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The effect of isodensity surface sampling on ESP derived charges and the effect of adding bondcenters on DMA derived charges

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Summary

The effect of sampling the electrostatic potential around a molecule on the quality of electrostatic potential derived charges is investigated. In addition, the effect of the number of expansion sites in a Distributed Multipole Analysis (DMA) on the quality of charges fitted to the DMA derived electrostatic potential is investigated. Sampling on constant electron density surfaces gives a better fit between the quantum mechanical potential and the potential derived from the fitted charges, compared to sampling on a van der Waals surface composed of intersecting spheres. The fit between the electrostatic potential derived from point charges and the quantum mechanical potential becomes poorer with increasing quality of the employed basis set. The inclusion of bondcenters into the calculations improves the fit between the Quantum Mechanical (QM) electrostatic potential and the DMA derived potential. The number of expansion sites needed for an accurate approximation of the QM electrostatic potential increases with increasing quality of the used basis set.

Introduction

Classical force field methods use Coulomb's law to describe the electrostatic interactions of molecules. This requires the use of point charges. Most force fields use a quick calculation of point charges based on electronegativity rules [1, 2]. Several methods exist to determine point charges from a Quantum Mechanical (QM) calculation. These methods can be subdivided into a class where charges are determined by some scheme that partitions the electron density over the atoms (Mulliken [3], Bader [4], Hirshfeld [5]) and a class where charges are optimized to reproduce the QM electrostatic potential (ESP) by employing a least-squares fit of the model (on point charges based) potential and the QM potential. From now on we will refer to these charges as QMESP charges. Methods in the latter class differ mainly by how and where the electrostatic potential is sampled in the surrounding molecular space [6, 7]. These methods sometimes have problems with statistically poorly determined charges on (buried) centers. The RESP method [8] was developed to deal with this problem by allowing the simultaneous fit of charges for multiple conformations.

However, using point charges to describe electrostatic contributions neglects the fact that an atom in the field of other atoms is polarized and exerts an electric force which is not spherically symmetric. By representing the molecular charge distribution as a set of multipoles on a number of centers, the electrostatic interaction can be modeled far more accurately [9, 10]. Stone [9, 10] has described a generally applicable method for the determination of distributed multipole moments from electron density determined using Quantum Mechanics (QM). However, most force field methods cannot handle multipoles and rely on atomic partial charges to describe electrostatic interactions. Exceptions are the tinker package by Ponder [11] and the DMAREL program [12]. The distributed multipoles can still be useful for point charge based force fields, since the Distributed Multipole Analysis (DMA) derived electrostatic potential can be used to obtain DMA derived charges (DMAESP charges).

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The advantage of these DMAESP charges over the conventional QMESP charges is a decrease in computational cost of two orders of magnitude. A procedure to calculate the DMAESP charges is available in our program *Molden* and has recently been developed independently by Winn et al. [13]. DMAESP charges are not equivalent to the monopoles which are the lowest rank of multipoles resulting from a DMA. These monopoles suffer from the same deficiency as charges derived from a Mulliken population analysis [3] in which the overlap density is equipartitioned over the contributing atoms, which is a quite arbitrary choice as explained by Williams [14]. In the DMA approach, the overlap density is shifted (see Equation 20 from our previous article [15]) to the nearest expansion site. In the standard approach this expansion site is an atomic site, which is an equally arbitrary choice as equipartitioning. The first objective of this work is to evaluate the quality of DMAESP charges in comparison with conventional QMESP charges.

The second objective of this work is to improve the quality of both ESP and DMAESP charges, by better sampling of the QM or DMA derived electrostatic potential around the molecule.

Methods

The quality of DMA derived charges versus QMESP charge

The agreement between DMAESP charges and conventional QMESP charges is limited by how well the DMA derived electrostatic potential approximates the QM electrostatic potential. From now on we will refer to the QM electrostatic potential as 'true potential'. Not shifting the overlap density to atomic sites should in principle produce the best agreement between the DMA potential and the QM potential. This method is only tractable for the smallest molecules, because the number of overlap sites scales with the square of the number of primitive Cartesian Gaussians used to describe the electron density and thus increases with basis set quality. It is expected that increasing the number of expansion sites will systematically improve the agreement between the true electrostatic potential and the DMA derived potential and that more expansion sites are needed as the quality of the basis set increases. We will compare the agreement between the DMAESP charges and those of the true ESP equivalent, for two DMA variants: the standard approach with only atomic expansion sites and a variant where bondcenters have been added.

