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Toward Improved Force Fields. 1. Multipole-Derived Atomic Charges

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The electrostatic energy component of classical force fields often includes some of the polarization energy component implicitly through the choice of atomic charges. In this and the subsequent articles we describe progress toward separating and accurately calculating both electrostatic and polarization energies. In the present contribution the distributed point charge representation of electrostatics is retained. Charges derived from several quantum chemical models including electron correlation at various levels are compared. We found that ignoring electron correlation in deriving charges for our force field can result in an error of several kcal mol^{-1} in free energy difference simulations, and that this error can be comparable to the effect of ignoring polarization. We conclude that the accurate treatment of polarization in force fields also requires an accurate treatment of electron correlation. The work is based on the relatively new MPFIT charge fitting procedure (Ferenczy, G. G. *J. Comput. Chem.* **1991,** *12,* 913*;* Chipot, C.; et. al. *J. Phys. Chem.* **1993,** *97,* 6628), which produces point charges comparable to conventional molecular electrostatic potential-derived charges. These new charges are slightly less polar and more transferable and contain more chemical sense, but they are still conformationally dependent. The significance of different levels of electron correlation in these charges was examined through regression analysis, to determine scaling relationships between the charges, and through free energy difference simulations, to determine the effect of using alternative charge sets. The free energy calculations indicate that the Becke−Lee, Yang, and Parr nonlocal density functional method gives charges similar to second-order Møller−Plessett perturbation theory. The charges are shown to be insensitive to the precision of the quadrature used in the density functional calculations. For polar molecules, these methods generally gave free energies of hydration which were significantly smaller than those computed using Hartree−Fock charges. When the Hartree−Fock charges are scaled to reproduce the higher quality charges, the error is usually reduced, but is still significant in some cases. Since many force fields effectively exploit the polarity of the Hartree−Fock charges to mimic the effects of polarization in an ad hoc way, this result has important implications for force field design, as mentioned above. It is suggested that the electron density calculated by the density functional method is a suitable starting point to derive distributed multipole sets for use in force fields which include explicit polarization.

Introduction

The development of accurate force fields is an important area of computational chemistry which has seen much progress in recent years. Nevertheless, the accuracy of the force fields depends as much on the care exercised during the parametrization and on a fortuitous cancellation of errors as on a rigorous treatment of the underlying physics. While the success of modern force fields in applications to appropriate problems is impressive, there is clearly much scope for improvement. Ideally, force field components should correspond to those of a quantum mechanical interaction energy decomposition scheme since this facilitates the separate improvement of the individual classical potentials and should also ensure the transferability of the parameters. Two areas where improvement would be much welcomed are (i) the implementation of polarization and (ii) the implementation of a more rigorous treatment of electrostatics which goes beyond the monopole approximation.

To lay the foundations for both of these improvements, we have investigated a relatively new method of deriving atomic point charges called MPFIT.[1,2] Because of its general nature, the method has applications far beyond the realm of traditional force fields. The method involves a fitting procedure to reproduce a distributed multipole analysis (DMA)[3] by a set of monopoles. As discussed in refs 1, 2, and 4 and further argued in this series of paper articles, this method has both conceptual and practical advantages over the more traditional potential-fitting procedure.[5] For example, the method may be adapted to describe induction effects within a monopole approximation since it may be used to reproduce an induced dipole on say atom A (Figure 1) by monopoles on the atom itself and those bonded to it,[6] i.e. atoms A, B, C, and D. This would enable polarization effects to be incorporated more fully, not only in force fields but also in Poisson−Boltzmann methods and hybrid quantum mechanics−molecular mechanics methods. Moreover, this multipole-fitting method can be extended beyond the monopole approximation by representing each multipole series at a single site by an equivalent distributed multipole series of lower rank. These *effective multipoles* are described in the following article. For the above reasons, the multipole-fitted distributed multipoles are the subject of the present detailed series of studies aimed at deriving parameters for accurate force fields.

