

Calculation and display of electrostatic potentials

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A general methodology is developed for incorporating accurate electrostatic information from ab initio molecular orbital calculations into molecular mechanics calculations. Examples are given of the method applied to simple aromatic organic molecules. A program has been developed for displaying the results of the ab initio calculations on a Silicon Graphics workstation. The technique developed here provides an alternative method for including electrostatic interactions in molecular mechanics calculations and is compared with other methods for determining atomic charges.

Keywords: electrostatic potentials, Silicon Graphics workstation, least-squares fitting, electron density

INTRODUCTION

The electrostatic interaction is particularly important in determining the geometry of molecules and polymers in the bulk. However, many of the techniques currently used within molecular modeling packages to determine the strengths of these interactions are extremely crude. Intermolecular interactions are dominated by three types of intermolecular forces: the short-range repulsive force that arises as two charge clouds interact with each other, the generally attractive long-range van der Waals interaction, and the electrostatic interactions that arise between local multipoles on both molecules. Molecular mechanics usually represents these forces using interaction potentials between atoms. The first two forces are usually represented by a pair-wise sum over atoms, involving functions such as Lennard-Jones or the Buckingham potential. In a typical calculation only pairs of atoms less than some cutoff distance (typically 8 Å) away from each other are considered to interact.

The electrostatic interaction can be represented in many ways. One approach is to use a single-center multipole expansion of the electrostatic potential. The dominant terms in this approach are the molecular charge and the dipole and quadrupole moments. Unfortunately this approach is known to converge very poorly, even at large distances from the molecule. An alternative is to distribute the multipoles over the molecules, usually choosing the atoms as the ex-

pansion centers. While this leads to improved convergence characteristics, a further simplification is to truncate this distributed multipole expansion at the first (monopole) term. This is the approach generally adopted within molecular modeling packages and is, by its nature, limited in accuracy. The electrostatic interaction in this latter approach is represented by interactions between charges at the atomic centers and is of the form $(q_i \times q_j)/r$, where q_i is the charge on the i th atom. These are extremely long-range interactions and it has been found for periodic systems, that special acceleration techniques like the Ewald method¹ are required to ensure that the summations converge.

Currently most molecular modeling programs use methods like those suggested by Del Re² and Gasteiger and Marsili³ to assign atomic charges. These techniques have the advantage that they are very quick and applicable to a wide range of organic molecules, but the charges produced are often crude in that they do not reproduce the overall dipole moment of a molecule and they do not reflect subtle electronic effects, such as resonance or induction. In particular they are defined by the topology of the molecule and take little account of its geometry.

In principle, *ab initio* molecular orbital calculations can calculate the electrostatic potential very accurately. Stone⁴ has shown how the distributed multipole analysis (DMA) method can be used to calculate crystal structures of small molecules on the basis of accurate *ab initio* calculations. Unfortunately, the DMA technique is not easily incorporated into standard molecular mechanics programs, as the technique assigns dipoles, quadrupoles and higher moments, as well as charges to each atomic center and currently the majority of molecular modeling packages are not capable of accepting this additional information.

Whereas the DMA method is essentially exact, less rigorous methods have often been used to analyze the wavefunction. The most popular of these is the Mulliken population analysis⁵ technique. This takes the electron density calculated by an *ab initio* program and partitions it between the atoms on the basis of the occupancy of each atomic orbital. For inner shell molecular orbitals this works very well, but for highly delocalized orbitals the partitioning is rather arbitrary because the atomic orbitals that contribute to each molecular orbital are not orthogonal. This leads to problems in the assignment of charge in the bonding orbitals.

An alternative approach, the method of potential-derived charges (PDC), is currently receiving a lot of attention. It involves least-squares fitting of the atomic charges to re-

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produce as closely as possible (in a least-squares sense) the electrostatic potential, which is calculated quantum mechanically at a set of points around the molecule.⁶⁻¹⁰ This has the advantage that the results can be incorporated into existing molecular modeling packages very easily. However, recent analysis of the technique indicates^{11,12} that the method required many more points than had been thought previously and also care has to be taken to ensure that the calculated charges are independent of the orientation of the molecule.

The procedure described here for the determination of atomic charges, is a development and implementation of a PDC approach to the fitting of the molecular electrostatic potential. In addition a program has been developed for displaying the electrostatic potential in an informative way.