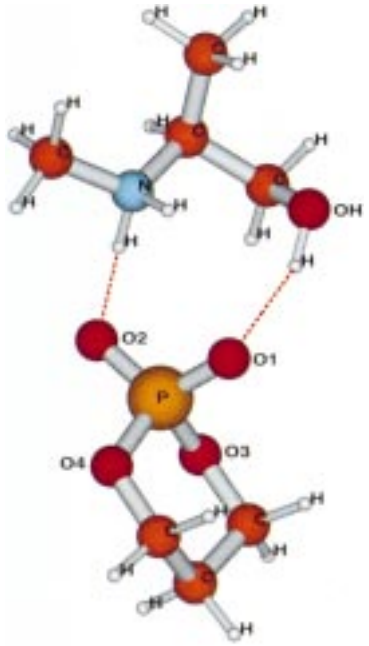

Figure 1. Test suite 'pa-complex' with highly localized charges.

The quality of the DMA derived potential can be inspected by visualizing the difference between the QM potential and the DMA derived potential. The quality of the charges will be judged by the root mean square of the difference in atomic partial charges derived from the QM potential and the DMA derived potential (Qrms) for a test suite of molecules. The mathematical background of electrostatic potentials, the charge fitting procedure and the DMA have been covered earlier in some detail [15]. The 2-(methylammonium)-propanol salt of a cyclic phosphoric acid (the so-called 'pa-complex') has highly localized charges; the phosphorus is strongly positive and two of the oxygens bonded to it carry a nearly full negative charge. An additional positive charge is located on the nitrogen atom and the complex has two hydrogen bonds, see Figure 1. For an accurate QM calculation diffuse functions on the negatively charged oxygens are required. This complex will serve as a test case for a highly inhomogeneous electrostatic potential.

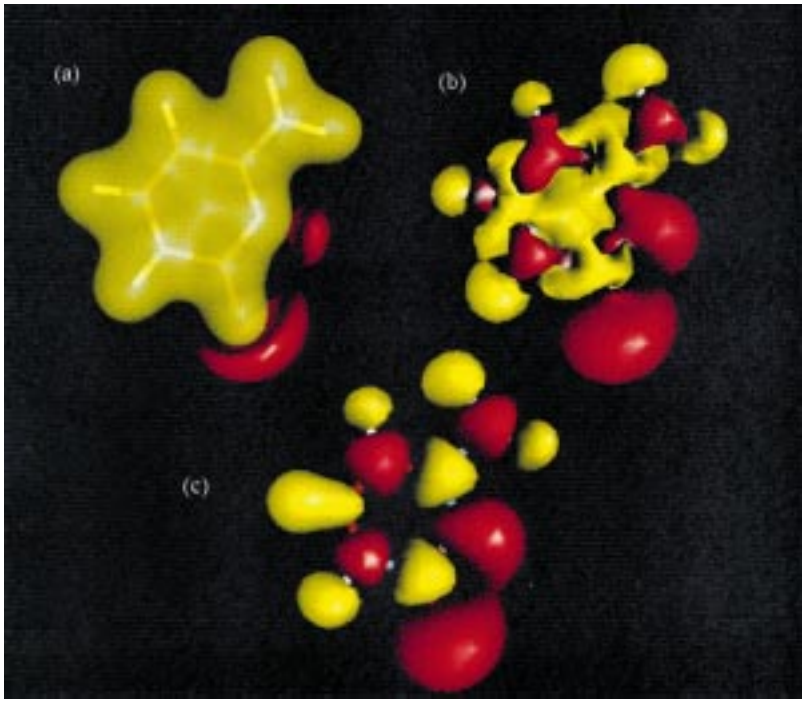

Figure 2. Isopotential surfaces (potential=+0.01 Hartree (yellow), −0.01 Hartree (red)) of the cytosine molecule for three types of potentials; (a) the QM electrostatic potential, (b) the DMA derived potential and (c) the ESP charges derived potential.

The effect of sampling on the quality of DMA derived charges and QMESP charges

The second objective of this work is an attempt to improve the quality of both ESP and DMAESP charges, by better sampling of the QM or DMA derived electrostatic potential around the molecule. The quality criterion in all ESP methods is a minimal quadratic sum of the deviation of the model potential from the QM electrostatic potential at the points used in the fit. Henceforth we will refer to it as the goodness-of-fit or GOF:

$$\mathrm{GOF} = \sqrt{\frac{\sum_i^m (V_i^o - V_i^c)^2}{n}}$$

where V_i^o is the QM electric potential and V_i^c the model potential which is given by Coulomb's law:

$$V_i^c = \sum_j^n \frac{q_j}{r_{ij}}$$

where i runs over the points sampling the electric potential (m in total) and j runs over the number of charges to be fitted (n in total). r_{ij} is the distance between point charge j and sampling point i. Large potentials and large deviations tend to be strongly expressed in the GOF giving unfairly great weights to the points nearby atoms. This may ultimately result in a poor fit of the potential at the sampling points with small potentials, and a decrease in quality of the charges associated with it. It is therefore crucial for the quality of the fit not to oversample large potential values. Williams experimented with the limit of the inner boundary of the van der Waals surface. The fit to the QM potential (rms and rrms) became worse at the smaller boundary and better at the larger boundary [16]. Singh and Kollman [17] located potential grid points in equally spaced shells located at 1.4, 1.6, 1.8 and 2.0 times the van der Waals radii. However, using such a van der Waals surface one employs the same van der Waals radii regardless of the different atomic environments. In contrast to a neutral oxygen, a negatively charged oxygen atom is likely to have an electron density distribution that extends further into space, which corresponds with a slightly larger van der Waals radius. Using a smaller radius will result in sampling points with a higher electron density with respect to the neutral oxygen. This in turn could lead to oversampling of high ESP values for some of the oxygen atoms with respect to others. The magnitude of this effect will increase with increasing level of detail