In this article we carefully assess the new multipole-fitting method by comparing the monopoles to conventional molecular electrostatic potential (MEP) derived charges.[5] (The new

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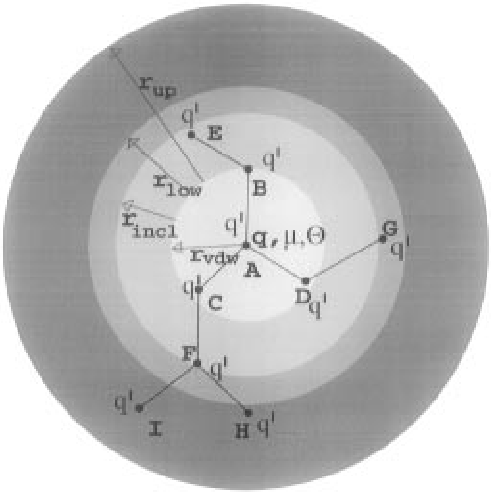


Figure 1. Schematic diagram to show how the multipole-fitting method works. Centers A−I represent atomic centers for which a DMA is available. The DMA is represented by charges, q, dipoles, μ, and quadrupoles, Θ, etc., which are reproduced by a set of charges q'.

charges are also potential-derived charges, but there are subtle differences in computation.) In addition, we assess the chemical meaning of the new charges using the criteria of Wiberg and Rablen.[7] Elsewhere it has been shown that the multipole-fitted charges are particularly transferable from one environment to another,[2] and so we have also investigated the conformational transferability[8] of these charges. Finally, we lay the foundations for the implementation of polarization by quantifying the effects of electron correlation on atomic charges. Such studies on the effect of electron correlation frequently[9−12] form an essential part of investigations of charge quality. Here this is important because electron correlation can have a differential effect on the lower and higher rank multipoles.[13,14] Unlike most other authors we have also extended our investigations to include the effect of charge magnitude on the free energy of hydration of some biologically relevant molecules. Traditionally, atomic charges have been calculated using molecular orbital methods, despite the known tendency to produce wave functions that are too polar.[15] Indeed, this polarity has been exploited in traditional force fields because molecules should be more polar in solution than in the gas phase. There is, however, no reason why these two sources of increased polarity should be related to each other. Consequently, a force field which includes explicit polarization should not be based on Hartree−Fock charges, otherwise the polarization energy may effectively be double-counted. Electron correlation has therefore been treated using both second-order Møller−Plessett perturbation theory and nonlocal density functional theory. Given the current importance of density functional theory,[16] it is particularly important to assess the quality of multipole-fitted charges derived from this source.

Methods

The multipole-fitting method[1] for deriving electrostatic potential-derived charges has the following benefits over the conventional approach. It is based on a DMA,[3] rather than on the potential calculated over a grid, and the sum of differences over the grid points is replaced by an integral. This largely eliminates the artifacts arising from the use of a numerical grid and considerably accelerates the computation. In addition, the charges are considerably more transferable from one molecule to another.[2]

A detailed description of the method is given in elsewhere,[1,2] but the basic methodology, including the introduction of a new parameter, r_{incl}, is described with the aid of Figure 1. Consider atom A, in Figure 1, as the center whose multipoles we wish to reproduce. The charges q' are determined so that they reproduce the electrostatic potential of the multipole series q, μ, Θ, ..., centered at A. The actual number of charges, q', involved in the fitting depends on the variable r_{incl}, since only charges, q', within $r_{\text{vdw}} + r_{\text{incl}}$ of the center A are considered. (r_{low} and r_{up} define the radii of the spherical shell where the reproduction of the electrostatic potentials is required. In the former version, charges within $r_{\text{vdw}} + r_{\text{low}}$ were involved in the fit.) Thus, in Figure 1, only charges at sites A, B, C, D, E, and F would be involved in the fitting. If we set r_{incl} to zero, then only A, B, C, and D would be involved in the fitting. The actual fitting is performed by integration over the outer region of the diagram from $r_{\text{vdw}} + r_{\text{low}}$ to $r_{\text{vdw}} + r_{\text{up}}$. Consequently, we expect the charges q' to reproduce the electrostatic potential of the multipole center in this region only. The other sites B to I at which the DMA is calculated would then be treated similarly, and the atomic charges reproducing each multipole series summed to give the total charge for each site. Here, r_{low} is always 2.0 Å, but r_{up} is either 5.0 or 15.0 Å; both values of r_{up} give essentially equivalent results.

