent to two atom spheres and concave portions when it is tangent to three spheres. The density of dots may be varied according to the computational needs. As already said, the triangulation of the surface, starting from Connolly's dots, raises problems, at low as well as at high density, due to the appearance of "holes" and "intersecting triangles". Juffer et al.<sup>214</sup> suggest a more complex procedure. High density dots on  $\Sigma_{MS}$  are first computed. A triangulation with the required density is performed on a sphere (72–100 elements). The vectors of nodes of the sphere ("spokes") and of dots on  $\Sigma_{MS}$ , referred to a common origin, are compared by computing scalar products. For each node, only the closest dot is selected and employed in the triangulation of  $\Sigma_{MS}$ . The procedure fails if a spoke intersects  $\Sigma_{MS}$  more than once.

Another definition has been recently proposed by Rauhut et al.<sup>215</sup> The surface dots are obtained making use of the marching-cube algorithm,<sup>216–218</sup> with a resolution of 0.216 bohr<sup>3</sup> for the cube. The flat mesh thus obtained is then projected on a  $\Sigma_{vdw}$  surface (factor  $f = 1.15$ ), with the introduction of a scaling factor for the area of the surface element

$$\Delta S_k = \Delta S_k^{\text{cube}} (1 + aD^2) \quad (50)$$

where  $D$  is the distance between the spherical surface element  $\Delta S_k$  and the flat one  $\Delta S_k^{\text{cube}}$ , and  $a = 0.2$  bohr<sup>-2</sup> is a parameter empirically selected.

We stop here our examination of triangulation procedures: other methods seem less convincing. The overview here reported reflects the importance of the problem, especially for macromolecules, and the widespread conviction that the apparent surface approach is the most powerful and accurate method to describe electrostatic contributions to the solvation energy. The experience based on numerical evidence indicates that methods apparently similar at a cursory inspection, may yield quite different performances, as to computing times and accuracy. If the shape of the cavity or the location of the  $s_k$  points are not appropriately chosen, one may obtain serious distortions of the reaction field  $\Phi_\sigma$ ; these effects are more evident at the ab initio level, because they influence the computed properties of the solute  $M$ . Problems of convergence in iterative procedures or series summation may also arise, as it is the case in classical models when the solute point charges lie close to the surface. It is our firm belief that the

approaches based on a collection of polytopes, first introduced in Pascual-Ahuir's doctoral thesis,<sup>178,219</sup> still represent the best combination of accuracy, efficiency, and simplicity.

## E. The Finite Difference Method (FDM)

The finite difference method (FDM) has been, and still is, widely employed in classical continuum studies: in the domain of the classical representation of large solutes, most applications employ the FDM or the ASC approaches.

The formulation of the electrostatic problem in the FDM is a little different from that given in section III.A. The starting point is a form of the Poisson equation in which the dielectric constant may depend on the position:

$$\vec{\nabla} \cdot [\epsilon(\mathbf{r}) \vec{\nabla} \Phi(\mathbf{r})] = -4\pi\rho(\mathbf{r}) \quad (51)$$

While the PCM might be adapted to treat systems with smooth boundaries, such as molecules surrounded by a region of variable  $\epsilon$ , it is currently applied to models with sharp boundaries, as described in section III.A. On the other hand, the FDM has been applied to salt solutions,<sup>220</sup> where  $\epsilon$  depends on  $\mathbf{r}$  through the concentration. Nonlinear effects, related to the ionic strength of the solution and not included in eq 51, have also been considered.<sup>221,222</sup>

The first application of the FDM is due to Warwicker and Watson.<sup>223</sup> The whole space, including solute as well as solvent, is mapped by a three-dimensional Cartesian grid. The differential equation 51 is replaced by a set of finite difference equations for each point of the grid, with seven-point formulas (a positive and a negative increment for each Cartesian axis). The linear system to be solved has coefficients determined by the  $\epsilon$  and  $\rho$  values, and by the grid spacing. The solution is a set of  $\phi$  values at the grid points. Iterative algorithms are applied, starting with  $\phi = 0$  everywhere. This version of the method presents several weak points which have been the target of successive refinements. The locations of the point charges describing the solute  $M$  in general do not coincide with the grid points. Rules for distributing each charge to the eight surrounding grid points have been given by Edmonds et al.<sup>224</sup> and by Gilson et al.<sup>225</sup> Analogously, the discontinuity in the dielectric constant at the cavity boundary has been smoothed out, alleviating the squared-off representation of the molecule.<sup>226</sup>

The calculation of the solute–solvent interaction energy  $W_{MS}$  and of the solvation free energy  $\Delta G_{el}$ , eqs 15 and 16, is rather unprecise. A double calculation has been suggested by Gilson and Honig;<sup>227</sup> the electrostatic energy is computed with and without solvent. The difference of the two results eliminates the self-energy of  $M$  and, in part, the finite difference spurious contribution to the Coulombic interaction. Another method, which reduces the cost of the second FDM calculation, has been proposed by Luty et al.<sup>228</sup>

The FDM calculations are rather computer intensive because of two reasons. The first is the slow convergence of the procedure. In the original Warwicker and Watson algorithm a Gauss–Seidel iteration scheme was adopted. Later, the simpler Jacobi

relaxation method was considered. In both cases, thousands of iterations are needed. More convenient are the successive over-relaxation (SOR) method, applied by Nicholls and Honig,<sup>229</sup> or the incomplete Cholewsky conjugate method, proposed by Davis and McCammon.<sup>230</sup> These methods can be very conveniently implemented for vector and parallel computing.

The second reason of inefficiency is the very large number of grid points. When the grid is too coarse, the results may be used only as a qualitative description. Reducing the spacing of the grid to reach the accuracy of other methods described in the preceding sections may be computationally prohibitive. The DelPhi program, developed by Honig's group,<sup>225</sup> introduces the "focusing" of a progressively smaller volume, by reducing the grid spacing in successive steps, normally down to 0.25 Å. Solvation energies obtained with a spacing of 1 Å are unreliable, but the 0.5 or 0.25 Å spacings seem to be sufficient. Harder to compute is the interaction between two or more solutes, for which the 0.25 Å spacing is just at the limit of acceptable accuracy. A comparison of DelPhi results with those obtained by the SM1 model of Cramer and Truhlar (see section IV.B.2) has been recently reported by Alkorta et al.<sup>231</sup>

We have not yet considered solvent polarization effects on the solute. The local dielectric constant (LDC) model, outlined in section III.B.1, was proposed in conjunction with an FD procedure for its solution; in fact, the replacement of point polarizable dipoles with regions having an appropriate dielectric constant makes easier the application of the FD formulas. The definition of atomic regions at constant, but different, values of  $\epsilon$ , is of course subject to some arbitrariness, and further refinements are expected.

## F. The Finite Elements Method (FEM)

Like the FDM, the FEM is a numerical method of differential type (by contrast, we recall that BEM is based on an integral formulation of the problem).

The FDM replaces the differential equations by algebraic ones, valid at a set of nodes within the domain, through the approximation of derivatives by finite differences, while the FEM replaces the domain by a set of finite domains (or elements), connected through their nodes, and reproducing at the nodes in an approximate way the behavior of the function in the subdomain. For example, in a triangular domain, the nodes are identified with the vertices, and the solution is expanded in terms of three functions, each having the appropriate value in a vertex and zero in the other two.

The FEM may be applied to surfaces (two dimensions) as well as to volumes (three dimensions). In our electrostatic problem 2-D FEM procedures will rely on an ASC formulation, while 3-D procedures will resort to a description of the potential in the whole space. The procedures of Zauhar and co-workers<sup>187-189</sup> we have quoted in section III.D.3 actually constitute an application of 2-D FEM. The last version of the computational code<sup>189</sup> seems to be quite effective.

More difficult is the 3-D implementation of the FEM. An interesting strategy has been elaborated by Orttung,<sup>232,233</sup> who has lately applied the method to other problems.

One of the advantages of the FEM with respect to the FDM is the easier construction of variable-size meshes and the easier handling of boundary conditions. The FEM appears to be the method of choice to treat electrostatic problems characterized by strong local anisotropies, a problem we shall consider in section VIII.

## G. The Description of the Solute Charge Distribution in Classical Models

The solute charge distribution  $\rho_M$  and the corresponding potential  $\Phi_M$  are in general reduced to a simple form. Definitions of  $\rho_M$  drawn from experimental data are now of very limited use (usually dipole moments in crude models). The approaches of wider use start from quantum mechanical calculations performed on the isolated molecule *M* or on interacting *M-S* pairs. The  $\rho_M$  function drawn from a QM calculation may be subjected to multipole decompositions, with one or many centers of expansion. Of wider use are the multicenter expansions. These may be reduced to the monopole term only (point charge expansions) or extended to higher angular momentum contributions. The most popular expansions are based on atomic charges (sometimes supplemented by atomic dipoles), but many other expansions are in use.

Claverie performed, before his untimely death, a lucid analysis of the methods for describing  $\Phi_M$  in terms of local expansions.<sup>234</sup> A more exhaustive review of this subject has been recently published.<sup>235</sup> In that review the appropriate attention is paid to the so-called potential derived (PD) atomic charges. These charges are obtained by a numerical fitting of the molecular electrostatic potential  $\Phi_M$  (MEP) at some distance or range of distances from the nuclei.<sup>165,166</sup> Many recent computational packages, such as AMBER<sup>236</sup> and GAUSSIAN92,<sup>239</sup> perform the evaluation of PD charges; the fitting procedures consider  $\Phi_M$  values in the region appropriate for the ASC calculation of solvent effects. The PD atomic charges were proposed in 1978 by Momany,<sup>237</sup> but it is fair to remark that the same fitting procedure, with charges not limited to the atoms, was of current use long before in our laboratory, where the first set of PD charges was obtained by Alagona in 1970.<sup>238-240</sup>

PD charges are now of widespread use in solvation energy calculations. We report here a limited number of quotations having some methodological relevance. To get accurate  $\partial\Phi_M/\partial\mathbf{m}$  values on the cavity surface requires a finetuning of the MEP fitting; the apparent charge  $\sigma$  and the corresponding potential  $\Phi_\sigma$  are quite sensitive to the numerical procedure adopted, and the best results are often obtained with some scaling of the computed PD charges.<sup>241-245</sup>

Analogous problems arise when other expansions of  $\rho_M$  are applied to evaluate solvation energies. This aspect has been considered by Claverie in one of his last papers,<sup>246</sup> based on the ASC approach.

Local expansions of  $\rho_M$  in charges or multipoles are of real chemical interest if the transferability is



Table 4. Classical Electrostatic Methods

author <sup>a</sup>	cavity shape	electrostatic approach	polarizable solute	description <sup>b</sup> of $\rho_M$
Born <sup>19</sup> 1920	sphere	MPE	no	$l_{\max} = 0$
Bell <sup>20</sup> 1931	sphere	MPE	no	$l_{\max} = 1$
Kirkwood <sup>21</sup> 1934	sphere	MPE	no	$l_{\max}$ unlimited
Onsager <sup>22</sup> 1936	sphere	MPE	yes	$l_{\max} = 1$
Bonnor <sup>112</sup> 1951	sphere	MPE	yes	$l_{\max}$ unlimited
Abraham <sup>109</sup> 1967	sphere	MPE	no	$l_{\max} = 2$
Friedman <sup>168</sup> 1975	sphere	IC	no	point charge/dipole
van Duijnen <sup>171</sup> 1987	sphere	IC + MPE	no	point charge, $l_{\max} = 1$
Abraham <sup>802,805</sup> 1978	sphere <sup>c</sup>	MPE	no	$l_{\max} = 0$
Scholte <sup>141</sup> 1949	spheroid	MPE	no	$l_{\max} = 1$
Buckingham <sup>143</sup> 1953	spheroid	MPE	yes	$l_{\max} = 1$
Thiebaut <sup>110</sup> 1972	spheroid	MPE	yes	$l_{\max} = 3$
Beveridge <sup>106</sup> 1976	spheroid <sup>d</sup>	MPE	no	$l_{\max}$ unlimited
Rivail-Rinaldi <sup>104,159</sup> 1982	ellipsoid	MPE	no	$l_{\max}$ unlimited
Westheimer <sup>139</sup> 1938	ellipsoid	MPE	no	point charges
Ehrenson <sup>140</sup> 1976	ellipsoid	MPE	no	point charges
Gómez-Jeria <sup>807</sup> 1990	ellipsoid <sup>d</sup>	MPE	no	general
Claverie <sup>51,52</sup> 1974	molecular	MPE	no	point charges
Orttung <sup>232,233</sup> 1977	molecular	FEM	yes	general
Tomasi <sup>58</sup> 1982	molecular	ASC	yes	general
Zauhar <sup>186</sup> 1982	molecular	ASC	no	point charges
Warwicker <sup>223</sup> 1982	molecular	FDM	no	point charges
Edmonds <sup>224</sup> 1984	molecular	FDM	no	point charges
Rashin <sup>97</sup> 1987	molecular	ASC	no	point charges
Honig <sup>225,227</sup> 1988	molecular	FDM	no	point charges
Claverie <sup>246</sup> 1988	molecular	ASC	no	pt charge/dipole/quadrupole
Abraham <sup>209</sup> 1988	molecular	ASC	no	point charges
Drummond <sup>184</sup> 1988	molecular	ASC	yes	point charges
Still <sup>220</sup> 1990	molecular	Gen.Born	no	point charges
Kanesaka <sup>810,811</sup> 1982	molecular <sup>d</sup>	FEM	no	$l_{\max} = 1$
Tomasi <sup>417</sup> 1986	cylinder <sup>d</sup>	ASC	no	point charges
Jayaram <sup>809</sup> 1990	cylinder <sup>d</sup>	MPE	no	point charges

<sup>a</sup> Reference name, not necessarily the first author. <sup>b</sup>  $l_{\max}$  is the maximum multipole order allowed in a one-center expansion of  $\rho_M$ . <sup>c</sup> Many layers with different dielectric constants  $\epsilon$ . <sup>d</sup> Two layers with different dielectric constants  $\epsilon$ .

insured. This problem has been considered many times in the past, but it must be taken up again in the framework of the solvation procedures, because of the coupling effects of the solvent reaction field on the separate contributions to  $\rho_M$ . The papers quoted above<sup>241-245</sup> consider this problem, but much work remains to be done.

Quantum mechanical solvent calculations allow the classical formulations to be checked by resorting to a controlled sequence of approximations, ending up with a very limited number of point charges. This perspective will be examined in section IV.C.

Atomic charges are also employed in the formulation of molecule-molecule pair potentials to be used in computer simulations.<sup>247</sup> Hybrid continuum and cluster models of solvation are expected to play an important role in future developments: the congruence of charges used in continuum methods and in cluster simulations is an aim worthy of further studies.

## H. A Summary of Classical Methods

Several among the procedures examined in the preceding sections have been conceived as parts of quantum mechanical methods, and their application to classical models has been considered as a marginal extension; other procedures have been developed as classical methods only. We collect in Table 4 a selection (very far from complete) of methodological proposals which have been employed in the classical approximation.

We recall here shortly the gist of a classical model and its most important parameters.

Point 1. The solute charge distribution  $\rho_M$  is determined a priori, with the methods examined in section III.G. An alternative approach<sup>58</sup> employs the full description of  $\rho_M$  as a linear combination of atomic orbital products (LCAO) or the analogous description of fragments, assuming transferability from molecule to molecule.<sup>248,249</sup>

Point 2. The solute charge distribution is frequently considered as unaffected by the solvent potential, or, in other cases, is subject to polarization. The polarization may be expressed in terms of central or local expansions (the dipole term only is generally retained), it may be described by introducing effective space-dependent dielectric constants,<sup>138</sup> or it may be represented by empirical expressions acting on the LCAO descriptions of local groups.<sup>248,250</sup>

Point 3. The solvent reaction field is described with one of the methods described in sections III.B-F: MPE, ASC, IC, FD, FE.

Point 4. The geometry of the solute is kept fixed. In some cases, e.g. in conformational studies, geometry changes may be included, by resorting to molecular mechanics.

These features are summarized in the above-mentioned Table 4.

## IV. The Quantum Problem

### A. General Aspects

In the preceding sections, we have considered in detail the classical formulations of the problem. The other face of the basic continuum model is the

quantum mechanical treatment of the solute  $M$ , embedded in the solvent reaction field. As already remarked, the formal problem is very simple; we add  $\hat{\gamma}'_{\sigma}$ , eq 7, to the solute Hamiltonian  $\hat{\mathcal{H}}_M^{(0)}$ , and we have to solve the Schrödinger equation:

$$[\hat{\mathcal{H}}_M^{(0)} + \hat{\gamma}'_{\sigma}(\mathbf{q}, \mathbf{Q}, \rho_M^{(f)}, \epsilon)]\Psi^{(f)}(\mathbf{q}, \mathbf{Q}) = E^{(f)}(\mathbf{Q})\Psi^{(f)}(\mathbf{q}, \mathbf{Q}) \quad (52)$$

We have added an index ( $f$ ) to indicate that the solution of this nonlinear problem is often determined iteratively, and we are interested in the final converged solution. We have also indicated that  $\hat{\gamma}'_{\sigma}$  depends on the solution of the equation,  $\Psi$ , through  $\rho_M$ . To avoid misunderstandings, we stress that the complete Hamiltonian in the fixed nuclei approximation must be employed (usually neglecting relativistic or magnetic terms).

The energy  $E(Q)$  may be partitioned into several components. In vacuo, as well as in the solvent, we have the kinetic energy of the electrons,  $T_{el}$ , and the potential energy terms concerning nuclei and electrons of  $M$ ,  $V_{nuc,nuc}$ ,  $V_{el,nuc}$ ,  $V_{el,el}$ ; these terms give different contributions, in solvent and in vacuo, only because of the change in the wave function induced by the reaction field. Additional energy terms represent the solute-solvent interaction,  $W_{MS}$ .

Because of the linearity of the electrostatic equations, eq 12, the  $\Phi_{\sigma}$  potential may be conveniently divided into two contributions, deriving from the nuclear and from the electronic charge distributions; we shall call them  $\Phi_{\sigma,nuc}$  and  $\Phi_{\sigma,el}$ , respectively. We have

$$\Phi_{\sigma} = \Phi_{\sigma,nuc} + \Phi_{\sigma,el} \quad (53)$$

Analogously, in the ASC approach, the  $\sigma$  charge can be partitioned as

$$\sigma = \sigma_{nuc} + \sigma_{el} \quad (54)$$

The interaction energy  $W_{MS}$  thus contains four terms:

$$W_{MS} = \int [\rho_{nuc}(\mathbf{r}, \mathbf{Q}) + \rho_{el}(\mathbf{r}, \mathbf{Q})] \times [\Phi_{\sigma,nuc}(\mathbf{r}, \mathbf{Q}) + \Phi_{\sigma,el}(\mathbf{r}, \mathbf{Q})] d\mathbf{r}^3 = W_{nuc,nuc} + W_{nuc,el} + W_{el,nuc} + W_{el,el} \quad (55)$$

where

$$W_{nuc,nuc} = \int \rho_{nuc}(\mathbf{r}, \mathbf{Q}) \Phi_{\sigma,nuc}(\mathbf{r}, \mathbf{Q}) d\mathbf{r}^3 \quad (56)$$

$$W_{nuc,el} = \int \rho_{nuc}(\mathbf{r}, \mathbf{Q}) \Phi_{\sigma,el}(\mathbf{r}, \mathbf{Q}) d\mathbf{r}^3$$

and so on.

The final energy is thus decomposed as follows:

$$E^{(f)}(\mathbf{Q}) = T_{el} + V_{nuc,nuc} + V_{el,nuc} + V_{el,el} + W_{nuc,nuc} + W_{nuc,el} + W_{el,nuc} + W_{el,el} \quad (57)$$

Here we have dropped, for simplicity, the superscript ( $f$ ) on the right hand side. In most papers this

decomposition is not mentioned: only the total potential  $\Phi_{\sigma}$  is considered, and the attention is focused on the electronic part of  $\rho_M$  and  $\hat{\gamma}'_{\sigma}$  (the nuclear part is treated in a completely classical way). We shall adopt here a similar abbreviation.

The most widely applied method to solve the electronic problem is the Hartree-Fock (HF). After expanding the one-electron functions (molecular orbitals) in a basis  $\{...|\mu\rangle...|\nu\rangle...\}$ , the HF equations are

$$\mathbf{FC} = \epsilon\mathbf{SC} \quad (58)$$

The matrix elements of the Fock matrix  $\mathbf{F}$  are modified, with respect to those appropriate in vacuo, primarily by the addition of the  $\hat{\gamma}'_{\sigma}$  contribution to the mono-electronic term  $\mathbf{h}$ , and secondarily because of the dependence of the bielectronic term  $\mathbf{G}$  on the electronic density  $\rho_{el}$ :

$$F_{\mu\nu} = h_{\mu\nu} + G_{\mu\nu}(\rho_{el}) + \langle\mu|\hat{\gamma}'_{\sigma}(\rho_{el})|\nu\rangle \quad (59)$$

The explicit expression of the  $\langle\mu|\hat{\gamma}'_{\sigma}|\nu\rangle$  elements depends on the method adopted to describe the reaction field potential,  $\Phi_{\sigma}$ . Three methods have been applied: (1) the multipole expansion (MPE); (2) the image charge (IC) approximation; and (3) the apparent surface charge (ASC) approach.

In the first case  $\Phi_{\sigma}$  is expressed as a sum of spherical harmonics; in the IC approximation,  $\Phi_{\sigma}$  is the potential of a set of point charges and point dipoles spread in the space around the cavity; in the ASC approach, the source of  $\Phi_{\sigma}$  are the point charges located on the cavity surface. All the elementary integrals needed for the three approaches have long been available in quantum chemical packages, with the exception of those involving spherical harmonics with high  $l$ , seldom used in molecular calculations in vacuo; programs are now available through the QCPE.<sup>105,251</sup>

An iterative solution of the HF equations 58 is adopted in the MPE and IC methods; approximate expressions of  $\hat{\gamma}'_{\sigma}$  in terms of multipole expansions or image charges are refined during the cycle of SCF calculations, taking into account the solvent polarization effect on  $\rho_{el}$  and  $\Phi_{\sigma}$  at the same time. The number of cycles is variable, depending on the parameters of the electronic problem, on the dielectric constant, and in particular on the shape of the cavity (limitations in the cavity shape are present in most of the methods belonging to the MPE and IC categories).

In the ASC approach, two strategies can be applied, as anticipated in section II.A. The first one consists of a two-step iterative procedure: (A) solution of the HF equations with a fixed  $\Phi_{\sigma}$  and (B) determination of a new  $\sigma$  charge distribution and a new  $\Phi_{\sigma}$ , by means of one of the algorithms described in section III.D. Steps A and B are repeated until convergence.

The alternative is a variational calculation of the free energy  $G_{el}^{(f)}$ ; this can be done by a modified SCF procedure, simultaneously optimizing the wave function and the reaction field, without external iterations. To examine the implications of this second option, we discuss first the thermodynamical status of the quantities we are computing. The energy  $E^{(f)}$ , eqs 52 and 57, corresponds to the work spent in

assembling nuclei and electrons of the solute M, i.e., in building up the charge distribution  $\rho_M^{(f)} = \rho_{el}^{(f)} + \rho_{nuc}$ , in the already polarized dielectric. The energy which may be recovered in a hypothetical thermodynamic cycle, i.e. the electrostatic free energy  $G_{el}$ , is<sup>58</sup>

$$G_{el} = \langle \Psi^{(f)} | \hat{\mathcal{H}}_M^{(0)} | \Psi^{(f)} \rangle + \frac{W_{MS}}{2} = \left\langle \Psi^{(f)} \left| \hat{\mathcal{H}}_M^{(0)} + \frac{\hat{\mathcal{V}}'_\sigma}{2} \right| \Psi^{(f)} \right\rangle = E^{(f)} - \frac{W_{MS}}{2} \quad (60)$$

This can be demonstrated by the charging parameter method applied in electrostatics and statistical thermodynamics.<sup>24,246,252</sup> Shortly, one defines an attenuated solute-solvent interaction potential, as the full potential  $U(\Omega)$  multiplied by a parameter  $\lambda$ , which ranges from 0 to 1 ( $\Omega$  is here the collection of solvent coordinates). A distribution  $g_S(\Omega; \lambda)$  of solvent particles corresponds to the attenuated potential  $\lambda U(\Omega)$ . The total interaction energy  $W_{MS}$ , computed with a given  $\rho_M$  and with the full interaction potential, depends linearly on  $g_S(\Omega; \lambda)$ :

$$W_{MS}(\lambda) = \int U(\Omega) g_S(\Omega; \lambda) d\Omega \quad (61)$$

This expression is equivalent to eq 55, if electrostatic interactions only are considered. The free energy change due to the building up of the solvent polarization, in the presence of the solute, is then

$$\Delta G = \int_0^1 W_{MS}(\lambda) d\lambda \quad (62)$$

If the solvent is a linear dielectric, i.e. if  $g_S(\Omega; \lambda)$  is proportional to the parameter  $\lambda$ , the factor  $1/2$  of eq 60 is obtained.

It is interesting to observe that the same result is found in a straightforward perturbation theory treatment of two interacting quantum systems, M and S. Let us write the total Hamiltonian as

$$\hat{\mathcal{H}} = \hat{\mathcal{H}}_M^{(0)} + \hat{\mathcal{H}}_S^{(0)} + \hat{\mathcal{H}}_{MS} \quad (63)$$

The zeroth-order Hamiltonian is  $\hat{\mathcal{H}}_M^{(0)} + \hat{\mathcal{H}}_S^{(0)}$ . The basis for the perturbation treatment is given by products of M and S states. For the subsystem M we consider only one state  $|\Psi\rangle$ , either in the rigid approximation (eigenstate of  $\hat{\mathcal{H}}_M^{(0)}$ ) or fully adapted to the environment ( $|\Psi^{(f)}\rangle$ ). In both cases we shall call  $E_M$  the associated energy term:

$$\langle \Psi | \hat{\mathcal{H}}_M^{(0)} | \Psi \rangle = E_M \quad (64)$$

Let us now concentrate on the perturbation treatment of the interaction energy and of the internal energy of S. We indicate with  $|K\rangle$  the states of S and with  $|\Psi, K\rangle$  the states of M + S. The zeroth-order energies of S are called  $\epsilon_K$ :

$$\hat{\mathcal{H}}_S^{(0)} |K\rangle = \epsilon_K |K\rangle \quad (65)$$

The second-order approximation for the total energy of the ground state,  $|\Psi, 0\rangle$ , is

$$E \approx E_M + \epsilon_0 + \langle \Psi, 0 | \hat{\mathcal{H}}_{MS} | \Psi, 0 \rangle - \sum_{K>0} \frac{|\langle \Psi, K | \hat{\mathcal{H}}_{MS} | \Psi, 0 \rangle|^2}{\epsilon_K - \epsilon_0} \quad (66)$$

We shall suppose that in the unpolarized ground state of the solvent there is no interaction, so that the first-order term vanishes. The perturbed wave function is

$$|\Psi_{MS}\rangle \approx |\Psi, 0\rangle - \sum_{K>0} |\Psi, K\rangle \frac{\langle \Psi, K | \hat{\mathcal{H}}_{MS} | \Psi, 0 \rangle}{\epsilon_K - \epsilon_0} \quad (67)$$

with the normalization factor

$$N^2 \approx 1 - \sum_{K>0} \frac{|\langle \Psi, K | \hat{\mathcal{H}}_{MS} | \Psi, 0 \rangle|^2}{(\epsilon_K - \epsilon_0)} \quad (68)$$

We now decompose the second-order corrected energy, eq 66, according to the Hamiltonian terms involved.  $E_M$  is the contribution of  $\hat{\mathcal{H}}_M^{(0)}$ . For  $\hat{\mathcal{H}}_S^{(0)}$ , we have a positive second-order contribution, representing the increase in energy of the perturbed system S:

$$\langle \Psi_{MS} | \hat{\mathcal{H}}_S^{(0)} | \Psi_{MS} \rangle \approx \epsilon_0 + \sum_{K>0} \frac{|\langle \Psi, K | \hat{\mathcal{H}}_{MS} | \Psi, 0 \rangle|^2}{\epsilon_K - \epsilon_0} \quad (69)$$

For the interaction  $\hat{\mathcal{H}}_{MS}$  we have a single negative term, double in magnitude:

$$\langle \Psi_{MS} | \hat{\mathcal{H}}_{MS} | \Psi_{MS} \rangle \approx -2 \sum_{K>0} \frac{|\langle \Psi, K | \hat{\mathcal{H}}_{MS} | \Psi, 0 \rangle|^2}{\epsilon_K - \epsilon_0} \quad (70)$$

In conclusion, both the electrostatic/statistical treatment and the quantum mechanical one lead to a simple interpretation: the  $1/2$  factor in eq 60 is due to the solvent polarization work, which is not contained in  $E^{(f)}$ , and is opposite in sign and half in magnitude with respect to the interaction energy. The factor is exactly  $1/2$  only in the linear response approximation, i.e. with linear dielectrics in the electrostatic language, or with a perturbation of the wavefunction truncated to first order in the quantum mechanical language.

The Schrödinger equation 52 we want to solve is of a nonlinear type, because  $\hat{\mathcal{V}}'_\sigma$  depends on  $\Psi$ . The variational principle can be applied to seek approximate solutions, but not in the standard form; in particular, the functional to be minimized does not correspond, for an exact eigenfunction  $\Psi^{(f)}$ , to the eigenvalue  $E^{(f)}$ . We avoid here the mathematical details<sup>253,254</sup> and we limit ourselves to recall that, in the case of a linear dielectric, the functional presenting an absolute minimum for  $\Psi = \Psi^{(f)}$  is

$$J(\Psi) = \frac{\langle \Psi | \hat{\mathcal{H}}_M^{(0)} + \hat{\mathcal{V}}'_\sigma(\Psi)/2 | \Psi \rangle}{\langle \Psi | \Psi \rangle} \quad (71)$$

This is just the electrostatic free energy  $G_{el}$ , eq 60.

**Table 5. Ab Initio Continuum Methods**

name	author <sup>a</sup>	cavity shape	electrostatic approach	Q M level	description <sup>b</sup> of $Q_M$
—	Christoffersen <sup>267</sup> 1976	sphere	MPE	SCF	$l_{\max} = 3$
DRF	van Duijnen <sup>365</sup> 1980	molecular	ASC	SCF	point charges
PCM	Tomasi <sup>57</sup> 1981	molecular	ASC	SCF	general
SCRf	Rivail <sup>105</sup> 1983	ellipsoid	MPE	SCF	$l_{\max}$ unlimited
PCM	Tomasi <sup>340</sup> 1983	molecular	ASC	SCF-EHP	general
PCM	Tomasi <sup>333</sup> 1984	molecular	ASC	3 × 3 CI	general
SCRf	Mikkelsen <sup>305</sup> 1987	sphere	MPE	SCF	$l_{\max} = 6$
SCRf	Mikkelsen <sup>308</sup> 1988	sphere	MPE	MCSCF	$l_{\max} = 6$
	Karlström <sup>362</sup> 1988	sphere	IC	SCF	point ch./dip.
	Karlström <sup>364</sup> 1989	sphere	IC	MCSCF	point ch./dip.
SCRf	Rivail <sup>265</sup> 1990	ellipsoid	MPE	SCF-MBPT	$l_{\max}$ unlimited
SCRf	Wiberg <sup>295</sup> 1991	sphere	MPE	SCF-MP2-CI	$l_{\max} = 1$
PCM	Olivares del Valle <sup>427</sup> 1993	molecular	ASC	SCF-MBPT	general
PCM	Aguilar <sup>179</sup> 1993	molecular	ASC	MCSCF-CI	general

<sup>a</sup> Reference name, not necessarily the first author. <sup>b</sup>  $l_{\max}$  is the maximum multipole order allowed in a one-center expansion of  $Q_M$ .

**Table 6. Semiempirical Continuum Methods**

name	author <sup>a</sup>	cavity shape	electrostatic approach	description <sup>b</sup> of $Q_M$
SRCF	Rivail <sup>53,54</sup> 1973-76	sphere	MPE	$l_{\max} = 7$
SRCF	Tapia <sup>55</sup> 1975	sphere	MPE	$l_{\max} = 1$
	Sakurai <sup>180</sup> 1987	molecular	ASC	general
PCM	Miertuš <sup>354</sup> 1988	molecular	ASC	general
SCRf	Rinaldi <sup>637</sup> 1983	ellipsoid	MPE	$l_{\max} = 6$
SCRf	Zerner and Karelson <sup>280</sup> 1986	sphere	MPE	$l_{\max} = 1$
AMSOL	Cramer and Truhlar <sup>314,318</sup> 1991	molecular	Gen Born	point charges
	Wang and Ford <sup>182</sup> 1992	molecular	ASC	point charges
PCM	Luque and Orozco <sup>355</sup> 1992	molecular	ASC	general
PCM	Basilevsky <sup>210</sup> 1992	molecular	ASC	general
PCM	Rauhut and Clark <sup>215</sup> 1993	molecular	ASC	general
COSMO	Klamt and Schüürmann <sup>192</sup> 1993	molecular	ASC	point charges

<sup>a</sup> Reference name, not necessarily the first author. <sup>b</sup>  $l_{\max}$  is the maximum multipole order allowed in a one-center expansion of  $Q_M$ .

The relationship between the Schrödinger equation 52 and the free energy functional has been first established by Yomosa.<sup>255</sup> A detailed formal elaboration of an SCF procedure which minimizes  $G_{el}$  has been given by Hoshi et al.<sup>180</sup>

In summary, if the dependence of  $\hat{\gamma}'_0$  on  $\Psi$  is explicitly taken into account, the variational solution of eq 52 yields  $\Psi^{(f)}$  and  $G_{el}$ . In the iterative solutions, whether elaborated in the ASC, in the MPE, or in the IC frameworks, the  $\hat{\gamma}'_0$  operator is held fixed at every step, and the standard formulation of the variational principle applies; at convergence, one obtains the same  $\Psi^{(f)}$ , but a different energetic quantity,  $E^{(f)}$ . The free energy  $G_{el}$  is then computed as a difference, eq 60. This procedure has been applied by Miertuš and Tomasi<sup>58</sup> and by many other authors. We emphasize the fact that the two approaches, formally equivalent, also give the same numerical results.<sup>191</sup>

One could ask why the  $G_{el}$  minimization method has seen relatively few applications at the quantum level and none, until today,<sup>191</sup> at the ab initio level. One reason is that it demands large memory resources to be competitive with the iterative methods; the latter, in turn, may run on small computers, also for medium-size molecules. Today, because of hardware improvements, the balance is shifting. Moreover, the formidable apparatus of matrices to be stored in core memory (see Hoshi et al.<sup>180,181</sup>) has now been reduced,<sup>191</sup> and the direct minimisation methods will surely find a wider application in the field of the ab initio quantum chemistry.

## B. A Survey of Quantum Methods

We report in Table 5 a selection of quantum mechanical ab initio continuum solvation methods and in Table 6 an analogous selection for semiempirical methods. The determination of the electronic wave functions is not always limited to the HF approximation. In the following pages we comment upon these methods.