Table 1. Comparison of the root mean square (Qrms) of the difference between DMAESP charges and QMESP charges for two types of electrostatic potential sampling; van der Waals surface sampling (VDW) and isodensity surface sampling. (1) QMESP charges; (2) DMA with atomic expansion sites; (3) DMA with bondcenter sites added

Compound	$Qrms_{1-2}^{VDW}$	$Qrms_{1-3}^{VDW}$	$Qrms_{1-2}^{ISO}$	$Qrms_{1-3}^{ISO}$
H_2O[a]	0.0002	0.00004	0.0007	0.0005
Tetrahydrofuran[a]	0.0202	0.0128	0.0111	0.0023
2-Methoxymethyl 5-Methoxy tetrahydrofuran[b]	0.0264	0.0120	0.0155	0.0032
Cytosine[b]	0.0164	0.0028	0.0105	0.0011
Pa-complex[b]	0.0269	0.0126	0.0187	0.0042
Benzene[b]	0.0061	0.0014	0.0031	0.0015

[a] 6-31g**.
[b] 3-21g.

of the basis set, since a more flexible basis set allows the atoms to extend further into space.

To avoid these problems we propose to sample the electrostatic potential on a number of surfaces with constant electron density or isodensity surfaces. This has the advantage of minimizing electron-cloud penetration effects. As two molecules approach each other their potentials are distorted by electron-cloud penetration effects [18]. Using isodensity surfaces ensures that local differences in electron-cloud penetration are small in the area where the electrostatic potential is sampled. The values of the electron density are chosen such that the isodensity surfaces approach best the van der Waals shells employed by Singh and Kollman. Sampling also affects the quality of DMAESP charges as compared to QMESP charges. The QM potential and the DMA derived potential (and the ESP charges derived potential) behave differently near the atoms (see Figure 2). When r (the distance to a particular atom) is small the QM potential is a function of the nuclear charge divided by r whereas a charges derived potential and the DMA derived potential, in first approximation, are a function of partial charge divided by r. Sampling too close to the atoms will therefore reduce the quality of DMAESP charges. As discussed above, both the quality of the QMESP/DMAESP charges and the correspondence between QMESP and the DMAESP are dependent on the quality of the basis set used; therefore we will present the basis set dependency as a separate topic. QMESP charges mentioned in this work were all calculated using the scheme by Singh and Kollman [17].

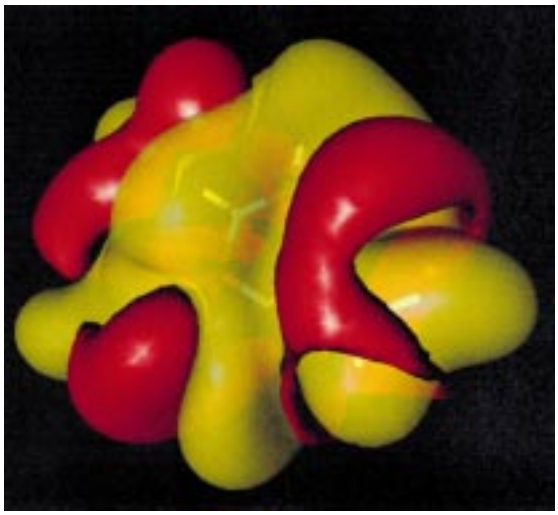

Figure 3. Graphical illustration of the difference between the QM electrostatic potential and the DMA potential with only atomic expansion sites for the cytosine molecule. Shown as surfaces with constant potential v. $+v$ = yellow and $-v$ = red. v = 0.0001 Hartree (0.06 kcal/mol).

