A graphical representation of the electrostatic potential and electric field on a molecular surface

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The graphics program presented, ARCHEM, draws the molecular electrostatic potential (MEP) on a molecular surface color-coded according to the magnitude of the potential. Vectors can be drawn on the surface to show the electric field surrounding the molecule and color-coded according to the magnitude of the field. The electrostatic potential (ESP) calculated from the wave function or from net atomic charges using GAUSSIAN 80 UCSF[1,2] can be plotted at points on a shell surrounding the molecule. For the neurotransmitter glycine zwitterion, the MEP is calculated from the wave function and from different point charge models, and the results are represented graphically.

Keywords: molecular surfaces, electrostatic potential

INTRODUCTION

A quantitative representation of the electrostatic properties of molecules can substantially enhance the intuition of the chemist. This is especially true in host–guest chemistry, where electrostatic properties are important for drug–receptor, substrate–enzyme or ion–ionophore interactions.

The electrostatic potential can be represented graphically in several ways. Isopotential surfaces are defined from the charge distribution of the molecule. Intersection of these surfaces with a plane generates isopotential contours. Plotting these contours surrounding the molecule is useful for showing interactions outward on the plane from the van der Waals surface; most favorable directions of attack can be extrapolated. If an isopotential surface is intersected with a set of parallel planes, then by drawing the resulting contours the isopotential surface is approximated. The shape and size of the volume enclosed by this surface for a substrate molecule may be important for molecular recognition by a receptor. MEP contours can be drawn that form the intersection of the isopotential surfaces and a surface defined by the van der Waals radii of the atoms.[3] Equivalently, the van der Waals surface can be drawn using the added dimension of color to designate ranges of the electrostatic potential (ESP).[4] These MEP representations are useful to simultaneously show both the steric and electrostatic properties of a molecule.

The ESP is a function of the charge distribution. It is most accurately determined from *ab initio* calculations using the electronic wave functions and nuclear coordinates. The ESP can be calculated less accurately from a net atomic charge model, where the electrons are assigned to the nuclei; a dielectric constant must be included in the calculations to account for the screening of the electrons. From both semiempirical and *ab initio* quantum mechanical calculations, the density matrix is used to determine net atomic charges via a Mulliken population analysis. A better method to obtain net atomic charges is to find the best charges that reproduce the dipole, quadrupole and the ESP calculated directly from the electronic wave functions and nuclear coordinates.[2] These charges are referred to as "potential derived charges."

Glycine is the simplest of neurotransmitters,[5] and it is small enough to calculate to a high level of accuracy. Understanding its MEP may provide insight into the properties "recognized" by the glycine receptor.

DESCRIPTION OF THE PROGRAM

ARCHEM calculates the ESP by the method of Politzer,[6] and it displays the results in several ways:

(1) If the MEP is calculated from GAUSSIAN 80 UCSF, one or more concentric circles are drawn on the van der Waals surface about each point where the ESP is determined (Color Plate 1).

(2) If the MEP is calculated from net atomic charges,

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one or two perpendicular sets of parallel circles are drawn, and the ESP is calculated for each segment of each circle. This kind of representation gives a crosshatching effect shown in Color Plate 2.

(3) The potential ranges can be shown in black and white by drawing different crosshatching patterns for each range.[7]

(4) Isopotential contours can be drawn either on the van der Waals surface or as parallel sets of planes passing through the molecule.

(5) The electric field can be represented on the van der Waals surface as vectors where the length of the vector is proportional to the magnitude of the electric field. A circle is drawn on the surface at the tail of each vector. Color Plate 3 illustrates the principle for glycine.

The following options are also available: stick drawing of the molecule inside the surface, scaling of atomic radii and/or constant extension of the atomic radii, full flexibility to reorient molecule and select window on the plotting surface, depiction of the outside or inside of the molecular surface with full hidden-line removal; and relaxed-eye or crossed-eye stereoscopic pairs.