THEORY

The quantum mechanical electrostatic potential $V_{qm}(r)$ around a molecule can be defined using the electron density $\rho(r)$, where r is a position in space:

$$V_{qm}(r) = \sum_{i=1}^N \frac{Z_i}{|r - R_i|} - \int \frac{\rho(r')}{|r - r'|} dr'$$

Here N is the number of atoms in the molecule, Z_i is the nuclear charge of atom i and R_i its position. The first term in this equation represents the potential of the positive charges of the atomic nuclei in the molecule. The second term is the potential due to the electrons around the molecule, which screen the nuclear interaction. Currently the GAMESS¹³ *ab initio* molecular orbital package calculates the molecular electrostatic potential, as well as other properties (like electron density, orbital amplitude and orbital density), as a two-dimensional grid in an arbitrary plane. This grid can be displayed as a contour diagram using standard graphics software, such as NAG or GINO.

Within the majority of molecular modeling packages the electron density is not available and the electrostatic potential is usually approximated as

$$V_{mm}(r) = \sum_{i=1}^N \frac{q_i}{|r - R_i|}$$

where q_i are effective charges, which in this work will be determined by least-squares fitting to the quantum mechanical electrostatic potential V_{qm} calculated at a set of points around the molecule.

Several procedures have been put forward for choosing the positions at which to calculate V_{qm} .⁶⁻¹² Because the electrostatic potential is a long-range potential, the sample points for the potential should not be too close to an atom. This is usually taken to mean that the sample points should lie outside the van der Waals surface of the molecule. On the other hand, it has also been shown that increasing the number of sample points a long way from the molecule has little effect on the charges. This is only to be expected as the long-range electrostatic potential will be dominated by the dipole contribution, which can be fitted exactly by an appropriate choice of atomic charges. The van der Waals surface is often defined by taking the outer surface of a set of spheres placed on each atom, the radius of each sphere

being determined by the element. In this work we propose to calculate the van der Waals surface from the electron density itself by calculating contours of the electron density around the molecule and then determining the electrostatic potentials at points on these contours.

Calling the sample points s_j , the GAMESS program has been modified to calculate $V_{qm}(s_j)$ at the N_s sample points. The charges q_i are determined by performing a least-squares fit of V_{mm} to the quantum mechanical electrostatic potential at the sample points. Defining the function F as

$$F = \sum_{j=1}^{N_s} V_{qm}(s_j) - V_{mm}(s_j)$$

or

$$F(q) = \sum_{j=1}^{N_s} \left(V_{qm}(s_j) - \sum_{i=1}^N \frac{q_i}{|s_j - R_i|} \right)$$

The derivative of F with respect to q_i is

$$\frac{\partial F(q)}{\partial q_i} = \sum_{j=1}^{N_s} \left(V_{qm}(s_j) - \frac{1}{|s_j - R_i|} \right)$$

and

$$\frac{\partial F^2}{\partial q_i} = 2F(q) \frac{\partial F(q)}{\partial q_i}$$

A least-squares fitting procedure finds the values of q_i that minimizes F^2 . As the derivatives of F^2 are linear in the parameters q_i they can be determined by solving a linear set of simultaneous equations. This approach is the same as that of the CHELP program¹⁴ available through the Quantum Chemistry Program Exchange (QCPE). Some researchers have required that constraints be added to the equations to reproduce the overall charge and dipole moment exactly. This option has been incorporated into this work through the use of Lagrangian multipliers. It is important that the molecular charge and dipole moment are correct, as they are the leading terms in the single center, multipole expansion of the electrostatic potential.

This procedure of fitting the atomic charge to the electrostatic potential is becoming a widely accepted procedure for determining suitable atomic charges in molecular mechanics calculations. In addition to the use of *ab initio* electrostatic potentials, recent work has shown that it is possible to use the MNDO and AM1 semi-empirical method, with suitable scaling, to calculate the wavefunction and electrostatic potential of the molecule to a similar degree of accuracy as an *ab initio* calculation.¹⁵⁻¹⁷

CALCULATION DETAILS

The molecules chosen to illustrate the method were selected from a group that is representative of linkages commonly found in aromatic polymers. The compilation of information on the energy required for torsional rotation,¹⁸ combined with the electrostatic analysis of the wavefunction reported here, should provide the foundation of a very useful database for the molecular modeling of aromatic polymers.