We recall that we are still examining the primitive model, i.e. a model addressed to evaluate the electrostatic component of the solute-solvent interaction energy, for an isotropic continuum medium. Some simple extensions of this model enter Tables 5 and 6; more complex models will be considered later. We remark also that some approaches have requested in their elaboration the proper consideration of nonelectrostatic contributions to  $\Delta G_{sol}$ ; these aspects will also be treated later.

Here we report some additional information and comments on the methods considered in Tables 5 and 6, without separation between ab initio and semiempirical methods, and tempering a chronological exposition with the indication of the successive developments of the approach.

The first models describing a quantum mechanical system placed within a cavity of a dielectric medium were elaborated to study solvated electrons.<sup>256-264</sup> The features of these systems prompted the introduction of specific simplifications not applicable to other

systems. The Schrödinger equation, for instance, reduces to the single electron one; the solution is found by means of ad hoc procedures, such as numerical quadrature in one dimension (the radial coordinate). However, these studies were important for the development of continuum solvation methods, because they brought out several methodological problems, such as those connected to relating macroscopic electrostatic properties with microscopic quantum descriptions; satisfactory solutions have been found in the prosecution of the studies.

### 1. One-Center Multipole Expansion Methods

The beginning of the activity of Rivail's group in the elaboration of quantum mechanical continuum methods is generally assigned to the year 1976.<sup>54</sup> The basic setup of the method was in fact detailed in a preceding paper,<sup>53</sup> which contains other items of interest, such as the determination of the dispersion component of the solvation energy and the search of the equilibrium geometry in solution.

In their 1976 paper, as well as in the preceding one, Rivail and Rinaldi adopted the MPE approach, in a spherical cavity, with the one-center expansion of  $\Phi_\sigma$  up to terms with  $l = 7$ . The quantum problem was dealt with by means of the CNDO semiempirical method. The extension to ellipsoidal cavities, already examined in section III.B.2 for the classical model,<sup>104</sup> was later extended to quantum systems in an ab initio version.<sup>105</sup> Again, the one-center expansion of  $\Phi_\sigma$  is employed, with  $l \leq 6$  (higher  $l$  values give, for the cases there examined, negligible contributions). The solution of the quantum problem is reached iteratively. The reaction field factors  $f_{ll'}^{mm'}$  are introduced both in the CNDO and in the ab initio SCF version. The Fock matrix is modified, with respect to a calculation in vacuo, according to

$$F_{\mu\nu} = F_{\mu\nu}^{(0)} + \sum_{l,l'} \sum_{m,m'} M_l^m f_{ll'}^{mm'} \langle \mu | M_{l'}^{m'} | \nu \rangle \quad (72)$$

In regular cavities the  $f_{ll'}^{mm'}$  factors have analytic expressions, and this property can be exploited to compute analytic first and second derivatives of the free energy with respect to nuclear coordinates.<sup>162</sup> Another improvement concerns the inclusion of electron correlation, by means of many-body perturbation theory.<sup>265</sup>

Extensions of the MPE approach to multicenter expansions of  $\Phi_\sigma$  and to cavities of general shape have been recently considered by Dillet et al.<sup>108</sup> (Distributed expansions with regular cavities are not convenient in SCF calculations.) In this case, the  $f_{ll'}^{mm'}$  factors do not have an analytic expression. The use of a multicenter expansion makes the limit  $l = 6$  quite satisfactory. (The test is made on formamide as a solute.) This new method is not yet implemented in quantum SCF versions.

No attention is paid, in the papers of Rivail's group, to the problem of quantum tails in the electronic distribution outside the cavity.

The Rivail–Rinaldi algorithm is quite flexible and it has been applied to numerous chemical problems. A computer program is now available.<sup>251</sup>

The first ab initio SCF-continuum method treating all the electrons of the solute on the same footing is that proposed by Hylton, Christoffersen, and Hall.<sup>266,267</sup> The method is of the MPE type in a spherical cavity, with inclusion of the reaction field potential operator in the Fock matrix. The Fock matrix is expanded over floating spherical Gaussian orbitals (FSGO) and in the evaluation of the matrix elements the specific features of this kind of basis set (no longer in use nowadays) are exploited. The one-center expansion of  $\Phi_\sigma$  is limited to  $l = 3$  (octopole). The authors give due emphasis to the problem of quantum tails of the electronic density outside the cavity; they introduce a "penalty function" forcing the electrons to be essentially inside the sphere. We have already considered this problem, which is neglected in other MPE formulations, in connection with the "renormalization" procedure in ASC methods. Under other aspects the method is similar to that of Rivail and Rinaldi we have already examined. An interesting proposal for the optimization of geometry of a solute cluster immersed in the cavity has been presented in a third paper.<sup>268</sup> Unfortunately this method, to the best of our knowledge, has not found further applications.

Tapia and Goscinski<sup>55</sup> present a general formulation for a dipolar reaction field. A direct variational solution of the quantum mechanical problem is searched, with the introduction of the  $J(\Psi)$  functional, eq 71, and the relationship of this approach with iterative procedures is discussed. The algorithm is here implemented at the CNDO level, for spherical cavities.

This method, which could be better qualified as "quantum-Onsager", has been named SCRf (self-consistent reaction field), an acronym used also for other methods not limited to dipole reaction fields in spherical cavities. The SCRf (or quantum-Onsager) method has been later implemented for a variety of semiempirical Hamiltonians (INDO, MNDO, AM1, PM3, etc.) and applied to several chemical problems, by Tapia and other authors.<sup>56,149,269–278</sup>

A special mention is due to the Karelson–Zerner group. These authors have applied the quantum-Onsager method to a number of chemical problems.<sup>279–292</sup> They also addressed several methodological questions, among which we quote the analysis of the arguments leading to the factor (1 or  $1/2$ ) in front of  $\hat{\mathcal{V}}'_\sigma$  in the basic equations of the quantum continuum model (eqs 52 and 60). The analysis is formally limited to the case of the dipolar operator, but may be extended to other forms of  $\hat{\mathcal{V}}'_\sigma$ . We already discussed this point in section IV.A. Another point of methodological and computational interest is the analysis<sup>288</sup> of artifacts occurring in the geometry optimization with numerical gradients, when the SCRf method is inserted<sup>281</sup> into the AMPAC<sup>293</sup> and MOPAC<sup>294</sup> semiempirical packages. We shall reconsider later this subject.

The quantum-Onsager model has been reformulated by Wong, Frisch, and Wiberg<sup>295</sup> in the ab initio framework. The pseudo-Hartree–Fock equation is solved iteratively. The model has been also implemented for the Møller–Plesset (MP2) and quadratic CI (QCI) methods, and it may be extended to higher

levels of the quantum molecular theory. The method is supplemented with efficient and compact subroutines for the evaluation of energy first and second derivatives with respect to geometrical parameters.<sup>296,297</sup> This implementation is part of GAUSSIAN91 package<sup>298</sup> and of the most recent version of it, GAUSSIAN92.<sup>299</sup> The continuum solvent calculation can be linked without difficulty to other facilities provided by the GAUSSIAN programs, such as several analyses of the solute wave function, computer-guided optimization of geometry (with a fixed cavity), evaluation of harmonic frequencies in the presence of the medium, etc.

This version of the *ab initio* continuum method fulfills almost all the expectations of a wide category of potential users: a program easy to handle, with very few parameters in the input (just the dielectric constant and the cavity radius) and with a rich output. Several applications have been presented by Wiberg's group<sup>300-303</sup> and quite probably a good number of papers by other authors have escaped our attention, given the wide diffusion of the GAUSSIAN programs and their readiness of use.

The perspective of a widespread application of this method in computational chemistry prompts us to repeat here some warnings already expressed in this review. The Onsager model has given a very important contribution to the understanding of phenomena occurring in solution; analogously, the SCRF (quantum-Onsager) approach, when properly applied, yields valuable insights, as most of the papers quoted in this section demonstrate. However, naive use of the quantitative values obtained with the SCRF method may lead to serious errors of interpretation.

We have already reported examples of the poor convergence of  $\Delta G_{\text{el}}$  with respect to the number of  $2^l$ -poles in the expansion of  $\Phi_{\sigma}$ . As an additional example we quote here an analysis of the performance of the sphere + dipole model (in its classical version), compared with more refined *ab initio* PCM calculations on the anomeric effect.<sup>304</sup> The conformational energy profiles are not reproduced at all (several conformations have a vanishing total dipole moment, for symmetry reasons, whence  $\hat{q}'_{\sigma} = 0$  in the dipolar approximation). Even more important is the failure of this approach to reproduce the correct trends in the conformational dependence of one of the basic quantities in the model, when the values of the other parameters are drawn from more accurate calculations or from experiment. For instance, compute  $\Delta G_{\text{el}}$  from the values of dipole  $\mu$  and polarizability  $\alpha$  of M, and cavity volume, or the latter from  $\Delta G_{\text{el}}$ ,  $\mu$ , and  $\alpha$ . In spite of these critical remarks and warnings, the Wong-Frisch-Wiberg computational procedure represents an important factor extending the consideration of solvent effects in applied quantum chemistry.

Mikkelsen et al.<sup>305</sup> adopt a multipole one-center expansion, with M inserted in a spherical cavity. The formal approach is not different from that of Rivail and Rinaldi.<sup>54</sup> The calculations are performed at the *ab initio* HF level. The authors are interested here in the study of solvent effects in the photoionization of small ions; for this reason they pay particular attention to the HF orbital energies. They also

compare the results obtained when M is the bare ion or when it includes the first solvation shell ( $M \equiv X(\text{H}_2\text{O})_n^{p\pm}$ ). In the latter case, the inaccuracy due to an oversimplified description of the solute-solvent interactions (electrostatic only) is minimized. In the same year Mikkelsen et al.<sup>306,307</sup> presented another formulation of the same model (one-center multipole expansion in a spherical cavity), passing through the definition of the ASC  $\sigma$ . The continuum approach is then extended with the introduction of an effective Hamiltonian in terms of medium field operators satisfying the Boson algebra and of Glauber transformations to derive an explicit time-dependent equation.

The method has been extended to MCSCF wave functions<sup>308</sup> and is applied to electron-transfer reactions in solution,<sup>307-310</sup> to photoelectron and Auger spectra, as well as to other photophysical processes.<sup>311-313</sup> Clearly we are going beyond the limits imposed by our definition of the basic continuum model, and we are entering a domain requiring a separate review. A short account on nonequilibrium solvation processes is given in section VII.

## 2. Multicenter Expansion Methods

The quantum continuum-dielectric models developed by Cramer and Truhlar<sup>314-318</sup> differ under several aspects from others examined in section IV.B. The quantum description is performed at the semiempirical level using the AM1<sup>293,319</sup> and PM3<sup>193,320,321</sup> methods. The electrostatics is treated at the extended Born level, with a cavity of molecular shape (interlocking spheres). The solute-solvent interactions are also parameterized in a semiempirical fashion, with parameters specific for each solvent. Until now, a full set of parameters has been published only for water.

As in all quantum continuum methods the matrix elements of the one-electron Hamiltonian, or the Fock matrix elements  $F_{\mu\nu}$ , are modified by introducing a term due to the solvent reaction field:

$$F_{\mu\nu} = F_{\mu\nu}^{(0)} + \delta_{\mu\nu} \frac{\epsilon - 1}{\epsilon} \sum_k q_k \gamma_{kl} \quad (73)$$

Here  $k$  and  $l$  are atomic indexes ( $l$  is the atom to which the basis function  $\mu$  belongs). The atomic charges  $q_k$  are obtained from Mulliken population analysis

$$q_k = Z_k - \sum_{\mu \in k} P_{\mu\mu} \quad (74)$$

and are determined self-consistently in the presence of the solvent. The Coulomb integrals  $\gamma_{kl}$  play a pivotal role. Their expression is taken from Still et al.,<sup>220</sup> with some additions and changes.  $\gamma_{kk} = 1/a_k$  is the inverse of an effective atomic radius, and  $\gamma_{kl}$  ( $k \neq l$ ) depends on the radii  $a_k$  and  $a_l$  and on the interatomic distance  $r_{kl}$ . The functional dependence is chosen so that the simple formula

$$\Delta G_{\text{el}} = - \frac{\epsilon - 1}{2\epsilon} \sum_{k,l} q_k q_l \gamma_{kl} \quad (75)$$

correctly yields the free energy of a system of charges in spherical cavities of the dielectric, in the limit of large interparticle distances (generalized Born equation<sup>322</sup>). There are a few semiempirical parameters in Cramer and Truhlar's expression of  $\gamma_{kl}$ . The optimization of the parameters is not based on the values of  $G_{el}$  alone, but on a more general expression of the solvation free energy, including other contributions. Besides the electrostatic one, the two most important terms are the cavitation and the dispersion energy; they are collected in the empirical formula

$$\Delta G_{CDS} = \sum_k \sigma_k A_k \quad (76)$$

Here  $\sigma_k$  a constant specific for each atom type and  $A_k$  is the solvent-accessible surface area of atom  $k$  (also depending on some geometrical parameters for its definition). The modeling of solute-solvent interactions in terms of solute surface area has a long history that we cannot resume here, for reasons of space. Equation 76 introduces further parameters, part of which (the  $\sigma_k$ 's) are simultaneously optimized with those contained in  $\gamma_{kl}$ , to fit a large set of experimental solvation free energies.

The model has been improved several times and adapted to cover different scopes. The latest available version (AMSOL 4.0<sup>323</sup>) is based on Dewar's AMPAC 2.1<sup>319</sup> and incorporates the parametrizations called SM1, SM1a, SM2, and SM3. An automatic geometry optimization facility is provided, based on numerical gradients. Our personal experience with AMSOL is limited; we confirm that good values of  $\Delta G_{hydr}$  are normally obtained for equilibrium compounds (compared to complete PCM calculations or to empirical group contribution estimates<sup>324</sup>). We signal considerable difficulties in achieving geometry optimization for the TS of some organic reactions; we suspect, however, that these problems are due more to the semiempirical part of the program than to the solvation model. In some cases more serious artifacts affect the results. As an example, we quote an ab initio study on the aldol condensation in aqueous solution, showing that a water molecule acts as a catalyst;<sup>325</sup> a parallel (unpublished) study<sup>326</sup> applying AMSOL suggests an increase of the activation energy when a water molecule is "added" to the "solute". However, this effect is also present in AMPAC calculations in vacuo and is simply not cancelled by the solvation contribution to the free energy profile, obtained with AMSOL. Cramer and Truhlar suggest that accurate potential energy surfaces can be obtained by adding the AMSOL solvation energies to high-level ab initio results computed in vacuo;<sup>327-330</sup> this procedure in most cases eliminates the largest source of error, i.e. the semiempirical approximation of the solute energy.

The approach recently developed by Gogonea and Osawa<sup>331,332</sup> is also based on Still's et al. approach<sup>220</sup> and has several aspects in common with that of Cramer and Truhlar. We shall examine this method in section V.C.4.

### 3. Apparent Surface Charge Methods

The polarizable continuum method (PCM) was first elaborated in the ab initio version.<sup>57</sup> It can be

described as an ASC approach, with a cavity of molecular shape. The tessellation of the spheres making up the surface was originally based on parallels and meridians and, later, on the inscribed pentakisdodecahedron; at the same time more refined shapes of the global surface were elaborated (see sections II.C and III.D.4).

The quantum mechanical calculation is performed making use of two nested cycles; the internal cycle calculates the  $q_k^{(m,f)}$  charges, from the  $\rho_M^{(m)}$  distribution; the external one determines an improved solute charge distribution  $\rho_M^{(m+1)}$ . As described in section III.D, the internal cycle may be replaced by a matrix inversion procedure or by an approximate closure relationship; the latter is computationally very effective. The number of external iterations needed to achieve a good convergency usually does not exceed 4.

In all the versions of the PCM program, attention is paid to a proper renormalization of the total apparent surface charge, i.e. to the effect of electronic density tails outside the cavity. A recent implementation,<sup>191</sup> based on the matrix inversion BEM formalism and the direct minimization of  $G_{el}$ , is not necessarily faster than the iterative one (the efficiency ratio depends only on the computer architecture); however, this approach allows one to clarify the mutual interaction between nuclear and electronic components of  $\rho_M$  and  $\sigma$ , to define better renormalization procedures, and to compute analytic first and second derivatives of  $G_{el}$  with respect to nuclear coordinates and other parameters, such as the dielectric constant  $\epsilon$  or the radii of the spheres defining the cavity. The derivatives with respect to the coordinates are necessary for efficient computer-driven geometry optimizations, and for the calculation of harmonic force fields and frequencies. The other derivatives are useful for extensions of the model to supercritical fluids, to derive expressions of the solvation enthalpy, to study the effect of temperature and pressure, etc.

In the standard PCM procedure the electrostatic free energy is given by eq 60, and the corresponding contribution to the solvation free energy is

$$\Delta G_{el} = G_{el} - E^{(0)} \quad (77)$$

where  $E^{(0)}$  is the energy eigenvalue of the Schrödinger equation in vacuo.

A semiclassical PCM version has been proposed by Miertuš and Tomasi;<sup>58</sup> in this approximation the polarization of the solute due to the solvent reaction field is neglected. The solvation free energy in this case is given by eq 16, i.e.:

$$\Delta G_{el}^{(0)} = \frac{1}{2} \langle \Psi^{(0)} | \hat{\mathcal{P}}_{\sigma}^{(0,f)} | \Psi^{(0)} \rangle = \frac{1}{2} \int \rho_M^{(0)} \Phi_{\sigma} d^3r \quad (78)$$

This quantity is the best approximation of  $\Delta G_{el}$  which can be defined within a rigid continuum model. The  $\Delta G_{el}^{(0)}$  values are routinely obtained in the standard PCM procedure, at the end of the first inner cycle (determination of the apparent surface charge for the  $\rho_M^{(0)}$  density computed in vacuo). We have accumulated during the years a large body of results,

which have been used as numerical evidence to set up a sequence of intermediate approximations, starting with  $\Delta G_{\text{el}}$  of eq 77 to end with very simple expressions. This subject will be considered in section IV.C.

It is very simple to adapt the PCM procedure to other levels of computational quantum mechanics. Persico and Tomasi<sup>333</sup> have employed the so called "half-electron Hamiltonian" with  $3 \times 3$  CI, a simple method which describes, with a low computational effort, the features of systems undergoing  $\sigma$  or  $\pi$  bond breaking.<sup>334</sup> Extensions of the procedure to excited states, using the simple electron-hole theory<sup>335</sup> or more refined versions<sup>336</sup> of this HF-like method, have been in use for a longtime.<sup>337-341</sup> Unrestricted Hartree-Fock (UHF) wave functions are also being used currently.<sup>342</sup> MCSCF, MBPT (levels 2-4), CASSCF, MR-SDCI, and other methods going beyond the HF approximation, have been implemented in the PCM procedure (see e.g. Aguilar et al.<sup>179</sup>). The description of electron correlation in solution will be treated in more detail in section IV.D.

There are several applications of the PCM to semiempirical descriptions of the solute wave function. The conjugation of semiempirical methods, based on ZDO, NNDO, or other similar approximations, with the PCM or other ASC approaches, gives several variants, concerning the calculation of the reaction potential  $\Phi_{\sigma}$  and of the Fock matrix elements.

An important step in the determination of  $\Phi_{\sigma}$  is to calculate the apparent surface charges  $q_k$ , eqs 31, 35, and 37:

$$q_k = \frac{\epsilon - 1}{4\pi\epsilon} \Delta S_k \bar{\nabla} \Phi_{M,\text{in}}(\mathbf{s}_k) \cdot \mathbf{n}_k \quad (79)$$

There are several methods for computing the semiempirical molecular electrostatic potential (MEP)  $\Phi_M$ , required in eq 79. These methods have been tested and discussed for the representation of MEP in vacuo.<sup>343-351</sup> They may be classified as "quasi-ab initio" or "direct" descriptions (with some variants within the two classes). In the "quasi-ab initio" descriptions the semiempirical wave function is de-orthogonalized and then expressed in terms of a Gaussian basis set. In the "direct" description the semiempirical wave function is used without modifications. The second class of methods is well represented by a recent proposal by Ford and Wang,<sup>350</sup> they introduce a semiempirical function to evaluate the nuclear contributions, with parameters calibrated against HF/6-31G\* results. The ab initio MEPS of a variety of molecules are accurately reproduced.

The evaluation of the  $\langle \mu | \hat{\mathcal{V}}_{\sigma} | \nu \rangle$  contributions to the Fock matrix elements, eq 59, presents similar options. The largest integrals are those with  $\mu$  and  $\nu$  belonging to the same atom. (Remember that  $\Phi_{\sigma}$  is reduced to a sum of  $q_k/|\mathbf{r} - \mathbf{s}_k|$  terms, with  $q_k$  not centered on any atom of M.) The discussion is now centered on the use of the Dewar-Sabelli-Klopman formula,<sup>352,353</sup> which includes empirical parameters fitting monopole, dipole, and quadrupole terms of the elementary charge distribution  $\mu^{*\nu}$  or of simpler alternatives. Apparently some of the latter give better results. The details of these methodological

investigations can be found in works of the last years.<sup>89,181,182,210,215,354,355</sup>

Miertuš and co-workers<sup>356</sup> presented a CNDO/2 version of PCM, based on a "quasi-ab initio" description of  $\hat{\mathcal{V}}_{\sigma}$ . To speed up calculations, the  $\sigma$  charge density is assumed constant over the spherical portion of the surface belonging to a given atom. On this portion of the sphere a few values of  $\sigma$  are computed (3 or 4), in points where the electrostatic potential has an extremum, and an average is then employed.

Chudinov et al.<sup>210</sup> point out that simple expressions of the elementary charge distribution  $\mu^{*\nu}$  give better results than the Dewar-Sabelli-Klopman formula, when applied to MNDO wave functions. To gain computational efficiency, they proposed a modified iterative scheme, reducing the number of SCF calculations, and revised definition of the surface elements.

The better performance of a simplified  $\mu^{*\nu}$  charge distribution is confirmed by Luque et al.,<sup>89</sup> using AM1 wave functions. When applying their most effective approximate formula, they also confirm that  $f = 1.2$  is the best scaling factor for the van der Waals radii used in the definition of the cavity. In a preceding paper, the same authors<sup>355</sup> compared the AM1 and MNDO versions of PCM. Quite recently the same authors<sup>357</sup> presented an optimized AM1 version of the method, yielding root-mean-square deviations of  $\Delta G_{\text{sol}}$  in the range of 1 kcal/mol for neutral solutes. The attention is here focused on the cavity radii for hydrogen. A factor  $f = 1.2$  is everywhere applied but, for hydrogens bonded to heteroatoms, smaller radii give a better agreement with the experimental results; the same was found in ab initio calculations.<sup>90</sup> The method is implemented in the MOPAC program.<sup>193</sup>

Wang and Ford<sup>182</sup> propose a still simpler expression of the  $\langle \mu | \hat{\mathcal{V}}_{\sigma} | \nu \rangle$  matrix elements for the AM1 and MNDO methods; their approximation allows one to avoid the calculation of the electric field due to the induced charges. Their version of the ASC approach (see section III.D.3) is based on the matrix inversion technique and the operator  $\hat{\mathcal{H}}_M^{(0)} + \hat{\mathcal{V}}_{\sigma}/2$ , interpreted by the authors as the effective Hamiltonian of the model; we have already discussed the generally accepted point of view on the status of this operator and its relationship with the Schrödinger equation and the free energy. This method has been applied to  $S_N1$  and  $S_N2$  reactions and to amino acid tautomerism.<sup>358</sup>

Rauhut et al.<sup>215</sup> point out that a full NDDO expression of the  $\langle \mu | \hat{\mathcal{V}}_{\sigma} | \nu \rangle$  integrals gives good results, when combined with the original PCM procedure<sup>57</sup> for the charge compensation and with the NAO/PC model<sup>359</sup> for the calculation of  $\Phi_M$  values on the cavity surface.

The matrix inversion ASC approach, with direct minimization of  $G_{\text{el}}$ , has been thoroughly elaborated by the Sakurai group.<sup>180</sup> They also extend the model to a nonhomogeneous continuum solvent, divided into regions with different dielectric constants. Hoshi et al.<sup>181</sup> present four approximated formulas for the calculation of the  $\langle \mu | \hat{\mathcal{V}}_{\sigma} | \nu \rangle$  integrals and of the corresponding differentials, leading to the evaluation of



$\bar{\nabla}\Phi_\sigma$ . In the last two approximations special care is taken to optimize the shape of the MEP near heteroatoms. The method has been implemented at the CNDO<sup>181</sup> and MNDO<sup>360</sup> levels and used to calculate hydration enthalpies of organic molecules. In a more recent paper,<sup>211</sup> MNDO, AM1, and PM3 semiempirical results are examined, to bring out the effects of some parameters of the method, such as the atomic radii defining the cavity, the number and shape of the surface elements, and the effect of correlation (II order Brillouin–Wigner/Epstein–Nesbet perturbation theory, applied to the MNDO Hamiltonian<sup>361</sup>).

We do not report here the formidable apparatus of matrices employed by Hoshi et al.<sup>180</sup> to present their method (the number and size of matrices to be stored during the calculations is probably the reason why this nice method has not yet been implemented in the ab initio framework). The method has been reported in Table 6 under the heading “PCM”, because it relies on the basic setup of the PCM. The only criticism we express to this elaboration of the matrix-inversion BEM procedure is that the formal consequences of the procedure here applied to renormalize  $\sigma$  have not been paid sufficient attention. A more appropriate renormalization of the two components  $\sigma_{el}$  and  $\sigma_{nuc}$ , eq 54, greatly improves the results and reduces the computational times.<sup>191</sup>

This method has been recently applied with appreciable results to more complex systems, such as the decarboxylation reaction catalyzed by cyclodextrins, to compare reaction parameters in vacuo, in homogeneous solution, and in heterogeneous media.<sup>211</sup>

The semiempirical (INDO/S CI) PCM formulation presented by Fox and Rösch<sup>189</sup> is addressed to spectroscopical problems and will be reviewed in section VII.C. The same holds for other semiempirical PCM approaches by the Basilevsky group, addressed to specific chemical problems (see sections VII.B).

Finally, we recall to the reader's attention that the COSMO method<sup>192</sup> (Klamt and Schürman, 1993), summarized in section III.D.3, has also been implemented in the MOPAC package,<sup>193</sup> in conjunction with semiempirical methods.

#### 4. Image Charge Methods

The model elaborated by Karlström<sup>362</sup> consists of a sphere encircled by a set of image point charges and dipoles, evaluated with the approximations given by Friedman.<sup>168</sup> The solute charge distribution is obtained by multipole decomposition of the  $\mu^*\nu$  elementary distributions (here  $\mu$  and  $\nu$  run over all the basis functions). The quantum problem is solved iteratively and the free energy is computed by subtracting half of the solute–solvent interaction  $W_{MS}$ , eq 60.

Karlström allows for solute displacements and geometrical relaxation inside the cavity. To avoid catastrophes (i.e. negative divergencies in the value of  $W_{MS}$ ), he introduces a repulsive potential function between the image elements and the solute nuclei,<sup>363</sup> of the type  $V = A/R_{im,nuc}^{12}$ , or between images and solute electrons,<sup>364</sup> of the type  $V = A[1 - \exp(-R_{im,el}/a)]^n$ ; here  $A$  and  $n$  are empirical constants ( $n = 12$ ). In the last paper Karlström extends his method to

CASSCF wave functions. The use of a spherical cavity greatly speeds up the calculations. We have already pointed out the deficiencies of this approach: the readjustment of the position of  $M$  inside the cavity may help in reducing these drawbacks. The results are however dependent on the form and parameters of the repulsion function.

#### 5. Direct Field Methods

The basic idea behind the direct reaction field (DRF) approach consists in replacing the reaction field operator  $\hat{\mathcal{V}}'_\sigma$  (eq 7), dependent on the solute charge distribution  $Q_M$ , with an operator based only on the single solute particles. This approach has been considered by Hylton et al. in their first paper,<sup>266</sup> but it has been extensively used by van Duijnen's group.

The first formulation of the DRF approach given by van Duijnen's group describes the medium as a set of interacting point polarizabilities.<sup>365,366</sup> Although not directly related to a continuum description of the medium, we use that formulation to clarify the meaning of the DRF formalism.

The Hamiltonian that approximates the energy of the whole system is written as

$$\hat{\mathcal{H}} = \hat{\mathcal{H}}_M^{(0)} + \hat{\mathcal{H}}^{DRF} \quad (80)$$

with

$$\hat{\mathcal{H}}^{DRF} = -\frac{1}{2} \sum_{ij} \sum_{p,q} \mathbf{F}_{ip}^\dagger \alpha_{pq} \mathbf{F}_{jq} \quad (81)$$

where indexes  $i$  and  $j$  run over the solute particles (electrons and nuclei) and  $p$  and  $q$  over the external polarizable points.  $\mathbf{F}_{ip}$  is the field of the particle  $i$  at the position of the polarizability  $p$ ,  $\alpha_{p,q}$  gives the dipole induced at  $q$  by a field applied at point  $p$  (response matrix element). With this formulation it is possible to get a direct solution of the corresponding Schrödinger equation (in contrast with the usual reaction field formulation which requires the knowledge of the solution  $\Psi$  to get the operator  $\hat{\mathcal{V}}'_\sigma$ ). The applications cover a wide range of solutes: structure of water dimers,<sup>366</sup> hydration and protonation free energies of amines and glycine,<sup>367</sup> proton transfer in the active sites of actinidin<sup>368</sup> and papain,<sup>369,370</sup> interactions between polypeptides.<sup>371</sup>

This approach opens some problems of interpretation. The use of the operator  $\hat{\mathcal{H}}^{DRF}$  of eq 80 does not correspond to the introduction of electrostatic polarization effects that are properly defined only when averaged distributions are used. The additional energy contributions have been interpreted as due to dispersion contributions (see section V.C.3). The direct considerations of the electron coordinates  $i$  and  $j$  has been interpreted as corresponding to a limiting case, in which electrons in the solute move much more slowly than those in the solvent; this approximation has been employed to study dynamical aspects of chemical reactions (see section VII.E).

Coming back to van Duijnen's methods, the original proposal has been recently recast in a more general formulation,<sup>372</sup> in which the continuum model plays a role. The whole material system is partitioned into

three subsystems: a "quantum motif"  $Q$ , which may be described by a wave function of any desired quality (until now the SCF level has been adopted in applications); a set of "classical motifs"  $A, B$ , etc., each represented by point charges and polarizabilities (at least one polarizability for each classical motif); and a continuous medium characterized by the static dielectric constant  $\epsilon$  and by the inverse of the Debye screening length  $\kappa^{-1}$  (to simulate finite ionic strengths).

The continuous contributions to  $\hat{\rho}_0$  are described within the ASC formalism, with apparent charges generated by the electric field of the quantum and classical motifs. In the latest version<sup>372</sup> the full DRF solution is given in matrix form. The matrix collects both surface charge and polarizable point contributions. The use of an average of the continuum contributions is suggested to get rid of an unphysical dispersion contribution. See ref 197 for further comments and ref 373 for a simplified version using perturbation theory techniques.

The linear DFR expressions are used in other discrete solvation models; see e.g. Basch and Hoz<sup>374</sup> for a recent version of this approach. Van Duijnen and co-workers suggest the possibility of considering the motifs  $Q + A + B + \dots$  as components of a single large molecule (e.g. a protein), but many applications refer to simpler solutes  $Q$ , with  $A, B$ , etc. representing a number of solvent molecules to be treated with computer simulations. This last type of application is a variant of the discrete solvation models supplemented with a description of the distant solvent electrostatic effects. As already stated in the introduction, we shall not include in the present survey this kind of approaches, which have given many valuable contributions to the study of chemical properties in solution, and deserve a separate review to document recent progresses.<sup>36-40</sup>

## 6. Virtual Charge Methods

The attempt of extending the Born model to a set of point charges led in the past years to the formulation of another variant of electrostatic continuum models, characterized by the introduction of a limited number of fictive charges not explicitly deduced from the electrostatic equations of a system composed of solute + dielectric solvent.

The first explicit formulation of this model is due to Klopman.<sup>375</sup> In this model an imaginary particle, called solvaton, is associated to each atom  $A$  of the solute. The charge of the solvaton,  $Q_A^S$ , is equal in magnitude and opposite in sign to the Mulliken charge  $q_A$ . The position of solvatons is not fixed; in the calculation of the interaction between  $Q_A^S$  and another atom with charge  $q_B$ , the solvaton is placed at the position of atom  $A$ ; the interaction of  $Q_A^S$  with  $Q_A$  is computed assuming a distance equal to the van der Waals radius of  $A$ . Interactions between solvents are discarded.

This classical formulation has been incorporated in a semiempirical SCF-MO procedure by Germeyer<sup>376,377</sup> and later reelaborated by Miertuš and Kysel<sup>378,379</sup> by Constanciel and Tapia,<sup>380,381</sup> and by others,<sup>382,383,322,384-401</sup> introducing corrections and additions, based in part on preceding formulations.<sup>402-404</sup>

The detection of formal errors in the first versions of the solvaton or virtual charge model (VCM), and the occurrence of unsatisfactory results, stimulated the elaboration of alternative formulations. Almost all the published papers, even those addressing specific applications, introduce some methodological changes. The efforts to supply this approach, so appealing in its original simplicity, with a sounder physical basis, led to models which are variants of the ASC methods.<sup>78</sup>

## C. A Strategy for Reducing the Quantum Problem

We have thus far considered the basic model: a solute at infinite dilution, immersed in a isotropic medium with linear dielectric properties, and described by a Hartree-Fock effective Hamiltonian.

In analyzing this model we have separated the computational problem into two parts, which are nevertheless coupled: electrostatics and quantum mechanics. In doing so, we have concentrated first on classical models, which may be considered as simplified representations of the whole problem. (The historical development has been different; the earlier models were exclusively classical and they incorporated an increasing amount of molecular information based on quantum mechanics.)

It is convenient now to start from the full quantum mechanical solution of the problem and to introduce a hierarchy of approximations leading, step by step, to more efficient algorithms, suitable for solutes of increasing size, but also to a reduction in the information contained in the computational results. The sequence of approximations we shall describe is accompanied by a set of protocols to check the quality of the results.

The general strategy is based on the "semiclassical approach" we developed in the past years to treat, on the same footing, intramolecular interactions, internal geometry relaxation, intramolecular interactions in vacuo, solvent effects, and electronic excitation. We cite a few papers from our group, reflecting the evolution of this approach.<sup>249,250,405-407</sup> Other authors have adopted the same basic concepts,<sup>408,409</sup> but without applications to solvent effects. Also the method elaborated by van Duijnen's group (see section IV.B.5) has many features in common with the approach here described.

In the semiclassical approach the basic units for the analysis are the charge distributions of molecular subunits. We shall define subunits in terms of localized orbitals (LO). The charge distribution associated with each subunit includes the proper share of nuclear charges, in order to be electrically neutral (special provisions are made for ions). We shall denote by  $\rho(g,0)$  the charge density of the chemical group  $g$  (e.g., the  $>C=O$  or the  $>N-CHO$  groups), by definition independent of the chemical environment. The  $\rho(g,0)$  functions, called prototypes, are expressed in a LCAO form, as the total charge distribution  $\rho_M$ . In fact, they derive from ab initio calculations on a suitable set of molecules, followed by a partitioning into LO and submitted to an averaging procedure.