Hidden-line removal is carried out by removing the line segments that are behind or inside of a sphere. Pen colors are assigned to each potential range. In order to send the line segments to the plotter in blocks of one color, a file for each pen color is opened and the plotting commands for each line segment are written to the appropriate file. Later, these eight files are appended and sent to the plotter. The area on the surface that lies within each potential range is determined by counting the number of segments of each color weighted according to the area per segment. Calculation of the areas of each potential range allows for quantifying the MEP. This methodology has proven useful in explaining potencies of several nicotinic agonists.[8,9]

ARCHEM is written in FORTRAN 77 for both a VAX computer and a Cyber 205 supercomputer.[10] The supercomputing facilities used for this work were those of the John von Neuman Center in Princeton, NJ. The standard coordinate files used by CHEM-X,[11] MACCS[12] or SYBYL[13] can be used as input. Output files are written in Hewlett-Packard Graphics Language and are sent to a multipen plotter.

QUANTUM MECHANICAL CALCULATIONS OF GLYCINE ZWITTERION

GAUSSIAN 80 UCSF was used to carry out three single-point crystal calculations on the zwitterion of glycine. The geometry was taken from the Cambridge Crystallographic database and the hydrogen positions optimized using MNDO.[14] The basis sets STO-3G, 6-31G and 6-31G* were selected. The option to calculate the ESP in a shell about the molecule was chosen. This data was used for two purposes: first, to plot the "dot" surface of the molecule, color-coded according to potential range (Color Plate 1 shows the result for the 6-31G* basis set), and second, to calculate the potential derived charges using ESPFIT.[2] The potential derived charges are those that best reproduce the ESP described above. A A single-point MNDO calculation was also performed on this structure for comparison. Seven sets of net atomic charges were generated from these calculations (i.e., the Mulliken and potential derived charges from the three GAUSSIAN 80 basis sets and the Mulliken charges from MNDO).

Table 1 shows the net atomic charges. There is little consistency in point charges—for example, N+ varies from +0.06 (MNDO) to −0.86 (6-31G). However, there are compensating charge alterations so that, for example, the NH_3+ group charge is about +0.6 for all models. Consequently, the MEPs generated from each of these sets of atomic charges are not so different. As seen by inspection of Color Plate 2, the MEP from atomic charges calculated by the relatively inexpensive MNDO method looks remarkably similar to the high-quality calculation of Color Plate 1. The differences can be seen more easily if from each MEP is subtracted a standard MEP, chosen as that calculated directly from the wave functions in GAUSSIAN 80 UCSF using the 6-31G* basis set. These difference MEPs are shown for the 6-31G* (Color Plate 4a) and STO-3G (Color Plate 4b) potential derived charges. It is interesting that the MEP from the 6-31G* potential derived charges does not match the MEP calculated directly from the 6-31G* wave functions particularly well (Color Plate 4a); this undoubtedly reflects the difficulty of calculating such a complex function from a limited number of point charges.

Table 1. Glycine zwitterionic X-ray structure net atomic charges from ab initio (GAUSSIAN 80) and semiempirical (MOPAC) calculations

		Mulliken			Potential derived		
Atom	MNDO	STO-3G	6-31G	6-31G*	STO-3G	6-31G	6-31G*
N1	0.0560	−0.3405	−0.8551	−0.8230	−0.1289	−0.0815	−0.1235
O2	−0.5804	−0.4929	−0.7282	−0.7336	−0.6793	−0.8880	−0.7825
O3	−0.4850	−0.4418	−0.6728	−0.6866	−0.6481	−0.8564	−0.7588
C4	0.3354	0.2413	0.7151	0.7515	0.6207	1.0708	0.8471
C5	−0.0390	−0.0589	−0.2834	−0.3323	−0.0185	−0.0068	0.0612
H6	0.1783	0.2833	0.4267	0.4312	0.2501	0.2308	0.2355
H7	0.2106	0.3156	0.4552	0.4587	0.2632	0.2256	0.2362
H8	0.2218	0.3234	0.4620	0.4650	0.2710	0.2335	0.2347
H9	0.0529	0.0864	0.2385	0.2343	0.0331	0.0316	0.0180
H10	0.0495	0.0840	0.2421	0.2349	0.0367	0.0403	0.0321

The electric field was calculated from 6-31G* potential derived charges. It is represented in Color Plate 3 as vectors originating at points on the solvent-accessible surface. The length of each vector is proportional to the magnitude of the field, and each vector is color-coded according to the magnitude of the field.

CONCLUSIONS

ARCHEM lets chemists produce high-resolution drawings of the electrostatic properties of molecules from quantum mechanical calculations without expensive graphics terminals. It usefully shows molecular electrostatic potentials (MEPs) in several representations of molecular surfaces. ARCHEM will be submitted to QCPE for general distribution.

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