Throughout this work, the DMA has been calculated from the wave function determined using CADPAC 5.1[17] with a 6-31G* basis set.[18] In most cases, the Hartree−Fock method[19] has been used in conjunction with a 6-31G* basis set for both the geometry optimization and the DMA calculation. Conventional molecular electrostatic potential (MEP) calculations were performed using GAUSSIAN 92/DFT;[20] charges determined to reproduce this MEP were obtained using the *Rattler* in-house fitting software.[8,21] In some cases, the AM1 semiemprical molecular orbital method,[22] as implemented in MOPAC 6.0,[23] was used to optimize the geometries. Density functional methods,[24] as implemented in CADPAC 5.1, were also used to calculate the wave function and hence the DMA. The Becke '88 functional[25] was used for exchange and the Lee−Yang−Parr functional was used for correlation[26] in the majority of the density functional calculations. This combination (denoted BLYP) has been shown to perform well in a number of applications,[16] but the local density approximation[27] (denoted LDA) was also used. Unless otherwise stated, the quadrature of the functionals was performed numerically using a high grid with about 15 000 points per atom. Very high, medium, and low grids were also used, which contained about 40 000, 6000, and 1500 points per atom, respectively. The charges were found to be essentially independent of the quadrature scheme used, and so this is not discussed further. Electron correlation has also been treated using second- or third-order Møller−Plessett perturbation theory (denoted MP2 or MP3).[28]

A set of five molecules (shown in Table 1) was chosen to test the convergence of the fitting procedure with the highest rank of the multipole to be fitted. The DMA for each molecule was obtained from Hartree−Fock (HF) 6-31G* wave functions. The variable r_{incl} was used to moderate the number of charge centers associated with each distributed multipole series. Initially r_{incl} was set at zero so that the program fits charges only to the nearest neighbors of an atom, but the effect of increasing r_{incl} to 2.0 Å was also investigated.

Once the dependence of the charges with rank had been studied, the multipole-fitted charges were compared to the conventional MEP-derived charges for 26 small molecules at their AM1 optimized geometry. A distributed multipole analysis was obtained at the HF/6-31G* level. From the DMAs, two sets of MPFIT charges were obtained using $r_{\text{incl}} = 0.0$ Å and $r_{\text{incl}} = 2.0$ Å. The corresponding conventional MEP-derived charges were also obtained.

TABLE 1: Variation of the Charge with DMA Rank. Using $r_{incl} = 2.0$ Å Reproduces the Distributed Multipole by Atomic Charges at Almost Every Center; Using $r_{incl} = 0.0$ Å Reproduces the Distributed Multipole by Atomic Charges on Neighboring Atoms Only