The prototypes  $\rho(g,0)$  may be refined or submitted to further simplifications. The refinement consists

in allowing for the polarizing effect of the electric field generated by the remainder of the molecule M, called  $\mathbf{F}(\mathbf{g}/\mathbf{M},0)$ . Under the influence of  $\mathbf{F}(\mathbf{g}/\mathbf{M},0)$  the electron density of the group g is modified to  $\rho(\mathbf{g}/\mathbf{M},0)$ . If we also take into account the polarization induced by the solvent reaction field, the charge distribution of g becomes  $\rho(\mathbf{g}/\mathbf{M},\sigma)$ . The recipes to get  $\rho(\mathbf{g}/\mathbf{M},0)$  or  $\rho(\mathbf{g}/\mathbf{M},\sigma)$  are given in refs 249, 405, 406, 407, and 410. This said, we move on to describing the sequence of approximations for the evaluation of solvent effects.

**Approximation 1.** This is the full PCM description of the system. The electrostatic contribution to the solvation free energy is computed as a difference:

$$\Delta G_{\text{el},1} = G_{\text{el}} - E^{(0)} \quad (82)$$

The  $G_{\text{el}}$  values define a potential energy surface in solution.

**Approximation 2.** The level of the theory is the same as in A1, but the solvation free energy is approximated as in eq 16:

$$\Delta G_{\text{el},2} = \frac{1}{2} \int \rho_{\text{M}}^{(f)}(\mathbf{r}) \Phi_{\sigma}^{(f)}(\mathbf{r}) d\mathbf{r}^3 \quad (83)$$

This approximation may be justified by invoking the virial theorem and by neglecting differences in the average electronic kinetic energies in vacuo and in solution. At this level, as well as in all the following approximations, the potential energy surfaces in solution are defined as the sum of the energy in vacuo plus the solvation free energy:

$$G_{\text{el},n} = E^{(0)} + \Delta G_{\text{el},n} \quad (84)$$

When eq 83 is applied to conformational problems, it introduces relative errors in low-energy conformational surfaces normally less than 0.2 kcal/mol ( $E^{(0)}$  is the same as in eq 82).

**Approximation 3.** The solute charge distribution is described in terms of the SCF wave function in vacuo. The solvation free energy has the form

$$G_{\text{el},3} = \frac{1}{2} \int \rho_{\text{M}}^{(0)}(\mathbf{r}) \Phi_{\sigma}^{(0)}(\mathbf{r}) d\mathbf{r}^3 \quad (85)$$

The iterative or matrix-inversion PCM calculations are no longer necessary. This approximation is the most detailed realization of the rigid model, which disregards the solute polarization effects. The associated error on  $\Delta G_{\text{el}}$  depends on the size of the molecule and on the basis set. With a relatively good basis set the differences between approximations 1 and 3, for the set of amino acids of relevance in biochemistry, lies between 6 and 12 kcal/mol. The relative errors on conformational surfaces are generally less than 0.6 kcal/mol.

**Approximation 4.** The prototype functions are here introduced; polarization effects due to the molecular remainder and to the solvent reaction field are allowed for. The resulting charge distribution is a sum of group contributions:

$$\rho_{\text{M},4} = \sum_{\mathbf{g}} \rho(\mathbf{g}/\mathbf{M},\sigma) \quad (86)$$

This definition can be applied in an iterative proce-

dure to get a better approximation of both  $\rho_{\text{M}}$  and  $\Phi_{\sigma}$ . Three cycles insure almost perfect convergence, but we normally stop the process after the first step. Here and in the following,  $\phi_{\sigma,n}$  is the reaction field potential pertinent to approximation  $n$  and computed from the charge density  $\rho_{\text{M},n}$ . The expression of the solvation free energy is

$$G_{\text{el},n} = \frac{1}{2} \int \rho_{\text{M},n}(\mathbf{r}) \Phi_{\sigma,n}(\mathbf{r}) d\mathbf{r}^3 \quad n = 4-8 \quad (87)$$

At this level, we do not need to perform ab initio calculations on M to determine  $G_{\text{el}}$ ;  $E^{(0)}$  can be computed by any method, and  $G_{\text{el},4}$  is given by eq 84. For the determination of conformational surfaces of large molecules one can resort to molecular mechanics (MM2<sup>411</sup> or MM3<sup>412,413</sup>) or to other force fields, such as AMBER,<sup>236,414,415</sup> in this case we find relative errors less than 0.5 kcal/mol.

**Approximation 5.** The prototype functions are polarized by the electric field due to the molecular remainder, not by the solvent reaction field:

$$\rho_{\text{M},5} = \sum_{\mathbf{g}} \rho(\mathbf{g}/\mathbf{M},0) \quad (88)$$

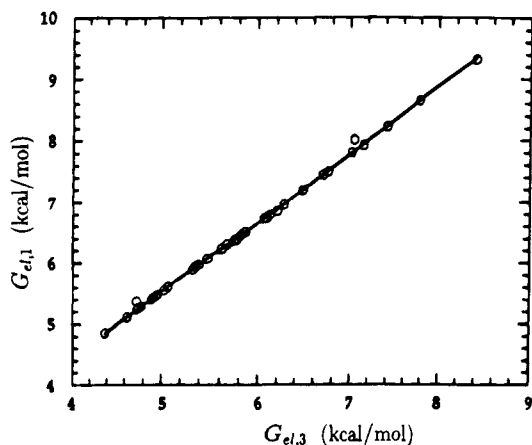
$E^{(0)}$  is again computed independently, for instance with molecular mechanics. This approximation neglects the polarization of the solute, as A3 does at a higher level. The relative errors in the same applications are less than 0.6 kcal/mol.

**Approximation 6.** The prototype functions are used without modifications.

$$\rho_{\text{M},6} = \sum_{\mathbf{g}} \rho(\mathbf{g},0) \quad (89)$$

Taking again  $E^{(0)}$  from molecular mechanics, the relative errors in conformational surfaces are of the order of 0.6–0.8 kcal/mol, with the exception of high-energy conformations, in which there is a partial reorganization of the electronic distribution (e.g., rotation around double C=C bonds or around the N–C(O) bonds in peptides).

**Approximation 7.** The prototype functions are replaced by simpler charge distributions. Several partitions of the molecular charge distribution into chemical subunits have been proposed, leading to the definition of local multipole developments (see ref 249 for a review); some of them have been applied to solvation models. Here we shall consider the procedure proposed by our group.<sup>166,416</sup> The  $\rho(\mathbf{g},0)$  distribution is replaced by the associated nuclear charges, plus one  $-2$  charge, or two  $-1$  charges, for each electron pair. The locations of the negative charges are determined by the LO charge centers and by the conservation of the dipole and quadrupole moments of the prototypes. The charge distribution  $\rho_7$  of the molecule is then given by a set of point charges, positive (the nuclei) and negative (usually a number smaller than the number of electrons). Further approximations can be introduced for the study of large molecules, by merging an increasing number of atomic or partial charges together. We quote, as an example, a study of solvent effects on DNA double helices with more than 1500 base pairs, subjected to internal deformations.<sup>417</sup> A simplified classical ver-



**Figure 2.** Correlation of  $G_{el,1}$  and  $G_{el,3}$  values (see text) for 35 conformations of 1,2-ethanediol diformate (ref 242).

**Table 7. Free Energy Changes ( $\Delta G_{el}$ , kcal/mol) in the Isomerization of *N*-Methylformamide in Water ( $\epsilon = 78.5$ ),<sup>a</sup> with Reference to the Trans Form**

approximation	TS(-30°)	TS(0°)	TS(+30°)	cis
1	29.96	27.89	27.26	2.00
2	27.30	28.95	28.75	3.54
3	26.20	26.90	26.42	1.99
4	27.40	29.30	29.00	3.70
5	23.22	26.65	25.58	1.78
6	20.40	23.57	23.17	1.52
7	21.00	24.07	23.62	1.82
8	18.00	19.69	19.59	0.00
in vacuo	25.55	24.20	23.42	1.94

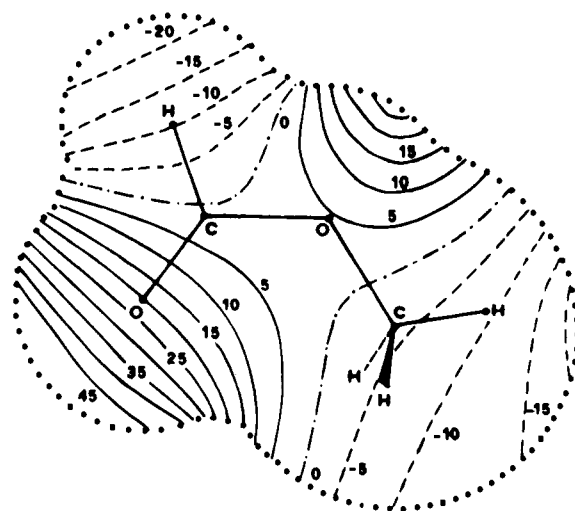
<sup>a</sup> SCF 4-31G calculations. For approximations 2–8,  $E^{(0)}$  is computed at the same ab initio level.

sion of the PCM was applied in the DNA calculations, and a more efficient algorithm for globular proteins is now under elaboration.

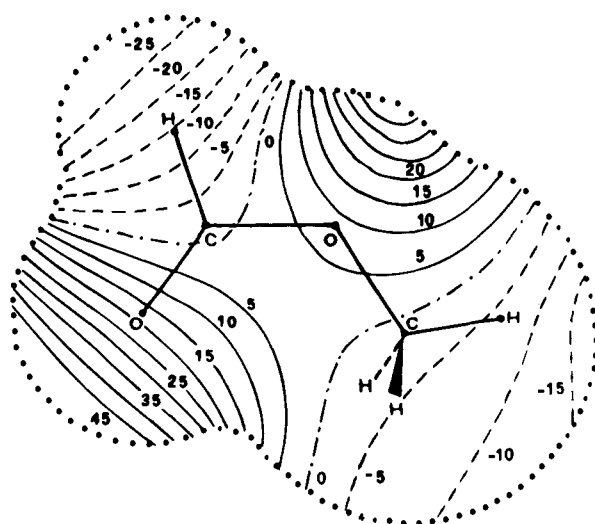
We report now some examples of the use of the sequence of approximations just described. Figure 2 compares  $G_{el,1}$  and  $G_{el,3}$  for a set of conformations of 1,2-ethanediol diformate.<sup>242</sup> As already said, approximation 3 is generally adequate for conformational energy differences.

A more delicate case concerns the solvent effects on some features of the *trans*-*cis* isomerization of *N*-methylformamide (see Table 7). While in the *cis* and *trans* conformations the  $CNR_1R_2$  group of amides is planar, both in vacuo and in solvent, the transition state is pyramidalized. In vacuo, the pyramidalization angle  $\theta$  is about 30°, with the *N*-substituents oriented on the side of the carbonyl group. In aqueous solution, the opposite happens: two transition states exist, with  $\theta \approx \pm 30^\circ$ , but  $\theta = -30^\circ$  is favored; for  $\theta \approx 0$  we have a supersaddle point. In Table 7 we report the  $\Delta G$  values for a set of geometries, with respect to the *trans* isomer. The data are taken from Alagona et al.,<sup>418,419</sup> with some additions. Other studies on the isomerization of amides have confirmed this view and found very good agreement with the available experimental data; Monte Carlo simulations have been run for *N,N*-dimethylacetamide,<sup>420</sup> PCM ab initio and semiempirical calculations for *N*-methylacetamide,<sup>421</sup> and a combined HF/MC method has been applied to *N,N*-dimethylformamide.<sup>422</sup>

The reaction field  $\Phi_\sigma$  is quite sensitive to the options and parameters of the calculations; therefore



**Figure 3.** Map of  $\phi_{\sigma,1}$  (standard PCM) in the molecular plane of *trans*-methyl formate, 4-31G SCF calculation.

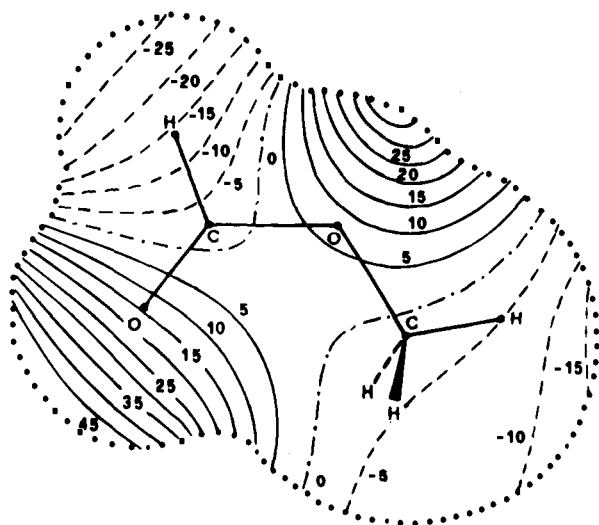


**Figure 4.** Map of  $\phi_{\sigma,4}$  (polarizable prototype functions approximation) in the molecular plane of *trans*-methyl formate, 4-31G SCF calculation.

it is useful to compare  $\Phi_\sigma$  maps computed with different approximations. In Figures 3, 4, and 5 we show the maps of  $\phi_{\sigma,1}$ ,  $\phi_{\sigma,4}$ , and  $\phi_{\sigma,6}$  for the *trans*-methyl formate, obtained with the 4-31G basis set and drawn in the molecular plane.<sup>418,419</sup> In all cases the agreement is almost perfect.

Another type of simplification regards the number of surface elements to be considered in ASC calculations. There are two steps where the number of tesserae might be conveniently reduced: (1) When the distribution  $\rho_M$  is a sum of local terms (localized orbitals, multipole expansions over atoms or bonds, point charges), it should be possible to simplify the calculation of the  $\sigma$  surface density, by neglecting the contribution of each local charge component to tesserae which are far enough. (2) In the same way, the self-polarization procedure might be speeded up by neglecting the interaction between surface charges in distant portions of the surface.

The  $r^{-2}$  dependence of the electric field on distance makes the introduction of approximations 1 and 2 a delicate task; probably the partial cancellation of solute and solvent polarization charges is the key feature of this problem. In our laboratory we are now



**Figure 5.** Map of  $\phi_{\sigma,6}$  (rigid prototype functions approximation) in the molecular plane of *trans*-methyl formate, 4-31G SCF calculation.

examining the opportunity of introducing such approximations in free energy calculations for large molecules. A somewhat similar philosophy underlies the use of the extended Born formula in the Still-Cramer-Truhlar treatments.<sup>220,314-318</sup>

#### D. The Inclusion of Electron Correlation

Several, among the quantum versions of the basic model we have examined in the preceding section, consider a description of the solute going beyond the Hartree-Fock level.

It is in fact an easy task to introduce in eqs 52 and 60 a more refined description of the wave function. The question deserves however a few words of comment. The introduction of correlation modifies the total charge distribution  $\rho_M$ ; for instance, the dipole moments of O and N bases are normally reduced. As a consequence, the solvent reaction potential  $\Phi_\sigma$  is also changed. On the other hand, the polarization induced by the solvent through the reaction field modifies in turn the electron correlation effects.

Parts of these mutual influences have been usually neglected in past work. The most frequent case is the neglect of correlation effects on the solvent polarization: the solute-solvent interaction operator  $\mathcal{V}'_\sigma$  is determined at the HF level and then included in the calculation of a correlated wave function.

To the best of our knowledge, the only analysis of the decoupling of the effects mentioned before has been made by the group of Olivares del Valle, in collaboration with us, using the PCM approach for many-body perturbation theory (MBPT) corrections to the HF picture.<sup>423-427</sup> The complete calculation, called PTDE in Olivares del Valle's terminology, is decoupled into two separate calculations. The first approximation, called PTE, consists of solving the PCM problem at the Hartree-Fock level only, to determine the solute wave function and the reaction potential. An MBPT correction to the energy is computed. In the second approximation, called PTD, the calculation of the reaction potential and of  $\Delta G_{el}$  is based on the MBPT corrected wave function, computed in vacuo.

#### E. Derivatives of the Free Energy

The calculation of the free energy derivatives is of interest for many applications of the continuum models. The variables with respect to which a derivation may be performed are of different nature, and we shall group them into three main classes:

(A) Parameters entering the formulation of the basic model. The main model parameters are the isotropic dielectric constant  $\epsilon$ , the solvent density, and the temperature. The corresponding derivatives are related to each other, as dielectric constant and density depend on temperature.

(B) External parameters. The systematic application of external electric and magnetic fields, static or oscillatory, permits to derive expressions for several first- and second-order molecular observables<sup>428,429</sup>.

(C) Internal geometrical parameters. The parameters defining the geometry of the solute also influence the cavity shape. It may be profitable in some case to decouple these two sets of variables, for instance to perform derivatives with respect to the nuclear coordinates at fixed cavity or to focus the attention on the derivatives of the cavity surface and volume.

Some of these derivatives cannot be computed in specific versions of the solvation continuous models. For example, it is meaningless to consider derivatives with respect to external fields in the extended Born models, based on nonpolarizable charge distributions. Quantum mechanical versions of the model may, in principle, give formally correct derivatives in the three cases outlined above. For this reason we shall refer to a quantum formulation, focusing on the derivatives of  $\Delta G_{el}$ .

It is convenient to adopt a short-hand notation for the first derivative of any quantity, based on superscripts: for instance, the first derivative of  $G_{el}$  with respect to a parameter  $\alpha$  will be indicated as  $G^{(\alpha)}$  and the second derivative with respect to  $\alpha$  and  $\beta$  as  $G^{(\alpha\beta)}$ . The calculation of  $G^{(\alpha)}$  and  $G^{(\alpha\beta)}$  can be greatly simplified by resorting to the matrix BEM formulation of the basic model. The  $G$  functional, expanded over a finite basis set  $\{\chi\}$  may be cast in the following form, using the notation of refs 430 and 431:

$$G = \text{tr} \mathbf{P} \mathbf{h}' + \frac{1}{2} \text{tr} \mathbf{P} \mathbf{G}'(\mathbf{P}) + V'_{\text{nuc,nuc}} \quad (90)$$

where

$$V'_{\text{nuc,nuc}} = V_{\text{nuc,nuc}} + \frac{1}{2} W_{\text{nuc,nuc}} \quad (91)$$

$W_{\text{nuc,nuc}}$  is the interaction between the component of the reaction field generated by the nuclear charges of  $M$  and the nuclear charges themselves (see eq 56).

The expression 90 is derived from the pseudo Hartree-Fock equation:

$$\mathbf{F}' \mathbf{C}' = \mathbf{E}' \mathbf{S}' \mathbf{C}' \quad (92)$$

with

$$\mathbf{F}' = \mathbf{h}' + \mathbf{G}' \quad (93)$$

$$\mathbf{h}' = \mathbf{h} + \frac{1}{2} (\mathbf{J} + \mathbf{Y})$$

$$\mathbf{G}' = \mathbf{G}(\mathbf{P}) + \mathbf{X}(\mathbf{P})$$

From the solution of eq 92 one obtains a first-order density matrix  $\mathbf{P}$ , expanded over the basis  $\{\chi\}$ . The other matrices have the following meaning:  $\mathbf{h}$  is the usual one-electron matrix;  $J_{\mu\nu}$  is the interaction of the solute electronic charge element  $\chi_{\mu}^*\chi_{\nu}$  with the component of the solvent reaction potential  $\Phi_{\sigma}$  generated by the nuclear charges of  $M$  (the one-electron operator  $W_{\text{el,nuc}}$ , eqs 55–57);  $Y_{\mu\nu}$ , vice versa, is the interaction between the nuclei of  $M$  and the component of  $\Phi_{\sigma}$  generated by the charge distribution  $\chi_{\mu}^*\chi_{\nu}$ ;  $\mathbf{G}(\mathbf{P})$  is the usual two-electron contribution to the Fock matrix;  $\chi_{\mu\nu}$  is the interaction between the charge distributions  $\chi_{\mu}^*\chi_{\nu}$  and the components of  $\Phi_{\sigma}$  generated by the electronic charge of  $M$ . Notice that the condition  $\mathbf{J} = \mathbf{Y}$  can be fulfilled, with an appropriate handling of the numerical procedures.<sup>191</sup>

Frisch et al.<sup>296</sup> have shown that

$$\text{tr}\mathbf{P}^{(\alpha)}\mathbf{F}' = -\text{tr}\mathbf{S}^{(\alpha)}\mathbf{P}\mathbf{F}'\mathbf{P} \quad (94)$$

This relation allows one to write a simple expression for  $G^{(\alpha)}$ :

$$G^{(\alpha)} = \text{tr}\mathbf{P}\mathbf{H}' + \frac{1}{2}\text{tr}\mathbf{P}\mathbf{G}'^{(\alpha)} - \text{tr}\mathbf{S}^{(\alpha)}\mathbf{P}\mathbf{F}'\mathbf{P} + V_{\text{nuc,nuc}}^{(\alpha)} \quad (95)$$

By differentiation of  $G^{(\alpha)}$  with respect to a second parameter  $\beta$ , one arrives at the formal expression of the second derivative  $G^{(\alpha\beta)}$ :

$$G^{(\alpha\beta)} = \text{tr}\mathbf{P}^{(\beta)}\mathbf{F}'^{(\alpha)} + \text{tr}\mathbf{P}(\mathbf{h}'^{(\alpha\beta)} + \frac{1}{2}\mathbf{G}'^{(\alpha\beta)} - \text{tr}\mathbf{S}^{(\alpha\beta)}\mathbf{P}\mathbf{F}'\mathbf{P} - \text{tr}\mathbf{S}^{(\alpha)}[\mathbf{P}^{(\beta)}\mathbf{F}'\mathbf{P} + \mathbf{P}'\mathbf{F}'^{(\beta)}\mathbf{P} + \mathbf{P}\mathbf{G}(\mathbf{P}^{(\beta)})\mathbf{P} + \mathbf{P}\mathbf{F}'\mathbf{P}^{(\beta)}]) + V_{\text{nuc,nuc}}^{(\alpha\beta)} \quad (96)$$

where  $\mathbf{S}$  is the overlap matrix and  $\mathbf{P}^{(\beta)}$  is obtained by solving the appropriate coupled perturbed Hartree–Fock equations (Frisch et al.<sup>296</sup>). Expressions 95 and 96 are valid for any type of parameters  $\alpha$  and  $\beta$ . These expressions have a formidable aspect but actually they are not much more complex than the corresponding derivatives  $E^{(\alpha)}$  and  $E^{(\alpha\beta)}$  for an isolated molecule, widely used in computational chemistry. The new integrals are of simple nature (typically one-electron integrals regarding first and second derivatives of the electric field).

The general expression may be considerably simplified when the nature of the  $\alpha$  and  $\beta$  parameters is specified. For example, if  $\alpha$  is the dielectric constant  $\epsilon$  the expression of  $G^{(\alpha)}$  is<sup>430</sup>

$$G^{(\epsilon)} = -\frac{4\pi}{(\epsilon - 1)^2} [2\text{tr}\mathbf{P}\mathbf{D}^{-1}\mathbf{J} + \frac{1}{2}\text{tr}\mathbf{P}\mathbf{D}^{-1}\mathbf{X} + \Phi_{\text{nuc}}^{\dagger}\mathbf{D}^{-1}\mathbf{q}_{\text{nuc}}] \quad (97)$$

We have introduced here the  $\mathbf{D}$  matrix collecting the geometrical information about the cavity and its tessellation (see section III.D.3);  $q_{\text{nuc},k}$  and  $\Phi_{\text{nuc},k}$  are the contributions, due to the nuclei of  $M$ , to the apparent point charge and to the electrostatic potential  $\Phi_M$ , for the surface element  $k$ .

The problem is more delicate when  $\alpha, \beta$  are geometrical parameters, for instance the radii of the van

der Waals spheres or the positions of the nuclei, normally identified with the centers of the spheres. In these cases, one needs the expression of the derivatives of the areas of the surface elements  $\Delta S_k$ . In the BEM procedures these terms are connected with the  $\mathbf{D}^{-1}$  matrix elements.

A relatively simple case is that of fixed-solute geometry. For example,  $\alpha$  can be an additional parameter  $\xi$ , scaling all the atomic radii  $R_k$  which define the cavity:

$$G^{(\xi)} = \text{tr}\mathbf{P}\mathbf{J}^{(\xi)} + \frac{1}{2}\text{tr}\mathbf{P}\mathbf{X}^{(\xi)}(\mathbf{P}) + \frac{1}{2}V_{\text{nuc,nuc}}^{(\xi)} \quad (98)$$

The  $G^{(\epsilon)}$  and  $G^{(\xi)}$  derivatives may be used to derive expressions of the solvation enthalpy  $\Delta H_{\text{el}}$ ,<sup>58</sup> and to study temperature- and pressure-dependent phenomena.

Analytical formulas have been obtained for all the cases occurring when the derivative involves nuclear coordinates and cavity surface. The algebra is rather involved because there are surface elements  $\Delta S_k$  cut by the intersection of two or more spheres. The most complex formulas occur in the calculation of the Hessian matrix elements  $G^{(\alpha\beta)}$ , when the parameters  $\alpha$  and  $\beta$  are two internal geometrical coordinates.<sup>431,432</sup> It is somewhat simpler to calculate the components  $G^{(\alpha)}$  of the gradient of  $G(\mathbf{Q})$ . Both quantities are obviously of great value in determining the critical points on the  $G(\mathbf{Q})$  hypersurface and the normal coordinates and frequencies.

It is tempting to avoid these complications by performing derivatives with respect to nuclear coordinates at fixed cavity. However we consider it necessary to test this approximation with more exact calculations. The bold approach of computing optimal geometries and vibrational frequencies with a fixed cavity has been adopted by Wong et al.<sup>295</sup> Their formulation is similar to that outlined above, but specialized for the quantum mechanical Onsager sphere + dipole model (called by the authors SCRf without any further specification). We have commented about this model in section IV.B.1; the relative crudeness of the model justifies neglecting the cavity surface derivatives. Surely in successive elaborations of this elegant method the spherical cavity and the dipole only field will be abandoned and surface derivatives will be considered.

When the cavity has a regular shape the evaluation of  $G^{(\alpha)}$  may be profitably performed by resorting to a multipolar expansion. An efficient program has been elaborated by Rivail's group<sup>162,251</sup> for ellipsoidal cavities. Using a multipole expansion the Hamiltonian and the resulting free energy are expressed in terms of the reaction field factors  $f_{ll'}^{nm}$  depending only on the geometry of the cavity and on  $\epsilon$  (see section III.B). The expression of  $G^{(\alpha)}$  may be thus obtained with standard procedures available in quantum chemistry packages. Rinaldi et al.<sup>162</sup> proceed a step further. The variation of any nuclear coordinate  $\alpha$  modifies the inertial axes and the Eulerian angles defining the ellipsoidal cavity; the  $f_{ll'}^{nm}$  factors are thus modified and their derivatives must be computed. Analytical expressions for these derivatives are available.<sup>104,159</sup>

Rivail's group is now considering cavities of more general shape, using the already quoted GEPOL

formalism.<sup>213</sup> A procedure for geometry optimizations based on approximate analytic gradients has been presented.<sup>433,434</sup>

Other authors have investigated methods to optimize the geometry of solutes: a comparative evaluation of the different approaches has not yet been performed. Klamt and Schüürmann<sup>192</sup> include in their COSMO method an evaluation of the derivatives of the energy with respect to atomic coordinates with a simplified expression. The areas and shapes of the tesserae, as well as the solute charge distribution  $q_M$ , are kept fixed. Chudinov and Napolov<sup>435,436</sup> propose a computational scheme for geometry optimizations, based on a partially numerical evaluation of the gradient, coupled with the analytical determination of the derivatives of surface elements. A strategy for geometry optimization based on the numerical evaluation of the gradient has been also proposed by Bonaccorsi et al.<sup>437</sup> To save time three variants of the method have been combined: (1) energy gradient computed at a fixed  $\sigma$  distribution; (2) gradient computed with fixed cavity and variable  $\sigma$ ; (3) gradient computed changing the cavity and  $\sigma$ .

Semiempirical methods using an ASC approach<sup>182,314–318</sup> compute the numerical energy gradient without any further approximation. The determination of saddle points is a more delicate task than the location of minima. Using the AMSOL program<sup>314–318</sup> we have found reasonable results (within the limits of the semiempirical method), but in some cases the search failed.

The evaluation of derivatives of the cavity surface and volume is of interest on its own, since there are several applications requiring a direct knowledge of these parameters. In general a tessellation of the surface is not necessary, and the computational task is thus reduced. We report here a list of pertinent references.<sup>187,198,199,201–204,331,332,438–440</sup> The reader will find the details of the various methods in the original papers.

## V. Definition of Equilibrium Thermodynamical Functions

### A. The Free Energy of Solvation

Up to now we have only considered the electrostatic component  $\Delta G_{el}$  of the total solvation free energy,  $\Delta G_{sol}$ . We shall now consider a more complete definition.

For molecular formulations of the solvation problem (simulations, effective Hamiltonians, and other approaches mentioned in section I) it is convenient to adopt Ben-Naim's definition of a solvation process.<sup>441–443</sup> According to Ben-Naim, the solvation process of a solute M in a solvent S consists of transferring M from a fixed position in the ideal gaseous phase to a fixed position in S, at constant  $T$ ,  $P$ , and chemical composition. The Gibbs free energy of solvation can be related to the work necessary to "build up" M in S,  $W(M/S)$ , also called the coupling work of M with S. Simple statistical arguments provide a connection between  $W(M/S)$  and a measurable free energy change. It is not necessary to report all the details here. The conclusion is that the following expression may be accepted as a fairly good

approximation to the solvation free energy:

$$\Delta G_{sol} = W(M/S) + RT \ln \left( \frac{q_{rot,g} q_{vib,g}}{q_{rot,s} q_{vib,s}} \right) - RT \ln \left( \frac{n_{M,g} \Lambda_{M,g}^3}{n_{M,s} \Lambda_{M,s}^3} \right) \quad (99)$$

Here  $q_{rot,g}$ ,  $q_{vib,g}$ ,  $q_{rot,s}$ ,  $q_{vib,s}$  are the microscopic partition functions for rotation and vibration of M, in gas phase and in solution;  $n_{M,g}$  and  $n_{M,s}$  are the numeral densities of M molecules;  $\Lambda_{M,g}$  and  $\Lambda_{M,s}$  are the momentum partition functions. There is an additional term,  $P\Delta V$ , which may be neglected, its value being normally less than  $10^{-3}$  kcal/mol. This expression is more general than the one we presented in 1981,<sup>338</sup> and later applied in other papers. Ben-Naim's derivation is not limited to dilute solutions and also avoids certain assumptions about the structure of the liquid state. The last term of eq 99 is the so called "liberation free energy" difference.<sup>442,443</sup> The sum of the first two terms, i.e. the solvation free energy at equal numeral densities in gas phase and solution, is indicated by Ben-Naim with an asterisk:  $\Delta G_{sol}^*$ . Notice that the usual thermodynamic relationships also hold for  $\Delta G_{sol}^*$ , in particular:

$$\Delta S_{sol}^* = - \left( \frac{\partial \Delta G_{sol}^*}{\partial T} \right)_P \quad (100)$$

$$\Delta H_{sol}^* = -\Delta G_{sol}^* - T\Delta S_{sol}^*$$

$$\Delta V_{sol}^* = - \left( \frac{\partial \Delta G_{sol}^*}{\partial P} \right)_T$$

The coupling work of M and S may be decomposed as follows:

$$W(M/S) = \Delta G_{el} + \Delta G_{cav} + \Delta G_{dis} + \Delta G_{rep} \quad (101)$$

We have already examined  $\Delta G_{el}$ .  $\Delta G_{cav}$  is a positive term, corresponding to the work spent in forming a suitable cavity in the liquid;  $\Delta G_{dis}$  is the dispersion contribution to the coupling work;  $\Delta G_{rep}$  is a repulsion term, assimilable, at the microscopic level, to the exchange–repulsion term of the perturbation theory for noncovalent interactions. In the following sections we shall analyze the methods available for the computation of the different components of  $\Delta G_{sol}$ .

### B. The Cavitation Energy

The introduction of a cavity formation energy term is a useful device to divide the evaluation of  $W(M/S)$  into separate and more manageable terms. As already said,  $\Delta G_{cav}$  corresponds to the work spent in forming, inside the liquid, a cavity of appropriate shape and volume, in the absence of solute–solvent interactions. In other words, during this hypothetical step the solute–solvent interactions are switched off. Once the cavity is formed, the other terms in  $W(M/S)$  are evaluated by switching on again the interactions, for instance by a charging parameter method, which ensures the status of a free energy to the final result.<sup>444</sup>

The concept of cavitation energy was introduced by Uhlig,<sup>445</sup> following a suggestion of Susskind and Kasarnowski<sup>446</sup> and then refined by Eley.<sup>447</sup> The approach was devised for, and later extensively applied to, the theory of solubility of gases into liquids. The literature on  $\Delta G_{\text{cav}}$  is influenced by this origin, and many tests and speculations concern the solvation of relatively inert gases into liquids of various nature and the related problem of the definition and evaluation of hydrophobic effects. It is not our aim to survey here the vast literature on these subjects, rich in debates opposing different views of the matter. We only remark that  $\Delta G_{\text{cav}}$  is but one of the components of  $\Delta G_{\text{sol}}$ , and an adequate treatment of all components is needed to draw firm conclusions from a comparison with experimental values.

For the evaluation of  $\Delta G_{\text{cav}}$  several formulas are available, based on the shape and size of the solute and on different parameters of the solvent: (1) surface tension (Uhlig), (2) surface tension with microscopic corrections (Sinanoglu), (3) isothermal compressibility (Gogonea and Osawa), and (4) geometrical parameters of the solvent molecules (Reiss, Pierotti). We may add that simulation methods are able to give a direct insight of the process of formation of a cavity and on the effect it has on the surrounding solvent molecules.<sup>448-456</sup>

The first three techniques mentioned here follow the same philosophy of the continuum dielectric approach. In fact, they do not rely on a detailed description of the discrete solute and make use of experimental bulk parameters of the solvent, in analogy with the dielectric constant of the electrostatic continuum model. The Reiss-Pierotti formulas derive from a theory based on a discrete model of fluids (the scaled particle theory); the original discrete formulation of the theory is no longer evident in the expression of  $\Delta G_{\text{cav}}$ , which depends again on pure solvent parameters.

### 1. Cavitation Energy from Surface Tension

We begin with the approach proposed by Uhlig.<sup>445</sup> The cavitation energy is simply proportional to the surface of the cavity, assumed spherical:

$$\Delta G_{\text{cav}} = 4\pi r^2 \gamma \quad (102)$$

where  $r$  is the radius of the cavity and  $\gamma$  the surface tension of the solvent.

This formula has been applied in many cases, also for the evaluation of the free energy of transfer between different solvents.

It is worth mentioning here a relationship<sup>457,458</sup> connecting the surface tension with the isothermal compressibility  $\kappa$  and density  $\delta$

$$\gamma^2 \frac{\kappa}{\delta} = A_0 \quad (103)$$

in the normal liquid range.  $A_0$  is temperature independent and invariant for a large set of organic solvents (including H-bonded liquids); it assumes different values for diatomic liquids and for rare gases. To the best of our knowledge this relationship has not yet been exploited to get cavitation energies.