Table 2. Distance to the surface with constant density for different oxygen atoms in the 'pa-complex'

Atom	Distance (in Å) to isodensity surface (density=0.0001 e/Bohr^3)
OH	2.17
O1	2.32
O2	2.28
O3	2.22
O4	2.22

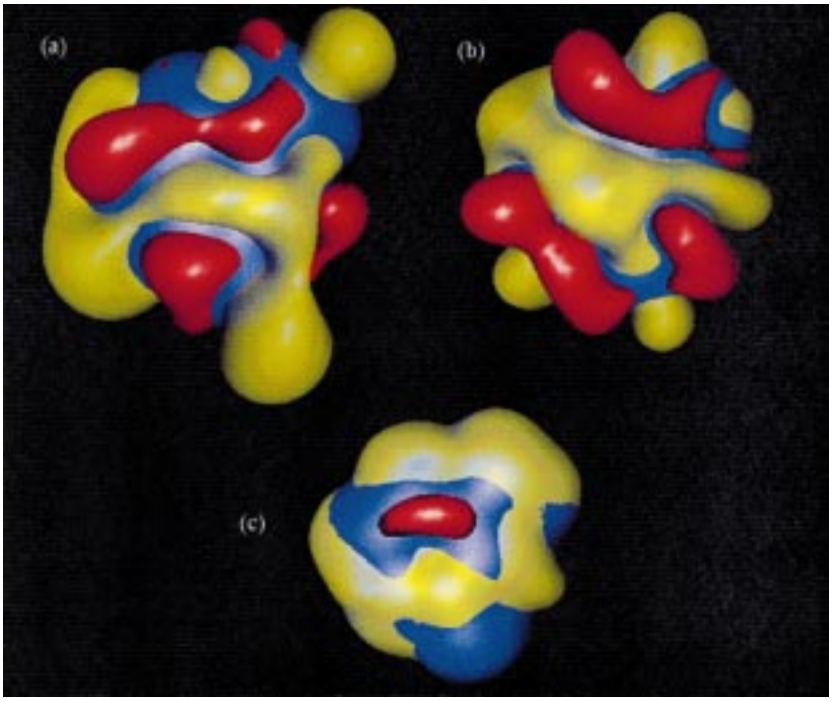

Figure 4. The difference of the QM electrostatic potential and the QMESP charges derived potential (a), the DMA potential derived with atomic expansion sites only (b) and the DMA potential derived with atomic and bondcenter expansion sites (c). Shown as surfaces with constant function values v; $+v$ = yellow and $-v$ = red. $v = 0.0001$ Hartree (0.06 kcal/mol) for (b) and (c), $v = 0.0005$ Hartree (0.31 kcal/mol) for (a). Also shown is the surface with constant density value 0.0001 e/Bohr^3 (blue color).

Results

DMA derived charges

In Table 1 two variants of DMAESP charges are compared with the true QMESP charges (charge set 1), using the root mean square differences of the atomic partial charges (Q_{rms}) as criterion. In the first variant, only the atoms were used as expansion sites (charge set 2). In the second variant, in addition bondcenters were included as expansion sites (charge set 3). Both van der Waals surface sampling and the isodensity surface sampling were performed. They are designated by VDW and ISO, respectively.

A comparison of the charges calculated with the two DMA variants shows that the addition of bondcenters (charge set 3) to only atomic expansion sites (charge set 2) reduces the Qrms values for both VDW surface sampling and isodensity surface sampling. The difference in Qrms values is about a factor 2 for VDW surface sampling and about a factor 5 for isodensity surface sampling, clearly showing the improved charges resulting from the isodensity surface sampling.

In Figure 3 the overall difference between the QM potential and the DMA potential with atomic expansion sites only is illustrated graphically for the cytosine molecule. This difference is positive (yellow) near the atoms and negative (red) between the atoms, i.e. the region of space closest to the bondcenters. This observation suggested that the agreement between both potentials could be improved by adding expansion sites at the bond centers.

The improvement of the fit is presented graphically in Figure 4, which shows the difference function between the QM electrostatic potential and three derived potentials:

(a) The electrostatic potential derived from QMESP charges.
(b) The DMA derived potential with atomic expansion sites only.
(c) The DMA derived potential with atomic and bondcenter expansion sites.

Figure 4 clearly shows that the error resulting from sampling the space outside the isodensity surface is larger for the DMA derived potential with only atomic expansion sites (b) than for the potential derived with bondcenter expansion sites added (c). The error sur-

Table 3. Comparison of the van der Waals surface sampling (VDW) and the isodensity surface sampling (ISO), based on the GOFs (in kcal/mol) and the differences (ΔD) between the dipole moment based on charges and the quantum mechanical dipole moment (D), both in Debye

Compound	GOF^{VDW}	GOF^{ISO}	ΔD^{VDW}	ΔD^{ISO}	D
H_2O[a]	1.5979	1.4567	0.0458	0.0434	2.1475
Tetrahydrofuran[a]	1.2738	0.8919	−0.0261	0.0036	1.9372
2-Methoxymethyl 5-Methoxy tetrahydrofuran[b]	1.0034	0.7873	−0.0021	0.0174	4.6624
Cytosine[b]	0.7394	0.6064	0.0491	0.0200	7.1521
Pa-complex[b]	0.9891	0.7784	0.0145	−0.0009	4.3139
Benzene[b]	0.9940	0.5128	0.0025	0.0020	0.0000

[a]6-31 g**.
[b]3-21 g.

faces extend further into space for smaller absolute values of the error v. This can be understood if one considers that close to the atomic sites the difference function always becomes strongly positive because of the different behaviour of the QM potential and the derived potentials in this region, as discussed above. It can also be seen that the DMA derived potentials are in far better agreement with the QM potential than the QMESP charges derived potential.