Ab initio molecular orbital calculations, using the GAMESS program,¹³ were performed on N-phenylphthalimide, N-phenylbenzamide, biphenyl, diphenyl methane, benzo-

phenone, diphenyl ether, methyl benzoate, diphenyl sulphide and diphenyl sulphone at their minimum energy configurations,¹⁸ using a 3-21G basis set.¹⁹ At their minimum energy conformation, the diphenyl molecules have a helical conformation, with the phenyl groups twisted through an angle that depends on the linking group. Benzophenone adopts the most planar structure, followed by diphenyl ether, while diphenyl sulphide and diphenyl methane are less planar. Diphenyl sulphone has a minimum energy configuration with the phenyl groups in a "roof" conformation. The geometries adopted by these molecules result from a competition between the repulsive interaction between the inner *ortho* hydrogen atoms of the phenyl groups, which tend to clash in the planar configuration, and the resonating power of the linking group between the two aromatic rings, which has its maximum effect in the planar configuration. N-phenylbenzamide is found to be flat, while N-phenylphthalimide and biphenyl have a torsion angle of about 64.5° and 29.0°, respectively, between the aromatic rings.

DETERMINING SAMPLE POINTS

The sample points are determined on a constant electron density contour around the molecule. This contour has been determined by constructing a three-dimensional cubic grid of points and calculating the electron density at each point. Each point in the grid is then taken in turn and its neighbors are examined to see if the required contour lies between the two points. If it does, a bisection method is used to search between the two points to locate the contour. The final point is stored and used to calculate the electrostatic potential. In addition the derivative of the electron density is calculated for each point on the contour. This information is used to determine the inner and outer surface of the contour and is needed also for the lighting algorithms that are used to display the results on a graphics workstation.

To establish which electron density contours should be used in determining the point charges, an analysis of three contours at 0.005, 0.001 and 0.0005 atomic units (au) was performed for all of the molecules considered here. (An atomic unit of electron density is defined as N_e/bohr^3 , where N_e is the number of electrons and 1 bohr = 0.52917 Å.) Each point on the contour was examined to find its distance from the nearest atom. Table 1 shows a summary of these results averaged over all of the molecules considered and compares the results with some accepted values of the van der Waals radii of the atoms. The 0.005-au contour can be seen to agree closely with the accepted van der Waals radius²⁰

Table 1. Average distance of contour from atoms (Å)

Atom	van der Waals radius ²⁰	Electron density (au)		
		0.005	0.001	0.0005
H	1.17	1.19	1.52	1.65
C	1.75	1.66	2.03	2.18
N	1.55	1.58	1.90	2.00
O	1.40	1.43	1.68	1.78
S	1.85	1.70	2.11	2.28

for the atom. This observation lends some support to the concept of van der Waals radii but it must be remembered that the values quoted here are averages. The 0.005-au contour can approach a hydrogen atom as closely as 0.92 Å and as far away as 1.71 Å. Other atoms show at most a 0.4-Å difference between the nearest and furthest atom to the contour.

Based on these results, the sampling points were chosen to lie on four contours; 0.005, 0.001, 0.0005 and 0.0001 au. These contours should sample the space around the van der Waals surface of the molecule, which is accessible to other nearby atoms and molecules. Because the lower density contours have a larger surface area more points will be associated with them, resulting in a bias toward getting the longer range electrostatic potential correct at the expense of the shorter range potential. This observation applies to most of the sampling procedures suggested in the literature.

RESULTS

Two approaches were adopted for fitting the charges to the potentials. In the first a single 0.005-au contour was taken and the charges were fitted to the points on this contour with no constraints as to the overall charge of the molecule or its dipole moment. This gives one some idea of the errors associated with this fitting procedure and the changes to be expected on going to a constrained fitting of the potential. In the second approach, points on all four contours were fitted and the overall results were constrained to give the correct molecular charge and *ab initio* dipole moments.