A simple formula related to eq 102 has been recently proposed by Tuñón, Silla, and Pascual-Ahuir:<sup>459</sup>

$$\Delta G_{\text{cav}} = \gamma S_M - RT \ln(1 - V_S n_S) \quad (104)$$

where  $S_M$  is the surface area of the cavity,  $V_S$  is the volume of a solvent molecule, and  $n_S$  is the numeral density of the solvent.

An empirical expression has been recently proposed by Simonson and Brünger:<sup>460</sup>

$$\Delta G_{\text{cav}} = C + \sum_i \gamma_i A_i \quad (105)$$

where  $A_i$  is the atomic accessible surface area, and  $C$  and  $\gamma_i$  are adjustable parameters. The quality of the fit is not significantly reduced when all the  $\gamma_i$  are reduced to a single value.

### 2. Cavitation Energy from Surface Tension with Microscopic Corrections

Some deficiencies of the preceding method have been interpreted as originating in the use of a macroscopic value of  $\gamma$  which does not take into account the effects of curvature at the microscopic scale. The theory of surface tension for curved surfaces has been laid down by Tolman<sup>461,462</sup> and successively refined for microscopic curvatures by Kirkwood and Buff<sup>463-466</sup> and others.<sup>467,468</sup> The version most widely adopted is that given by Sinanoglu<sup>469-473</sup> within the context of a general treatment of molecular interactions in solutions, mainly based on a discrete representation of the liquid.

The cavitation free energy is given by

$$\Delta G_{\text{cav}} = k_S^g (V_S/V_M) \gamma \Sigma \quad (106)$$

Here  $\Sigma$  is the cavity area (the formula has been developed for spherical cavities and then extended to arbitrary shapes).  $k_S^g (V_S/V_M)$  is a correction factor, characteristic of the solvent and depending on the ratio of the molecular volumes of  $S$  and  $M$ . It can be developed in the expression:

$$k_S^g (V_S/V_M) = 1 + \left( \frac{V_S}{V_M} \right)^{2/3} (k_S^g(1) - 1) \quad (107)$$

where  $k_S^g(1)$  is estimated from solubility data. Actually Sinanoglu's formulation is more complex than this schematic overview; he also introduces separate microscopic factors  $k_S^S$  and  $k_S^E$  for the cavitation entropy and energy. As a consequence, different formulas can be found in the various papers referring to Sinanoglu's approach.

A detailed worked-out example has been reported by Birnstock et al.<sup>474</sup> with application to the conformational enthalpy changes of several solutes. Revised versions of Sinanoglu's method have been proposed by Blaisten-Barojas et al.<sup>475</sup> and by Moura-Ramos et al.,<sup>476-479</sup> with several applications.<sup>480,481</sup>

### 3. Cavitation Energy from Isothermal Compressibility

Quite recently Gogonea and Osawa<sup>331,332</sup> reconsidered a suggestion of Oakenfull and Fenwick<sup>482</sup> to



estimate  $\Delta G_{\text{cav}}$  through the relationship:

$$\frac{\partial G}{\partial V_T} = -V \frac{\partial P}{\partial V_T} = \frac{1}{\beta_T} \quad (108)$$

Whence

$$\Delta G_{\text{cav}} = \frac{V_{\text{cav}}}{\beta_T} + \text{constant} \quad (109)$$

Here  $\beta_T$  is the isothermal compressibility and  $V_{\text{cav}}$  is the volume of the cavity (this formula contains an error of sign in ref 482).

Gogonea and Osawa support their proposal with the results of molecular dynamics simulations of liquid water, published by Postma et al.<sup>450</sup> The energy necessary to create a cavity in water correlates quite well (correlation coefficient 1.000) with  $V_{\text{cav}}$  computed from the thermal radius of the cavity:

$$\Delta G_{\text{cav}} = 0.0426V_{\text{cav}} - 0.1173 \quad (110)$$

(energies in kcal/mol, volumes in  $\text{\AA}^3$ ). The slope 0.0426 is substantially different from the experimental value of  $\beta_T^{-1} = 0.318$ . The surface tension and the compressibility formulas (without corrections) pick up different single aspects of the cavity formation process; a more comprehensive approach is outlined in the next section.

#### 4. Cavitation and Scaled Particle Theory

The formulation given by Pierotti<sup>483-485</sup> is based on the scaled particle theory (SPT) of Reiss and co-workers,<sup>6-8</sup> already mentioned in the introduction as one of the cornerstones of the physical approach to solutions. In its original formulation the SPT reduces the fluid molecules to hard spheres; the theory was later extended to rigid bodies with more complex shapes and recently applied<sup>486</sup> to the evaluation of  $\Delta G_{\text{cav}}$ .

Pierotti adds an interaction energy term to evaluate the solubility of gases in liquids, with the assumption that there is no entropic contribution to the solute-solvent interaction. As to the cavitation free energy, it is expanded in powers of  $R_{\text{MS}}$ , i.e. the radius of the sphere which excludes the centers of the solvent molecules (sum of the solute and solvent radii,  $R_{\text{MS}} = R_M + R_S$ ):

$$\Delta G_{\text{cav}} = K_0 + K_1 R_{\text{MS}} + K_2 R_{\text{MS}}^2 + K_3 R_{\text{MS}}^3 \quad (111)$$

The coefficients  $k_i$  are expressed in terms of some of the properties of the solvent (molecular radius  $R_S$ , numeral density  $n_S$ ) and of the solution (pressure  $P$ , temperature  $T$ ):

$$K_0 = RT \left[ -\ln(1-y) + \frac{9}{2} \left( \frac{y}{1-y} \right)^2 \right] - \frac{4\pi R_S^3 P}{3} \quad (112)$$

$$K_1 = -\frac{3RT}{R_S} \left[ \frac{y}{1-y} + 3 \left( \frac{y}{1-y} \right)^2 \right] + 4\pi R_S^2 P$$

$$K_2 = \frac{3RT}{R_S^2} \left[ \frac{y}{1-y} + \frac{3}{2} \left( \frac{y}{1-y} \right)^2 \right] - 4\pi R_S P$$

$$K_3 = \frac{4\pi P}{3}$$

with  $y = 4\pi R_S^3 n_S / 3$ . The expression of  $\Delta H_{\text{cav}}$  is deduced through the Helmholtz equation:

$$\Delta H_{\text{cav}} = \Delta G_{\text{cav}} - T \left( \frac{\partial G_{\text{cav}}}{\partial T} \right)_P \quad (113)$$

which requires the knowledge of the thermal expansion coefficient  $\alpha_P$  of the solvent.

A modified expression of  $\Delta G_{\text{cav}}$ , similar to Pierotti's and valid when the solvent is water, has been proposed by Stillinger, who incorporated in the theory also the radial distribution function of pure water and the experimental surface tension.

#### 5. Comparison of Cavitation Models

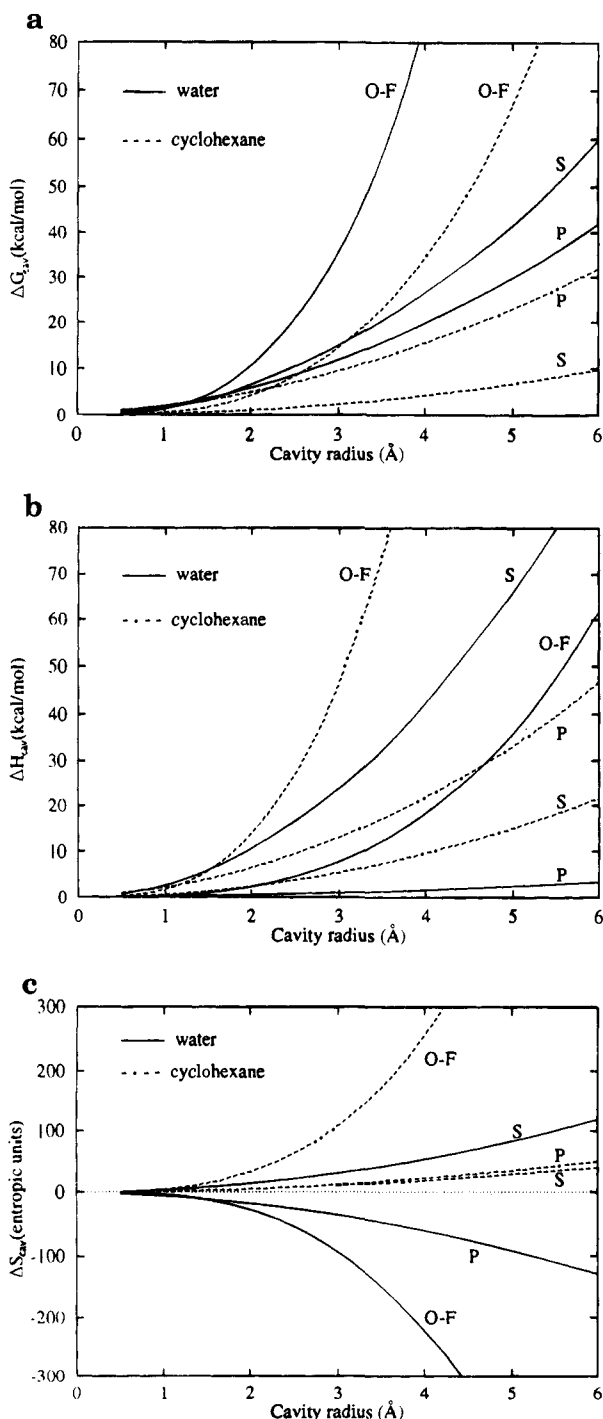
The various expressions of  $\Delta G_{\text{cav}}$  and  $\Delta H_{\text{cav}}$  have been used in many papers, giving rise to diverging conclusions. The main reason is that  $\Delta G_{\text{cav}}$  is not an observable; an evaluation of the merits of an expression for  $\Delta G_{\text{cav}}$  (as well as for  $\Delta H_{\text{cav}}$  and  $\Delta S_{\text{cav}}$ ) cannot rely on direct comparisons with thermodynamic data. On the other hand, the results of computer simulations of real liquids are influenced by the quality of the intermolecular potential.

An example of systematic analysis of thermodynamic data, comparing Pierotti's and Sinanoglu's cavitation free energies, has been presented by Abraham and Nasehzadeh<sup>487</sup> without definitive conclusions. As a general trend, Pierotti's formula works fairly well for solvents of small size, even when they are polar, protic, or hydrogen bonded (methanol, water); the deficiencies of the approach are more evident for solvents with large and not spherical molecules (such as the series of *n*-alkanes and 1-alcohols). The cavity, in Pierotti's formulation, has a spherical shape; to apply the same concepts to molecules described in terms of overlapping spheres, Claverie et al.<sup>102</sup> proposed the following expression:

$$\Delta G_{\text{cav}} = \sum_i^{\text{spheres}} \frac{A_i}{4\pi R_i^2} \Delta G_{\text{cav}}(R_i) \quad (114)$$

where each sphere, with radius  $R_i$ , contributes with a weight depending on the portion of its surface which is exposed to the solvent ( $A_i$ ). A similar formulation is used in our PCM implementation of Pierotti's expressions.

In Figure 6, parts a, b, and c, we report  $\Delta G_{\text{cav}}$ ,  $\Delta H_{\text{cav}}$ , and  $\Delta S_{\text{cav}}$  in water and cyclohexane, for a spherical solute, as functions of the cavity radius. The Oakenfull-Fenwick, Sinanoglu, and Pierotti formulas have been applied. The numerical parameters ( $\gamma$ ,  $\beta_T$ , etc.) are experimental values; they have not been calibrated to reproduce thermodynamical data. It is evident that there is not agreement among the three methods; the most striking differences are found in the  $\Delta S$  and  $\Delta H$  values, rather than in  $\Delta G$ , a common



**Figure 6.** Thermodynamical functions for the formation of a spherical cavity in water and cyclohexane, according to different models [(O-F) Oakenfull-Fenwick; (S) Sinanoglu; (P) Pierotti]: (a)  $\Delta G$ ; (b)  $\Delta H$ ; (c)  $\Delta S$ .

feature when comparing thermodynamical quantities evaluated by means of different models.

As already observed,  $\Delta G_{cav}$  is not directly measurable; estimates of  $\Delta G_{cav}$  are drawn from experimental data of various origins only on the basis of ad hoc assumptions. These assumptions are generally criticized, with the exception, perhaps, of those concerning the solubility of noble gases. In our opinion there is a need of systematic investigations of cavities of different shapes and sizes, based on MC or MD simulations with potentials made of well-defined and separate terms: repulsion, dispersion, and electrostatic (if any). Another approach is to evaluate all

terms in eq 101, in order to compare total computed solvation free energies with experimental values. We shall see in section V.E that by using Pierotti's formulas it is possible to obtain fair agreement in a number of cases, but it is not certain that this relatively good performance is not due to a compensation of errors.

The strategy of introducing empirical calibration procedures, such as the one suggested by Gogonea and Osawa, or that implemented in the AMSOL package,<sup>323</sup> surely reduces the errors, at least when the method is applied to solutes in their equilibrium geometry. (Notice that Cramer and Truhlar<sup>314-318</sup> combine  $\Delta G_{cav}$  and  $\Delta G_{dis}$  in a unique term, parameterized to reproduce  $\Delta G_{sol}$  of stable species.) However, there is no guarantee that the application to other structures, e.g. transition states, yields results of comparable accuracy.

## C. The Dispersion Energy

### 1. General Aspects

Dispersion forces are ubiquitous (in contrast with other interactions that may or may not be active, depending on specific features of the molecular systems) and play an important role in many phenomena occurring in liquid system.

Theoretical treatments of varying complexity have been proposed, ranging from quantum electrodynamics to simple phenomenological formulations. The literature on this subject is quite abundant and the analysis of the dispersion interaction is an important chapter in all books dealing with molecular interactions. Among many excellent books and reviews, we quote here a few titles,<sup>488-494</sup> reflecting in this choice our personal taste.

Exhaustive formal analyses at the standard quantum mechanical time-independent level are available for bimolecular systems and for small clusters. Less detailed, for obvious reasons, are the treatments of larger systems, namely liquids and solutions. We do not need here a complete summary of such analyses; we shall recall the few points which are sufficient for our purposes.

The dispersion terms cannot be treated within a simple Hartree-Fock description, as they are related to electron correlation effects. However, it is convenient to remark some analogies between the dispersion and the inductive interactions, which are included in a Hartree-Fock treatment.

The interaction of a molecule M and of a nearby system S (molecule, supermolecule, portion of the solvent) is represented by a Hamiltonian term,  $\mathcal{H}_{MS}$ , containing Coulombic attractions and repulsions between nuclei and electrons of M and S. We may replace  $\mathcal{H}_{MS}$  with its multipole expansion and retain for simplicity, at least in a qualitative discussion, only dipole terms. The molecule M may possess a permanent dipole (i.e., a nonvanishing mean value of the dipole operator,  $\langle \Psi_M | \mu | \Psi_M \rangle$  in the absence of S) and/or an induced dipole (i.e., a variation of  $\langle \Psi_M | \mu | \Psi_M \rangle$ , due to the electric field generated by S). The same holds for the system S. At sufficiently large M-S distances, and neglecting electron correlation, one may write the overall wave function as

**Table 8. Evolution of Microscopic Theories for Dispersion Interactions**

Two Bodies	
two atoms in vacuo	London, <sup>496</sup> Slater and Kirkwood, <sup>497</sup> Kirkwood, <sup>498</sup> Mueller <sup>499</sup>
two spherical molecules in vacuo (considering only pair interactions between constituent atoms)	Hamaker <sup>500</sup>
two spherical molecules immersed in a solvent	Hamaker <sup>500</sup>
an assembly of molecules with bond-bond interactions and approximate spatial average	Huron and Claverie <sup>501,502</sup>
Three bodies	
three atoms in vacuo	Axilrod and Teller, <sup>503</sup> Muto, <sup>504</sup> Bade and Kirkwood, <sup>505,506</sup> Kestner and Sinanoglu <sup>507</sup>
two atoms in solvent with third atom correction	Sinanoglu <sup>508</sup>
two spherical molecules in solution (pair interactions with third atom correction)	Vilker et al. <sup>509</sup>

a product of  $\Psi_M$  and  $\Psi_S$ ; in this case, the  $\mathcal{H}_{MS}$  contribution to the total energy is limited to electrostatic and inductive terms, that is, the interactions of permanent and induced dipoles (multipoles). These are the forces which are responsible for the  $\Delta G_{e1}$  contribution to the solvation free energy. Even at shorter M-S distances it is possible to discriminate such terms from others, with suitable energy decomposition schemes.<sup>88,495</sup>

With a more complex form of the wave function, taking into account the electron correlation, another interaction term arises. Consider the dipole-dipole interaction of M and S, and subtract from the dipole operators (functions of the positions of the particles) their mean values (constants). In this way the electrostatic and induction terms are eliminated. What is left is an interaction operator, which does not average to zero if we consider that the electron density and dipole of M are influenced by the "instantaneous" positions of the electrons of S, and vice versa, i.e., if we allow for a correlation in the motions of the electrons of M and S. This is the origin of the dispersion energy term.

The nonadditivity of electrostatic induction components is described by the quantum continuum models we have examined in the preceding sections. (The description of nonadditive electrostatic effects is still present in the continuum description of systems containing more than a solute molecule, as we shall discuss in section VI.D.) It would be convenient to have a computational model which introduces these nonlinear effects at the same level of accuracy as for the electrostatic ones.

The modeling of dispersion interactions in solution may be based either on a discrete molecular description of the liquid or on a continuum dielectric model. Both approaches are based upon theories for dispersion forces in simpler systems. We sketch in Table 8 the basic steps which have led to the formulation of discrete models.

In the last 15 years, there has been remarkable progress in the formal perturbation theory analysis

of interactions involving few bodies. These improvements in our understanding of dispersion and dispersion-related terms have not yet been transferred to models for liquids, as the necessary calculations are too expensive. The simple additive approach of Hamaker<sup>500</sup> is still used to support the interpretation of experimental results.

The formal theory for the continuum dielectric approach was elaborated by Lifchitz in 1955<sup>510,511</sup> (see also Dzyaloshinsky et al.<sup>512</sup>). The theory is expressed in terms of quantum electrodynamics. The continuum medium is characterized by its spectrum of complex dielectric frequencies.

Simpler formulations have been later derived from this theory (for a review see Mahanty-Ninham<sup>490</sup>). We mention here the treatments proposed by McLachlan<sup>514</sup> and by Linder,<sup>515-518</sup> both rich in suggestions for the implementation of efficient computational models for solutions.

McLachlan's approach focuses on the dispersion forces acting on two molecules immersed in a fluid and avoids the use of a cavity. This model is thus less suited to treat  $\Delta G_{dis}$  contributions in the basic model (a solute at infinite dilution) we have considered until now. Several points of McLachlan's approach could be exploited however to model more complex material systems.

Linder's approach makes explicit use of a cavity and of the reaction field. A couple of methods now in use are based on this approach, generalizing with respect to the simple case of a dipolar solute into a spherical cavity sketched by Linder in his formulation of the theory.

We have contrasted in these introductory pages the discrete and the continuum approach. In the practical implementations we shall now consider, that the differences are not so definite. In fact in several models which may be considered as belonging to the discrete approach, a continuous distribution of solvent molecules is assumed; also in models derived from the continuum electrodynamic approach, strong simplifications lead to the neglect of some features of the original theory, such as the consideration of retardation effects. However, at least one difference remains, namely that continuum-derived methods take somewhat into account nonadditive effects. We present in Table 9 the approaches we shall examine here.

## 2. Pair-Potential Energy Approaches

The discrete approaches are generally based on the use of pair potentials. The units composing a pair in the expression of a pair potential may be solute and solvent molecules, or suitable portions of them: atoms, bonds, chemical groups.

It is convenient to consider, in parallel, another potential of different physical origin, related to the quantum mechanical effects of mutual penetration of the electron charge distributions of the partners. This potential gives origin, in ground state molecules, to repulsive forces, therefore it will be called "repulsion potential". It is also sometimes called "exchange potential" because its main component in the perturbation theory of intermolecular forces is related

**Table 9. Some Methods To Compute  $\Delta G_{\text{dis}}$** 

authors	cavity	method
Huron-Claverie <sup>50</sup> 1972	general shape	pair potential + continuum distribution
van Duijnen et al. <sup>365-373</sup> 1980		direct reaction field
Rinaldi et al. <sup>519</sup> 1986	regular	reaction field
Aguilar-Olivares del Valle <sup>520</sup> 1989	general shape	reaction field
Floris-Tomasi <sup>521-523</sup> 1989	general shape	pair potential + continuum distribution
Frečer-Miertis <sup>524</sup> 1991	general shape	pair potential
Cramer-Truhlar <sup>314-318</sup> 1991	general shape	empirical
Gogonea-Osawa <sup>331,332</sup> 1993	general shape	empirical

to the consideration of exchange operators among the electrons of the two partners.

Dispersion potentials are conveniently expressed as a truncated asymptotic expansion in powers of  $1/r$  (for the delicate formal problems connected with these expansions see, e.g., Jeziorski and Kołos<sup>525</sup>). We report here an expression we shall use later

$$U_{\text{ms}}(\text{dis}) = \sum_{k=6,8,10} d_{\text{ms}}^{(k)} r_{\text{ms}}^{-k} \quad (115)$$

where the indexes  $m$  and  $s$  indicate subunits belonging to the molecules  $M$  and  $S$  respectively (as already said, in some cases  $m$  and  $s$  may coincide with  $M$  and  $S$ , respectively). We report here, for comparison, a similar expression for the repulsion term

$$U_{\text{ms}}(\text{rep}) = \sum_{k \geq 12} d_{\text{ms}}^{(k)} r_{\text{ms}}^{-k} \quad (116)$$

Often an alternative expression, more directly related to the physical interpretation of the interaction, is used

$$U_{\text{ms}}(\text{rep}) = c_{\text{ms}} e^{-\gamma_{\text{ms}} r_{\text{ms}}} \quad (117)$$

Dispersion and repulsion potentials are collected in some methods into a single term:  $U_{\text{ms}}(\text{dis-rep}) = U_{\text{ms}}(\text{dis}) + U_{\text{ms}}(\text{rep})$ .

The powers  $r_{\text{ms}}^{-k}$  in expansion 115 are based on the formal theory of two-body interactions. The first term,  $d_{\text{ms}}^{(6)}$ , may be approximated in several ways, using e.g. the well-known London formula:

$$d_{\text{ms}}^{(6)} = -\frac{3}{2} \alpha_{\text{m}} \alpha_{\text{s}} \frac{\bar{I}_{\text{m}} \bar{I}_{\text{s}}}{\bar{I}_{\text{m}} + \bar{I}_{\text{s}}} \quad (118)$$

or the more complex Slater-Kirkwood<sup>497</sup> or Mueller-Kirkwood<sup>498,499</sup> formulas. These formulas have been elaborated for atomic systems, and in these systems the mean excitation energies  $\bar{I}_{\text{m}}$  (or the first ionization potential which often replaces  $\bar{I}_{\text{m}}$ ) and the isotropic polarisabilities  $\alpha_{\text{m}}$  have a clearly defined operational meaning. In applying such approximations of  $d_{\text{ms}}^{(6)}$  to molecular systems we have to introduce important changes. The polarisabilities are no longer isotropic; they are tensorial quantities. The approximation still remains poor if the molecule contains several atoms and it is then necessary to partition the polarizable body into smaller subunits ("segments"), each characterized by its own polarizability. In the last case the quantities entering the definition of  $d_{\text{ms}}^{(6)}$  (as well as of the other  $d_{\text{ms}}^{(k)}$  coefficients) no longer have a counterpart in physical observables and must be computed with the ad hoc methods based on arbitrary

partitions of the charge distribution. If the segmentation is extended to the last factor of the London function, even more arbitrary assumptions on the mean excitation energies must be introduced. The situation is still worse for the other  $d_{\text{ms}}^{(k)}$  components.

Moreover, the calculation of  $\Delta G_{\text{dis-rep}}$  is rather complex and presents other problems. To illustrate these problems, which have been partly solved by making use of other approximations, we resume here one of the first attempts to use molecule-molecule pair potentials (Huron and Claverie<sup>501</sup>).

The reference molecule  $M$  is surrounded by a small cluster of solvent molecules  $S$ . The dispersion potential is limited to the dipole-dipole term, with the following expression:

$$U_{\text{MS}}(\text{dis}) = -\frac{x}{4} \frac{\bar{I}_{\text{M}} \bar{I}_{\text{S}}}{\bar{I}_{\text{M}} + \bar{I}_{\text{S}}} \sum_{u=1}^{B_{\text{M}}} \sum_{v=1}^{B_{\text{S}}} \{r_{uv}^{-6} \text{Tr}[\mathbf{T}_{uv} \mathbf{A}_u \mathbf{T}_{uv} \mathbf{A}_v]\} \quad (119)$$

where  $B_{\text{M}}$  and  $B_{\text{S}}$  are the number of bonds of  $M$  and  $S$ ,  $\bar{I}_{\text{M}}$  and  $\bar{I}_{\text{S}}$  are the molecular mean excitation energies,  $\mathbf{T}_{uv}$  is the tensor:

$$\mathbf{T}_{uv} = 3 \frac{\mathbf{r}_{uv}}{r_{uv}} \otimes \frac{\mathbf{r}_{uv}}{r_{uv}} - \mathbf{1} \quad (120)$$

and  $\mathbf{A}_u$  is the polarizability tensor of bond  $u$ , to be computed with ad hoc procedures (see Claverie<sup>102</sup>). Recall that in eq 119 there is no dissection of the mean excitation energy factor.

Another elegant expression for  $U_{\text{MS}}(\text{dis})$  has been proposed by Amos and Crispin.<sup>526</sup> Although elegant this expression is hard to use for liquids and gives deceiving results.

To improve the results Huron and Claverie have found it necessary to introduce in eq 119 an empirical factor  $x$ , the value of which should lead to numerical agreement between the molecule-molecule pair potential and a simpler expression based on the assumption that the interaction energy between two molecules may be reduced to the sum of independent atom-atom contributions.<sup>527,528</sup>

$$U_{\text{MS}}(\text{dis}) = \sum_{\text{m}} \sum_{\text{s}} d_{\text{ms}}^{(6)} r_{\text{ms}}^{-6} \quad (121)$$

The atom-atom potentials are here used only to get a value for the calibration factor  $x$ . The calculation of  $\Delta G_{\text{dis}}$  uses the potentials of eq 119 in a cluster of molecules mimicking the first and second solvation shell and performing an approximate Boltzmann average by modifying position and orientation of the molecules belonging to the first solvation shell.<sup>501,502,529</sup>

It is clear that this approach is unsatisfactory under many aspects. It has been in fact abandoned in favor of atom-atom isotropic potentials (eqs 115-117) with coefficients drawn from experimental data (see for example Pertsin and Kitaigorodsky<sup>528</sup>) or from calculations. (See also a recent systematic investigation by Miertüs and co-workers,<sup>524</sup> which reconsider a set of approximations, reviewed at the end of this section.)

The methods developed by Claverie and coworkers in Paris and by our group in Pisa adopt the atom-atom approximation. In both methods the average dispersion-repulsion energy may be written as

$$\langle E_{\text{dis-rep}} \rangle = \int \dots \int U(\Omega) g(\Omega) d\Omega \quad (122)$$

where  $\Omega$  stands for the set of all the coordinates of the molecules,  $g(\Omega)$  is a distribution function and  $U(\Omega)$  is expressed as a sum of two-body  $U_{\text{ms}}(\text{dis-rep})$  potentials. Expression 122 may be rewritten in terms of continuous distribution functions  $\varrho_{\text{ms}}(\mathbf{r}_{\text{ms}})$ :

$$\varrho_{\text{ms}}(\mathbf{r}_{\text{ms}}) = N_s n_s g_{\text{ms}}(\mathbf{r}_{\text{ms}}) \quad (123)$$

where  $N_s$  is the number of atoms of type  $s$  present in each solvent molecule,  $n_s$  is the macroscopic density of the solvent, and  $g_{\text{ms}}$  is a correlation function depending on the relative position of  $s$  and  $m$ . The distribution of atoms  $m$  in the solute is known; the geometry of  $M$  is kept fixed. We have

$$\begin{aligned} \langle E_{\text{dis-rep}} \rangle &= \sum_{m \in M} \sum_{s \in S} \int U_{\text{ms}}(\mathbf{r}_{\text{ms}}) \varrho_{\text{ms}}(\mathbf{r}_{\text{ms}}) d\mathbf{r}_{\text{ms}}^3 = \quad (124) \\ &= n_s \sum_{s \in S} N_s \sum_{m \in M} \sum_k d_{\text{ms}}^{(k)} \int r_{\text{ms}}^{-k} g_{\text{ms}}(\mathbf{r}_{\text{ms}}) d\mathbf{r}_{\text{ms}}^3 \end{aligned}$$

The use of eq 117 instead of eq 116 introduces minor changes in the notation.

The distribution functions  $g_{\text{ms}}(\mathbf{r}_{\text{ms}})$  are in general unknown. Experimental measurements, computer simulations, and integral equation methods (such as the RISM procedure) give estimates of angularly averaged distribution functions  $g_{\text{ms}}(r_{\text{ms}})$  and only indirect and partial information about their anisotropy. The various methods we are considering here differ in the evaluation of the  $g_{\text{ms}}(r_{\text{ms}})$  functions.

The integrals appearing in eq 124 may be safely limited to  $r_{\text{ms}}$  larger than a certain minimum value; around each center  $m$  there will be a region in which no  $s$  atoms can be found. We may consider these forbidden spaces as spheres with suitable radii  $R_{\text{ms}}$ . (One can expect  $R_{\text{ms}}$  to be somehow related to the van der Waals radii of  $m$  and  $s$ .) The union of all the spheres, with  $s$  fixed and  $m$  ranging over the whole set of  $M$  atoms, defines a cavity  $C_s$  with surface  $\Sigma_s$ . We have thus recovered the concept of molecular cavity.

When the set of the  $\Sigma_s$  surfaces is known, we may replace the volume integrals in eq 124 with surface integrals. To do so we have to define auxiliary vector functions  $\mathbf{A}_{\text{ms}}^{(k)}(\mathbf{r}_{\text{ms}})$  such that

$$\vec{\nabla} \cdot \mathbf{A}_{\text{ms}}^{(k)}(\mathbf{r}_{\text{ms}}) = d_{\text{ms}}^{(k)} r_{\text{ms}}^{-k} g_{\text{ms}}(\mathbf{r}_{\text{ms}}) \quad (125)$$

Expression 124 is thus reduced to:

$$\langle E_{\text{dis-rep}} \rangle = n_s \sum_{s \in S} N_s \sum_{m \in M} \sum_k \int_{\Sigma_s} \mathbf{A}_{\text{ms}}^{(k)} \cdot \mathbf{n}_\sigma d\sigma \quad (126)$$

where  $\mathbf{n}_\sigma$  is the outer normal to the surface  $\Sigma_s$  at position  $\sigma$ . This integral may be evaluated numerically with a suitable tessellation of the surface (see later).

The explicit expressions of the  $\mathbf{A}_{\text{ms}}^{(k)}$ 's are different in the several versions of the method we are here considering; however, they are always recast in a simpler form:

$$\mathbf{A}_{\text{ms}}^{(k)}(\mathbf{r}_{\text{ms}}) = f_{\text{ms}}^{(k)}(r_{\text{ms}}) \mathbf{r}_{\text{ms}} \quad (127)$$

where an isotropic function  $f_{\text{ms}}^{(k)}$  is introduced.

In the several versions of Claverie's method<sup>50,246,530</sup> the integrals of eq 124 are computed numerically using a Koborov grid<sup>531</sup> (maximum number of points for each sphere defining  $C_s$ , 610). In the versions of our PCM set of programs, the tessellation of the cavity is of the same type used to compute  $\Delta G_{\text{el}}$  (see section III.D.4); the maximum number of points for each sphere defining  $C_s$  is 60.

The atom-atom isotropic functions  $g_{\text{ms}}(r_{\text{ms}})$  are replaced in the Claverie approach by calibration factors  $K_{\text{ms}}^{\text{D}}$  and  $K_{\text{ms}}^{\text{R}}$ , respectively for the dispersion and the repulsion contributions; in this case the  $f_{\text{ms}}^{(k)}(r_{\text{ms}})$  functions assume a simple analytical form. The numerical values of the  $K_{\text{ms}}$  factors are obtained in preliminary calculations in which an appropriate number of solvent molecules (90-150) are described as rigid spheres in a close packing. The  $K_{\text{ms}}$  factors are not transferable; they must be reevaluated for each new couple of molecules; approximate expressions are however provided to get simpler computational recipes.<sup>50</sup>

A simpler formulation based on a calibration factor not depending on the solute has been proposed by Kihara and John;<sup>532</sup> apparently this method has not found many applications.

In the PCM computational scheme<sup>521-523</sup> we discard the use of calibration factors, preferring to adopt explicit expressions for  $g_{\text{ms}}(\mathbf{r}_{\text{ms}})$ . In the simplest version, the one we recommend for routine calculations, the so-called "uniform approximation" is adopted. Each  $g_{\text{ms}}(\mathbf{r}_{\text{ms}})$  function is reduced to a step function:

$$\begin{aligned} g_{\text{ms}}(\mathbf{r}_{\text{ms}}) &= 0 \quad \text{for } \mathbf{r}_{\text{ms}} \in C_s \\ g_{\text{ms}}(\mathbf{r}_{\text{ms}}) &= 1 \quad \text{for } \mathbf{r}_{\text{ms}} \notin C_s \end{aligned} \quad (128)$$

The  $\mathbf{A}_{\text{ms}}^{(k)}$  functions have in this case a simple analytical expression:

$$\mathbf{A}_{\text{ms}}^{(k)}(\mathbf{r}_{\text{ms}}) = \frac{d_{\text{ms}}^{(k)}}{(k-3)r_{\text{ms}}^k} \mathbf{r}_{\text{ms}} \quad (129)$$

An alternative formula for  $\mathbf{A}_{\text{ms}}^{(\text{rep})}$  is based on eq 117:

$$\mathbf{A}_{\text{ms}}^{(\text{rep})}(\mathbf{r}_{\text{ms}}) = -C_{\text{ms}} \left[ \frac{1}{\gamma_{\text{ms}} r_{\text{ms}}} + \frac{2}{\gamma_{\text{ms}}^2 r_{\text{ms}}^2} + \frac{2}{\gamma_{\text{ms}}^3 r_{\text{ms}}^3} \right] e^{-\gamma_{\text{ms}} r_{\text{ms}}} \mathbf{r}_{\text{ms}} \quad (130)$$

(Note that in ref 522, this formula contains a couple of misprints.)

As a test we have compared the  $\Delta G_{\text{dis-rep}}$  evaluated in the uniform approximation, with the results obtained using numerical  $g_{\text{ms}}(r_{\text{ms}})$  functions; the latter were derived from RISM-HNC calculations, based on the same two-body potential<sup>523</sup> of eqs 115 and 116, with the same  $d^{(k)}$  coefficients. In this case the evaluation of the  $A_{\text{ms}}^{(k)}$  functions is preceded by a numerical one-dimensional integration. This analysis also permits one to check (and essentially to confirm) the values of the  $R_{\text{ms}}$  radii which define the cavity  $C_s$ , previously based on van der Waals radii.<sup>521</sup> Similar unpublished analyses based on Monte Carlo derived  $g_{\text{ms}}$  functions confirm the above reported conclusions.

