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Theoretical
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Perspective

Perspective on "Electrostatic interactions of a solute with a continuum. A direct utilization of ab initio molecular potentials for the prevision of solvent effects"

Miertus S, Scrocco E, Tomasi J (1981) Chem Phys 55: 117

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Abstract. This paper provides an overview of the title paper by Miertus, Scrocco and Tomasi, including the impact that it has had on the theoretical description of solvation by means of continuum models.

Key words: Continuum models – Polarizable continuum method – Solvation

Current continuum solvation models provide not only qualitative insights into a wide variety of chemical phenomena in condensed phases, but in most cases are the best compromise between computational efficiency and reliability for the estimation of solvent effects. Achievement of the present status has resulted from tremendous research effort made by different groups around the world.

The initial attempts to account theoretically for solvent effects were made in the 1930s [1], but the suitability of these models for understanding chemical events in condensed phases was limited by their intrinsic simplicity. Thus, it was not until the 1970s, when continuum models were implemented within the quantum mechanical framework [2], that an accurate theoretical representation of solvent effects became possible. The last decade of this century has witnessed the spectacular growth of this new area of research [3]. It is expected that in the next century continuum methods will be the most used approach for the study of solvent effects in chemical systems.

The contribution made by Miertus, Scrocco and Tomasi (MST) and published in their 1981 *Chem Phys* paper [4] is one of those pioneering works in the development of implicit solvation methods. The relevance of this contribution in modeling and predicting chemical processes in solution can be appreciated from inspection of the citations received by this paper in the scientific literature (Figs. 1, 2). Figure 1 shows that MST's paper had achieved nearly 600 citations by 1997. More remarkably, the number of citations has been increasing in the last few years, showing that this a paper which will have a large impact on future research. The citation profile for the 1980s shows a slow increase in the number of citations, while the increase is very sharply during the 1990s. The low slope of the plot in the period until 1990 is due to the fact that most of the work performed with the polarizable continuum method (PCM) developed at Pisa was necessarily aimed at testing and refining the basic physical and mathematical assumptions of the model. The fast growth in the number of citations shown in the second half of Fig. 1 can be explained by two different factors. First, the availability of very efficient versions of the algorithm, which include treatments for computing the dielectric reaction field and also nonelectrostatic effects. Second, the formidable increase in computer power and the implementation of the algorithm in widely used quantum chemistry programs. This has facilitated the application of the PCM to the study of an increasingly large number of systems and processes in diverse chemical fields.

The increasing acceptance of the PCM by the chemistry community is reflected in Fig. 2, which shows the distribution by chemistry areas of the publications referencing MST's original article in 1988 and a decade later. Inspection of Fig. 2 reveals a number of features about the evolution of the PCM. In 1988 nearly 60% of the studies were published in journals of quantum and computational chemistry, and nearly 30% in journals of physical chemistry. A decade later the contribution of quantum and computational studies had sensibly diminished to around 25%, and that of physical chemistry had increased to nearly 40%. More importantly, new areas of applications have clearly emerged, especially in

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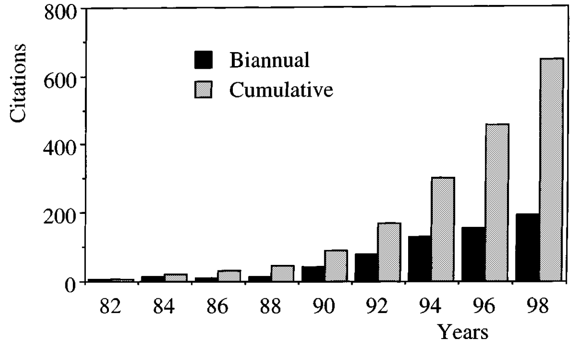

Fig. 1. Profile of citations in the scientific literature of "Electrostatic interactions of a solute with a continuum. A direct utilization of ab initio molecular potentials for the prevision of solvent effects" by Miertus, Scrocco and Tomasi (1981) *Chem Phys* 55: 117