Unconstrained fitting

An indication that the PDC method provides a reasonable description of the electrostatic potential is given by comparing the charge and dipole moment given by the point charge distribution with the *ab initio* values. The charge for the molecules considered here should, of course, be zero. But, because our sample points lie inside some electron density, this is not quite true. Deviations from zero by up to 0.09 electrons were observed. The dipole moment of the molecule reflects the electrostatic potential at very large distances and is calculated routinely by most *ab initio* packages from the wavefunction. The dipole moment predicted by the unconstrained PDC method is shown in Table 2 and

Table 2. Dipole moments (Debye)

	<i>Ab initio</i>	PDC	Gasteiger	Mulliken
Benzophenone	3.278	3.558	2.382	4.333
Diphenyl ether	1.470	1.570	2.021	3.628
Diphenyl sulphide	2.302	2.229	1.038	0.606
Diphenyl methane	0.074	0.073	0.124	0.164
Diphenyl sulphone	7.002	7.695	3.638	5.346
Biphenyl	0.001	0.001	0.001	0.003
Methylbenzoate	1.906	2.054	0.293	1.632
N-phenylbenzamide	3.802	3.965	2.283	2.392
N-phenylphthalimide	3.468	3.394	1.878	3.696

is compared with the other charge methods and the *ab initio* calculations.

The agreement between the *ab initio* and unconstrained PDC results is very good, leading to some confidence that the potential-derived charges describe the electrostatic potential well at both large and small distances. As has been found in other work,⁷ the Gasteiger and Mulliken charges predict very poor dipole moments and appear to be quite unreliable in this respect.

Constrained optimization

It is possible to constrain the charges so as to obtain the overall *ab initio* molecular charge and dipole moments exactly. This ensures that the long-range potential is correct, at the expense of a poorer fit to the *ab initio* sample points. As has been seen, the dipole moments calculated from an unconstrained fitting of the innermost contour are already in good agreement with the *ab initio* values. In this section the charges were determined by fitting them to the electrostatic potential at point on the 0.005-, 0.001-, 0.0005- and 0.0001-au electron density contours. Typically there were about 500 points per atom and a standard deviation of about 0.007 au was obtained for the fit.

Table 3 shows the overall charge of some of the functional groups in the systems considered and compares the results of the PDC method with those of other well-known approaches.

The Gasteiger method predicts the ether group to be the most negatively charged group, with the methylene and sulphone groups being the only positively charged groups. On the whole the Gasteiger method seems to underestimate the magnitude of the charge on highly charged atoms. The Mulliken method, on the other hand, predicts a very negatively charged ether group and, rather surprisingly, a large positive charge on the sulphide. The Mulliken method also predicts a positive charge for the carbonyl group. It was noted that the Mulliken method predicts charges for the hydrogen atoms that are more positive than the corresponding charges from PDC calculations.

According to Morrison and Boyd,²¹ electrophilic attack of substituted benzene rings may be classified as shown in Table 4. Classification of the substituents on the basis of charge alone is difficult. In electrophilic attack an important

consideration is the stability of the transition state leading to the formation of the carbonium ion intermediate. Both activity and selectivity are governed by the transition state. If the transition state is early, its height will be influenced by the local electrostatic interactions around the carbon atom at which substitution takes place, with a more negatively charged carbon favoring substitution. Other important considerations are the stereo-specific requirements of approach of the electrophile. Approach to the *ortho* position would see some steric hindrance not found by approach to the other carbon atoms of the ring.

A detailed breakdown of the charge distribution for the potential-derived charges is given in Table 5, which shows the charge on the *ortho*, *meta* and *para* carbon atoms of the phenyl groups in the molecules considered. In some cases the two *ortho* and two *meta* positions have slightly different charges and the average of each pair is shown in the table. On the basis of atomic charges the only *meta*-directing groups are the ketones, sulphones and ethanoates, which is in agreement with experiment. The amide group in N-phenylbenzamide is *meta* directing for the phenyl group attached to the carbonyl of the amide group and *ortho*, *para* directing for the phenyl group attached to the nitrogen. All the other groups are *ortho*, *para* directing as is found experimentally.