The coupling of continuum calculations with RISM and computer simulation approaches also gives information about the last important methodological point we are going to discuss.

The quantity we have computed is actually an internal energy. A well-known technique to get a free energy from an internal energy is based on the so-called charging process, previously discussed in section IV.A in connection with the electrostatic problem. Let us recall it here briefly. The solute-solvent potential  $U(\Omega)$  is multiplied by a parameter  $\lambda$ , ranging from 0 (no interaction) to 1 (full or unchanged interaction);  $g_{\text{S}}(\Omega; \lambda)$  is the distribution function for the attenuated potential  $\lambda U(\Omega)$ . The free energy change is given by the integral:

$$\Delta G = \int_0^1 d\lambda \left[ \int d\Omega U(\Omega) g_{\text{S}}(\Omega; \lambda) \right] \quad (131)$$

According to the picture given by the charging parameter method, a solvent reorganization process accompanies the progressive turning on of the interaction. Equation 131 is quite general;  $G$  and  $U(\Omega)$  may be total values or partial contributions. In the latter case,  $g(\Omega; \lambda)$  is the distribution resulting from a full interaction of some kind (for instance, cavitation and electrostatic) plus an attenuated interaction of some other kind (for instance, dispersion-repulsion). Actually, we have adopted a partition of the charging process into three separate steps: cavitation, electrostatic, and dispersion-repulsion. The use of the SPT (Pierotti's formulas) and of the classical electrostatic picture for the reaction field corresponds to integrations with suitable (and distinct) charging parameters to get  $\Delta G_{\text{cav}}$  and  $\Delta G_{\text{el}}$ .

The description of the reorganization accompanying dispersion-repulsion charging processes presents some special problems, as Claverie and co-workers first pointed out.<sup>246</sup> In their short analysis, they give a clear view of the situation, pointing out that the most delicate cases are those concerning nonpolar solutes, without giving however any suggestion for the solution of this problem.

A set of isotropic  $g_{\text{ms}}(r_{\text{ms}})$  functions, computed with the RISM-HNC method, with the same two-body potentials as above, but containing now an explicit charging parameter  $\lambda$ , permits one to get, via the PCM pair dispersion procedure outlined above, a numerical solution of eq 131. The values found for a few hydrocarbons in water (and methanol) are quite encouraging. The integrand is almost constant, with a weak linear dependence on  $\lambda$ . The approximation

$$\Delta G_{\text{dis-rep}} \approx E_{\text{dis-rep}} \quad (132)$$

introduces errors lower than 5% and decreasing with the size of the hydrocarbon. Moreover, the  $\Delta G_{\text{dis-rep}}$  values obtained in such a way are quite similar to the  $\langle E_{\text{dis-rep}} \rangle$  values obtained with the uniform approximation, which already have, by definition, the status of a free energy.

The continuum approach based on atomic pair-potential functions appears to be, especially in the PCM version, an efficient computational method, able to yield reliable  $\Delta G_{\text{dis-rep}}$  at least for closed-shell solutes. It is worth reporting some data about the dissection of this quantity into its  $k$  components ( $k = 6, 8, 10$  dispersion terms, negative;  $k = 12$  repulsion term, positive). For a sample of 42 hydrocarbons in water we found that  $|\Delta G_{\text{rep}}|$  is in the average 15.8% of  $|\Delta G_{\text{dis}}|$ , with a standard deviation of 0.93. The three components of  $\Delta G_{\text{dis}}$  with  $k = 6, 8, 10$  contribute to the total according to the following percent ratios, respectively;  $90.01 \pm 0.32\%$ ,  $8.60 \pm 0.26\%$ ,  $1.38 \pm 0.10\%$ . The  $\Delta G_{\text{dis-rep}}$  values have a good linear correlation with the van der Waals surface,  $S_M$ , and the volume  $V_M$  of the hydrocarbons:<sup>522</sup>

$$\Delta G_{\text{dis-rep}} = -0.03208 - 0.0767S_M \quad (133)$$

( $R = 0.9959$ ,  $\sigma = 0.345$  kcal/mol,  $n = 21$ )

$$\Delta G_{\text{dis-rep}} = -1.26850 - 0.07469V_M \quad (134)$$

( $R = 0.9969$ ,  $\sigma = 0.302$  kcal/mol,  $n = 21$ )

Both surface and volume appear to be good predictors of  $\Delta G_{\text{dis-rep}}$  for hydrocarbons in water (as well as in methanol and in cyclohexane), and in passing to larger globular hydrocarbons  $S_M$  probably will be a better predictor, as other not fully analyzed tests indicate. Less abundant is the computational evidence we have for other solvents and for polar solutes, but the results should be comparable to those shown here.

A last point which deserves mention is the quality of the atom-atom potentials. There are many sets of pair potentials available in the literature (space limitations prevent a survey). The computed  $\Delta G_{\text{dis-rep}}$  values are not insensitive to the choice of the pair potential; attention should be paid to a proper selection of parameters. The  $\Delta G_{\text{dis-rep}}$  values reported above for hydrocarbons in water were computed with potentials supplied by Vignér-Maeder and Claverie,<sup>533</sup> but other sets give similar results.

It would be convenient, however, to reconsider the question of the pair potentials again. Pair potentials drawn from experimental data could describe, in principle, a portion of the nonadditive dispersion effects we mentioned at the beginning of this section.

**Table 10. Comparison of  $\Delta G_{\text{dis-rep}}$  Values (kcal/mol) Obtained with Approximations A–E of Freer et al.<sup>524</sup> for a Set of Solutes in Water**

solute	A	B	C	D	E
CH <sub>4</sub>	-24.58	-8.56	-5.10	-7.05	-6
C <sub>2</sub> H <sub>6</sub>	-34.35	-10.44	-6.47	-9.02	-8
C <sub>3</sub> H <sub>8</sub>	-38.18	-11.48	-7.04	-9.98	-9
C <sub>4</sub> H <sub>10</sub>	-39.91	-12.32	-7.60	-10.66	-10
H <sub>2</sub> O	-4.21	-4.62	-3.40	-4.45	-4
CO <sub>2</sub>	-4.43	-6.47	-4.64	-6.13	-5
H <sub>2</sub> CO	-8.77	-6.71	-4.72	-6.95	-6
NH <sub>3</sub>	-11.72	-6.40	-5.08	-6.71	-6
HNCO	-7.89	-7.92	-6.01	-7.94	-7
CH <sub>3</sub> OH	-13.38	-7.65	-5.22	-7.12	-6
C <sub>2</sub> H <sub>5</sub> OH	-21.40	-9.51	-6.32	-9.04	-8
C <sub>3</sub> H <sub>7</sub> OH	-26.70	-11.64	-7.01	-9.95	-9
CH <sub>3</sub> NH <sub>2</sub>	-17.40	-7.97	-5.97	-8.18	-7

A carefully planned application of the reaction field methods that we shall examine later could give an independent set of parameters with explicit inclusion of nonadditive effects. We have found this strategy quite effective for introducing nonadditive classical induction effects in two-body potentials to be used in ion–water simulations,<sup>534</sup> a subject that will be treated more in detail in section VI.D.

The discrete pair potential approach has been the subject of a recent effort by Miertüs and coworkers,<sup>524</sup> to collect a representative set of models in a coherent ladder of approximations. The analysis is limited to the dipole–dipole dispersion term, supplemented by a  $r^{-12}$  repulsion term for the solvent molecules of the first solvation layer. These authors define five levels of approximation, using: (A) molecule–molecule-type formulas, (B) atom(solute)–molecule formulas, (C) atom–atom formulas, (D) atom–atom-type formulas, with inclusion of specific mutual solute–solvent molecular orientations, and (E) a combination of approximation D, for the first shell, and approximation C (rotationally averaged quantities) for the other shells.

London-type formulas are used for all models, with parameters drawn from quantum mechanical calculations according to methods detailed in ref 98. The solvent is modeled in layers (10 is the maximum number of layers considered in the calculations, but convergence is completely achieved within four layers). Solvent packing numbers for solvent molecules (or atoms) in each solvation shell are introduced, with special algorithms to discriminate between accessible and sheltered positions of each atomic van der Waals surface.<sup>354</sup> The five approaches have been coded and the program is operative. We report in Table 10 a small selection of the published results concerning water as solvent.

Approximation A is quite poor and approximation B gives too negative values, especially for solvents other than water. Approximations C–E give results of comparable magnitude, which satisfy the expected trends for homologous series in different solvents. The values obtained with these approximations are comparable with those obtained using the PCM pair dispersion procedure (for hydrocarbons the best agreement is found with approximation C).

### 3. Reaction Field Based Approaches

A simple version of this approach is the direct reaction field model (DRF), implemented by van

Duijnen and co-workers;<sup>365–373</sup> we have already considered the electrostatic DRF model in section IV.B.5.

The method is based on a model in which a quantum mechanical solute interacts with a medium described as a collection of point-polarizable dipoles. The interaction term in the Hamiltonian  $\hat{\mathcal{H}}_M = \hat{\mathcal{H}}_M^{(0)} + \hat{\mathcal{H}}^{\text{DRF}}$  is written as

$$\hat{\mathcal{H}}^{\text{DRF}} = -\frac{1}{2} \sum_{ij} \sum_{p,q} \mathbf{F}_{ip}^{\dagger} \alpha_{pq} \mathbf{F}_{jq} \quad (135)$$

where  $i$  and  $j$  run over the particles of the solute,  $p$  and  $q$  over the external polarizable dipoles (see also section IV.B.5).  $\mathbf{F}_{ip}$  is the field generated by particle  $i$  (electron or nucleus) at point  $p$ . The  $\alpha_{pq}$  tensor gives the moment induced at  $q$  by a field applied to point  $p$ ; the nondiagonal terms  $p \neq q$  arise from the interaction between induced dipoles.

In contrast with the reaction potential operator  $\hat{\mathcal{V}}_0$  we have used in preceding sections, defined in terms of an expectation value,  $\hat{\mathcal{H}}^{\text{DRF}}$  is a linear operator embodying, in principle, induction as well as dispersion contributions. What is left after subtracting the classical induction (or polarization) terms, is considered a measure for dispersion interactions (in the dipole–dipole approximation). The dispersion term is here overestimated because this direct evaluation neglects the frequency dependence of polarizability, which implies a time lag in the induced dipole with respect to the applied field. The overestimation of  $E_{\text{dis}}$  may be put under the form of an upper bound which is a generalization of a similar upper bound for two spherical systems (the Alexander upper bound). According to the authors, a good guess for the correction factor should be near 2; they support this guess with tests on two H atoms and two harmonic oscillator models and with test calculations on the water dimer.

Ángyán and Jansen<sup>535</sup> have tested the performances of the DRF method on a set of atom–atom systems. They found that the correction factor ranges between 2 and 15 and give some hints for the explanation of this apparently erratic behavior. It must be considered that in van Duijnen's idea the DRF is a simple method to get from Hartree–Fock calculations an estimate of the dispersion energy for large systems in solution. This being the goal, the approach may endure heavy empirical corrections if experience will suggest their introduction.

The use of models based on the concept of a reaction field coupled to that of a cavity has been advocated, as said at the beginning of this section, by Linder.<sup>515–518</sup> Linder worked out this model for the case of a polarizable point dipole in a spherical cavity.

More realistic versions of Linder's model have been elaborated by Rinaldi, Costa Cabral, and Rivail<sup>519</sup> and by Aguilar and Olivares del Valle.<sup>520</sup> The two approaches are inserted in the framework of the multipole expansion model of the Nancy group, and in the ASC model (in the PCM formulation), respectively. This makes a noticeable difference in the practical implementation and in calculations, but the formal elaboration is similar in the two cases, and

we may give here a unified sketch of the formalism, contrasting later the two realizations.

The reduction of Linder's theory to a form suited for molecular calculations given by the two groups allows one to write an effective Hamiltonian of the type:

$$\hat{\mathcal{H}}_M = \hat{\mathcal{H}}_M^{(0)} + \hat{\mathcal{V}}_o + \hat{\mathcal{V}}_{\text{dis}} \quad (136)$$

The  $\hat{\mathcal{V}}_o$  operator regards the classical electrostatic polarization terms and has here the same definition given in section II.A. We recall that it depends on the solute charge distribution  $\varrho_M$  and on the static dielectric constant  $\epsilon_0$ . The term added here,  $\hat{\mathcal{V}}'_{\text{dis}}$ , depends on  $\varrho_M$  and on the dielectric permittivity  $\epsilon_\infty$ , the square of the optical refractive index extrapolated to infinite frequency.

$\hat{\mathcal{V}}_{\text{dis}}$  is formulated in the framework of the London approximation, that is, in terms of the mean excitation energies of the solvent and solute molecules, and of the solute multipole polarizability  $\alpha$ . In addition,  $\hat{\mathcal{V}}_{\text{dis}}$  will also depend on the coefficients of the second rank the reaction field tensor  $\mathbf{g}$ . Using a spherical tensor formalism, we have

$$\hat{\mathcal{V}}_{\text{dis}} = \sum_{p,q} G_{pq} \alpha_{pq} \quad (137)$$

$$p = \{l_1, m_1\} \quad -l_1 \leq m_1 \leq l_1 \quad 0 \leq l_1 \leq \infty$$

$$q = \{l_2, m_2\} \quad -l_2 \leq m_2 \leq l_2 \quad 0 \leq l_2 \leq \infty$$

The  $G_{pq}$  elements collect the transition energy factor and the components of the reaction field tensor  $\mathbf{g}$ :

$$G_{pq} = -\frac{1}{8} \frac{\bar{E}_M \bar{E}_S}{\bar{E}_M + \bar{E}_S} g_{pq}(\epsilon_\infty) \quad (138)$$

The  $\alpha_{pq}$  are elements of the matrix

$$\alpha = 8\mathbf{Q}\mathbf{D}^{-1}\mathbf{Q} \quad (139)$$

where

$$Q_{KL} = \langle M_K M_L \rangle - \langle M_K \rangle \langle M_L \rangle \quad (140)$$

and

$$D_{KL} = \langle \nabla^2 M_K M_L \rangle \quad (141)$$

with  $M_K$  and  $M_L$  denoting a multipole moment operator.

The  $\mu - \nu$  element of  $\hat{\mathcal{V}}_{\text{dis}}$ , in the Hartree-Fock formulation, and referred to the basis set functions  $\xi_\mu$  and  $\xi_\nu$ , may be written in the following form:

$$\begin{aligned} F_{\mu\nu}^{\text{dis}} = & \sum_{p,q} G_{pq} \left\{ \sum_K \left[ \langle \mu | M_p M_K | \nu \rangle R_{Kq} + \right. \right. \\ & \left. \left. R_{pK}^\dagger \langle \mu | M_K M_q | \nu \rangle - \sum_n R_{pK}^\dagger \langle \mu | \nabla^2 M_K M_q | \nu \rangle R_{nq} \right] - \right. \\ & \left. \frac{1}{2} \sum_K \left[ \sum_{\lambda,\sigma} P_{\lambda\sigma} \langle \mu | M_p | \lambda \rangle \langle \nu | M_K | \sigma \rangle + \right. \right. \\ & \left. \left. R_{pK}^\dagger \langle \lambda | M_K | \mu \rangle \langle \sigma | M_q | \nu \rangle \right] \right\} \quad (142) \end{aligned}$$

$R_{Kq}$  and  $R_{pK}^\dagger$  are elements of the intermediate ma-

trices  $\mathbf{R} = \mathbf{Q}\mathbf{D}^{-1}$  and  $\mathbf{R}^\dagger = (\mathbf{Q}\mathbf{D}^{-1})^\dagger$ . Note that the elements collected in the second summation in  $K$  depend on the density matrix elements  $P_{\lambda\sigma}$ :

$$\hat{\mathcal{V}}_{\text{dis}} = \frac{\bar{E}_M \bar{E}_S}{\bar{E}_M + \bar{E}_S} \sum_i [\hat{\mathcal{A}}(i) + \hat{\mathcal{B}}(i)] \quad (143)$$

The  $\hat{\mathcal{A}}$  operators correspond to the first summation of eq 142, and the  $\hat{\mathcal{B}}$  operators to the second summation:

$$\hat{\mathcal{A}}(i) = 2 \sum_{p,q} G_{pq} \sum_K \left[ M_p(i) M_K(i) R_{Kq} + R_{pK}^\dagger M_K(i) M_q(i) - \sum_n R_{pK}^\dagger \nabla^2 (M_K(i) M_q(i)) R_{nq} \right] \quad (144)$$

$$\hat{\mathcal{B}}(i) = 2 \sum_{p,q} G_{pq} \sum_K \left[ -\frac{1}{2} \sum_{\lambda,\sigma} P_{\lambda\sigma} (M_p(i) | \lambda \rangle \langle \sigma | M_K(i) + R_{pK}^\dagger M_K(i) | \lambda \rangle \langle \sigma | M_q(i)) \right] \quad (145)$$

This formulation singles out a term [the sum of the one electron operators  $\hat{\mathcal{B}}(i)$ ] which depends on the electron density matrix. Both approaches, by the Nancy and the Badajoz groups, try to avoid, as much as possible, external parameters. So the components of  $\alpha$  are computed with a variational procedure using the same basis set used for solvation processes. The Rivail-Cartier method<sup>536</sup> has been used in both cases. The mean excitation energies are replaced by the first ionization potential in the Koopmans approximation, computed with MINDO/3 wavefunctions in ref 519 and with a 6-31G basis set in ref 520.

The differences between the Nancy and Badajoz approaches are related to the different general strategies of the solvation procedures followed by the two groups. Rivail and Rinaldi use multipolar expansions in elliptical cavities. The multipole approach implicit in eq 137 may be developed without changes. The calculations reported in ref 519 refer to the use of the dipole term ( $l = 1$ ) alone, but the extension to higher terms is straightforward. In fact in ref 537, which is a preliminary communication, giving much more details than those here reported about the formal justification of the method, a study of the convergency of  $\Delta G_{\text{dis}}$  with  $l$  ranging from 1 to 4 is reported. (In this communication,  $\Delta G_{\text{dis}}$  is computed separately and not included in the Hamiltonian.)

Also the Badajoz papers limit the treatment of polarizability to the dipole term. So  $\alpha$  and the related  $\mathbf{Q}$  and  $\mathbf{D}$  matrices, eqs 140 and 141, are expressed in terms of dipole moment operators only. The method is however conceived as a part of the PCM procedure, therefore the next step is to define a new apparent charge surface distribution,  $\sigma_{\text{dis}}$ , which derives from the fluctuating electric field and is computed with the same prescriptions as the electrostatic contribution (see section III.D). The first term,  $\sigma_{\text{dis}}^{00}$ , may be computed in two different ways: the first consists of following the same routes as in the calculation of  $q^{00}$  (see eq 37 and following), but applying a dielectric constant  $\epsilon_\infty$ ; the second consists of defining a continuous uniform distribution of atomic polarizability  $\alpha(s)$  ( $s$  stays for the solvent



**Table 11. Solvation Energies (kcal/mol) for Some Solutes in Water (6-31G Calculations)**

solute	method	$\Delta G_{el}^a$	$\Delta G_{dis}^a$	$\Delta G_{el} + \Delta G_{dis}^a$	$\Delta G_{el} + \Delta G_{dis}^b$
H <sub>2</sub> O	SCF	-9.14	-3.92	-13.06	-13.09
	PTE3	-8.58	-4.23	-12.82	-12.78
NH <sub>3</sub>	SCF	-5.60	-4.88	-10.48	-10.50
	PTE3	-5.41	-5.32	-10.73	-10.63
HF	SCF	-10.43	-3.18	-13.62	-13.68
	PTE3	-9.72	-3.44	-13.16	-13.22
CH <sub>4</sub>	SCF	-0.57	-8.16	-8.73	-8.65
	PTE3	-0.30	-9.01	-9.30	-8.82

<sup>a</sup>  $\Delta G_{el}$  and  $\Delta G_{dis}$  separately computed from the same  $\rho_M$ , only  $\Delta G_{el}$  is included the effective Hamiltonian. <sup>b</sup> Both  $\hat{\mathcal{V}}'_\sigma$  and  $\hat{\mathcal{V}}'_{dis}$  included in the effective Hamiltonian.

atoms) and in applying the Green theorem as we have explained in connection with eq 125 and following. It is interesting to note that the two procedures give numerical results in fairly good agreement. The use of a  $\sigma_{dis}$  distribution spread on the solute cavity corresponds to the use of an infinite multipole expansion in the evaluation of  $\rho_M$ .

This generality is paid by the introduction of a third iterative cycle in the PCM procedure, this last being performed at fixed  $\rho_M$  and  $\sigma$  and affecting the  $\hat{\mathcal{B}}(i)$  component of eq 143. The iterative computational machinery may be thus resumed.<sup>427</sup> The interaction operators of the Hamiltonian 136 are supplemented with a couple of indexes:

$$\hat{\mathcal{H}}_M = \hat{\mathcal{H}}_M^{(0)} + \hat{\mathcal{V}}'_\sigma^{(kl)} + \hat{\mathcal{V}}'_{dis}{}^{(klm)} \quad (146)$$

The outer cycle regards SCF calculations performed at  $l$  and  $m$  fixed values; at each step  $\hat{\mathcal{V}}'_\sigma$  and  $\hat{\mathcal{V}}'_{dis}$  are updated. The second cycle regards the determination of  $\hat{\mathcal{V}}'_\sigma$  ( $l$  varies,  $k$  and  $m$  are fixed) and does not involve SCF calculations; these two cycles correspond to the normal PCM iteration cycles (see section IV.B.3). The third inner cycle determines  $\hat{\mathcal{V}}'_{dis}$  ( $m$  varies at given  $k, l$ ). The modification induced by this cycle (no additional SCF calculations) mainly concerns the  $\hat{\mathcal{B}}(i)$  operator of eq 143.

Olivares del Valle and Aguilar proceed a step further. They introduce in this algorithm the solute electron correlation calculated at the PTE3 level (see section IV.D), i.e. using third-order many-body perturbation theory for the description of the wave function and of the ensuing molecular energy, while the interaction terms are computed at the SCF level. We compare in Table 11 a few numerical values for small solutes in water (from ref 427). Apparently the introduction of  $\hat{\mathcal{V}}'_{dis}$  in the effective Hamiltonian does not produce great changes with respect to the evaluation of  $\Delta G_{dis}$  as a separate and additive contribution (compare the last two columns). The introduction of electron correlation effects leads to changes of modest entity, ranging from -1 to 2%. Extrapolation of these values to larger systems and nonequilibrium geometries (e.g. reaction transition states) and to excited states is for the moment impossible.

To conclude, both the Nancy and the Badajoz reaction field methods appear to give sensible results and the approach deserves further studies. In fact, many weak points could be corrected, for instance the use of orbital energies in the London-like formula.

Also notice that repulsion contributions to  $\Delta G$  are not taken into account: this limitation may be more or less important according to the strength of the attractive (electrostatic and/or dispersive) interactions. Improved continuum methods may be suitable for reference studies, i.e. to check and to ameliorate the empirical pair potential methods we have already examined and the surface-only procedures we shall examine in the next section; the latter are much faster, but they require renewed calibrations and tests when applied to new classes of solvents.

#### 4. Cavity Surface-Dispersion Energy Relationships

The idea of relating the dispersion energy to the surface of the cavity is quite appealing. This approach may be connected to an older one (still in use and subject to recent improvements), that relates the total solvation free energy to the molecular surface.<sup>206,207,447,538-555</sup>

$$\Delta G_{sol} = \sum_k \gamma_k \Sigma_k + C \quad (147)$$

We have here partitioned the surface area  $\Sigma$  into group components,  $\Sigma_k$ . The factor  $\gamma_k$  has been associated, in the earlier works, to the surface tension.

We shall not introduce here an analysis of this chapter of the computational and modelistic theory of solvation thermodynamic functions, rich of interesting remarks and analyses, and useful when applied to specific classes of solute-solvent systems.

The analyses reported thus far make evident that expressions such as eq 147 should be more simply parametrized if limited to the dispersion energy  $\Delta G_{dis}$ . In principle it is possible to model also  $\Delta G_{el}$  via surface contributions (see section IV.B.3), but the very nature of Coulombic interactions complicates the parametrization, each contribution depending on the nature of the vicinal groups and on the topography of the molecule. (The electric field acting on the surface element  $\Sigma_k$  also depends on molecular groups not directly linked to  $k$ , but near in space.)

The dispersion forces decay as  $r^{-6}$ ; therefore, a partitioning such as that of eq 147 is less dependent on the nature and spatial distribution of the nearby solute groups. Numerical evidence for this relative insensitivity to the molecular remainder has been also provided by Floris et al.<sup>522</sup> and by Bachs et al.<sup>90</sup>

The description of  $\Delta G_{dis}$  in terms of contributions proportional to the area has been proposed by Still et al.<sup>220</sup> and employed by Cramer and Truhlar<sup>314-318</sup> and by Gogonea and Osawa.<sup>331,332</sup> We shall give here a few additional details about the strategy followed by Cramer and Truhlar, because the corresponding AMSOL program<sup>323</sup> is widely distributed and it will probably be used by some readers of this review. The hydration free energy is written as

$$\Delta G_{tot}(aq) = \Delta G_{ENP}(aq) + \Delta G_{CDS}(aq) \quad (148)$$

We are here interested in  $\Delta G_{CDS}(aq)$ . With this index the authors emphasize that the term contains cavitation, dispersion, and solvent structural reorganization effects. Actually, as we shall see later, it contains other terms as well. The definition of  $\Delta G_{CDS}$  is

$$\Delta G_{\text{CDS}} = \sum_k \sigma_k A_k(\beta_k) \quad (149)$$

$A_k$  is the solvent-accessible surface area depending on atom  $k$ . It corresponds to the portion of a sphere of radius  $\beta_k = R_k^{\text{vdW}} + R_S^{\text{vdW}}$  exposed to the solvent. In other words, it is the portion assigned to  $k$  of the surface  $\Sigma$  of the same cavity used in the PCM pair contribution expression for  $\Delta G_{\text{dis}}$  in its simplest version.<sup>521-523</sup> The parameter  $\sigma_k$  is interpreted as a surface tension but the  $\sigma_k$  values are obtained by a fitting procedure, and the correspondence with experimental surface tension values is lost. In the different versions of the AMSOL program there are different parameters to be simultaneously optimized with reference to experimental  $\Delta G_{\text{sol}}$  values; namely three parameters,  $\rho_k^{(0)}$ ,  $\rho_k^{(1)}$ , and  $q_k^{(0)}$ , related to the electrostatic contribution  $\Delta G_{\text{ENP}}(\text{aq})$ , and the parameter  $\sigma_k$  for  $\Delta G_{\text{CDS}}$ . The limitation to water as solvent simplifies the multiple regression procedure. The authors remark that it is effectively possible to separate the optimization of the  $\sigma_k$ 's from the set of the other three parameters. There are now available  $\sigma_k$  parameters for  $k = \text{H, C, N, O, F, P, S, Cl, Br, and I}$ .<sup>318</sup>

We have reported the definition of  $\Delta G_{\text{CDS}}$  in the section concerning dispersion contributions because it seems to us that there is a tendency in some users of the AMSOL program to assimilate  $\Delta G_{\text{CDS}}$  to dispersion contributions. Actually  $\Delta G_{\text{CDS}}$  contains all the contributions not described by  $\Delta G_{\text{ENP}}$ : two terms of opposite sign, namely  $\Delta G_{\text{cav}} + \Delta G_{\text{rep}}$  and  $\Delta G_{\text{dis}}$ , plus the rotational and vibrational contributions to  $\Delta G_{\text{sol}}$ . Cramer and Truhlar clearly emphasize this point, with the additional proviso that vibrational contributions (including zero-point energy differences) could be computed separately. As to these terms there is always an ambiguity in computational methods with parameters obtained by fitting experimental energies. The tendency is now to supplement semiempirical molecular energies in vacuo with a separate evaluation of zero-point contributions (or vibrational contribution to the free energy, when this last quantity is considered); Cramer and Truhlar foresee a similar evolution for semiempirical calculations in water.

Gogonea and Osawa<sup>331,332</sup> separate the cavitation and dispersion contributions. For the latter, an approach based on a continuum + pair contribution expression is considered as preferable, but for hydrocarbons they use an empirical formula:

$$\Delta G_{\text{dis-rep}} = \sum_k \nu_k A_k + \nu_0 \quad (150)$$

with parameters ( $k = \text{H and C}$ ) obtained by fitting the values of

$$\Delta G_{\text{dis-rep}} = \Delta G_{\text{sol}} - \Delta G_{\text{cav}} \quad (151)$$

The correlation coefficient is satisfactory;  $r = 0.9982$ .

Bachs et al.<sup>90</sup> apply the same formula, eq 137, with  $\nu_0 = 0$ , to fit theoretical results computed with the pair potential method of Floris and Tomasi.<sup>521-523</sup>

They obtain a good correlation for a set of 23 polar and nonpolar molecules in water.

## D. The Molecular Motion Energy Contributions

Coming back to eq 99 we have to describe the other component of  $\Delta G_{\text{sol}}$ , namely:

$$\Delta G_{\text{mm}} = \Delta G_{\text{sol}} - W(\text{M/S}) =$$

$$RT \ln \left( \frac{q_{\text{rot,g}} q_{\text{vib,g}}}{q_{\text{rot,s}} q_{\text{vib,s}}} \right) - RT \ln \left( \frac{n_{\text{M,g}} \Lambda_{\text{M,g}}^3}{n_{\text{M,s}} \Lambda_{\text{M,s}}^3} \right) \quad (152)$$

Let us start with the last term.  $\Lambda_{\text{M}}^3$  is the momentum partition function and  $n_{\text{M}}$  is the numeral density of M, in the gaseous and in the liquid state. We shall use as reference states the ideal gas at 1 mol/L concentration and the ideal solution at the same concentration; in this case the two densities are equal. If other standard states are used there will be an additional term, which is easy to compute. For example, if the standard states refer to an ideal gas at 1 atm and to a hypothetical dilute ideal solution in which the mole fraction of M is unity, this additional term will be:  $RT \ln(RT n_{\text{S}})$ , where  $n_{\text{S}}$  is the number density of the solvent S.

Ben-Naim<sup>442,443</sup> calls the quantity  $-RT \ln(n_{\text{M}} \Lambda_{\text{M}}^3)$  "liberation free energy" and interprets it as the additional amount of free energy (entropic contribution) gained when M is allowed to wander into the entire volume at its disposal in the reference state. In our simple basic model (infinite isotropic solutions, no chemical association/dissociation processes) this contribution is equal to zero. Obviously there will be problems in which these assumptions are no more valid (e.g., the crossing of a membrane, a dissociation process). The translational contribution here considered has been treated in the past by invoking further modelistic considerations. The translational contribution may be reduced to the logarithm of the ratio between the volumes available in the gas phase and in solution:  $RT \ln(V_{\text{gas}}/V_{\text{sol}})$ . The question is whether the entire volume of the solvent is available for M. In crystals or glasses each molecule is confined into a specific site and motions are limited to a "free space"  $v_{\text{M}}$ , with dimensions depending upon the characteristics of the interaction potential (for a water molecule in liquid water  $v_{\text{M}}$  has been estimated by Némethy and Scheraga<sup>556</sup> to be 0.26 cm<sup>3</sup>/mol). In the ideal gaseous phase there are no limitations to the motion. Because of this additional freedom gas molecules are said to have a "communal entropy" not possessed by molecules in a rigid matrix. In solution a part or the whole of the communal entropy will be recovered.<sup>557</sup>

This concept stimulated, in the past, several discussions and proposals to compute the effective volume in solution.<sup>558-564</sup> We have adopted it with modelistic considerations, on the basis of the cell theory of liquids, in our first papers on this subject.<sup>338,565</sup> The use of the communal entropy concept in the theory of liquids has been sharply criticized by Ben-Naim, who considers it "obsolete".<sup>443</sup> The approximation we are using here, of assimilating the free volume to the whole volume of the solution, has

**Table 12. Barrier Height for the Methyl Torsion and Related Contribution to the Molecular Free Energy, Computed in the Hindered Rotor Approximation (kcal/mol) (4–31G SCF Calculations from Alagona et al.<sup>419</sup>)**

molecule		barrier height		$-RT \ln(q_{tors})$	
		$\epsilon = 1$	$\epsilon = 78.5$	$\epsilon = 1$	$\epsilon = 78.5$
<i>N</i> -methylformamide	T	0.17	0.62	-1.10	-0.83
	C	0.67	0.80	-0.87	-0.83
	TS	1.15	1.34	-0.79	-0.76
methyl formate	T	0.71	1.09	-0.93	-0.82
	C	0.18	0.87	-1.03	-0.87
	TS	1.14	1.10	-0.79	-0.80

been also implicitly assumed by Pierotti in the evaluation of  $\Delta G_{cav}$ . The controversy has continued until very recently. Sharp et al.<sup>196,566</sup> make use of the volume entropy concept in their work on the hydrophobic effect, which is based on a modification of the Flory–Huggins theory.<sup>567–572</sup> As a test case, they consider  $\Delta G_{sol}$  of a set of alkanes in water. Giesen, Cramer, and Truhlar, in contrast, find a better agreement using the simple ideal solution theory; the set of alkanes they consider is somewhat more extended, but also the van der Waals radii employed to calculate molecular surfaces and volumes are different. The application of Flory–Huggins theory to dilute solutions of small molecules has been criticized on theoretical grounds also by Ben-Naim and Mazo<sup>574</sup> and by Abraham and Sakelariou.<sup>575</sup>

The contribution related to vibrational degrees of freedom presents some problems of different nature. The evaluation of  $\ln(q_{vib,g})$  is now generally performed using ab initio calculations. Current computational packages (e.g. GAUSSIAN<sup>299</sup>) give the frequencies in the harmonic approximation. This approximation is not sufficient for large amplitude–slow frequency modes, which must be treated separately. We shall discuss in another section the evaluation of molecular vibrations in the continuum model. We may anticipate here that a reliable computerized method to get harmonic frequencies in solution is not yet available.

When only the ratio  $\ln(q_{vib,g}/q_{vib,s})$  is considered, we may note that in most cases, for medium-sized molecules the solvent effect is almost negligible. The solvent effect may be important in large amplitude–slow frequency vibrational modes. The computation of these contributions may be performed in parallel with the corresponding one in vacuo, thus reducing the effect of some approximations (the definition of the normal coordinate for a mode of this kind does not imply a simple route for the calculation of the corresponding frequency). We report in Table 12 the barrier height for the methyl-hindered rotation and the corresponding contribution to  $\Delta G$  in *N*-methylformamide (MFA) and methyl formate (MF) in the trans (T) and cis (C) conformations and at the transition state (TS) for the T–C conversion, computed in vacuo and in water solution,<sup>419</sup> with the hindered rotor approximation.<sup>576</sup> The change in the energy barrier is sharp in some cases, but the effect on the vibrational contribution to  $\Delta G_{sol}$  is small.

Some of the couplings among modes involving large amplitude motions will be surely different in vacuo and in solution, because of specific solvation effects. This problem requires further investigation.

Another problem involving molecular vibrations in solution regards the occurrence of specific interactions with solvent molecules, especially the formation of solute–solvent hydrogen bonds. The theory of these motions has been amply developed.<sup>577</sup> We feel that the continuum approach is able to give a sensible description of these effects (see section VII.D on molecular vibrations) and for the moment we have used approximate routes based on continuum calculations supplemented by supermolecule calculations. Further studies would improve the description.