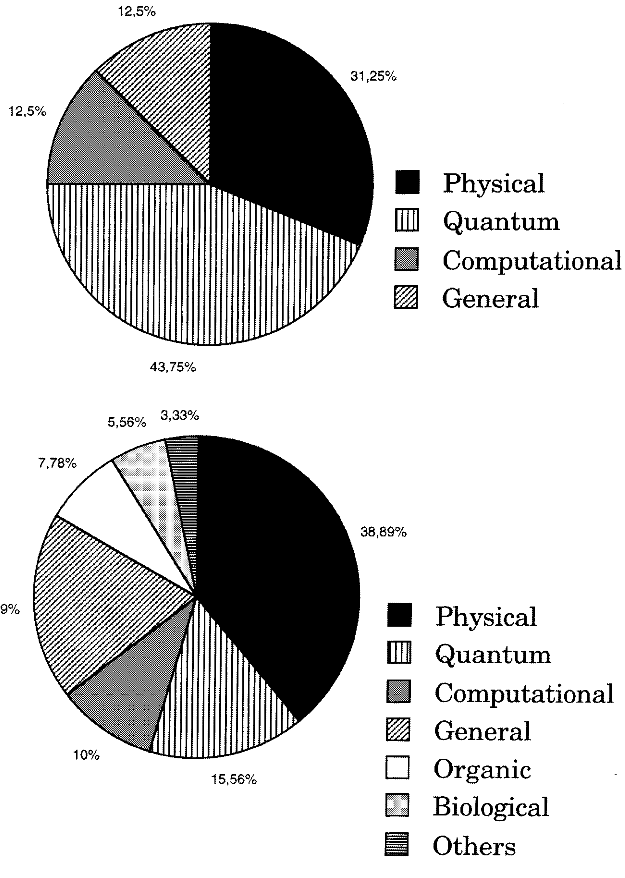

Fig. 2. Distribution by chemistry areas of the publications referencing *Chem Phys* 55: 117 (1981) in 1988 (top) and 1998 (bottom). Chemistry areas are defined according to the main scope of the journal where the citation was made

organic chemistry and biochemistry–medicinal chemistry. Overall, this can interpreted as the result of the progressive impact of implicit continuum models in the research conducted in very diverse areas of chemistry.

Let us now examine the significance of MST's contribution at the time of the publication of their paper and in the following years. The article in *Chem Phys* reported the basic features of the PCM for solving the electrostatic problem in a homogeneous continuum dielectric medium. This was accomplished by reformulating the Poisson equation in terms of a boundary-element problem related to the discretization of the apparent charge density accounting for the solvent reaction field on the solute cavity surface. Compared to other methods proposed to treat the dielectric response in continuum calculations, the approach adopted by MST is characterized by three different features. First, whereas simpler spherical or ellipsoidal cavities facilitated solving the Poisson equation, MST utilized a cavity adapted to the molecular shape, which was built up from a set of interlocking spheres centered on the nuclei, allowing a more realistic treatment of the solute/solvent interface. Second, the discretized set of apparent surface charges was determined from the total electrostatic potential computed at selected points (tesserae) on the cavity. As an observable, the computation of the electrostatic potential [5] could be rigorously performed without any approximation, whereas other methods at that time utilized a truncated expansion of the solute charge distribution. Finally, once the set of apparent charges is known, their interaction with the solute is treated by adding a perturbation operator to the gas-phase solute Hamiltonian. Owing to the mutual dependence between the solute wavefunction and the apparent charges on the cavity, MST discussed a self-consistent procedure to achieve self-consistency.