Isodensity surface sampling vs. van der Waals surface sampling

For the 'pa-complex' in our test suite, distances of different oxygen atoms to the surface with density value 0.0001 e/Bohr^3 are given in Table 2. It can be seen that the extension in space varies up to 0.15 Å from a hydroxyl oxygen (OH), to the negatively charged oxygen bonded to phosphorus (O1).

For the same compound this isodensity surface for two different basis sets (3-21g and 6-31g*+) and a van der Waals surface of intersecting spheres, scaled by a factor of 1.4, are shown in Figure 5. This van der Waals surface approximates the isodensity surface quite well for the medium sized basis set but it lies well inside the isodensity surface of the bigger basis set.

van der Waals surface sampling will include more higher density points for the medium size basis set than for the larger basis set. This is equivalent to sampling more points with a lower electrostatic potential, since higher electron density means more shielding of the nuclear charge. Only for the medium quality basis set, isodensity surfaces at density values 0.0001, 0.00001 and 0.000001 e/Bohr^3 are fairly well approximated by van der Waals surfaces located at 1.4, 1.6 and 1.8 times the van der Waals radii, respectively.

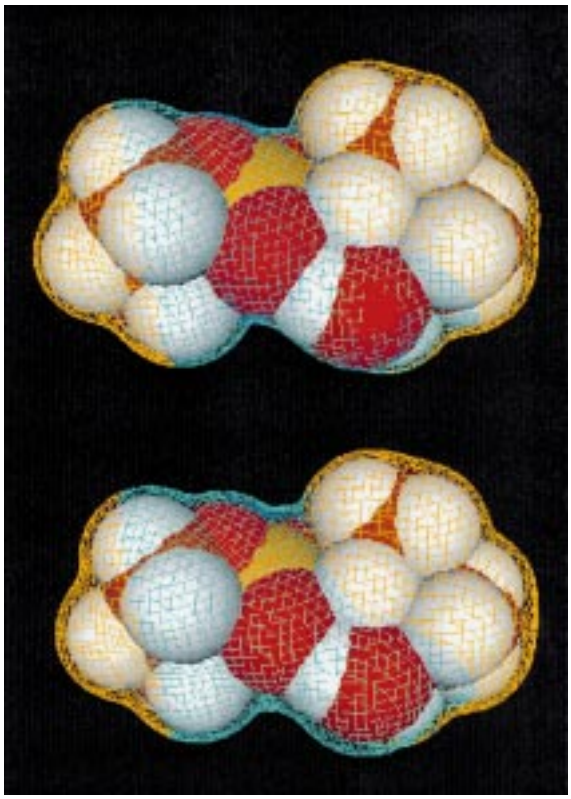

Figure 5. Isodensity surface with density value 0.0001 e/Bohr^3 for two different basis sets (3-21g (top) and 6-31g*+ (bottom)). The electrostatic potential is color coded on the surface (positive values orange, negative values blue). The van der Waals surface of intersecting spheres with a van der Waals radius scaled by a factor 1.4 is shown as a solid surface.

Comparison of the goodness-of-fit between VDW surface sampling and isodensity surface sampling