Note that we have included here the zero-point corrections, which could be computed separately when one is interested in the evaluation of  $\Delta H_{sol}$ . From the practical point of view the only important contribution in the zero-point correction comes from high-frequency motions involved in solute–solvent specific interactions.

The term  $RT \ln(q_{rot,g}/q_{rot,s})$  in expression 152 does not present problems as far as the gas-phase partition function is concerned. The partition function in solution depends on the dynamics of rotation of M in solution. There will be effects due to the disruption of specific solute–solvent interactions. There is here a large space open for modelistic studies, which should be based on a coupling of molecular dynamics simulation and continuum model calculations. We have performed the first steps in this direction, but we have, for the moment, established only some bounds for the empirical barrier height hindering the rotation of M along the three axes of inertia.

To conclude, it seems to us that the evaluation of the molecular motion contribution to  $\Delta G_{sol}$  may be at present performed with a reasonable degree of accuracy, for simple solutes of small and medium size having a relatively rigid molecular framework. Things actually are more complex when one considers other solutes, for example dimers  $M_1$ – $M_2$  or trimers  $M_1$ – $M_2$ – $M_3$ , held together by relatively weak interactions.

The reader surely has noted that in this subsection we have based our exposition almost exclusively on the elaboration performed by the Pisa group. We are in fact not aware of systematic elaborations of this subject performed by other groups, within the continuum models.

## E. Solvation Free Energy of Some Simple Solutes. Some Conclusions

We have examined the methods today available to compute all the elements of  $\Delta G_{sol}$  detailed in eqs 99 and 101. We may now try to draw some tentative conclusions from the numerical evidence at our disposal.

We report in Table 13 a set of  $\Delta G_{sol}$  values computed with the standard procedure ( $\Delta G_{el}$  at the 6-31G\*\* SCF level,  $\Delta G_{cav}$  with the Pierotti formula,  $\Delta G_{dis-rep}$  with the PCM continuum pair potential approach in the uniform approximation,  $\Delta G_{mm}$  with the routes given in section V.D) drawn from ref 66. In the same table we also report the corresponding  $\Delta G_{el}$  values. (Unfortunately other data, including optimal geometries and the separate values of  $\Delta G_{cav}$  and  $\Delta G_{dis-rep}$  have been lost in the interim.)

The agreement between computed and experimental  $\Delta G_{sol}$  values is quite good. Note that no calibra-

**Table 13. Comparison of Experimental Solvation Values of Some Esters (Solvent Water,  $T = 298.15$  K, Values in kcal/mol) with Computed Values and with  $\Delta G_{el}$  Values (SCF Calculations, 6-31G\*\* Basis Set)<sup>66</sup>**

solute	$\Delta G_{sol}(\text{exp})^a$	$\Delta G_{sol}(\text{calc})$	$\Delta G_{el}$
acetic acid methyl ester	-3.31	-3.75	-8.42
acetic acid ethyl ester	-3.09	-3.51	-8.16
propanoic acid methyl ester	-2.93	-3.34	-8.00
acetic acid propyl ester	-2.85	-3.25	-7.86
butanoic acid methyl ester	-2.83	-3.22	-7.90
propanoic acid ethyl ester	-2.80	-3.21	-7.80
formic acid methyl ester	-2.78	-3.18	-7.82
acetic acid 1-methylethyl ester	-2.64	-3.03	-7.66
formic acid ethyl ester	-2.64	-3.02	-7.64
acetic acid butyl ester	-2.55	-2.96	-7.55
formic acid propyl ester	-2.48	-2.88	-7.50
propanoic acid propyl ester	-2.45	-2.85	-7.50
acetic acid 2-methylpropyl ester	-2.37	-2.77	-7.37
formic acid 2-methylpropyl ester	-2.21	-2.58	-7.16
formic acid 2-methylbutyl ester	-2.13	-2.52	-7.10
formic acid 1-methylethyl ester	-2.02	-2.43	-7.04

<sup>a</sup> Experimental values from Cabani et al.<sup>324</sup>

tion and/or scaling factors have been introduced. (The occurrence of casual compensation among errors of different origin is of course possible.)

The correlation is given by the following linear relationship:

$$\Delta G_{sol}(\text{exp}) = 1.03\Delta G_{sol}(\text{calc}) + 0.33 \text{ kcal/mol}$$

$$r = 0.999 \quad (153)$$

where  $r$  is the regression coefficient. The correlation between  $\Delta G_{sol}(\text{exp})$  and  $\Delta G_{el}$  is of the same quality:

$$\Delta G_{sol}(\text{exp}) = 1.09\Delta G_{el} - 4.78 \text{ kcal/mol}$$

$$r = 0.998 \quad (154)$$

$\Delta G_{el}$  is in this case a good predictor of  $\Delta G_{sol}(\text{calc})$ :

$$\Delta G_{sol}(\text{calc}) = 1.06\Delta G_{el} - 4.44 \text{ kcal/mol}$$

$$r = 0.998 \quad (155)$$

In passing to other sets of solutes of homogeneous nature we have found analogous correlations between  $\Delta G_{sol}(\text{exp})$  and  $\Delta G_{sol}(\text{calc})$ , with some differences in the intercept, but with slopes close to unity and  $r > 0.9$ . The number of compounds in each chemical family for which reliable  $\Delta G_{sol}(\text{exp})$  values are available is in general small, and these correlations are of limited statistical weight. Correlations of similar quality have been also obtained for a more limited number of solutes in nonpolar solvents.

The correlation between  $\Delta G_{sol}$  and  $\Delta G_{el}$  seems to hold when extended to a heterogeneous set of polar molecules. We have drawn from our files calculations regarding 102 polar molecules (including polyfunctional molecules, heterocycles, and aromatic compounds) in water. The calculations have been performed over the years, and the specimen is not uniform, especially as to the basis set. We are thus compelled to limit the correlation to  $\Delta G_{sol}(\text{calc})$  values:

$$\Delta G_{sol}(\text{calc}) = 0.91\Delta G_{el} - 5.09 \text{ kcal/mol}$$

$$r = 0.90 \quad (156)$$

When the examination is extended to nonpolar solutes in water, and to nonpolar solvents, the

correlation between  $\Delta G_{sol}$  and  $\Delta G_{el}$  fails. There is however a good correlation between  $\Delta G_{sol}$  and  $W(M/S) = \Delta G_{el} + \Delta G_{cav} + \Delta G_{dis-rep}$ .

Continuum methods compare well with molecular dynamics free energy perturbation methods (MD-FEP). A comparison has been performed by Orozco, Jorgensen, and Luque,<sup>578</sup> using 6-31G\* SCF wave functions in the PCM calculations, and standard pair potentials for the MD. The PCM solvation free energies included cavitation, dispersion, and repulsion terms. The average error for  $\Delta G_{hyd}$  over a set of eight neutral solutes is 1.5 kcal/mol for MG-FEP and 0.8 kcal/mol for PCM. For another set of 13 solutes, accurate Monte Carlo calculations yield an average error of 1.1 kcal/mol.<sup>247</sup>

We may thus tentatively suppose that all the efforts required to better compute the  $\Delta G_{mm}$  contributions, eq 152, are not necessary if the goal is to get an appreciation of  $\Delta G_{sol}$ . Reasonable estimates for rigid polar solutes in water could be obtained from  $\Delta G_{el}$  with an appropriate scaling. The  $\Delta G_{el}$  values depend on the basis set, and we have noted that the correlation between  $\Delta G_{sol}(\text{exp})$  and  $\Delta G_{el}$  improves in passing to larger basis sets. When  $\Delta G_{cav}$  and  $\Delta G_{dis-rep}$  are added, an empirical scaling could be also applied to values referred to nonpolar solvents and to hydrocarbons in polar solvents.

These (provisional) conclusions drawn from ab initio PCM calculations justify the expectation that simpler methods including parametrization and/or scaling may give good estimates of  $\Delta G_{sol}$  without including the  $\Delta G_{mm}$  term, which is harder to evaluate.

Cramer and Truhlar have published a detailed report<sup>318</sup> of the performances of the AMSOL model in three different versions, AM1-SM1a, AM1-SM2, and PM3-SM3. For the 117 neutral polar solutes they have used in their calibration procedure (the calibration set also includes 33 hydrocarbons and 28 ions) we found the following correlations:

$$\Delta G_{sol}(\text{exp}) = 0.901\Delta G_{sol}(\text{SM2}) - 0.017 \text{ kcal/mol}$$

$$r = 0.876 \quad (157)$$

$$\Delta G_{sol}(\text{exp}) = 0.882\Delta G_{sol}(\text{SM3}) - 0.117 \text{ kcal/mol}$$

$$r = 0.853 \quad (158)$$

The same definition of parameters and the same strategy of optimization has been used in the two cases, and the differences are only due to the internal parameters of the AM1 and PM3 semiempirical Hamiltonians.<sup>293,320,321</sup> The linear regression between experimental solvation values and  $\Delta G_{ENP}$ , computed with the SM2 and SM3 sets of parameters for the same set of 117 solutes, yields

$$\Delta G_{sol}(\text{exp}) = 0.330\Delta G_{ENP}(\text{SM2}) - 0.79 \text{ kcal/mol}$$

$$r = 0.615 \quad (159)$$

$$\Delta G_{sol}(\text{exp}) = 0.234\Delta G_{ENP}(\text{SM3}) - 0.87 \text{ kcal/mol}$$

$$r = 0.399 \quad (160)$$

At least a loose correlation between  $\Delta G_{sol}(\text{exp})$  and  $\Delta G_{ENP}$  (or  $\Delta G_{el}$ , in our terminology) is expected for polar solutes in water. Apparently, this correlation is lost during the calibration of the AMSOL param-

**Table 14. Linear Regression Parameters for Model Predictions against Experimental  $\Delta G_{\text{hyd}}$  Values**

model	authors	no. of points	slope	intercept (kcal/mol)	$r$
SASA	Ooi et al. <sup>551</sup>	26	0.9526	-0.041	0.977
GB/SA	Still et al. <sup>220</sup>	21	1.0379	-0.091	0.955
FDPB	Jean-Charles et al. <sup>581</sup>	14	0.7246	-0.770	0.813
SM2	Cramer and Truhlar <sup>318</sup>	49	0.9543	-0.001	0.975

eters; in fact, the parametrization has considered the experimental  $\Delta G_{\text{sol}}$  values, rather than their separate components, which have no experimental counterparts. A reasonable explanation for the poor  $\Delta G_{\text{sol}}/\Delta G_{\text{ENP}}$  correlation calls on the use of Mulliken charges, which do not reproduce the molecular electrostatic potential with a sufficient accuracy. The fact that  $\Delta G_{\text{ENP}}$  cannot be used alone for neutral polar molecules is not extremely significant; in fact this method, as well as other semiempirical methods, is addressed to the evaluation of a specific quantity,  $\Delta G_{\text{sol}}$  in this case, and not of its separate components. To validate Cramer-Truhlar's method one should examine the results of linear regression between experiment and theory for compounds not included in the calibration set. The data are unfortunately scarce, but for a set of seven neutral compounds<sup>318</sup> we found quite a good regression coefficient:  $r(\text{SM2}) = 0.965$ .

In a more recent review Cramer and Truhlar<sup>579</sup> compare linear regressions for  $\Delta G_{\text{sol}}$  obtained with AMSOL and other semiempirical methods. We draw from their analysis the data reported in Table 14. Here the set of solutes also includes nonpolar molecules. More details can be found in ref 579. We may conclude this overview by reporting our impression that the objective of predicting  $\Delta G_{\text{hyd}}$  values for molecules in their equilibrium geometry with computationally inexpensive methods is almost reached. Further refinements undoubtedly will increase the confidence degree in the calculation of a quantity so hard to derive from experiments.

We have not considered in this review a new semiempirical procedure proposed by Hehre and included in the Spartan program.<sup>580</sup> We are obliged to the courtesy of Professor H.-J. Hofmann, who has given us some information about this procedure. The program is quite fast, with results in some cases comparable to AMSOL, but with some problems, for instance in the determination of tautomeric equilibria.

## VI. Chemical Applications

As we pointed out in the Introduction, this review is mainly addressing the examination of methodological aspects. For this reason we shall not consider in exhaustive detail the wealth of chemical applications, rapidly increasing in number and variety.

In several cases the application is accompanied by some methodological innovation, but it would be difficult to single out these aspects without giving a broader view of the problems for which they have been elaborated. We shall limit ourselves to a few

**Table 15. Thermodynamical Properties for the Chemical Processes Involving Tautomeric Changes between the Neutral and Zwitterionic Forms of Glycine (kcal/mol)**

	$(\text{NT})_{\text{aq}} \rightarrow (\text{ZW})_{\text{aq}}$		$(\text{NT})_{\text{gas}} \rightarrow (\text{ZW})_{\text{gas}}$	
	computed <sup>a</sup>	experimental <sup>b</sup>	computed <sup>c</sup>	experimental <sup>c</sup>
$\Delta G$	-7.2	-7.7	-16.5	-
$\Delta H$	-9.6	-9.9	-19.5	-19.2
$-T\Delta S$	2.4	2.2	3.0	-

<sup>a</sup> The values are here modified with respect to the original references<sup>93,582</sup> by inclusion of dispersion and thermal contributions. <sup>b</sup> Haberfield, P. *J. Chem. Educ.* **1980**, *97*, 346. <sup>c</sup> Gaffney, J. S.; Pierce, R. C.; Friedman, L. *J. Am. Chem. Soc.* **1977**, *99*, 4293.

themes, emphasizing the general aspects, rather than the specific chemical interest of the results.

The themes we have selected are as follows: (A) equilibria in chemical reactions, (B) reaction mechanisms, (C) molecular observables, and (D) use of continuum models in computer simulations.

## A. Chemical Equilibria

The first aspect of interest in the study of chemical reactions regards the chemical equilibrium conditions. The evaluation of solvent effects on a chemical equilibrium might be more reliable than the determination of absolute solvation energies because some cancellation of errors should occur. This is actually the case for several classes of reactions which have been extensively studied; some examples, regarding the AMSOL method, can be found in the two reviews<sup>318,579</sup> and other papers<sup>327-579</sup> by Cramer and Truhlar; analogous results hold for other systems.

The most extensively studied equilibria regard tautomeric processes, isomerizations, acid-base equilibria, and condensation reactions.

Even in this set of simple reactions there are cases in which differential solvent effects play an important role. The examination of these cases sheds more light on the features of solvation and may be helpful in improving the computational procedures. As an example we quote one of the first chemical equilibria studied with adequate tools, i.e. the equilibrium between neutral (NT) and zwitterionic (ZW) forms of glycine in water (Bonaccorsi et al.<sup>93,582</sup>). To compute free energy and enthalpy changes for this tautomerization reaction, we have found it necessary to modify the definition of the cavity around the two polar heads of the ZW form:  $\text{H}_3\text{N}^+-\text{CH}_2-\text{COO}^-$ . This effort showed the way to subsequent cavity modeling for charged solutes. We report in Table 15 the values for the  $(\text{NT})_{\text{aq}} \rightarrow (\text{ZW})_{\text{aq}}$  process, as well as for the  $(\text{NT})_{\text{gas}} \rightarrow (\text{ZW})_{\text{gas}}$  process, compared with experimental data.

An accurate comparison of experimental and computed trends of  $\Delta G$  and  $\Delta H$  values for sets of related reactions surely will bring important refinements in the solvation models. Analogous considerations hold for the selection of the quantum level necessary for a reliable description of the thermodynamics of reactions. We limit ourselves to a simple example, again, drawn from the studies of Silla's group in Valencia,<sup>583-585</sup> concerning the protonation of organic solutes. The inversion of the relative basicities of

amines and alcohols in solution, with respect to the gas-phase values, can be easily interpreted only by applying an appropriate model to describe solvent effects (the PCM in this example) with wave functions of a good level of accuracy. On this topic see also Rguini et al.<sup>164</sup>

More experience gained in similar studies on other reactions may lead to improve a computational strategy valid also for other chemical applications.

Phase-transfer processes provide another example of chemical equilibria, characterized by  $\Delta G$  values of direct chemical (and biochemical) interest, that may also be used as a guide to improve the models. The most expedient way to use  $\Delta G_{\text{transf}}$  values in practical applications (for instance, to predict the properties of molecules as potential drugs) probably exists in fitting the computed solvation energies with empirical relationships, as proposed e.g. by Miertuš and Moravek.<sup>586</sup> We have already quoted our exploitation of  $\Delta G_{\text{transf}}$  calculations to get indirect clues on the more convenient values for the factor  $f_K$  modifying the van der Waals radii  $R_K$  in the definition of molecular cavities.<sup>91</sup> Another analysis of  $\Delta G_{\text{transf}}$  results has been recently considered by Silla's group,<sup>587</sup> they develop two expressions of  $\Delta G_{\text{transf}}$  based on statistical mechanics, and relate them to Ben-Naim's formulation.<sup>443</sup> This elaboration allows a better understanding of hydrophobic effects and justifies the application of surface-only formulas in calculating the solubility of hydrocarbons,<sup>207,459,588</sup> the large amount of literature on this subject deserves a careful analysis that we cannot do here.

The recent study of Sakurai's group on the decarboxylation reaction catalyzed by cyclodextrins<sup>589</sup> shows in a different way how continuum models may be modified and adapted to describe the more challenging problems of anisotropic media. The attention is here focused on the activation energy, and the modelistic considerations are aimed at the description of the dielectric properties of reaction centers in the enzyme, but the approach could be also exploited for equilibrium properties.

## B. Reaction Mechanisms

The study of reaction mechanisms is one of the more challenging problems faced by interpretative theoretical chemistry. A connected problem is to describe the reaction processes with details and reliability sufficient to derive quantitative information of chemical interest, such as the reaction rate.

There are several clever shortcuts that enable to provide useful information, without much effort, about the two aspects outlined above. We shall follow however the most systematic approach, based on the study of the properties of the energy hypersurface, with the aim of stressing analogies and differences with the corresponding studies in vacuo.

The energy hypersurface  $E(\mathbf{Q})$  in vacuo [or, better, the energy hypersurfaces  $E_n(\mathbf{Q})$ ] defined in the space  $\{\mathbf{Q}\}$  of the nuclear coordinates has its counterpart in the  $G(\mathbf{Q})$  surface in solution. The formal analogy between the two functions has been highlighted many times, see e.g. Laidler and Polanyi<sup>590</sup> and Tomasi and Bonaccorsi.<sup>69</sup> There are however some differences which deserve a few comments.

Let us identify  $G(\mathbf{Q})$  with  $E(\mathbf{Q}) + W(M/S)$  (see eq 99); it is then a free energy function, from which the translational, rotational, and vibrational contributions, including the zero point energy, have been omitted. In this sense, for a solute  $G(\mathbf{Q})$  has the same status as  $E(\mathbf{Q})$  for a free molecule. However,  $G(\mathbf{Q})$  depends on the temperature through the solvent properties: the dielectric constant, which enters the  $\Delta G_{\text{el}}$  component, the surface tension or other constants for  $\Delta G_{\text{cav}}$ , and so on. In most studies performed up to now  $\Delta G_{\text{cav}}$  and  $\Delta G_{\text{dis-rep}}$  have been neglected; in many cases these terms exhibit small changes in the portion of the  $\{\mathbf{Q}\}$  space of interest for a reaction, but it is safer to use the whole  $G(\mathbf{Q})$  function.

In many chemical reactions,  $G$  also depends upon the position and the orientation of the solute in the collective material system. We shall examine some cases when dealing with anisotropic systems. The situation is not different from that found in passing from systems in vacuo without influence of external fields to models in which directing external fields are active.

To describe the portion of the  $G(\mathbf{Q})$  surface of interest for a generic reaction we need a solvation method able to treat two or more solutes separated by the solvent, otherwise applications would be limited to isomerizations. This point will be considered in section VII. When a method to compute  $G(\mathbf{Q})$  functions is available, we may proceed as in vacuo, limiting the study to the determination of the critical points (minima and saddle points) of the reaction coordinate and of the corresponding energy profile; larger portions of  $G(\mathbf{Q})$  are needed for a dynamical study of the reaction. The dynamics of reactions in solution presents additional problems which will be analyzed in section VII.

The static solvent effects we are considering here influence the geometrical and energetic data extracted from the  $G(\mathbf{Q})$  surface. To get an interpretation of the reaction mechanism, these results must be analyzed by tools selected in the large panoply of methods elaborated by theoretical chemists.

Classical solvation methods are of little use for the determination of the geometrical and energetic features of reactions. A preliminary description of these features may be obtained by resorting to semiempirical methods, which are however of little reliability for the analysis of the electronic effects. A complete and reliable analysis must be based on ab initio calculations.

The experience drawn from the analysis of many reactions is often quite useful to facilitate the interpretation of a new mechanism. A few basic effects, combined in several ways, give rise to the complexity of real chemical problems. The confidence gained in the interpretation of chemical reactions in vacuo may lead however to significant errors when directly applied to reactions in solution. The interaction between two reactants always replaces solute-solvent interactions, often of similar nature, and the reaction is ruled by a subtle balance that must be carefully appreciated.

An example is given by the symmetric  $S_N2$  reactions  $X^- + H_3CX \rightarrow XCH_3 + X^-$  which exhibit

important differences in the energy profile in vacuo and in solution. Monte Carlo simulations first,<sup>591,592</sup> integral equation,<sup>41</sup> molecular dynamics,<sup>593</sup> free energy perturbation,<sup>594</sup> and PCM continuum calculations later<sup>595,596</sup> have provided the first examples of known reaction profiles in solution successfully reproduced by calculation. When comparing the two energy profiles, one finds that more than one-half of the energy barrier present in solution is due to differential effects acting at the stage of close contact between reactants, when local solute-solvent interactions are replaced by interactions between reactants. The same effects are presents in other reactions, even when blurred by other more evident solvent effects.<sup>596-598</sup>

For this reason we have considered it convenient to reformulate the Kitaura and Morokuma<sup>88</sup> energy decomposition for two molecules A and B interacting in solution.<sup>599</sup> The A-B noncovalent interaction is plagued by basis set superposition errors (BSSE), which are minimized with suitable basis sets.<sup>600-603</sup> The study of relatively large molecular systems with such basis sets is computationally very demanding. A reasonable correction of BSSE with standard bases is given by the counterpoise (CP) procedure,<sup>604</sup> which we have extended to the separate terms of the Kitaura and Morokuma decomposition.<sup>495</sup>

To use the approach of ref 495 in solution we have introduced a "partial desolvation" term in the expression of  $G_{el}(R_{AB})$ , related to the presence of solute-solvent interactions preceding the close contact between A and B. An extension of the CP-corrected decomposition analysis<sup>495</sup> to MP2 and MP3 wave functions in vacuo as well as in solution is now under elaboration (Cammi and Tomasi, in progress).

A sensible estimate of the simultaneous effects due to noncovalent A-B interactions and to the reaction field (obviously one of the two partners A-B may be a solvent molecule) may be obtained also by studying the effects of external fields on the A-B interactions,<sup>605</sup> an approach we have found very useful to interpret the initial steps of reactions in solution. In this field the application (and extension) of recent techniques for the evaluation and the analysis of noncovalent interactions in supermolecular systems could be an important aid in understanding chemistry in solution.

Another point that may be related to the first steps of a reaction in solution is a full account of the free energy for solute aggregations. We have expressed our optimistic view on the calculation of full  $G$  for almost rigid molecules in solution, including thermal molecular motion effects, in section V.D. We must relate here our difficulties to get reliable results when the solute is composed by two or more loosely bound molecules. The main difficulty is related to the description of the rotational motions, for which definition of the appropriate partition function is not trivial. Another problem (related to the first one) is the determination of the pertinent  $G(\mathbf{Q})$  surface, markedly flatter than in vacuo and extremely sensitive to the basis set, the CP corrections, etc. Here again the difference between surfaces in vacuo and in solution is due to differential interaction effects. As an example we quote the study of formamide,

acetamide, *N*-methylformamide, and *N*-methylacetamide dimers.<sup>606</sup>

Let us now move to the heart of the reaction, ie. the region of  $\{\mathbf{Q}\}$  where bonds are broken and formed. The effect of the solvent may be seen as a deformation of the energy hypersurfaces, with changes in the topology and topography of the crossing regions, and changes in the topography of the single surfaces. The surface crossing problems have not yet been studied in a significant number of cases, and also our knowledge of single surface problems is limited.

A topological deformation of the surface may represent an important change in the reaction mechanism; a recent example is given by the study of Tuñón et al. on the transition structures of Friedel-Craft reactions.<sup>607</sup> Another example is given by the first reaction studied with the PCM approach: the reduction of a carbonyl group by  $\text{LiBH}_4$ .<sup>608</sup> The structure of the transition state leads to the formulation of a mechanism different from that found at the same computational level in vacuo.<sup>338</sup>

The attention is thus far concentrated on reactions with a simple mechanism, for example proton transfer reactions, of the type  $\text{AH} + \text{B} \rightleftharpoons \text{A}^- + \text{HB}^+$ . We report a short and not complete list of studies mainly addressed at bringing out cases in which the solvent shifts the balance from reactants to products, or vice versa.<sup>55,270,277,362,610-616</sup> The energy profile (often the results are presented as a one-dimensional cut) must be determined with a good accuracy, because solvent-induced distortions may be of a lesser extent than artifacts due to the insufficiency of the computational level, the shape of the cavity or the geometry optimization.

In many reactions one or a few solvent molecules play an active role. In such cases the necessary number of solvent molecules must be included in the "solute" system, with a corresponding enlargement of the  $\{\mathbf{Q}\}$  space. In a recent study,<sup>326</sup> a technique has been proposed to distinguish general solvent effects from specific catalytic effects.

The last example leads us to consider another related subject. The electronic wave function obtained with continuum quantum methods is a good source of information to interpret reaction mechanisms in solution. Theoretical chemistry has made available a large set of methods, based on the partitioning of the  $\rho_m$  charge distribution into subunits and on the elaboration of suitable indices.<sup>235</sup> Among these indices we quote the atomic populations, obtained with Mulliken's,<sup>617</sup> Bader's,<sup>618</sup> and Weinhold's<sup>619</sup> procedures, the MO energy differences,<sup>620</sup> and the electrostatic fields exerted by local subunits.<sup>410,621,622</sup>

The experience of solvent effects on these indices is rapidly accumulating, and other indices, specific for solution problems, are being devised. Among the latter we quote indices based on the value of the reaction field potential  $\Phi_\sigma$  in specific regions of the solute. A wealth of information is enclosed here, which may be used directly or to explain the solvent effect on other indices, such as atomic charges, electrostatic fields and MO energies.<sup>419</sup> The examination of the  $\Phi_\sigma$  and  $\nabla\Phi_\sigma$  values, now displayed in a

large number of papers, is highly recommended, because it may spur the ingenuous researcher to devise new exploitations of this information.

The solvent shifts of MO energies has been the subject of several papers.<sup>69,305,427,623-626</sup> Two of these papers<sup>69,427</sup> show how sensitive the MO energy shifts are to the shape of the cavity and to the electron correlation effects. Caution should be taken when drawing conclusions from MO energy shifts computed with low accuracy.

The so-called stereoelectronic effects are all influenced by the solvent. A typical example is the anomeric effect,<sup>304,327,627-633</sup> for which an interpretation in terms of semiclassical fields has been found enlightening.<sup>304</sup> Here again simple solvation models, based on a point dipole in a spherical cavity, cannot be used for an interpretation, even when they are valuable to detect solvent effects on the stability of molecular conformations. With more detailed models the influence of the medium, expressed in terms of the reaction potential  $\Phi_\sigma$  or of the reaction field, complements and modifies the effects due to the chemical subunits of the molecule, which are expressed, for uniformity, in terms of the electric potential (of field). Other formulations, not based on semiclassical fields, may be of course employed. The indices used for the interpretation in vacuo will be in this case modified by the solvent.

The deformation of excited-state energy surfaces induced by the solvent can be even more important than in the ground state. As an example, we quote a study on the photoisomerization of the DCM dye (a substituted styrylpyran), applying both the Onsager and the solvaton models.<sup>634</sup>

### C. Molecular Observables

The calculation of molecular observables is straightforward in quantum mechanical continuum solvation procedures. However, it is well known that several primary, derivative, and induced observables<sup>635</sup> of isolated molecules require a sophisticated level of theory and suitably large basis sets to get reliable values. The same holds for observables in solutes; the solvent does not introduce simplifications.

For this reason many of the calculations of molecular observables published in the past years have an exploratory character, rather than being accurate studies. We quote here some examples of observables which have been the object of calculation: vibrational polarizabilities,<sup>636</sup> circular dichroism,<sup>637-639</sup> nuclear quadrupole coupling constant,<sup>640,641</sup> and spin-spin coupling constants.<sup>642</sup> These examples have been drawn from the activity of Rivail's group only, one of the most interested in the evaluation of spectroscopic properties with potentially adequate methods. Other examples may be found in papers quoted in section IV.B. Observables related to vibrational and electronic spectroscopy will be considered in section VII.

A special role is played by the electrostatic properties, such as multipole moments or the MEP, because of their direct connection with  $\Delta G_{el}$ . Occasional comments about these and other related properties can be found in many papers. As a general rule, an increase of charge separations and of multipole moments is observed in passing from an isolated

molecule to the solution. We can cite here more specific studies on neutral solutes by our group<sup>249,418,419</sup> and on small anions by Luque et al.<sup>643</sup> Geometrical and electronic relaxation of the solute may cooperate significantly, as shown by Cramer and Truhlar on nucleic acid bases.<sup>644</sup>

We have not quoted here papers reporting the calculation of molecular observables with more crude methods, mainly based on effective solvation semiempirical formulations (references may be found in section IV.B.6). These applications may give a rough rationale of changes of the properties in a set of related molecules, and parallel, in our opinion, the use of empirical solvent parameters, like Kosower's  $Z$  value,<sup>645</sup> Kamlet and Taft's  $\alpha$ ,  $\beta$ ,  $\pi^*$  solvatochromic parameters,<sup>646</sup> Dimroth and Reichardt's  $E_T$  parameters,<sup>647</sup> Guttman's acceptor and donor numbers,<sup>648,649</sup> and many others. The large literature on this subject is well covered by detailed reviews. (The updated 1990 edition of Reichardt's monograph<sup>650</sup> is recommended.)

The recent progress in the continuum methods should stimulate a renewed interest in establishing connections between these empirical parameters and similar formulations drawn from computations. In such a way a better physical understanding of the parametric relationships and a greater confidence in their use could be reached. Previous attempts in this direction have shown that such an approach may give important results, but a decisive effort has been thus far impeded by the crudeness of the available computational procedures.

In conclusion, not much accurate work on molecular properties has been done until now, probably because reliable continuum models were not available until recently. There are several fields in which accurate estimates of molecular properties in solution are urgently requested, for example the hyperpolarizabilities in nonlinear optics,<sup>651</sup> which may differ from the gas phase values by a factor up to 3. The few calculations make use of a spherical cavity.<sup>651,652</sup>

The situation is now changing, and we hope that the new expressions for energy derivatives presented in section IV.E will be of some help. There are some examples of recent calculations indicating more clearly the prospects for the future. In a recent paper Cremer et al.<sup>653</sup> use a combination of IGLO calculations with good basis sets with our PCM procedure (the code is called PISA-IGLO<sup>654</sup>) to calculate NMR chemical shifts in solution for stannyl compounds and  $\text{BH}_3\text{NH}_3$ . The story of this last compound is instructive. Schleyer and co-workers<sup>655</sup> correctly pointed out that the deviation between computed and experimental values for  $^{11}\text{B}$  chemical shift found for this compound was basically due to a shortening of the B-N distance occurring in solution. They found a better agreement with experimental chemical shifts, when the IGLO calculation in vacuo was performed at a geometry optimized with the PCM (solvent cyclohexane). Cremer et al.<sup>653</sup> confirmed Schleyer's findings, with the addition that a parallel effect of similar magnitude is due to solvent electrostatic effects, as distinct from geometrical deformations (in this case the solvent is water).



## D. Applications in Computer Simulations

We have remarked several times that continuum models benefit from the results of computer simulations. In this short section we point out that simulations may exploit some continuum methods and results.

One of the most delicate problems in chemical simulations concerns the boundary conditions. Given the finite number of molecules in the simulation procedure, appropriate boundary conditions must be imposed if the researcher is not interested in modeling a finite cluster. We cannot review the large literature on this subject; suffice it to say that all the definitions have drawbacks.

Among the various proposals, one is to surround the finite cluster with a dielectric continuum. The first proposal of this kind, according to our files, came from Barker and Watts;<sup>656</sup> several other proposals and analyses have been presented<sup>657-667</sup> among which there is the already quoted paper by Romano.<sup>103</sup> Some of the papers address the evaluation of the appropriate dielectric constant (see also Allen and Tiddesley's book<sup>31</sup>). Classical versions of continuum methods must be employed here. Friedman,<sup>168</sup> in his paper on the image charge method, suggests it is appropriate to describe boundary conditions in simulations. These proposals do not satisfy fully the boundary requirements of simulations and present some problems themselves. For example, working with a fixed cavity, spurious effects arise when a molecule comes too close to the cavity boundary from inside. More recent formulations of the classical continuum model can give more satisfactory results.

Another problem that plagues the simulation of certain chemical systems is the inadequacy of two-body potentials. Using three-body potentials considerably increases the computational costs, without a complete elimination of the artifacts.<sup>668</sup> It is well known that the most important source of non additive many-body effects in polar systems is the classical electrical polarization.

The most annoying artifacts concern polar solutions containing highly charged ions. A simple expression for the correction of pair potentials, based on classical continuum models, has been proposed and tested by Berendsen et al.<sup>669</sup> The numerical values of parameters have been obtained by performing several trial simulations, with different combinations of the values.

More recently, Floris et al.<sup>534</sup> used PCM calculations to get effective two-body potentials with a full account of many-body polarization terms. Applications to a large number of cation-water systems is quite satisfactory.<sup>670</sup> Molecular dynamics simulations give a correct representation of hydration numbers and of solvation layers. Particularly interesting is the case of  $\text{Ca}^{2+}$ , for which an interpretation of the somewhat puzzling experimental results is given, in terms of a dynamical equilibrium between two structures, with eight and nine water molecules, respectively, in the first shell.

## VII. Dynamical Effects in the Continuum Model

### A. The Role of the Continuum Approach in the Description of Chemical Dynamical Phenomena

We consider in this section some phenomena for which a static description of the solvent is not sufficient. More physics can be added to the basic model examined in the first sections of this paper, in particular for the description of time dependent phenomena, among which are the dynamics (and kinetics) of chemical reactions.

We cannot review exhaustively the impressive number of recent methodological and applicative contributions in this field, supported, and spurred, by new experimental evidence based on innovative techniques. The continuum representation of solvent effects plays an important role in the evolution of this branch of the physicochemical research, but obviously does not constitute the unique element of theories and models. It would be quite interesting, and useful for future progress, to have a coherent overview of the evolution of continuum models in this field. This overview would bring out that the general trend toward chemical, rather than physical, models (see section I) is presently active in this specific field.