The boundary-element solution adopted by MST made it necessary to solve two computational problems inherent to the physical model in the PCM. First, since the solvent reaction field originates from the total electrostatic potential, including both solute and solvent contributions, the self-polarization between the solvent apparent charges also had to be considered in determining the solvent reaction field. This question was addressed by introducing a second iterative procedure coupled to the self-consistent procedure mentioned previously. The second problem is related to the escape of tails of the solute electron density from the solute cavity. This lost electron density throws the solvent response originating from the continuous electron distribution and the discrete set of nuclei out of balance, leading to a completely biased description of the reaction field. It was then necessary to introduce a charge compensation factor to balance properly the polarization due to nuclei and electrons.

The original PCM has been further refined by the Pisa group over the years. Some of the recent modifications of different physical and mathematical features of the model are examined in the following lines. One focus of interest has been the building up of the solute/solvent interface, which has been reformulated to obtain a finer description of the cavity [6]. Another point that has deserved particular research effort has been the treatment of charge compensation, and different correction procedures have been examined [7]. The model, which was originally formulated considering exclusively the solution to the electrostatic problems, was later extended to include nonelectrostatic contributions to solvation [8]. The iterative procedure adopted to solve the problem of using the self-consistent procedure has been reformulated using other procedures, such as matrix-inversion or closure approaches [9]. Another relevant focus of interest has been the implementation of analytical expression for the free-energy derivatives [10], and their implications for geometry optimization or calculations of polarizabilities. It is also worth noting the efforts made to reformulate nonequilibrium solvation in the computational scheme of the PCM [11]. Finally, very recently many efforts have been devoted to the extension of the PCM, initially devised to deal with an isotropic homogeneous medium, to more complex systems, including anisotropic dielectrics and/or ionic solutions [12]. Even though these topics comprise just a fraction of the research developed in the framework of the PCM in the last few years, they suffice to illustrate how implicit solvation methods can be further elaborated in order to obtain a more precise description of solvation and to extend these methods to the study of chemical systems of increasing complexity.

Several groups have also made relevant contribution to the evolution of the original PCM. A related model based on conductor-like screening (COSMO) has been developed recently by Klamt and Schüürmann [13]. Likewise, another approach to the PCM has been proposed in which the cavity surface is determined in terms of an electronic isodensity surface [14]. Olivares del Valle and coworkers [15] have focused their attention on aspects such as the inclusion of correlation effects in the PCM, or on the role of nonadditive effects in solute–solvent interactions. Pascual-Ahuir et al. [16] have paid most attention to the problem of the definition of the cavity surface. The work done in Barcelona has focussed mainly on the parametrization of the PCM to treating aqueous and nonaqueous solvents, as well as the application of the PCM to the study of biochemical systems [17, 18]. Finally, we and others have made new methodological developments to allow the implementation of the PCM in molecular dynamics or in Monte Carlo calculations [19].

The list of topics mentioned above is far from being complete, and the reader is addressed to several reviews [3, 18] that offer a comprehensive view of solvation models and their applications; however, the preceding lines suffice to illustrate well the evolution and refinement of the original PCM, and how it has been reformulated and improved as new chemical challenges have been considered. Nowadays, the PCM-based versions are powerful tools for understanding a variety of chemical phenomena in condensed phases, and the accuracy achieved in determining solvent-related properties permits quantitative predictions to be formulated in some cases. These encouraging features, in conjunction with the exploration of new methodological advances, allows us to envisage that the method will be applied to an increasingly large number of chemical fields, covering more complex systems and chemical processes in condensed phases.