Table 4. Effect of groups on electrophilic substitution

Activating: <i>Ortho</i> , <i>para</i> directors	Deactivating: <i>Meta</i> directors
Moderately activating	
—OCH ₃	—COOH (—COOR)
—NHCOCH ₃	—SO ₃ H
	—CHO
Weakly activating	—COR
—C ₆ H ₅	
—CH ₃	

Table 5. Potential-derived charges on carbon atoms in phenyl groups

Molecule	Position in phenyl group		
	<i>Ortho</i>	<i>Meta</i>	<i>Para</i>
Benzophenone	−0.12	−0.16	−0.10
Diphenyl ether	−0.42	−0.05	−0.27
Diphenyl sulphide	−0.29	−0.10	−0.21
Diphenyl methane	−0.31	−0.09	−0.21
Diphenyl sulphone	−0.13	−0.17	−0.11
Biphenyl	−0.21	−0.14	−0.14
Methylbenzoate	0.00	−0.20	−0.07
N-phenylbenzamide			
N-phenyl	−0.40	−0.07	−0.25
C-phenyl	−0.09	−0.17	−0.10
N-phenyl phthalimide	−0.38	−0.09	−0.20

Table 3. Electronic charge of functional groups

Molecule	Group	PDC	Gasteiger	Mulliken
Benzophenone	carbonyl	0.110	−0.096	0.032
Diphenyl	ether	−0.593	−0.457	−0.789
Diphenyl	sulphide	−0.339	−0.090	0.528
Diphenyl	methane	−0.081	0.071	−0.027
Diphenyl	sulphone	−0.027	0.015	−0.558
Methylbenzoate	ethanoate	0.164	−0.092	−0.031
N-phenylbenzamide	amide	−0.126	−0.166	−0.359
N-phenylphthalimide	phthalimide	−0.303	−0.358	−0.300

GRAPHICS DISPLAY

An important aspect of any technical research is the ability to convey results in a simple and understandable way. Computer graphics, in conjunction with molecular modeling, have been very useful in this respect. Here a method is proposed using the three-dimensional graphics facilities provided by the Silicon Graphics 4D/20 workstation to display the results of complicated *ab initio* calculations in a simple and comprehensible way.

Three-dimensional solid images are displayed on graphics workstations by dividing the image surfaces into simple polygons (a so-called wire mesh representation), displaying the polygons as filled surfaces, using hidden-line removal and, finally, lighting the object in as realistic a manner as possible.

The construction of a wire mesh representation is a non-trivial process; recently several articles²²⁻²⁵ have proposed alternative ways of approaching the problem. The algorithm adopted here is based on the work of Boissonnat²⁴ and is very similar to the polyhedral propagation method.²⁵ The surface chosen for display is the set of sample points on an electron density contour as defined in the previous section.

- (1) Each sample point is analyzed in turn and a list of its N nearest neighbors is determined, where N depends on the surface but is normally between 6 and 9.
- (2) A starting triangle on the surface is selected and used to initialize a boundary, the inside of which will be tessellated with triangles. The boundary is maintained as a linked list of pointers to lines moving round the contour in a clockwise direction.
- (3) The boundary is grown by considering each edge of the existing boundary and choosing a new point (from the list of nearest neighbors to the points on the edge) that is not inside the boundary and that forms a new triangle with the largest possible angle. The new point can be
 - (a) part of the boundary, in which case only points adjacent to the current contour edge are considered and the size of the boundary shrinks as two edges are deleted and one new edge is added
 - (b) a point outside the boundary, in which case the boundary is grown by deleting one edge and adding two edges.
- (4) As each edge is defined, a list of lines is updated with the new edge. The process of growing the new boundary is continued until all of the points are inside the contour or until there are no more points available in the vicinity of the contour. In the latter case a new boundary is started out of the remaining points by choosing a new seed triangle and starting again. Problems do occur when two surfaces approach each other closely, as this algorithm will tend to cause hopping between the surfaces. This problem can be overcome by allowing lines only between points whose normals point in a similar direction. Information on the normal to a surface can be obtained from the *ab initio* calculation by differentiating the expression for the electron density with respect to the Cartesian coordinates. The normal information is also important in defining a smooth color shading of the solid image under lighting conditions.

- (5) After all the points have been considered, the list of lines is processed into a list of triangles.