The continuum models used until recently are of a simple structure. Let us take as an example the important case of charge-transfer reactions.<sup>671</sup> We may notice that the theories of Marcus<sup>672-676</sup> and Hush,<sup>677</sup> as well as the earlier formulation of the theory of Levich and Dogonadze,<sup>678,679</sup> use continuum models where the solute is structureless and the solvent isotropic. These models are, in other words, extensions of the Born model (section III.B.1). The description of the solvent structure and dynamics around the charged species has been improved in different directions: application of a quantum electrodynamic theory of continuous media in terms of appropriate Green functions of the medium;<sup>680</sup> elaboration of structured continuum models, based on nonlocal dielectric theory; introduction of several concentric layers of solvent at low dielectric constant (very detailed reviews of these subjects are available;<sup>681-683</sup> see also section VIII). All the approaches mentioned here refer again to simple spherical solutes.

The availability of more detailed experimental data and of more realistic computer experiments has led in recent years to a further elaboration of models, embodying refined continuum approaches. See for instance ref 684 for a review on the recent progress in this field.

The case of charge-transfer reactions is just one example of a wide class of dynamical phenomena in which the same evolution from "physical" to "chemical" models occurs. It is clear that we cannot include in this paper a review of the role played by the continuum approximation in this field.

After these introductory considerations, let us define more exactly what are the subjects considered in this section. We shall consider the first steps of the evolution of the "chemical" basic model to treat a few selected problems of dynamical nature. In several cases the models here considered do not contain time as an explicit parameter; conventional

quantum chemistry is not at ease in treating time-dependent phenomena and prefers to resort to static pictures; time evolution is introduced at a later stage, or alternatively a complex phenomenon is dissected into separate steps, each treated with a time-independent formalism.<sup>340</sup> A few simple formulations, some of which of very tentative character, are explicitly time-dependent. The starting point is the experience gained in the studies of the basic static model. This line of evolution is very promising, in our opinion, and of fundamental importance in assessing methods able to describe dynamical aspects of phenomena of direct chemical interest.

## B. Computational Methods

A basic ingredient in the evolution outlined in the preceding section is the implementation of methods able to compute  $G_{el}$ , and related energetic quantities, in a medium characterized by a polarization vector  $\mathbf{P}(t)$  depending on time. We have defined up to now a  $\mathbf{P}$  vector independent of time, with the additional assumption of an infinite linear isotropic medium. Here we retain the hypotheses of isotropicity, infinity, and linearity.

The best approach to treat problems characterized by the presence of a  $\mathbf{P}(t)$  function is provided by the quantum electrodynamics theories we have mentioned. This approach will not be followed here, and it will remain in the background, as a useful reference for simpler models.

The quantum electrodynamical picture is consistent with a description of  $\mathbf{P}$  in terms of an expansion over normal modes (with frequency  $\nu$ ) of the polarization of the dielectric:

$$\mathbf{P} = \sum_{\nu} \mathbf{P}_{\nu} \quad (161)$$

$\nu$  may be a discrete or a continuum index.

A concise and clear exposition has been given by Levich.<sup>685</sup> The model can be simplified by replacing the summation of eq 161 with two terms alone, often called the fast and slow contributions to  $\mathbf{P}$ :

$$\mathbf{P} = \mathbf{P}_{fast} + \mathbf{P}_{slow} \quad (162)$$

$\mathbf{P}_{fast}$  is connected to polarization of the electron charge clouds and  $\mathbf{P}_{slow}$  to nuclear motions of the solvent molecules. It is convenient to recall here the typical times for these processes. Electronic relaxation times are of the order of  $10^{-16}$ – $10^{-15}$  s; vibrational relaxation occurs in the range  $10^{-14}$ – $10^{-12}$  s and rotational diffusion in  $10^{-11}$ – $10^{-9}$  s; translational times are of the order of  $10^{-9}$  s or more. The fast component of  $\mathbf{P}$  is clearly related to electronic polarization,  $\mathbf{P}_{fast} \equiv \mathbf{P}_{el}$ , and the slow component collects the other terms; it is often called the orientational polarization ( $\mathbf{P}_{slow} \equiv \mathbf{P}_{or}$ ), but a less specific definition, such as “inertial” component ( $\mathbf{P}_{slow} \equiv \mathbf{P}_{in}$ ) is preferable. A more precise definition of  $\mathbf{P}_{slow}$ , based on the characteristic times reported above, will be convenient in some cases.

The static value of  $\mathbf{P}$ ,  $\mathbf{P}_{stat}$ , and the fast component,  $\mathbf{P}_{fast}$ , can be defined in terms of experimental quantities, namely the static and optical susceptibilities:

$$\chi_{stat} = \frac{\epsilon_0 - 1}{4\pi} \quad (163)$$

$$\chi_{fast} = \frac{\epsilon_{\infty} - 1}{4\pi} \quad (164)$$

where  $\epsilon_0$  and  $\epsilon_{\infty}$  are the static and optical dielectric constant (the latter assimilated to  $n^2(\infty)$ , the square of the refraction index at very large frequency). There is no direct operational definition of  $\chi_{slow}$ . However, assuming the partition  $\mathbf{P} = \mathbf{P}_{fast} + \mathbf{P}_{slow}$ , we may also define  $\chi_{slow}$  as<sup>179,686</sup>

$$\chi_{slow} = \frac{\epsilon_0 - \epsilon_{\infty}}{4\pi} \quad (165)$$

This model has been applied to systems in which there is an evolution in time of the charge distribution of the solute,  $q_M(t)$ . It is assumed that  $\mathbf{P}_{fast}$  follows, without appreciable time lag, the evolution of the electric field,  $-\nabla\Phi_M^{(0)}(t)$ , while  $\mathbf{P}_{slow}$  feels the total electric field experienced by the system at an earlier time. In several applications the “earlier time” can be assumed to precede beginning of the time evolution of  $q_M(t)$ . In this case  $\mathbf{P}_{slow}$  is, at any time, the corresponding contribution to  $\mathbf{P}$  in the static, or initial, situation. This model has been developed and applied by many authors: we quote here Marcus<sup>672–676</sup> and Hynes<sup>686,687</sup> as typical and well-known examples, but the list could be quite longer, especially if one would include analogous models with some differences in the basic assumptions.

The “chemical” realizations of this model to our knowledge are based on the apparent surface charge approach (ACS, see sections III.D and IV.B.3) and more specifically on some modifications of the iterative PCM procedure.

The first formulation is due to Bonaccorsi et al.<sup>339</sup> The method was elaborated for the study of solvent effects on electronic spectra; in this case it is reasonable to assume that the “earlier time” (E) immediately precedes the transition from state 1 to state 2; the actual time (A) immediately follows the jump (in absorption as well as in emission). At time E we perform a normal PCM calculation; the solvent is in equilibrium with  $q_M$  for electronic state 1. From the surface charge  $\sigma_E$  thus obtained, it is easy to separate the orientational (slow) contribution on the basis of the equation

$$\sigma_E = \sigma_{E,fast} + \sigma_{E,slow} \quad (166)$$

The charge distribution  $\sigma_{E,fast}$  is obtained by repeating the PCM calculation using  $\epsilon_{\infty}$  instead of  $\epsilon_0$ . The perturbation  $\hat{\gamma}'_s$  associated with  $\sigma_{E,slow}$  is then introduced in the Hamiltonian as a permanent contribution, and the calculation is repeated with the dielectric constant  $\epsilon_{\infty}$ , to determine the wave function of state 2 and the charge distribution  $\sigma_A$ . This procedure describes vertical transitions, at fixed nuclear geometry. (For this and other approximations see comments in papers by Bonaccorsi et al.<sup>340,341</sup> and by Sheykh et al.<sup>688</sup>) The program has been developed

at the ab initio SCF level, with use of the electron-hole potential (EHP) method<sup>335</sup> for excited states.

A more general version of this method has been recently elaborated by Aguilar et al.<sup>179</sup> The surface charge distribution  $\sigma_{E,slow}$  is here computed directly. This requires the explicit consideration of special electrostatic boundary conditions at the cavity surface, different from those valid in the static case. A compact expression of the free energy functional is also given. The computational package is no longer limited to the study of electronic transitions and allows one to make calculations at the SCF (RHF, UHF), MCSCF, and CI levels. The renormalization of the surface charges  $\sigma_{slow}$  and  $\sigma_{fast}$  plays an important role, as in the equilibrium model. The renormalization conditions are

$$\int_{\Sigma} \sigma(\mathbf{s}) d^2s = -\frac{\epsilon_0 - 1}{\epsilon_0} Q_M = Q_{fast} + Q_{slow} \quad (167)$$

$$Q_{slow} = \int_{\Sigma} \sigma_{slow}(\mathbf{s}) d^2s = -\frac{\epsilon_0 - \epsilon_{\infty}}{\epsilon_0} Q_M \quad (168)$$

$$Q_{fast} = \int_{\Sigma} \sigma_{fast}(\mathbf{s}) d^2s = -\frac{\epsilon_{\infty} - 1}{\epsilon_{\infty}} (Q_M + Q_{slow}) \quad (169)$$

The formulation of Basilevsky and Chudinov<sup>689,690</sup> is similar to that of Aguilar et al.,<sup>179</sup> although cast in a different form. The elaboration of the formalism is extended<sup>689</sup> to get the characteristic equation which determines the complex-valued frequencies  $\omega_{\nu}$  of the dielectric spectrum  $\epsilon(\omega)$ , necessary for dynamical treatments. In the implementation of the method, Basilevsky and Chudinov prefer, for technical reasons, an expression of the solute wave function in terms of CI expansions. In such a way the original idea of Marcus,<sup>672</sup> of using  $\mathbf{P}_{slow}$  as a dynamical variable, is extended to a collection of variables  $Y_{ab}$ , with indexes  $a$  and  $b$  running on the configurations included in the calculation.<sup>690</sup>

$$Y_{ab} = -\int d^3r \int_{\Sigma} d^2s \frac{\sigma_{slow}(\mathbf{s}) Q_{ab}(\mathbf{r})}{|\mathbf{s} - \mathbf{r}|} \quad (170)$$

where the  $Q_{ab}$  is a single state or transition density involving the configurations  $a$  and  $b$ . We note that  $\sigma_{slow}$  defines a two-dimensional continuum set of dynamical variables, which can be defined also for single-configuration (SCF) wave functions. This continuum may be discretized, when a description of  $\sigma$  in terms of point charges is adopted. In addition, the shape and location of the cavity surface may also be considered as a dynamical variable. The CI approach of Basilevsky and Chudinov has been applied, and extended, in a set of papers.<sup>691-695</sup>

We shall consider again the question of the dynamical variables in section VII.E.

### C. Solvent Effects on Electronic Spectra

Much attention was paid in the 1950s to the elaboration of models for the interpretation of solvent effects on the electronic states of a solute M, and on the frequency shift for absorption and emission spectra. Here we are interested in the approach

pioneered by Bayliss,<sup>696</sup> essentially on the basis of classical arguments, and then recast in a quantum mechanical formalism, using second-order perturbation theory as the starting point, by Ooshika,<sup>697</sup> McRae,<sup>698</sup> and many others.<sup>699-703</sup> Several detailed reviews are available; we refer to those given by Basu,<sup>704</sup> Mataga and Kubota,<sup>705</sup> Amos and Burrows,<sup>706</sup> and Suppan.<sup>707</sup>

The model is based on the use of the reaction potential concept, with partition into inertial (slow) and electronic (fast) components. In light absorption processes we are concerned with the energy difference between the solute in its ground state (GS) in equilibrium with the solvent, and in the excited state (EX) that experiences the inertial components of the GS reaction potential and the fast component related to the EX charge distribution. In fluorescence processes the energy difference regards the EX state in equilibrium with the solvent and the GS state feeling the inertial EX reaction potential and a fast contribution due to the GS charge distribution. This model is justified because the lifetime is in general long enough ( $\sim 10^{-8}$  s) to ensure solvent equilibration prior to the photon emission.

A number of approximations are then introduced, regarding both the solute model (reduced to a point dipole inside a spherical cavity), and the application of the second-order perturbation theory. In this way it is possible to write a compact formula, in which the main terms correspond to the Bell-Onsager formula for the solvation energy, computed with ground- or excited-state dipole moments ( $\mu_{GS}$  and  $\mu_{EX}$ ), and with the dielectric constants  $\epsilon_0$  and  $\epsilon_{\infty} = n^2$ . We report here McRae's expression<sup>698</sup> in Mataga-Kubota's formalism:<sup>705</sup>

$$\Delta \tilde{\nu}_{abs} = (A + B + C) \frac{n^2 - 1}{2n^2 - 1} + E_{abs} \left[ \frac{\epsilon_0 - 1}{\epsilon_0 + 2} - \frac{n^2 - 1}{n^2 + 2} \right] + F_{abs} \left[ \frac{\epsilon_0 - 1}{\epsilon_0 + 2} - \frac{n^2 - 1}{n^2 + 2} \right]^2 \quad (171)$$

$$\Delta \tilde{\nu}_{fluor} = (A + B + C) \frac{n^2 - 1}{2n^2 - 1} + E_{fluor} \left[ \frac{\epsilon_0 - 1}{\epsilon_0 + 2} - \frac{n^2 - 1}{n^2 + 2} \right] + F_{fluor} \left[ \frac{\epsilon_0 - 1}{\epsilon_0 + 2} - \frac{n^2 - 1}{n^2 + 2} \right]^2 \quad (172)$$

Terms  $A-F$  are functions of the properties of the solute: oscillator strength, dipole moments  $\mu_{GS}$  and  $\mu_{EX}$ , cavity radius  $a$ , etc. The dipole moments of the solute are present in the  $C$ ,  $E$ , and  $F$  functions:

$$C = \frac{\mu_{GS}^2 - \mu_{EX}^2}{hca^3} \quad (173)$$

$$E_{abs} = \frac{2\mu_{GS} \cdot (\mu_{GS} - \mu_{EX})}{hca^3} \quad (174)$$

$$E_{\text{fluor}} = \frac{2\mu_{\text{EX}} \cdot (\mu_{\text{GS}} - \mu_{\text{EX}})}{hca^3} \quad (175)$$

$$F_{\text{abs}} = \frac{6\mu_{\text{GS}}^2(\alpha_{\text{GS}} - \alpha_{\text{EX}})}{hca^6} \quad (176)$$

$$F_{\text{fluor}} = \frac{6\mu_{\text{EX}} \cdot (5\mu_{\text{EX}} - 2\mu_{\text{GS}})(\alpha_{\text{GS}} - \alpha_{\text{EX}})}{hca^6} \quad (177)$$

The solvent shift is thus reduced to a dispersion contribution, related to the  $A + B$  function, which produces a red shift, and to electrostatic contributions. The separation between inertial and fast polarization makes the difference between the absorption and emission shifts. The electrostatic contribution may lead to a blue shift, if  $\mu_{\text{EX}} < \mu_{\text{GS}}$ .

The other models mentioned at the beginning of this section lead to analogous formulas, with minor modifications. It is noteworthy that a different approach pioneered by Abe<sup>708</sup> leads to similar formulas (see e.g. Amos and Burrows<sup>706</sup>). Abe considers a discrete molecular picture of the solution, not introducing the reaction field picture, and performs appropriate averages on the molecule-molecule interactions.

All the methods mentioned thus far have not been conceived for numerical calculations, but rather to interpret and rationalize experimental data. Some of the factors appearing in the  $A-F$  functions can be estimated from experimental data, but often the analysis has been limited to the detection of a linear correlation with the dielectric constant function of eqs 171 and 172. As an example of successful application of this approach, we mention the studies of Ito et al.<sup>709</sup> on  $\Delta\nu_{\text{abs}}$  of ketones, of Robertson et al.<sup>710</sup> on  $\Delta\nu_{\text{abs}}$  of azulene, and of Kubota and Yamakawa<sup>711</sup> about the  $\Delta\nu_{\text{abs}}$  of pyridine and acridine  $N$ -oxides.

These formulas have been recast more recently in a form suitable for molecular calculations. The SCRF computational model of Tapia and Goschinski (a dipole reaction field for a spherical cavity, we recall) is suited for an immediate transcription of McRae's theory. Raudino, Zuccarello, and Buemi have developed some variants of this approach, using them in actual calculations on systems of chemical and biochemical interest.<sup>149,712-717</sup> The most detailed description is given in ref 714. The SCF ground state calculation is performed at the INDO/5 semiempirical level, the excited-state wave function via a single excitation configuration interaction procedure (SECI). Perturbation theory is applied to approximate the energy term connected with the solvent fast polarization, i.e. with the response to the change of the solute dipole due to the electronic transition.

Tapia's approach is improved by introducing in the reaction potential operator multipoles with higher  $l$  values. (In this paper the authors consider the rhodopsin system, which is rather asymmetric, and they find necessary to include terms up to  $l = 20$ .) The dispersion contributions are evaluated with an atom-atom Lennard-Jones (6-12) potential assuming that the solvent distribution is uniform.

This computational model has also been applied to systems exhibiting local and large-scale anisotropies

(effects of dielectric saturation, solutes near a lipid membrane-water interface).<sup>718-720</sup> In every case the cavity is spherical.

Another version of McRae's model, suited for molecular calculations, has been elaborated by Karelson and Zerner;<sup>283,284,291,721</sup> a detailed description is given in ref 721. A spherical cavity and a dipole reaction field are assumed; GS and EX wave functions are computed using INDO/S-CIS procedures (with the parameters obtained by Zerner<sup>722,723</sup>). The attention is focused on the Hamiltonian models to be used for the description of the electronic excitation process. A first model (A) defines the Hamiltonian as  $\hat{\mathcal{H}}_{\text{M}} = \hat{\mathcal{H}}_{\text{M}}^{(0)} + \hat{q}'_{\sigma}$ ; the interaction operator  $\hat{q}'_{\sigma}$  is determined at the SCF level for the ground state, and the same  $\hat{\mathcal{H}}_{\text{M}}$  is adopted in the CI calculation for the excited states; two terms, representing the work for slow and fast solvent polarization, are added to the total computed energy. In a second model (B), a different Hamiltonian is defined:  $\hat{\mathcal{H}}_{\text{M}} = \hat{\mathcal{H}}_{\text{M}}^{(0)} + \hat{q}'_{\sigma}/2$ ; no slow polarization term is added. Two variants of models A and B, called A1 and B1, are obtained by defining  $\hat{q}'_{\sigma}$  through a "mean" reaction field (an average of ground and excited state  $\Phi_{\sigma}$ ). All the four models are meant to represent electronic transition processes, with reasonable assumptions about the behavior of the solvent polarization in a very short time scale. However, these models are not equivalent among themselves, as shown also by the (relatively small) differences in the numerical results. Notice that the use of the  $\hat{\mathcal{H}}_{\text{M}}$  Hamiltonian in an iterative SCRF procedure is not equivalent to the minimization of the  $J(\Psi)$  functional (eq 71, section IV.A).

The computational models considered thus far are limited to spherical cavities. An ASC method accepting cavities of general shape has been proposed by Bonaccorsi et al.<sup>339-341</sup> This method has already been viewed in section VII.B; we add here that two versions have been presented for vertical (i.e. without changes in the geometry) absorption/emission processes. The first one, computationally more demanding, builds up iteratively a unique effective Hamiltonian for the GS and EX states, while the second version uses two different Hamiltonians. In this case the GS and EX wave functions are no longer orthogonal, but the effect of the fast component of  $\mathbf{P}$  is not so large as to compromise the ordering of the lowest energy levels of the solute. The model has also been extended to consider geometry rearrangements prior to the fluorescence or phosphorescence emission.

The same procedure has been applied by Fox et al.,<sup>189</sup> in conjunction with the semiempirical INDO/S-CI method. They compare it with a finite elements method, studying several rodlike molecules with charge-transfer transitions.

A more accurate PCM procedure to evaluate energy differences in light absorption phenomena has been recently presented by Aguilar et al.<sup>179</sup> (for comments see section VII.B).

Ooshika-McRae's model, which we have discussed here in formal and computer-suited formulations, singles out from a complex dynamical phenomenon two distinct steps that can be treated without explicit use of a time-dependent formalism. For each step,

we may consider an equilibrium polarization of the solvent (both  $\sigma_{\text{fast}}$  and  $\sigma_{\text{slow}}$  updated according to  $Q_M$ ), as well as nonequilibrium situations. We have discussed the expression of the free energy for the equilibrium situation in section IV.A. It is possible to define a free energy functional also for nonequilibrium polarization,<sup>179,686,687</sup> but attention must be paid in the application of this formalism to spectroscopic problems. The emission lifetimes (fluorescence and, a fortiori, phosphorescence) are normally long enough to ensure a complete relaxation of the inertial component of the polarization. However, time-resolved fluorescence studies may give information about the dynamics of this process. The reorganization of the solvent may be accompanied by changes in the solute geometry. Continuum methods may treat, at least in an approximate way, these phenomena too, but it is convenient to consider such processes as a specific case of chemical reactions, a subject that has been treated in section VI.

## D. Molecular Vibrations

The study of the vibrations of the solute presents dynamical aspects and may be considered in this section.

Let us first consider a model employed for many years to treat solvent effects on the properties of a vibrating solute. Some of the assumptions of the basic continuum model are maintained (isotropic dielectric medium without dispersion, infinite dilution). The vibrating solute is reduced to an oscillating dipole within a spherical cavity; this is an extension of Bell–Onsager model for a static solute. The expression of the solvent shift  $\Delta\nu$  is given by the so-called Kirkwood–Bauer–Magat formula:<sup>724</sup>

$$\frac{\Delta\nu}{\nu} = C \frac{\epsilon_0 - 1}{2\epsilon_0 + 1} \quad (178)$$

where  $C$  is a constant depending on the properties of the vibrating system.

Actually two separate derivations lead to the same eq 178, but with two different expressions for  $C$ . Kirkwood's derivation has not been the object of a specific publication; it was used for the first time by West and Edwards.<sup>725</sup> According to this model the frequency shift is due to an instantaneous change of the polarization of the medium as the molecule vibrates. The effect on the solvation free energy  $\Delta G_{\text{el}}(x)$ , where  $x$  is the elongation of the oscillator, may be evaluated with Bell's model, eq 23, using the Taylor expansion of the solute charge distribution  $\mu$ :

$$\mu = \mu_0 + \mu_1 x + \mu_2 x^2 + \dots \quad (179)$$

The modification  $\Delta k$  of the force constant is

$$\Delta k = \frac{\partial^2}{\partial x^2} \Delta G_{\text{el}}(x) \approx -2 \frac{\mu_1^2 + 2\mu_0\mu_2}{a^3} \frac{\epsilon_0 - 1}{2\epsilon_0 + 1} \quad (180)$$

The constant  $C$  in eq 178 is thus

$$C_K = - \frac{\mu_1^2 + 2\mu_0\mu_2}{a^3 k} \quad (181)$$

where  $a$  is the radius of the spherical cavity. West and Edwards<sup>725</sup> apply a more complex formula, suggested again by Kirkwood, corresponding to a dipole out of centre in the spherical cavity.

Bauer and Magat<sup>724</sup> remarked that the interaction with the medium modifies the static properties of the oscillator. In particular the equilibrium length  $l$  will be increased by an amount  $x_0$  which may be evaluated as

$$x_0 = \frac{1}{k} \frac{\partial^2}{\partial x^2} \Delta G_{\text{el}} = 2 \frac{\mu_0 \mu_1}{a^3 k} \frac{\epsilon_0 - 1}{2\epsilon_0 + 1} \quad (182)$$

The force constant  $k$  may be related to the length of the oscillator by an expression of the type

$$k = k_0 + fx \quad (183)$$

where  $f$  is an anharmonicity factor depending on the mathematical expression of the potential function (e.g. a Morse oscillator). The constant  $C$  in this model is

$$C_{\text{BM}} = \frac{f}{k^2} \frac{\mu_0 \mu_1}{a^3} \quad (184)$$

The Kirkwood–Bauer–Magat model has been refined (with extensions to polyatomic molecules) by many authors.<sup>726–735</sup> The dipole-in-a-sphere model has also been used to elaborate formulas for IR and Rahman intensities.<sup>727,728,736–743</sup> More recently the Bauer–Magat formula has been tested versus ab initio calculations.<sup>297</sup>

The relatively abundant literature, of which we have only quoted some significant examples, is based on the classical picture of the dielectric medium. Other approaches not based on a continuum model have been employed in more recent times and are presently applied with success. It is however beyond the scope of this review to examine these methods.

The application of quantum mechanical continuum methods to vibrations has been considered only in recent years. The schematic analysis of Kirkwood–Bauer–Magat model reported above shows that there are two kinds of effects to be considered. The first one is of static nature (Bauer–Magat model in our example) and the second one is of dynamical nature (Kirkwood model).

Considering typical vibration times (ranging in the interval  $10^{-14}$  to  $10^{-11}$  s) it is evident that the separation of  $\mathbf{P}$  into inertial and fast contributions ( $\mathbf{P} = \mathbf{P}_{\text{in}} + \mathbf{P}_{\text{el}}$ ) must be reexamined with care, taking into account the characteristics of the specific solute vibrations and the properties of the solvent.

Olivares del Valle and Tomasi<sup>744</sup> examined a sequence of models, for the case of the vibrations of M–H groups in isolated MH monomers and in hydrogen-bonded dimers (MH–MH). The ASC approach in the PCM formulation has been used for the evaluation of the potential energy as a function of the molecular elongation  $x = R - R_{\text{eq}}$ , with separate evaluation of mechanical and electrical anharmonicity contributions. The corresponding dipole moment  $\mu(x)$  is also computed, in order to determine the absorption intensities.

The models examined in this and subsequent works<sup>745,746</sup> are summarized in the following.

(1) The cavity is fixed, with the shape suitable for the equilibrium geometry, and the apparent charge distribution is also kept fixed as found in equilibrium calculations:

$$\sigma_1 = \sigma[\epsilon_0, \varrho_M(\mathbf{R}_{\text{eq}})] \quad (185)$$

here we have put in evidence that the calculations are performed using the static value  $\epsilon_0$  of the dielectric constant.

(2) The cavity shape is kept fixed as in 1, and  $\sigma$  is computed using the solute charge distribution  $\varrho_M(\mathbf{R})$  for each elongation  $x$ :

$$\sigma_2 = \sigma[\epsilon_0, \varrho_M(\mathbf{R})] \quad (186)$$

(3) The cavity is still fixed and  $\sigma$  is split in two parts: the first one is related to  $\epsilon_0$  and to the  $\varrho_M(\mathbf{R}_{\text{eq}})$  distribution; the other one is related to the optical dielectric constant  $\epsilon_\infty$  and to the difference  $\varrho_M(\mathbf{R}) - \varrho_M(\mathbf{R}_{\text{eq}})$  (equilibrium and instantaneous charge distribution):

$$\sigma_3 = \sigma[\epsilon_0, \varrho_M(\mathbf{R}_{\text{eq}})] + \sigma[\epsilon_\infty, \varrho_M(\mathbf{R}) - \varrho_M(\mathbf{R}_{\text{eq}})] \quad (187)$$

(4) The cavity follows the nuclear displacements, and  $\sigma$  is computed using at each geometry the corresponding wave function:

$$\sigma_4 = \sigma(\epsilon_0, \varrho_M(\mathbf{R})) \quad (188)$$

In this set of models both  $\sigma$  and the position of the cavity surface have been considered as possible dynamical variables (see section VII.B). Model 1 assumes a completely static description with charges frozen at the equilibrium values; model 4, on the other hand, assumes a perfect following, without any time lag.

The static description 1 gives poor results for the MH (and (MH)<sub>2</sub>) systems thus far examined, particularly when one considers displacements large enough to feel overtones and anharmonicity contributions. Model 4 neglects all the delay effects, which have an important role in proton-transfer processes and presumably in accurate studies of M–H vibrations. Models 2 and 3 yield estimates of the properties of M–H vibrations, particularly of the harmonic frequency, in reasonable agreement with scanty available experimental data. These models (and others of similar nature, not considered here for brevity) try to mimic the dynamical behavior, for which more refined formal elaborations (e.g. Baňacký and Zayak<sup>747,748</sup>) have not yet found a computational realization.

The modeling of M–H vibrations cannot be considered completely satisfactory, and further efforts are necessary. The results obtained thus far, however, are sufficient to have a guess on the frequency shift  $\Delta\nu(\text{M–H})$  for groups involved in hydrogen bonds with solvent molecules, and for the related changes of the zero-point energy of the solute. Reference 745 points out the importance of an accurate description of the surface charge distribution.

In passing to vibrations with lower frequencies the completely static description becomes untenable. A case studied with some attention is the bending vibration of water, including effects due to electron correlation. (A summary of the results can be found in ref 746.) For slow vibrations, especially when involving large amplitude motions, approximation 4 seems to be preferable.

Wiberg and co-workers<sup>297</sup> have elaborated a method to compute the harmonic frequencies of the solute in the framework of the GAUSSIAN programs. The procedure to get analytical expressions of the second-order derivatives with respect to normal coordinates is quite elegant and effective.

The method, to our knowledge, is limited to the case of a spherical cavity with a dipole reaction field; in the evaluation of the harmonic frequencies the cavity and the reaction field are kept fixed. The model is thus a version of approximation 1 presented above; some inconveniences of this approximation are probably smeared out in medium-size molecules, but the results obtained with this procedure must be taken with caution.

## E. Dynamical Aspects of Chemical Reactions

The static descriptions of the chemical reactions in solution with continuum models have been considered in section VI.B. We shall examine now some dynamical aspects of the reactions, using again the continuum model.

The starting point is represented by the  $G(\mathbf{Q})$  hypersurfaces, defined in section VI.B, as the analogue in solution of the  $E(\mathbf{Q})$  hypersurfaces.<sup>590</sup> For a given reaction the space of the nuclear coordinates in solution  $\{\mathbf{Q}\}$  may differ from that in vacuo,  $\{\mathbf{Q}_v\}$ , as already said, because some solvent molecules may play a specific role, and their coordinates must then be inserted in the  $\{\mathbf{Q}\}$  space.

The presence of the solvent introduces other changes in the dynamics of reactive processes. The relative motions of the atoms of the reacting system are subject to friction and random forces. These forces act during the whole reaction process, but their effect will be more evident in two distinct steps, the approach of reactants in bimolecular processes (as well as the separation of products) and the crossing of the energy barrier. Continuum models are giving important contributions to the study of diffusion processes, especially in the case of structured anisotropic media. We shall not consider this topic here.

The solvent friction effects during the crossing have a remarkable influence on the rate constant. They are generally described using Kramers<sup>749</sup> or Grote–Hynes<sup>750</sup> theories, based on the Langevin and generalized Langevin equations, and successive modifications.

Kramers formulation is directly related to the continuum description of the medium: the “hydrodynamic” friction constant  $\xi$  does not make reference to a discrete solvent. In the Grote and Hynes model, the time correlation function  $\langle RR(t) \rangle$  of the solvent random forces  $R$  enters the expression of the friction constant,  $\xi(t) = (1/kT)\langle RR(t) \rangle$ . In this way they introduce corrections related to the discreteness of the solvent random motions.

However, other factors could be considered. During a large part of the reactive trajectory of a system of medium size, the solvent has time enough to rearrange itself, and the  $G(\mathbf{Q})$  surface calculated in the equilibrium approximation may suffice. There are however limited regions of the trajectory where this approximation is no longer acceptable because large changes in the solvent polarization should occur in a short time; dielectric solvent retardation effects are here important. It is then necessary to increase the number of dynamical variables, by adding to the solute degrees of freedom one or more solvent coordinates.

A limiting case may here be considered as an example. In the outer-sphere electron-transfer reaction mechanism between two spherical ions, there is no change in the first solvation shell radii during the ET process, according to Marcus' model.<sup>672-676</sup> The barrier for the electron transfer appears in a "solvent coordinate"  $s$  which measures deviations from the equilibrium distribution of the solvent. The  $s$  coordinate has been defined by Zusman<sup>751</sup> in terms of an electrostatic continuum model as

$$s = \int_{\text{solv}} (\mathbf{F}_R^0 - \mathbf{F}_P^0) \cdot [\mathbf{P}(\mathbf{r}) - \mathbf{P}_R^{\text{eq}}(\mathbf{r})] \, d\mathbf{r} \quad (189)$$

where  $\mathbf{F}_K^0$  is the electric field in vacuo generated by the solute ( $K = R$ , reactants;  $K = P$ , products),  $\mathbf{P}_R^{\text{eq}}$  is the equilibrium polarization of the solvent and  $\mathbf{P}(\mathbf{r})$  is the actual time-dependent polarization (see also Alexandrov<sup>752</sup> and Calef and Wolynes<sup>753</sup>).

Another definition of  $s$  has been recently given by Cossi et al.<sup>754</sup> using the PCM algorithm. In this case  $s$  is defined in terms of the radii of the cavities surrounding the two ions. The dynamical effects are represented by deviations of these radii from the equilibrium values.

A decisive step in the definition of combined solute and solvent coordinates is presented in some papers by van der Zwan and Hynes<sup>755</sup> and by Lee and Hynes.<sup>687</sup> The continuum model is recast in terms of an explicit solvent coordinate  $s$  depending on the distance between two solute partners in the reaction.

The physical modeling of the reactive dynamics has progressed much in the last years. An excellent introduction to this field may be found in the clear and authoritative review by Hynes.<sup>756</sup> In the last years, progress in this field has been stimulated by the increasing reliability and efficiency of computer simulations, by the use of new experimental techniques and by recent developments in the basic underlying theory.<sup>757</sup>

A "deluge" of papers, to quote Weaver from his recent review,<sup>684</sup> cover electron-transfer (ET) reactions, with a variety of approaches. There is, however, a clear tendency to extend continuum models from ET to reactions of other type, such as proton transfer,  $S_N2$ ,  $S_N1$ , etc. We cannot extend the present review to a systematic examination of these recent methods and applications, not even limiting it to methods in which the continuum model plays a key role. The subject well deserves a separate review. We shall limit ourselves to outlining how the process of "chemical appropriation", mentioned in the introduction, is developing also in this field. For poly-

atomic complex systems the use of a single dynamical coordinate  $s$ , as in Marcus' theory of ET and in its generalizations, may not be sufficient. An increase in the number of coordinates is also suggested by the availability of more sophisticated solute wave functions.

Both the polarization vector  $\mathbf{P}_{\text{in}}$  and the corresponding reaction potential  $\hat{q}'_{\sigma,\text{in}}$  may generate a three-dimensional continuum of coordinates. A set of dynamical variables of a lower dimensionality is given by the  $\sigma_{\text{in}}$  charge distribution, in methods using the apparent surface charge (ASC) approach. In the PCM the set of coordinates is reduced to a discrete number, related to the radii defining the cavity and to the set of surface charges  $q_{\text{in},k}$ ; the index  $k$  runs over the representative points selected on the solute surface.

These possibilities have been exploited in preliminary studies of several groups. Truhlar and co-workers<sup>758</sup> use  $\mathbf{P}_{\text{in}}$  without resorting to apparent charges. A solvent coordinate  $s_\alpha$  is defined for each internal coordinate  $Q_\alpha$  of the solute; this formulation allows one to extend to molecules in solution the algorithms and concepts of the variational transition state theory. The main advantage of this model is its generality, which makes it suitable for the treatment of large classes of reactions.