References

1. (a) Born M (1920) Z Phys 1: 45; (b) Bell RP (1937) Trans Faraday Soc 27: 797; (c) Onsager L (1936) J Am Chem Soc 58: 1486; (d) Kirkwood J (1935) J Chem Phys 3: 300
2. (a) Rinaldi D, Rivail JL (1973) Theor Chim Acta 32: 57; (b) Rivail JL, Rinaldi D (1976) Chem Phys 18: 233; (c) Tapia O, Goscinski O (1975) Mol Phys 29: 1653; (d) Constancie R, Tapia O (1978) Theor Chim Acta 48: 75; (e) Klopamn G (1967) Chem Phys Lett 1: 200
3. (a) Tomasi J, Persico M (1994) Chem Rev 94: 2027; (b) Rivail JL, Rinaldi D (1995) In: Leszczynski J (ed) Computational chemistry. Review of current trends. World Scientific, New York, pp 139–74; (c) Tapia O, Bertrán J (eds) (1996) Solvent effects and chemical reactivity. Kluwer, Dordrecht; (d) Cramer CJ, Truhlar DG (1999) Chem Rev (in press)
4. Miertus S, Scrocco E, Tomasi J (1981) Chem Phys 55: 117
5. Scrocco E, Tomasi J (1973) Top Curr Chem 42: 95
6. (a) Pomelli CS, Tomasi J (1998) Theor Chem Acc 99: 34; (b) Pomelli CS, Tomasi J (1999) J Comput Chem (in press); (c) Barone V, Cossi M, Tomasi J (1997) J Chem Phys 107: 3210
7. (a) Mennucci B, Tomasi J (1997) J Chem Phys 106: 5151; (b) Cossi M, Mennucci B, Pitarch J, Tomasi J (1998) J Comput Chem 8: 833
8. (a) Floris FM, Selmi M, Tani A, Tomasi J (1997) J Chem Phys 107: 6353; (b) Floris FM, Tani A, Tomasi J (1993) Chem Phys 169: 11
9. (a) Coitiño EL, Tomasi J, Cammi R (1995) J Comput Chem 16: 20; (b) Cammi R, Tomasi J (1995) J Comput Chem 16: 1449
10. (a) Cammi R, Cossi M, Tomasi J (1996) J Chem Phys 104: 4611; (b) Cammi R, Cossi M, Mennucci B, Pomelli CS, Tomasi J (1996) Int J Quantum Chem 60: 1165; (c) Cossi M, Tomasi J, Cammi R (1995) Int J Quantum Chem Symp 29: 695
11. (a) Cammi R, Tomasi J (1995) Int J Quantum Chem Symp 29: 465; (b) Aguilar MA, Olivares del Valle FJ, Tomasi J (1993) J Chem Phys 98: 7375
12. (a) Cances E, Mennucci B, Tomasi J (1997) J Chem Phys 107: 3032; (b) Mennucci B, Cances E, Tomasi J (1997) J Phys Chem B 101: 10506; (c) Mennucci B, Cossi M, Tomasi J (1995) J Chem Phys 102: 6837; (d) Mennucci B, Cossi M, Tomasi J (1996) J Phys Chem 100: 1807
13. Klamt A, Schüürmann G (1993) J Chem Soc Perkin Trans 2: 799
14. Foresman JB, Keith TA, Wiberg KB, Snoonian J, Frisch MJ (1996) J Phys Chem 100: 16098
15. (a) Olivares del Valle FJ, Aguilar MA (1992) J Comput Chem 13: 115; (b) Contador JC, Aguilar MA, Olivares del Valle FJ (1997) Chem Phys 214: 113
16. Pascual-Ahuir JL, Silla E, Tuñon I (1994) J Comput Chem 15: 1127
17. (a) Orozco M, Hernández B, Luque FJ (1998) J Phys Chem B 102: 5228; (b) Colominas C, Luque FJ, Orozco M (1996) J Am Chem Soc 118: 6811; (c) Orozco M, Lopez JM, Colominas C, Alhambra C, Busquets MA, Luque FJ (1996) Int J Quantum Chem 60: 1179
18. Orozco M, Alhambra C, Barril X, Lopez JM, Busquets MA, Luque FJ (1996) J Mol Model 2: 1
19. (a) Colominas C, Luque FJ, Orozco M (1999) J Comput Chem (in press); (b) Varnek AA, Wipff G, Glebov AS, Feil D (1995) J Comput Chem 16: 1