The triangle list can be displayed, either as a mesh or as a solid filled object with different lighting conditions and different properties for the surface, using FORTRAN sub-routines provided in the Silicon Graphics library. Normals to the surface are required to provide features like lighting effects and shading. The defined surface is color coded to represent the size and sign of the electrostatic potential. Thus areas of positive potential are colored progressively from green to blue, with green denoting a zero potential. Similarly the negative areas of electrostatic potential are colored from green to red. Color contrast techniques can be used to enhance the distinction between positive and negative electrostatic potential. A similar approach was proposed by Purvis and Culberson²⁶ to represent the gradient of the electron density.

Examples of such displays are shown in Color Plates 1-5. A common feature of these plots is the blue (positive) edge of the benzene ring and its slightly negative center. This charge distribution accounts for the commonly observed edge-to-face packing of aromatic units in crystals.²⁷ Color Plate 1 shows that there is a distinction between the charge distribution of the "inner" and "outer" surfaces of the phenyl rings in biphenyl. Color Plate 2 shows the concentration of charge in the lone pairs of the sulphide group in diphenyl sulphide. The charge separation becomes much less significant farther away from the molecule. Color Plate 3 shows how the amide group in N-phenylbenzamide polarizes the molecule, with a larger negative charge in the π -system of the phenyl group attached to the nitrogen of the amide. Finally, Color Plate 4 shows a large difference in the charges of the π -systems between the phthalimide and phenyl groups in N-phenylphthalimide, the phenyl ring being much more negatively charged.

The techniques described here can be used to display other properties. For example, Color Plate 5 shows a plot of the 0.001-a.u. electron density contour of N-phenylbenzamide, color coded according to the error between the full *ab initio* potential and the approximate PDC charge fitted potential. As can be seen there is no real systematic error in the potential for this particular contour.

CONCLUSIONS

Several workers have pointed out that the charges are quite sensitive to the number of sampling points chosen. In some cases it has been recommended that a thousand sample points per atom are needed for stability. While it is important to understand the limitations of the algorithms being used, it should be remembered that the procedure being adopted to represent the electrostatic potential involves approximations. There are errors in the electrostatic potential that can only be overcome by considering higher multipoles on each center. Given the flawed nature of the model, the stability of the charges to the number of points becomes less important: whatever the number of sample points chosen, there will still be errors in the electrostatic potential. It has been proposed by several workers that such inadequacies can be overcome by fitting distributed dipoles and charges to the *ab initio* potential. Unfortunately, although this would be

possible and would give much more reliable results for such systems, the results can not as yet be incorporated into standard modeling packages. Another problem with this approach is that the incorporation of charges into molecular modeling packages neglects the fact that the charges have been determined at a fixed geometry. Within the modeling packages they will be used in other conformations, for which they were not determined. Thus the number of points required for convergence is not so important a shortcoming as are the assumption that charges remain static as the geometry of a molecule is varied and the lack of convergence of the multipole expansion.

The PDC method provides an effective way of deriving atomic charges that reproduce the medium- and long-range electrostatic potential in a form that can be incorporated into standard molecular modeling packages. In addition the potential-derived charges appear to be chemically significant in that they are able to explain some of the features encountered in electrophilic attack of substituted benzene rings. There are however, difficulties in the application of the method to larger systems, because of the time-consuming nature of the *ab initio* calculation.

The Gasteiger method seems to produce charges that are, on the whole, too small to give reliable electrostatic potentials in either the long or medium range, and the dipole moments predicted by this method are unreliable.

The Mulliken charges for hydrogen appear to be too large and the method is especially unreliable for those molecules containing sulphur. This may be because the nonorthogonality of the orbitals becomes more acute in this case due to the difference in the sizes of the atoms.