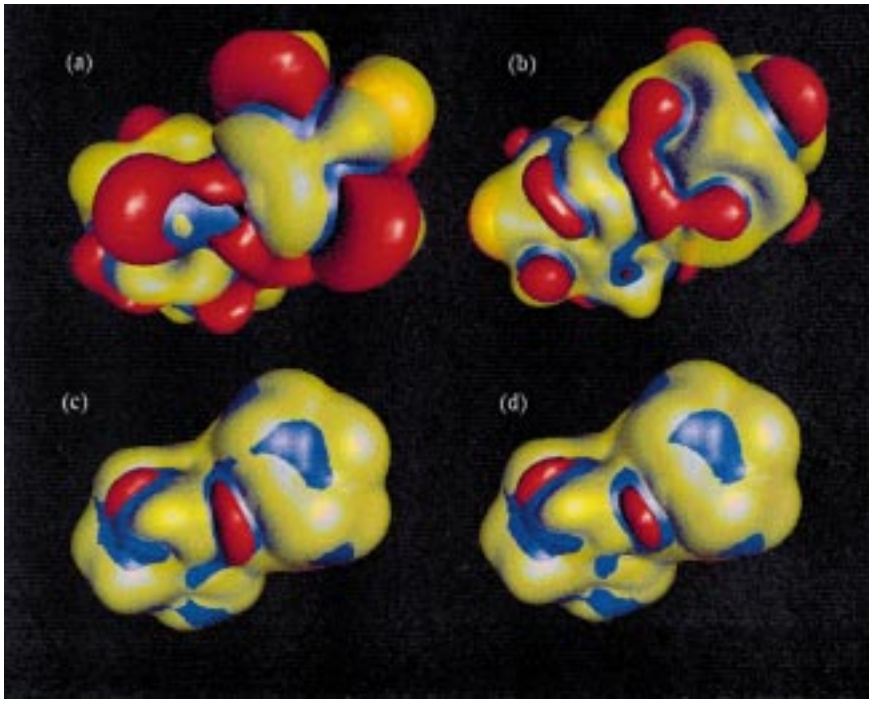

Figure 6. The difference function of the QM electrostatic potential (3-21g basis set) and (a) QMESP charges derived potential; (b), (c), (d) three variants of the DMA derived potential. Shown as surfaces with constant function value v for the 'pa-complex'. $+v$ = yellow and $-v$ = red. $v = 0.0001$ Hartree (0.06 kcal/mol) for (b), (c), (d) and $v = 0.0005$ Hartree (0.31 kcal/mol) for (a). The surface with constant density value 0.0001 e/Bohr^3 is shown in blue.

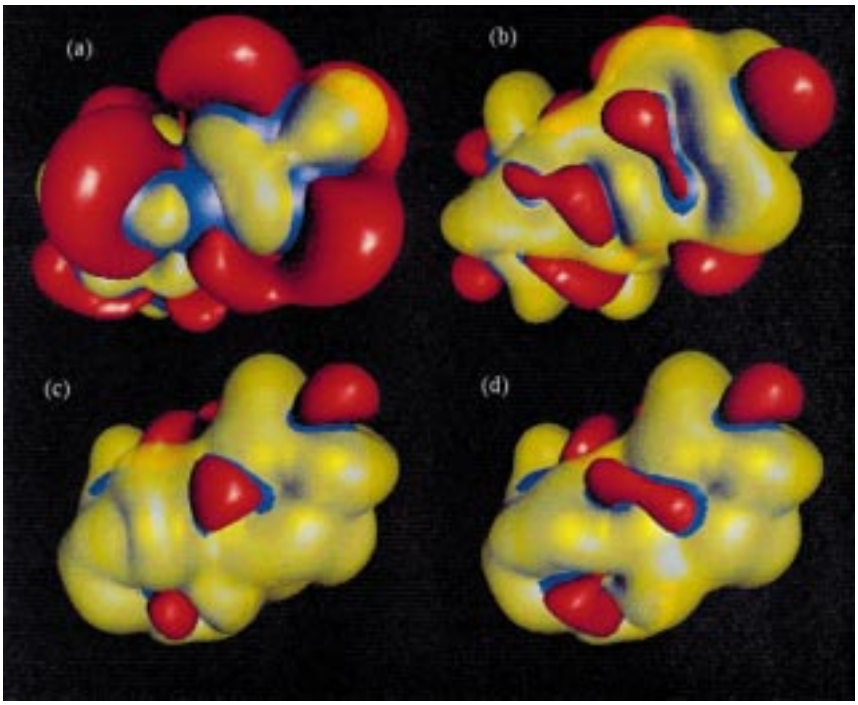

Figure 7. The difference function of the QM electrostatic potential: (6-31g*+ basis set) and (a) QMESP charges derived potential; (b), (c), (d) three variants of the DMA derived potential. Shown as surfaces with constant function value v for the 'pa-complex'. $+v$ = yellow and $-v$ = red. $v = 0.0001$ Hartree (0.06 kcal/mol) for (b), (c), (d) and $v = 0.0005$ Hartree (0.31 kcal/mol) for (a). The surface with constant density value 0.0001 e/Bohr^3 is shown in blue.