Basilevski-Chudinov's approach<sup>689-695</sup> is formulated in the framework of the PCM computational scheme. A configuration interaction (CI) formulation of the solute wave function is adopted.<sup>692,693</sup> The CI formulation leads to the definition of a larger set of dynamical variables  $Y_{ab}$  (see eq 170), each one involving a couple  $a, b$  of configurations. This formulation has been used to describe the dynamics of the reaction in the limit of the Born-Oppenheimer (BO) approximation.<sup>691,695</sup> It is in fact customary to examine dynamical phenomena in solution with the aid of two extreme models, namely the BO and the self consistent (SC) ones; the former assumes that electron motions in the solute are slower than in the solvent, the latter the opposite. The BO approximation may suggest the use of a direct reaction field (DRF, see section IV.B.5) approach, while the SC approximation requires equilibration of both components of  $\mathbf{P}$  with an averaged distribution of the solvent (it is also called mean field approximation).

Basilevski and Chudinov have compared the SC and BO limits with realistic molecular calculations, in a case where it is necessary to consider a reaction coordinate  $p$ , drawn from the nuclear conformation space  $\{\mathbf{Q}\}$ . For the  $S_N2$  reaction  $\text{Cl}^- + \text{H}_3\text{CCl} \rightarrow \text{ClCH}_3 + \text{Cl}^-$  they found no significant differences between the SC and BO limits.<sup>694</sup> In this study the reaction coordinate  $p$  is discretized in a finite number of points,  $p_\alpha$ . For each integer  $\alpha$  the equilibrium value of the set  $\{q_k(\alpha)\}$  of apparent surface charges and the corresponding solute charge distribution  $q_M(\alpha)$  are computed. Then for each  $\alpha$  a set of nonequilibrium values, one for each  $\beta \neq \alpha$  is obtained. The nonequilibrium solvent charges are denoted with  $\{q_k(\alpha, \beta)\}$ ; for each  $\alpha, \beta$  pair there will be a solute charge distribution  $q_M(\alpha, \beta)$  obtained with the solute at the geometry  $p_\alpha$  and the apparent charges  $\{q_k(\beta)\}$ . In this way a two-dimensional  $G_{\text{el}}(\alpha, \beta)$  surface is

obtained; the first coordinate corresponds to  $p$  with equilibrium solvation, the second is a solvent variable. Basilevski and Chudinov do not treat explicitly the problems related to the shape of the cavity; the  $\alpha$  and  $\beta$  indices cannot be too different, otherwise unphysical effects arise in the evaluation of  $G_{el}(\alpha, \beta)$ , due to the excessive displacement of the  $\{q_k(\beta)\}$  charges with respect to the solute van der Waals surface.

We note that the couple  $\alpha, \beta$  corresponds to the couple "earlier" (E)–"actual" (A) introduced by Aguilar et al.<sup>179</sup> (see section VII.B). The formulas given in the latter work correspond to the SC limit. In another paper Aguilar et al.<sup>759</sup> define the main solvent dynamical variable in terms of the cavity shape, testing again the model on a  $S_N2$  reaction. In the reaction there is a net flow of representative points on the potential hypersurface starting from the reactant side and reaching the product side. For this kind of trajectories there will be a dielectric friction retarding the motion; as a result, the barrier is higher and displaced toward the products. The backward trajectories will feel a similar retardation effect; at the equilibrium the net flux will be zero. For each trajectory we define an appropriate delay for the center of each sphere defining the cavity. The position of the nucleus I is a function of the reaction coordinate,  $\mathbf{s}_I = \mathbf{s}_I(p_\alpha)$ . The corresponding sphere, however, is not centered in  $\mathbf{s}_I(p_\alpha)$ , but in a point corresponding to an earlier time,  $\mathbf{s}_I(p_\beta) = \mathbf{s}_I(p_\alpha) - \Delta\mathbf{s}_I(p_\alpha)$ . Here  $p_\beta$  precedes  $p_\alpha$  along the reaction coordinate. The positional delay is assumed to depend on the velocity of atom I and on the rate of change of its electric charge.

A novel feature in the description of dynamical aspects of reactions is the introduction of a full quantization of  $\mathbf{P}_{el}$  presented by Kim and Hynes.<sup>757</sup> The quantization of  $\mathbf{P}_{el}$  is performed via a coherent state formulation, coupled with a MCSCF representation of the wave function. This feature makes the extension to larger basis sets and to larger solutes relatively easy. The approach is applied to a rapidly growing number of chemical problems; we quote here applications to  $S_N1$  reactions,<sup>760–763</sup> proton transfer,<sup>764</sup> and  $S_N2$ .<sup>765</sup> A recent review on the results thus far obtained with the Kim and Hynes approach<sup>765b</sup> gives a clear indication of its potentiality. The examples shown here indicate that several groups are working at the formulation of a "classical" model. Much more work is needed, but the perspective of using these rather sophisticated continuum models in extensive chemical calculations in a time not too far away is realistic.

To end this section, we detail an attempt to model, via the continuum PCM approach, the effect of stochastic solvent fluctuations on chemical reactions.<sup>766</sup> An explicit consideration of stochastic fluctuations is not possible in the primitive model; the mean force potential (i.e.  $G$ ) averages out the fluctuations,  $G$  being the minimum of the free energy functional. We have to abandon the canonical description, and the computed energetic quantity loses the status of a free energy. We may thus invoke local fluctuations in energy, with frequency, intensity, and duration to be appreciated with the aid of molecular

dynamics simulations in pure solvent.<sup>767–769</sup>

Suitable supermolecule calculations on solvation clusters allow the connection of energy fluctuations, and related changes in the structure of the first solvation shells, to changes in the solvent reaction potential; in the PCM the latter may be modeled by altering some of the  $\{q_k\}$  charges, via appropriate  $\lambda_k(t)$  factors. In such a way it is possible to follow the reaction dynamics and to compute the reaction kinetic parameters with a given set of  $\lambda_k(t)$  values. This has been done for a  $S_N2$  reaction with the assumption that  $\lambda_k(t) = \lambda_k(0)$ . (The mean lifetime of a solvent fluctuation is longer than the time required to cross the barrier for the  $S_N2$  reaction here considered.) An average over the possible  $\{\lambda_k(t)\}$  values must be performed. Solvent fluctuations can be introduced in the study of chemical reactions in more effective ways; however, as shown by this example, alternate applications of the continuum model are possible, and the sampling of a two-dimensional space (that of the apparent charge distribution  $\sigma$ ) may replace a more demanding sampling of solvent conformations.

### VIII. Inhomogeneities and Anisotropies in the Solvent

The modeling of the solvent as an infinite linear isotropic dielectric medium with  $\epsilon$  described by a step function

$$\epsilon = 1 \quad \text{in the cavity} \quad (190)$$

$$\epsilon = \epsilon_0 \quad \text{out of the cavity}$$

obviously is not a suitable approximation in many cases. We shall consider in this section some modified versions of the basic model not involving time dependency. It is convenient to collect all the modifications under the common heading "anisotropies" and to introduce then a classification of these anisotropies.

The anisotropies may have a local character, or act on a large scale. Local anisotropies are limited to a portion of space near the solute or to other finite regions of space; large-scale anisotropies may affect the whole infinite medium, or larger portions of the space out of the cavity.

#### A. Local Inhomogeneities

The presence of a solute induces a local disturbance in the distribution of the solvent (the so-called cybotactic regions). The effect of these disturbances is evident in the radial distribution functions of the solvent atoms, which typically exhibit a positive deviation corresponding to the first solvation layer, followed by a more or less pronounced oscillatory behavior reaching the unit value characteristic of the bulk solvent.

These disturbances are more evident when the solvent is a supercritical fluid, or when there is a strong solute–solvent interaction, as in the case of charged solutes in polar solvents. We do not consider here the case of supercritical fluids (quite interesting, indeed), and we focus our attention on charged solutes. The local anisotropies induced in the solvent may be reduced, to a first approximation, to the combination of two effects: dielectric saturation and electrostriction, acting in opposite directions. It is



generally accepted that dielectric saturation is more important than electrostriction, although recent computer simulation studies<sup>92</sup> show that for singly charged ions the two effects are comparable.

The nonlinear effects on the polarization may be expressed in terms of a series development of the polarization vector  $\mathbf{P}$  with respect to the electric field  $\mathbf{F}$ .<sup>24</sup>

$$\mathbf{P} = \chi\mathbf{F} + \xi F^2\mathbf{F} \quad (191)$$

The expansion is generally truncated to the second term, related to the third power of  $F$ . Experimental data on nonlinear effects derive from measurements of the dielectric displacement  $\mathbf{D}$ , performed by superposing a weak alternating field to a strong dielectric field; the quantity accessible to measurements is thus an incremental (field-dependent) dielectric constant  $\epsilon_F$ .

We have

$$\mathbf{D} = \mathbf{F} + 4\pi\mathbf{P} = \epsilon_0\mathbf{F} + 4\pi\xi F^2\mathbf{F} \quad (192)$$

and

$$\epsilon_F = \frac{\partial D}{\partial F} = \epsilon_0 + 12\pi\xi F^2 \quad (193)$$

The nonlinearity is defined as

$$\frac{\Delta\epsilon}{F^2} = \frac{\epsilon_F - \epsilon_0}{F^2} = 12\pi\xi \quad (194)$$

When  $\mathbf{F}$  is the field produced by the solute, a direct determination of  $12\pi\xi$  is not possible and experimental values have been used as indirect check of models describing  $\epsilon(F)$ . We have reported eqs 192–194 as a help for the reader interested in a reappraisal of the literature.

### 1. Continuous $\epsilon(F)$ Functions

When the solute is a spherical ion it is immediate to transform  $\epsilon(F)$  into  $\epsilon(\mathbf{r})$ . The explicit dependence of  $\epsilon$  upon  $\mathbf{r}$  is also used for nonspherical solutes, with or without a net positive charge.

We report here a selection of the many functional expressions proposed in the literature for  $\epsilon(\mathbf{r})$ .<sup>770–789</sup> The seminal papers of Debye,<sup>790</sup> Sack,<sup>791,792</sup> Onsager,<sup>22</sup> and Kirkwood<sup>793</sup> give the background of these formulations. The thermodynamics of ion solvation constitutes the principal (if not unique) test of their validity. Some expressions (e.g. ref 776) are merely empirical fittings of numerical results, others are based on intuition (e.g. refs 772 and 780) or selected on the basis of their simple analytical form.<sup>779</sup>

The first attempt of a more rigorous derivation is due to Booth,<sup>773</sup> on the basis of Onsager–Kirkwood–Frölich methods. Until recent times the Debye–Sack theory had been neglected because of the claims of inadequacy expressed by Onsager and Kirkwood, but it has been recently vindicated by Ehrenson<sup>789</sup> with a careful analysis (see also the works of Kakitani and Mataga<sup>794</sup> and of Bucher and Porter<sup>781</sup>).

The most used  $\epsilon(\mathbf{r})$  function is that proposed by Block and Walker,<sup>779</sup> for its simplicity and because it has been adopted by Abboud and Taft<sup>795</sup> and by

Abe<sup>796</sup> in papers with high impact:

$$\epsilon(\mathbf{r}) = \epsilon_0 \exp\{-\kappa/r\} \quad (195)$$

with  $\kappa = a \log \epsilon_0$  and  $a =$  ion radius.

Other expressions have been less used, in spite of their more consistent theoretical formulation. We quote here the formulas proposed by Booth,<sup>773</sup> Bucher and Porter,<sup>781</sup> and Ehrenson.<sup>789</sup> According to Booth we have

$$\epsilon(\mathbf{r}) = n^2 + \frac{\alpha\pi N\mu(n^2 + 2)}{F} L(y) \quad (196)$$

where  $y = [\beta\mu(n^2 + 2)F]/kT$  and  $L(y) = [\coth y - 1/y]$  is the Langevin function. Here  $n$  is the refractive index;  $N$ , the number of solvent molecules per unit volume;  $F$ , the field strength;  $T$ , the absolute temperature; and  $\alpha$  and  $\beta$  are numerical constants ( $4/3$  and  $1/2$  respectively, in the simplest formulation).

The expression derived by Bucher and Porter reads

$$\epsilon(\mathbf{r}) = 1 + \frac{\epsilon_\infty - 1}{\epsilon_\infty + 2} + \frac{4\pi\mu r^2}{Fv} L(y) \quad (197)$$

with  $y = [\epsilon(\mathbf{r}) + 2]F\mu/[3kT r^2\epsilon(\mathbf{r})]$  and  $v$  is the volume occupied by a solvent molecule. The expression given by Ehrenson is similar to eq 197. It must be remarked that even implicit transcendental expressions like eq 197 can be easily used when applied to the evaluation of  $\Delta G_{el}$  solvation energies for spherical ions.

The examination of the  $\Delta G_{el}$  values for a set of ionic solutes is an indirect way of assessing the relative merits of the various expressions of  $\epsilon(\mathbf{r})$ . Actually, the calculation of  $\Delta G_{el}$  benefits from the substitution of the step function, eq 190, with an expression for  $\epsilon(\mathbf{r})$  smoothing the change from  $\epsilon = 1$  to  $\epsilon = \epsilon_0$  (bulk). However, the functional dependences 195–197, as well as several others, are almost equally effective under this respect.

Ehrenson<sup>789</sup> has shown that the Block–Walker expression belongs to a family of functions, all leading to an analytical solution for the radial potential  $\Phi(r)$  of a dipole at the centre of a spherical cavity:

$$\epsilon_n(\mathbf{r}) = \epsilon_0 \exp(-\kappa_n/r^Z) \quad (198)$$

with  $Z = 1/n$ ,  $n = 1, 2, 3$ , etc., and  $\kappa_n$  fixed by the boundary conditions. Several  $n$  values give equally reasonable values of  $\Delta G_{el}$  (ion). Abraham et al.<sup>797</sup> remarked that starting from Stiles'  $\epsilon(\mathbf{r})$  function<sup>780</sup> it is possible to derive other expressions, giving reliable values of  $\Delta G_{el}$  (ion). Stiles' function is

$$\epsilon(\mathbf{r}) = \epsilon_a(\epsilon_0/\epsilon_a)^{f(r)} \quad a \leq r \leq b \quad (199)$$

$$f(r) = 1 - \left[\frac{b-r}{b-a}\right]^2 \quad (200)$$

where  $\epsilon_a$  is the dielectric constant of the internal zone (set equal to 2),  $a$  is the ion radius and  $b$  another radius at which the dielectric function assumes the bulk value  $\epsilon_0$ . Abraham et al.<sup>797</sup> replace  $f(r)$  with the following expression:

$$f(r) = 1 - \left[ \frac{b-r}{b-a} \right]^n \quad (201)$$

with  $n = 2.0, 1.0, 0.5, 0.1$ . For each  $n$  value there is an optimum value of the parameter  $b$ .

Stiles, on the other hand, remarks that a simple linear relationship between  $\epsilon_a$  and  $\epsilon_0$  gives practically equivalent results.

It is clear that the examination of the  $\Delta G_{el}$  (ion) values cannot give a definitive answer. Other arguments put forward in this debate (e.g. congruence with shell models) have an indirect impact. Quite probably a better insight will be possible when reaction field potentials for nonspherical solutes, obtained with accurate and reliable computer simulations, will be available. A comparison with  $\Phi_c$  values computed with continuum methods will permit more precise assessment of the physical eligibility of the various  $\epsilon(\mathbf{r})$  functions.

As a help for this future investigation, we have recently elaborated a version of the PCM procedure which uses  $\epsilon(\mathbf{r})$  functions.<sup>798</sup> This PCM version maintains many of the features of the original isotropic version (quantum mechanical formulation, cavities of general shape, calculation of the electric field  $\mathbf{F}$  without approximations, etc.) and accepts  $\epsilon(\mathbf{r})$  functions of any type (up to this time calculations have been performed with the simple Block-Walker and Stiles' expressions only). The most important difference with respect to the isotropic version is that the electrostatic problem is no longer treated with a boundary element method (BEM) but rather with a finite element method (FEM), to take into account the effects due to the three-dimensional distribution of apparent charges  $q_b$  (remember that only in isotropic media the apparent polarization charge may be reduced to a surface charge  $\sigma$ ).

## 2. Step Functions

An alternate way to describe local anisotropies consists in replacing the one-step dielectric function 190 with a multistep function. Within each domain  $\epsilon$  is constant. This is a particular case of a more general problem in which the whole external space is partitioned into exclusive domains, with sharp boundaries each characterized by its own dielectric constant. A general solution for this problem in the framework of quantum mechanical continuum cavity models has been elaborated by Bonaccorsi et al.<sup>417</sup> and later by Hoshi et al.<sup>181</sup> These general formulations are of interest for large-scale anisotropies and will be considered in the next section.

The one-layer model for a spherically symmetric ion is defined by

$$\begin{aligned} \epsilon &= 1 & \text{for } r < a \\ \epsilon &= \epsilon_a & \text{for } a \leq r < b \\ \epsilon &= \epsilon_b & \text{for } r \geq b \end{aligned} \quad (202)$$

The expression analogous to Born's eq 22 is in this case:

$$\Delta G = \frac{1}{2} \left\{ \frac{1 - \epsilon'_a}{\epsilon'_a} \frac{Z^2}{a} + \frac{1 - \epsilon_b}{\epsilon_b} \frac{Z^2}{b} \right\} \quad (203)$$

with

$$\epsilon'_a = \epsilon_a \left( \frac{(1 - \epsilon_a)(1 - \epsilon_b)}{\epsilon_b} \frac{a}{b} + 1 \right)^{-1}$$

The one-layer expression for a dipole in a spherical cavity has been first derived by Oster<sup>799</sup> as a generalization of Onsager's model. The expression for a general charge distribution inside a spherical cavity with a one-layer model has been developed by Beveridge and Schnuelle;<sup>800</sup> it is a generalization of Kirkwood's model (classical representation, no solvent polarization effects). A different generalization, to concentric multiple layer models with a single point charge has been considered by Abraham et al.<sup>801</sup> The classical multipole expansion method, used by Beveridge and Schnuelle, provides formidable mathematical expressions when applied to the case of a general distribution in multilayer models (we note, in passing, that the apparent surface charge (ASC) expressions are by far simpler to write and to implement in computational codes).

Abraham and co-workers have used their model, and in particular the simple one-layer model, in a set of papers on  $\Delta G_{el}$  for spherical ions<sup>797,801-805</sup> in a variety of solvents, with quite encouraging results. The free parameters of this model, namely the radii  $a$  and  $b$  and the dielectric constant  $\epsilon_a$  of the layer, may be assigned very reasonable values; namely,  $a$  is the ion radius,  $b - a$  is the radius of one solvent molecule,  $\epsilon_a = n^2$  (alternatively  $\epsilon_a = 2$ ).

The same one layer model has been considered in a still unpublished study (Bonaccorsi et al.,<sup>806</sup> see also Tomasi et al.<sup>68</sup>) with some differences with respect to Abraham's approach. The total values of  $G_{sol}$ ,  $H_{sol}$ ,  $S_{sol}$ , including also cavitation and dispersion-repulsion terms, are computed, instead of  $\Delta G_{el}$ ,  $\Delta H_{el}$ ,  $\Delta S_{el}$ , with the same set of parameters used by Abraham, with even better results.

The PCM procedure permits the extension of this approach to polyatomic ions in nonspherical cavities and in particular to ions in which the charge is localized in a portion of the molecule (for example protonated organic molecules). In these cases the additional layer no longer has a spherical symmetry and covers only a portion of the solute surface.

There are several other papers using layered models. We shall not report here, although interesting under many aspects, further applications of spherical concentric models. We quote some examples of extensions to nonspherical shapes. Gómez-Jeria and Morales-Lagos<sup>807,808</sup> have published the formulas for a general distribution within prolate or oblate ellipsoidal cavities surrounded by one or two layers of the same symmetry. Jayaram and Beveridge<sup>809</sup> have considered the case of an arbitrary charge distribution in a coaxial dielectric continuum. A layered model with a nonspherical cavity has been formulated by Kanesaka et al.<sup>810</sup> and used to study the IR intensity of the C-H stretch in  $\text{CH}_3\text{Cl}$ .<sup>811</sup> The extension of these layered models to properties other than  $\Delta G_{sol}$  has not yet been undertaken systematically.

One-layer and two-layer models are easier to use than continuous  $\epsilon(\mathbf{r})$  models; on the other hand the

continuous description is aesthetically more appealing, and a good  $\epsilon(\mathbf{r})$  model is closer to the physical reality than layered models. Other reasons suggesting a choice between these two options will probably become decisive when local anisotropy models are applied to different phenomena, for example of dynamical nature.

### 3. More than One Solute Molecule

The last type of local anisotropy we shall consider is due to the presence of another solute molecule. Formally the problem is simple when the surrounding medium is represented by a continuum dielectric. Explicit formulation in the multipole expansion approach, and coding of the corresponding computational procedure, are however complex tasks. The apparent surface charge approach is by far more convenient.<sup>250</sup>

The inclusion of local anisotropies around each solute is feasible, either in the  $\epsilon(\mathbf{r})$  or in the layered model. This last has been coded and applied in test PCM calculations. Tests on the free energy profile for the approach of a couple of ions (of opposite as well as of equal charge) have been performed. The results show that the monotonic energy profile given by the basic continuum model is modified by the presence of local minima, roughly corresponding to solvent-separated ion pairs. Models including an appropriate  $\epsilon(\mathbf{F})$  function quite probably would give a more realistic description of this phenomenon, often considered as an example showing the intrinsic inability of the continuum models to describe specific solvent effects at the molecular scale.

The problem of two ions approaching in a continuum medium has been considered by many authors, often using a rough version of the basic PCM model. More detailed studies have been performed e.g. by Rashin<sup>812</sup> and by Contreras et al.<sup>813</sup> The description of two or more solutes separated by the solvent is of primary interest in treating bimolecular reactions, as already observed in section VI.B.

## B. Large-Scale Inhomogeneities

There is a wide variety of large-scale inhomogeneities, regarding different areas of the physicochemical domains. We cannot give a systematic survey, even if limited to methods using a continuum model. Suffice it to say that inhomogeneities of this kind are important in liquid-surface phenomena (liquid-air, liquid-liquid, liquid-solid), in the study of dispersions, micelles, vesicles, capillarity phenomena, membranes, bidimensional phases, dissolution of solids, etc., of interest in different disciplines such as catalysis, electrochemistry, biochemistry and biophysics, environmental sciences, etc.

In reality all these phenomena are connected by some common features acting at the molecular level. In many cases a simple classical formulation of the continuum model has been employed, and this level of accuracy may provide an interpretation of the basic aspects of the phenomenon. The evolution of the research leads however to finer descriptions, in which the chemical details of the problem are considered. We shall limit ourselves to a few examples directly

related to the quantum methods exposed in this review, without any claim of completeness.

### 1. Two Semi-infinite Dielectrics

The simplest case is that of two semi-infinite dielectrics separated by a plane. The two dielectric model may be applied to liquid-vapor, liquid-liquid, and liquid-solid systems. Near the separation surface the physicochemical parameters depend upon the nature of the interface, the chemical composition of the two subsystems, and other factors (typically the temperature and the presence of electric fields).

An accurate modeling of these local conditions depends on the availability of experimental data and computer simulation results (also physical methods for the study of solutions may give valuable contributions). Continuum methods exploit, *prima facie*, information coming from other sources, but may give a support for refinements of the model. This is one of the fields in which the interaction among different approaches, which we advocated in the Introduction, may give fruitful results.

One has not, in general, much information about density and dielectric constant profiles in the interface region (a third factor, i.e. the occurrence of electric fields in the contact region between two neutral dielectrics,<sup>814</sup> is generally neglected). One of the simplest cases is the interface between a polar liquid (e.g. water) and a hydrocarbon (e.g. benzene); for Monte Carlo simulations on this system see Linse.<sup>815</sup> There is a small admixture of molecules belonging to the two phases, and the small deviations of density with respect to the bulk values are limited to one molecular diameter. The separation surface is an almost perfect plane, with scattered "fingering" (i.e. small capillary waves of molecules of one phase protruding in the other one). Bonaccorsi et al.<sup>816</sup> have studied the conditions of equilibrium of linear primary alcohols and amines ( $C_nH_{2n+1}X$  with  $X = OH$  or  $NH_2$  and  $n = 1-8$ ) at water-hydrocarbon interfaces; they find a buoyancy equilibrium on the surface for the solutes with  $n > 1$ , with the polar head in the aqueous solution and the hydrocarbon tail in the other medium. Calculations have been performed with the standard PCM procedure, supplemented by another set of apparent charges on the separation surface.

In a further study Bonaccorsi et al.<sup>817</sup> improve the method and present sets of two dimensional maps of  $G$  for  $CH_3OH$  and  $CH_3NH_2$  in the whole water-benzene system. We have already noted that the energetic quantity coming out from the calculation is a "starred" quantity (i.e.  $G^*$ ) in Ben-Naim's terminology, namely a quantity computed assuming that the solute occupies a fixed position in the liquid. In infinite isotropic liquids the value of  $G^*$  does not depend upon the position one has selected: to calculate more precisely the free energy one has to consider an additional term, the "liberation free energy", easy to compute. In restricted systems  $G^*$  depends on the position; in the case presented here it depends on the distance  $z$  of the solute from the interface and on the Eulerian angle  $\Omega$  defining its orientation:  $G(z, \Omega)$ . The improvements of the computational model mainly regard the description of the

portion of space not allowed to the solvent. When the solute is close to the boundary surface, there may be not enough space to accommodate a solvent molecule. In the case of liquid–liquid boundaries this space cannot be left void, therefore the boundary is modified by introducing a local concavity or convexity, such as to fill the void with the most appropriate solvent.

Dispersion contributions, computed with a suitable modification of the model elaborated for isotropic liquids,<sup>521</sup> introduce minor changes in the  $G(z, \Omega)$  surfaces.<sup>818</sup> Floris<sup>819</sup> has shown that the energy profile for the crossing of the boundary in water–benzene and similar systems is given by the combination of electrostatic ( $\Delta G_{el}$ ) and cavitation ( $\Delta G_{cav}$ ) effects, while dispersion–repulsion contributions play a minor role (for an example see ref 67).

Unpublished studies on water–air systems have been performed by Bonaccorsi within the same approach. The preliminary results on the preferred orientation of the solvent molecules, as well as of solute molecules bearing an OH group, such as  $\text{CH}_3\text{OH}$  and  $\text{C}_6\text{H}_5\text{OH}$ , are in agreement with molecular simulation<sup>820–824</sup> studies and with second-harmonic generation experiments.<sup>825,826</sup> In addition, calculations give an estimate of the surface potential within the suggested estimate ( $+80 \pm 60 \text{ mV}$ )<sup>827</sup> and not far from a recent experimental determination.<sup>828</sup> However these values depend critically upon the choice of the cavity radius for H atoms (a reduction of  $R_H$ , suggested by Luque et al.,<sup>90,357</sup> gives a better agreement).

A similar approach has been used for the study of the desolvation of a substrate molecule entering the lock of an enzyme.<sup>829</sup> The enzyme is modeled as a large continuum dielectric body, with a planar (or moderately convex) surface and an indentation able to host the interactive portion of the substrate molecule. A complete version of the electrostatic problem (treated with the PCM formalism, at the quantum level) is accompanied by a set of faster versions to be used in routine calculations. The primary goal of this research is in fact the elaboration of an index based on the molecular electronic potential (MEP), to be used in the selection of appropriate enzyme–ligand interactions, a task requiring fast (but accurate) calculations.

Sakurai's group has recently considered decarboxylation reactions catalyzed by cyclodextrins with the aid of a two dielectric model.<sup>589</sup> The calculation of the activation energy is performed at MNDO level, using their version of the quantum ASC model (see section IV.3). The intramolecular cavity of cyclodextrin is approximated by a cylindrically shaped dielectric with  $\epsilon = 2.0$ . The pseudomolecular complex formed by the organic substrate and the cylinder is embedded into a medium with  $\epsilon = 80$ . The results agree with experimental evidence, in spite of the simplicity of the model.

## 2. More Complex Systems

We have delved into our files to give this overview of two dielectric models, because PCM and related ASC approaches represent, in our opinion, the most advanced elaborations presently available to describe

chemical phenomena at liquid–liquid and liquid–gas interfaces.

There is a larger number of studies on more complex anisotropic systems, such as a slab of liquid confined between two parallel conducting or dielectric walls, a cylindrical portion of liquid with appropriate boundary conditions, liquid wetting layers, etc. In most cases the attention is not paid to a refinement of the continuum model but rather to the specific properties of the system. In many studies the image charge approach results in being the most convenient, owing to its simplicity in the description of the solutes; for this reason we prefer not to extend this review further by treating subjects not of direct pertinence. It will suffice to repeat that also in these fields it is possible and convenient to apply more refined continuum models to describe chemical properties.

Several methodological progresses, worthy of further development, have appeared in the literature. For example we quote a study of liquid wetting layers, by Tarazona et al.,<sup>830</sup> introducing a “piecewise” dielectric constant, similar to those we have considered in multilayered models of local anisotropies.

Neither do we try to review the applications of continuum electrostatic methods to membranes, inverted micelles, or vesicles; a review by Honig et al.<sup>831</sup> may be suggested as a first guide in a field that has shown important progresses in recent years.

## C. Large-Scale Anisotropy in Homogeneous Dielectrics

As the last subject of this section we shall consider a linear nonisotropic dielectric. In this case the scalar permittivity  $\epsilon$  must be replaced by a tensor  $\epsilon$ . The problem is of interest for crystals (the dielectric model may be also applied to solids), liquid crystals, the interior of membranes, and limited portions of other liquids that for any reason exhibit a local order.

We shall consider the case of an infinite liquid, described by a linear nonisotropic dielectric, whose boundaries are limited to the solute surface and to infinity. Little attention has been paid to the evaluation of the solvation energy in liquids with long-range anisotropy. Studies on liquid crystals, which represent an important example of systems with tensor permittivity  $\epsilon$ , have been mainly addressed to the formulation of a theory of the pure liquid.<sup>24,832–837</sup> When internal and reaction cavity fields are necessary, as in the extensions of Onsager and Kirkwood–Frölich theories for the evaluation of the permittivity, the reaction field is reduced to that of a distributed dipole density, and the formal problem is solved with a transformation of the coordinate system:<sup>833</sup>

$$x \rightarrow x' = x \epsilon_{xx}^{1/2} \quad \text{etc.}$$

which is not suitable for the implementation of a quantum model.

The Laplace equation for anisotropic dielectrics takes the form

$$4\pi Q = -\text{tr}(\epsilon \nabla^2 \Phi) = -\left[ \epsilon_{xx} \frac{\partial^2}{\partial x^2} + \epsilon_{yy} \frac{\partial^2}{\partial y^2} + \epsilon_{zz} \frac{\partial^2}{\partial z^2} \right] \Phi \quad (204)$$

where we have chosen the suitable coordinate system to put  $\epsilon$  in diagonal form. This expression reduces to  $\nabla^2\Phi = 0$  only when  $\epsilon_{xx} = \epsilon_{yy} = \epsilon_{zz}$ .

It is reasonable to assume a step expression, analogous to eq 190, for our homogeneous dielectric. This being the basic assumption, the reaction field operator  $\hat{\mathcal{V}}_R$  to be inserted in the Hamiltonian

$$\hat{\mathcal{H}} = \hat{\mathcal{H}}^0 + \hat{\mathcal{V}}_R \quad (205)$$

is due not only to the apparent surface charge distribution  $\sigma$  as in the isotropic dielectric case, but also to an apparent volume charge distribution  $q_b$  (here  $\hat{\mathcal{V}}_R = \hat{\mathcal{V}}'_\sigma + \hat{\mathcal{V}}'_b$ ).

Mennucci et al.<sup>83b</sup> have implemented this model in the PCM formalism. Two versions have been considered: one treats the electrostatic problem without any further approximation, and the  $\sigma$  and  $q_b$  charge distributions are determined self-consistently, including the polarization effects on the solute charge distribution  $q_M$  as in the isotropic case; the other version considers  $q_b$  as a small perturbation, and calculates it with perturbation theory, using the self-consistent expressions for  $q_M$  and  $\sigma$ , and including at each SCF cycle the approximate expression of  $\hat{\mathcal{V}}'_\sigma$  in the Hamiltonian. The method may be considered as an admixture of BEM and FEM techniques, the former used for  $\sigma$ , and the latter for  $q_b$ .

A comparison with the  $\epsilon(\mathbf{r})$  PCM procedure considered in section VIII.A.1 may be of some help in the appreciation of the two computational strategies. In the  $\epsilon(\mathbf{r})$  problem the  $\sigma$  distribution disappears, and unless  $\epsilon(\mathbf{r})$  is a step function, we have instead a  $q_b$  distribution varying in a limited range of distances. (When the solute is of a large size, and the net charge is localized, the use of a mixed model is preferable; however, the  $\sigma$  charge description is preserved for the portions of the solute far from the net charge.) In the anisotropic homogeneous problem, on the other hand, the  $q_b$  distribution is spread out over a large portion of space, and the most important contribution to  $\hat{\mathcal{V}}_R$  comes from  $\hat{\mathcal{V}}'_\sigma$ . The computational strategy is thus different in the two cases.

Computational times are definitely longer in the anisotropic model than in isotropic ( $\epsilon = \text{constant}$ ), by a factor  $\sim 5$  for the simpler formulation using perturbation theory for  $q_b$ , and by a factor  $\sim 10$  for the exact formulation. The model has not yet been extensively applied to chemical problems, but some initial results deserve mention. The orientation of a polar solute in an anisotropic liquid is dictated by the effect of the  $q_b$  distribution. When such a solute experiences an appropriate electronic excitation (e.g.  $n \rightarrow \pi^*$  excitation of a C=O chromophore) the energy profile for different orientations of the solute changes remarkably, and the study of the evolution of the system after electronic excitation should include an extra coordinate, i.e. the orientation of the solute with respect to the axes of  $\epsilon$ .

## IX. Concluding Remarks

The continuum description of the solvent has provided in the past some very useful models for the interpretation of thermochemistry, reactivity, and spectroscopy in solution. In the last 20 years, several

approaches have been devised to perform accurate calculations of free energy surfaces as functions of the solute internal coordinates. Quantum chemistry in solution has become an almost perfect counterpart of the well-established quantum chemistry of isolated molecules. The implementation of continuum methods in connection with different kinds of semiempirical and ab initio treatments, and the development of automatic geometry optimization algorithms, will certainly favor the trend to consider "adding the solvent" as a standard option available to quantum chemists. The accuracy of the results has improved, when all the relevant components of the solvation free energy (not only the electrostatic one) have been properly taken into account, either by specific theoretical developments or by semiempirical parametrizations.

One of the distinctive advantages of continuum methods with respect to MM, MC or MD, namely that of offering a quantum mechanical treatment of the solute, is now challenged by the development of combined force field/quantal approaches. As continuum methods are generally much less demanding of computer resources, and their application is straightforward, they are ideally suited for the investigation of hypersurfaces. Moreover, the continuous description of part of the system can be combined in different ways with quantal or classical discrete models, and with elements of macroscopic physics (layers, phase boundaries, anisotropies, etc). Such methods will be certainly part of the equipment of the theoretical chemist tackling biophysical or biochemical problems in the next future.

Because of the consistence and relative simplicity of their physical foundations, the continuum models lend themselves to further theoretical elaborations, with the aim of clarifying a wealth of dynamical processes in photophysics and in chemical reactivity. Computational tools have also been provided, in order to test different physical hypotheses and to quantify dynamical solvent effects and their dependence on the features of specific chemical processes: the answers we expect from these studies are, once more, on the way from physics to chemistry.

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