REFERENCES

- 1 Ewald, P.P. Die Berechnung optischer und elektrostatischer Gitterpotentiale. *Ann. Physik* 1921, **64**, 253–287
- 2 Del Re, G. A simple MO-LCAO method for calculating the charge distribution in saturated organic molecules. *J. Chem. Soc.* 1958 4031–4040
- 3 Gasteiger, J. and Marsili, M. Iterative equalization of orbital electronegativity: A rapid access to atomic charges. *Tetrahedron* 1980, **36**, 3219–3222
- 4 Stone, A.J. Distributed multipole analysis, or how to describe a molecular charge distribution. *Chem. Phys. Lett.* 1981, **83**, 233–239
- 5 Mulliken, R.S., Electron population analysis on LCAO-MO [linear combination of atomic orbitals] molecular wavefunctions. *J. Chem. Phys.* 1955, **23**, 1833–1840
- 6 Momany, F.A., Determination of partial atomic charges from *ab initio* molecular electrostatic potentials. Application to formamide, methanol and formic acid. *J. Chem. Phys.* 1978, **82**, 592
- 7 Cox, S.R. and Williams, D.E. Representation of the molecular electrostatic potential by a net atomic charge model. *J. Comp. Chem.* 1981, **2**, 304–323
- 8 Singh, U.C. and Kollman, P.A. An Approach to computing electrostatic charges for molecules. *J. Comp. Chem.* 1984, **5**, 129–145
- 9 Chirlian, L.E. and Francl, M.M. Atomic Charges derived from electrostatic potentials. *J. Comp. Chem.* 1987, **8**, 894–905
- 10 Williams, D.E. Representation of the molecular electrostatic potential by atomic multipole and bond dipole models. *J. Comp. Chem.* 1988, **9**, 745–763
- 11 Woods, R.J. Khalil, M., Pell, W., Moffat, S.H. and Smith Jr., V.H. Derivation of net atomic charges from molecular electrostatic potentials. *J. Comp. Chem.* 1990, **11**, 297–310
- 12 Breneman, C.M. and Wiberg, K.B. Determining atom-centered monopoles from molecular electrostatic potentials. The need for high sampling density in the formamide conformational analysis. *J. Comp. Chem.* 1990, **11**, 361–373
- 13 Guest, M.F. and Kendrick, J. *GAMESS Manual* Daresbury Laboratory, Warrington, UK
- 14 Chirlian, L.E. and Francl, M.M. *QCPE Bulletin* 1987, **7**, 524
- 15 Luque, F.J., Illas, F. and Orzco, M. Comparative study of the molecular electrostatic potential obtained from different wavefunctions. The reliability of semiempirical MNDO wavefunctions. *J. Comp. Chem.* 1990, **11**, 416–430
- 16 Besler, B.H., Merz, K.M. and Kollman, P.A. Atomic charges derived from semiempirical methods. *J. Comp. Chem.* 1990, **11**, 431–439
- 17 Ferenczy, G.G., Reynolds, C.A. and Richards, W.G. Semiempirical AM1 electrostatic potentials and AM1 electrostatic derived charges: A comparison with *ab initio* values. *J. Comp. Chem.* 1990, **11**, 159–169
- 18 Kendrick, J., The calculated energetics of torsional motion in six diphenyl molecules: benzophenone, diphenyl ether, diphenyl sulphide, diphenyl sulphone, diphenyl methane and biphenyl. *J. Chem. Soc., Faraday Trans. 2*, 1990, **86**, 3995–4000
- 19 Binkley, J.S., Pople, J.A. and Hehre, W.J., Self-consistent molecular orbital methods. 21. Small split valence basis sets for first-row elements. *J. Amer. Chem. Soc.* 1980, **102**, 939–947
- 20 Gavezzotti, A. The calculation of molecular volumes and the use of volume analysis in the investigation of structured media and of solid-state organic reactivity. *J. Am. Chem. Soc.* 1983, **105**, 5220–5225
- 21 Morrison, R.T. and Boyd, R.N. *Organic Chemistry* Allyn and Bacon Inc., Boston (1969) 346
- 22 Bower, A. Computing Dirichlet tessellations. *The Computer J.* 1981, **24**, 162–166
- 23 Watson, D.F. Computing the *n*-dimensional Delaunay tessellation with application to Voronoi polytopes. *The Computer J.* 1981, **24**, 167–172
- 24 Boissonnat, J.-D. Geometric structures for three-dimensional shape representation. *ACM Trans. Graphics* 1984, **3**, 266–286
- 25 Koide, A., Doi, A. and Kajioka, K. Polyhedral approximation approach to molecular orbital graphics. *J. Mol. Graphics* 1986, **4**, 149–155
- 26 Purvis, G.D. and Culbertson, C. On the graphical display of molecular electrostatic force fields and gradients of the electron density. *J. Mol. Graphics* 1986, **4**, 88–92
- 27 Williams, D.E. and Star, T.L., Calculation of the crystal structure of hydrocarbons by molecular packing analysis. *Comput. Chem.* 1977, **1**, 173–177