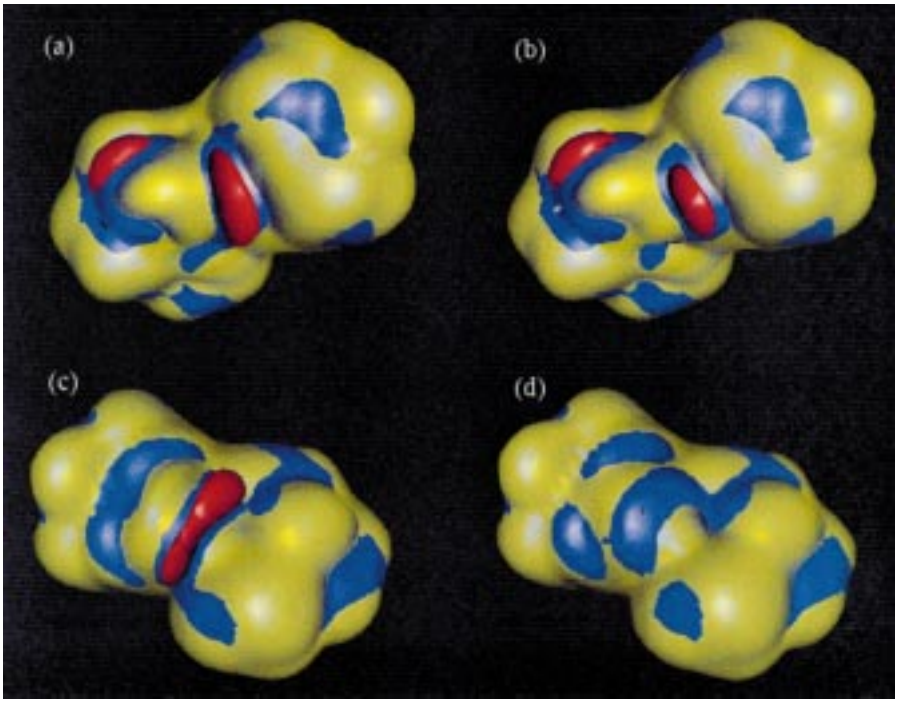

Figure 8. The difference function of the QM electrostatic potential (3-21g basis set) and DMA derived potential; (a) front-side view and (c) back-side view of 'pa-complex' for bond center sites only. (b) and (d) the same with hydrogen bond center sites added. Shown are surfaces with constant function value v, $+v$ = yellow and $-v$ = red. v = 0.0001 Hartree (0.06 kcal/mol). The surface with constant density value 0.0001 e/Bohr^3 is shown in blue.

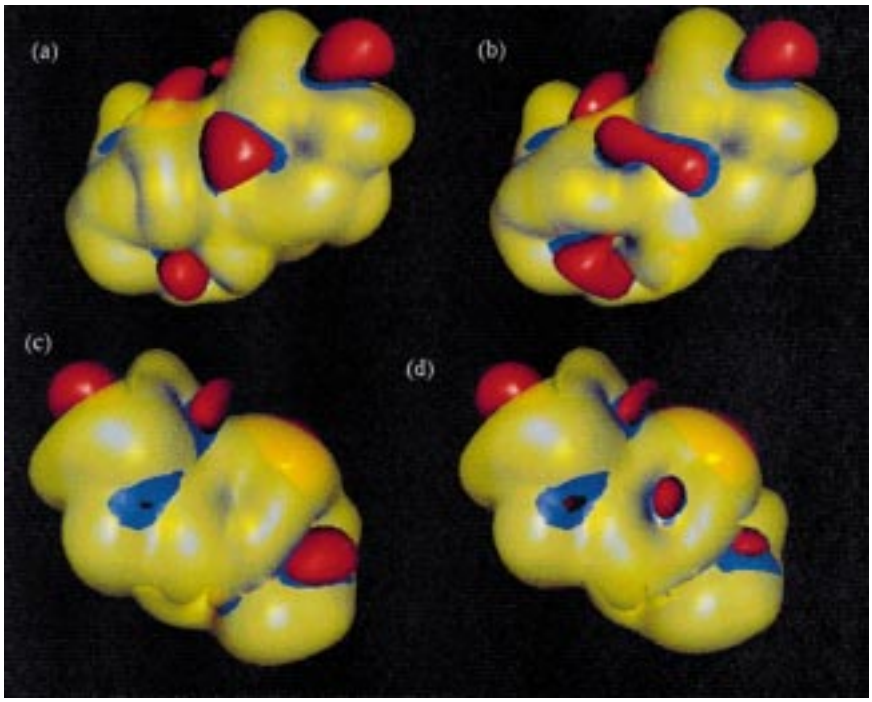

Figure 9. The difference function of the QM electrostatic potential (6-31g*+ basis set) and DMA derived potential; (a) front-side view and (c) back-side view of 'pa-complex' for bond center sites only. (b) and (d) the same with hydrogen bond center sites added. Shown are surfaces with constant function value v, $+v$ = yellow and $-v$ = red. v = 0.0001 Hartree (0.06 kcal/mol). The surface with constant density value 0.0001 e/Bohr^3 is shown in blue.

Table 4. The GOF (in kcal/mol) as a function of the basis set quality for van der Waals surface sampling (VDW) and isodensity surface sampling (ISO). Data presented are for the 'pa-complex'

Basis set	GOF^{VDW}	GOF^{ISO}
sto3g	0.8237	0.6904
3-21g	0.9891	0.7784
6-31g*+	1.0905	0.6275

Table 5. Root mean square values (Qrms) of the deviation of DMAESP charges from QMESP charges as a function of basis set quality and sampling method, van der Waals surface sampling (VDW) and isodensity surface sampling (ISO). Data for the 'pa-complex'. (1) QMESP charges; (2) DMA with atomic expansion sites; (3) DMA with bondcenter sites added

Basis set	$Qrms_{1-2}^{VDW}$	$Qrms_{1-3}^{VDW}$	$Qrms_{1-2}^{ISO}$	$Qrms_{1-3}^{ISO}$
sto3g	0.0160	0.0084	0.0096	0.0033
3-21g	0.0269	0.0126	0.0187	0.0042
6-31g*+	0.0347	0.0282	0.0255	0.0181

(see Table 3) shows that the isodensity surface sampling yields significantly better goodness-of-fit values. There is also a general trend towards better correspondence with the QM dipole moment when isodensity surface sampling is used, although this trend is not as strong as with the GOF values.

