

Electrostatics and computational modelling Editorial overview

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Received 5 June 1990

Accepted 30 June 1990

Key words: Electrostatics; Computational methods; π - π Interactions; New directions

An accurate treatment of electrostatic interactions has always been crucial to solving problems of intermolecular interaction. Severe difficulties due to the long-range nature of electrostatic potentials, their many-centred additivity and the interference of solvent and polarisability have continued to plague efforts in this area. Yet such interactions underlie crucial features of molecular systems such as the free energy of solvation, the stabilisation of transition states by the alignment of solvent dipoles, the recognition of ligands by biological receptors and the properties of polymeric materials. For chemists interested in the design of new compounds or in gaining new insights into chemical reactivity, obtaining information about modern advances in the treatment of electrostatics is made difficult by the fragmentation of the subject in the literature. Furthermore, chemists have the option to use a number of commercial software packages in which the electrostatic handling may be very different and hard to ascertain.

In choosing articles for inclusion into this special issue of the *Journal of Computer-Aided Molecular Design*, the goal has been to illustrate how the nature of the electrostatic modelling problem, and methods for its solution, can be modified according to the total number of atoms in the system. In addition, emphasis has been placed upon the various graphical techniques which are becoming commonplace, especially with the power of modern workstations. The examples illustrating the applications in each paper comprise structures of biological importance, or systems of interest in the study of reactions in the gas-phase and solution. Despite this, the concepts outlined should have wide applicability to problems such as the design of new materials, dyes, catalysts and superconducting ceramics.

In solvents such as water, or DMSO, which possess large molecular dipole moments and high bulk effective dielectric constants, the solvation energy due to the interaction with the monopoles,

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and higher electrostatic moments of given solutes can often be large. The inclusion of this term into the conformational energy of solutes is therefore essential in understanding the accessible conformations to a particular species in solution. This not only has consequences for the conformational properties of bound forms upon molecular receptors, but is also crucial in the desolvation contribution to the energetics of binding. In the first article the problem of developing an effective treatment of such terms which is rapid enough to be incorporated into the classical potential functions used in empirical force field approaches (molecular mechanics and dynamics) is addressed. Its application to proteins is indicative of the power of modern methods in obtaining reasonable estimates of solvation energies.

Most electrostatic calculations rely upon the assumption that partial charges can be placed at the atomic nuclei. Where do these partial charges come from? A number of methods have been devised for obtaining values. The most rigorous methods for computing such charges involve computing the wavefunction for a particular molecule and then evaluating the molecular electrostatic potential (MEP) about the molecule in three-dimensional space. Fitting procedures are then used to generate partial charges which reproduce the quantum-mechanical MEP. Unfortunately, this approach is clearly a function of the particular set of nuclear coordinates. In addition, the accuracy of the quantum-mechanical calculation is also dependent upon the number of atoms in the molecule. Further problems arise for (a) flexible molecules whose partial charges will depend upon the conformation, (b) systems which interact with external fields or (c) systems which shift conformation when moved from one phase into another. Methods for rapidly recomputing the partial charge distribution must be found and this rules out *ab initio* or semi-empirical approaches given the present limitations of processing power. A rapid approach to obtaining such a distribution, given an initial set of nuclear coordinates, is outlined in the second paper. The CHARGE2 program currently enjoys wide use within the modelling community and is reliable and fast enough to begin to allow recomputation of molecular electrostatics as a function of conformation.

Tackling fundamental electrostatic modelling problems particularly in applications requiring the formation of complexes between two or more molecules needs new models. For example, in studies on biological systems, hydrogen bonds must be accurately represented by computational models of the potential energy. Such non-covalent bonds are principally electrostatic in nature and can appear to show a modicum of directionality. In the third article, a comparison of the molecular electrostatics produced by a Mulliken charge distribution and that arising from spreading the charge by a distributed multipole analysis (DMA) is made. The role of molecular graphics in aiding the interpretation of wavefunction properties is also outlined, since comparison was greatly aided by the real-time display of the molecular electrostatic field using colour-coded arrows. Although the use of this type of graphical representation has been applied to complex proteins, its application to understanding the advantages and limitations of various types of quantum-mechanical models in smaller systems is less well-known. Yet the use of molecular graphics to visualise properties other than pure structure is probably the best reason to invest in modern graphics display hardware. For example, attention has been paid to the role of graphics in understanding reactivity by the graphical analysis of frontier orbital properties, or in visualising molecular electrostatics and surface features.

Questions then arise as to the most useful graphical representation to select when considering these non-physical properties, and much work remains to be done, especially in displaying confor-

mationally dependent features. These issues are introduced, and discussed using a range of studies upon chemical reactivity, in the last paper of this special issue.

In putting together this special issue, we were encouraged by the progress that has been made in the realistic treatment of molecular electrostatics. The introduction of the effect of external solvent and other environmental influences, has begun to allow the study of subtle effects in intermolecular recognition. In addition, empirical force fields which use higher multipoles to introduce anisotropic effects are under active development, and will probably become widespread over the next five years as processors get faster.

A recent paper by Hunter and Sanders [J. Am. Chem. Soc., 112 (1990) 5525] has highlighted a simple but potentially important extension to the way electrostatic charges can be distributed. In their attempts to simulate the staggered stacking patterns known to be adopted by porphyrin rings, they placed half an electron at a fixed distance (charge node) above and below each π carbon atom, set the nucleus to unit positive charge and calculated the most stable two-body interaction. Hitherto, the use of point charges, placed at the nucleus resulted in a parallel, co-centred overlap of conjugated π -systems but these author's simple, intuitive technique gave an answer in complete accord with experiment. The methodology has been incorporated into a large molecular mechanics package and the results have been reproduced. Extensions into lone-pairs and intramolecular interactions are currently continuing.

The idea is essentially a naive extension of the DMA method reported by Price and Richards in this issue but is not restricted by slow computation on static coordinate sets. The implications of this kind of step forward (if it proves to be as important as it first seems) are legion; previous studies of π - π interactions which must include expensive computations on biological subjects could have been misleading at best; molecular mechanics studies of the stacking patterns in proteins should be re-assessed. The possibility of using a fast charge calculator (*vide infra*), coupled with the ability to vary the length of these extended charge nodes, could lead to a fast way to tackle polarisation phenomena. Simulations involving hydrogen bonding could be improved and the effect of π -systems on solvent and hydrophobic interactions is expected to show relevant specificity.

Despite the exciting new possibilities discussed in this issue, significant problems remain. More work is needed on the polarisation of the charge as two molecules approach each other although distributing density might open up possibilities. Similarly, defining the redistribution of charge as the conformation of a flexible molecule changes is beginning to look likely. Of crucial importance to many industrial applications is the development of models which will allow the calculation of the electrostatic contribution to the free energy change associated with the partitioning of a given compound between two phases and the associated entropy contributions. More work needs to be done on the electrostatic effects within extended, highly charged systems such as zeolites and their interactions with dipolar solvents and guest molecules.

Given the current rapid growth in the awareness of Coulombic forces in molecular recognition and reaction phenomena, it should not be long before another collection of papers on this topic will appear in a future issue of this journal.