Basis set effects

Basis set quality influences the fit between the QM electrostatic potential and derived potentials. This effect is clearly shown by the GOF values presented in Table 4. The effect is most pronounced for van der Waals surface sampling. There the GOF becomes significantly worse with increasing basis set quality. For isodensity surface sampling the GOF is not only better but also does not significantly increase with increasing basis set quality.

Besides affecting the fit, basis set quality also affects the reliability of the DMAESP charges. Independent of sampling method and the DMA variant used, the deviation of DMAESP charges from QMESP charges deteriorates with increasing basis set quality as shown by the Qrms values in Table 5.

The larger the basis set one selects to calculate the QM electrostatic potential, the less is the fit with derived potentials and the less charges can be approximated by any less compute-intensive method. However, by addition of more expansion sites to the DMA analysis, DMA derived potentials can be systematically improved.

The deteriorating agreement with increasing basis set flexibility between QM electrostatic potential and derived potentials and the improvement in fit by adding additional expansion sites is illustrated graphically in Figures 6–9. The decrease in fit is understood by considering that the ratio atomic plus overlap sites versus atomic plus bondcenter sites becomes increasingly unfavorable with increasing flexibility of the basis set used. Figures 6 (3-21g basis set) and 7 (6-31g*+ basis set) show the difference function between the QM electrostatic potential and four derived potentials for the molecular 'pa-complex':

(a) The electrostatic potential derived from ESP charges.
(b) The DMA derived potential with atomic expansion sites only.
(c) The DMA derived potential with atomic and bondcenter expansion sites.
(d) The DMA derived potential with atomic, bondcenter and hydrogen-bond center expansion.

Comparison of Figures 6 and 7 shows the basis set effect; the systematic improvement as a result of the addition of expansion sites is clearly illustrated in going from (a) to (d) in both Figures 6 and 7.

The improvement of the fit between the QM electrostatic potential and DMA derived potentials as an effect of the addition of hydrogen bondcenter expansion sites on top of atomic and bondcenter sites is shown in more detail in Figures 8 and 9 where we zoom in on potentials (c) and (d) above.

The effect of the addition of hydrogen-bondcenter expansion sites on the quality of the fit is most significant at the back side of the molecule where the spacial extension of electron density is less pronounced. The locations where the DMA derived potential still deviates from the QM potential could be identified as oxygen lone pair sites.

Timings

Table 6 shows a comparison of times needed to calculate QMESP charges (t_{QMESP}) and DMAESP charges (t_{DMAESP}) as a function of the number of basis functions used to describe the QM electron density. The ratio t_{QMESP} / t_{DMAESP} increases in favor of the DMAESP charges with increasing number of basis

Table 6. Comparison of the calculation time of QMESP charges (t_{QMESP}) and DMAESP charges (t_{DMAESP}) as a function of number of basis functions used. Timings are in s

Compound	t_{QMESP}	t_{DMAESP}	t_{QMESP}/t_{DMAESP}	Basis functions
H_2O[a]	4.28	0.26	16.5	25
Benzene[b]	53.2	1.4	38.0	66
Cytosine[b]	84.5	2.0	42.3	82
Tetrahydrofuran[a]	165.5	3.7	44.7	115
2-Methoxymethyl 5-Methoxy tetrahydrofuran[b]	253.0	5.4	46.9	118
Pa-complex[b]	619.3	11.0	56.3	166

[a] 6-31 g**.
[b] 3-21g.

functions, ranging from 16 for small systems to 56 for larger systems.

Conclusions

Calculations on a set of test molecules with wide variety of charge distributions were performed to establish the quality of the DMA derived electrostatic potentials and the effect of the sampling method on the quality of charges fitted to a DMA derived potential. The advantage of DMAESP charges over the conventional (QMESP) charges is a decrease in computational cost of a few orders of magnitude. It was found that the quality of the DMA derived electrostatic potential can be systematically improved by adding additional expansion sites to the DMA analysis and that more sites are needed with increasing basis set quality. The same procedure improves the DMAESP charges as well. Sampling the electrostatic potential on isodensity surfaces instead of sampling on a van der Waals surface improves both ESP and DMAESP charges. Using the isodensity sampling method and a sufficiently large number of expansion sites, DMAESP charges can be calculated in good agreement with the conventional QMESP charges, with typical errors being smaller than 1%.

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