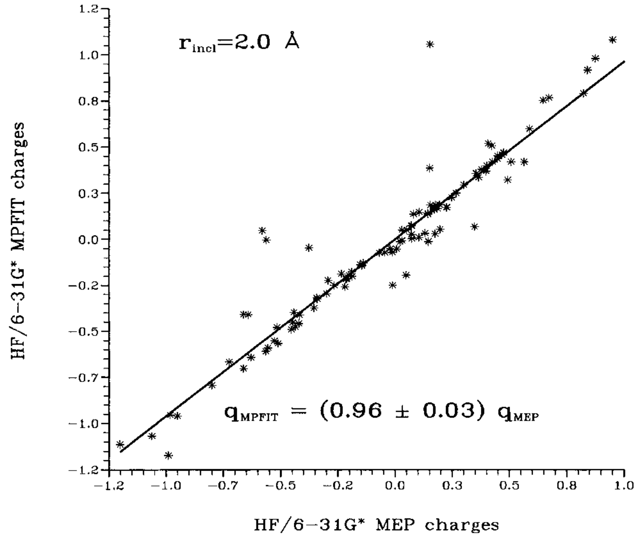
		$r_{incl} = 2.0$ Å						$r_{incl} = 0.0$ Å		
molecule	atomic no.	rank 4	rank 5	rank 6	rank 7	rank 8	rank 9	rank 4	rank 5	rank 6
$CH_3CH_2OCH_3$	6	−0.211	−0.005	0.087	0.135	0.159	0.177	0.167	0.167	0.167
	6	0.447	0.380	0.370	0.369	0.368	0.366	0.638	0.638	0.638
	8	−0.412	−0.456	−0.477	−0.486	−0.490	−0.493	−0.741	−0.741	−0.741
	6	−0.132	0.025	0.078	0.091	0.099	0.109	0.718	0.718	0.718
	1	0.139	0.100	0.086	0.082	0.079	0.076	−0.068	−0.068	−0.068
	1	0.053	0.015	0.004	0.003	0.003	0.001	−0.136	−0.136	−0.136
	1	0.053	0.017	0.006	0.005	0.005	0.003	−0.136	−0.136	−0.136
	1	−0.033	−0.027	−0.032	−0.037	−0.039	−0.041	−0.147	−0.147	−0.147
	1	−0.029	−0.024	−0.029	−0.033	−0.035	−0.037	−0.147	−0.147	−0.147
	1	0.025	−0.030	−0.056	−0.069	−0.075	−0.080	−0.059	−0.059	−0.059
	1	0.051	0.004	−0.018	−0.030	−0.036	−0.040	−0.045	−0.045	−0.045
	1	0.051	0.003	−0.019	−0.031	−0.037	−0.041	−0.046	−0.046	−0.046
$HCONH_2$	8	−0.485	−0.491	−0.492	−0.492	−0.492	−0.492	−0.536	−0.536	−0.536
	6	0.572	0.584	0.587	0.588	0.588	0.588	0.743	0.743	0.743
	7	−0.791	−0.794	0.793	−0.792	−0.792	−0.792	−0.859	−0.859	−0.859
	1	0.394	0.394	0.393	0.393	0.393	0.393	0.395	0.395	0.395
	1	0.324	0.323	0.323	0.322	0.322	0.322	0.353	0.353	0.353
	1	−0.012	−0.017	−0.018	−0.018	−0.019	−0.019	−0.096	−0.096	−0.096
CH_3COCH_3	8	−0.488	−0.492	−0.495	−0.495	−0.495	−0.495	−0.490	−0.490	−0.490
	6	0.543	0.541	0.527	0.527	0.527	0.526	0.577	0.577	0.577
	6	−0.096	−0.079	−0.046	−0.032	−0.026	−0.021	−0.234	−0.234	−0.234
	1	0.032	0.028	0.020	0.016	0.014	0.013	0.073	0.073	0.073
	1	0.018	0.013	0.003	0.000	−0.002	−0.003	0.059	0.059	0.059
	1	0.018	0.013	0.003	0.000	−0.002	−0.003	0.059	0.059	0.059
	6	−0.096	−0.079	−0.046	−0.032	−0.026	−0.021	−0.234	−0.234	−0.234
	1	0.028	0.020	0.016	0.014	0.013	0.011	0.073	0.073	0.073
	1	0.018	0.013	0.003	0.000	−0.002	−0.003	0.059	0.059	0.059
	1	0.018	0.013	0.003	0.000	−0.002	−0.003	0.059	0.059	0.059
NH_3	1	0.332	0.332	0.332	0.332					
	7	−0.997	−0.997	−0.997	−0.997					
	1	0.332	0.332	0.332	0.332					
	1	0.332	0.332	0.332	0.332					
	1	0.332	0.332	0.332	0.332					
CH_4	1	−0.030	−0.024	−0.022	−0.022	−0.022	−0.022			
	6	0.121	0.095	0.088	0.087	0.087	0.087			
	1	−0.030	−0.024	−0.022	−0.022	−0.022	−0.022			
	1	−0.030	−0.024	−0.022	−0.022	−0.022	−0.022			
	1	−0.030	−0.024	−0.022	−0.022	−0.022	−0.022			

The chemical sense of MPFIT charges was investigated for a number of methyl−X compounds (where X = Li, BeH, BH_2, CH_3, NH_2, OH, F, H, and CH_3) at their HF/6-31G* geometry. The methyl group charges were derived with r_{incl} set at both 0.0 and 2.0 Å, and with $r_{up} = 15$ Å. The dipole moment of the C−H bond in methane, ethane, and acetylene was also investigated and compared to experiment.

To assess the conformational dependence of the multipole-fitted charges, five different conformations of propanol were investigated.[8] Multipole-fitted charges were calculated for each optimized conformation using both the BLYP density functional method and the MP2 method. For each conformation, the dipole moment was calculated with the charges derived for the conformation under consideration (the correct charges). It was also calculated with the charge sets derived from each of the other conformations (effectively incorrect charges for the conformation being considered). The conformational transferability was then assessed by comparing the various classical dipole moments with the corresponding calculated quantum mechanical one.

The significance of electron correlation on the point charges used in molecular mechanics calculations and its implications for modeling polarization have been assessed by determining point charges for the 28 small molecules at their AM1 geometries. Hartree−Fock, MP2, and density functional multipole-fitted charges were obtained. The density functional calculations used different quadrature densities and basis sets and employed both the BLYP and LDA functionals. Regression analyses of the form $y = mx$ were performed to determine the relationship between these charges. (It was fortunate that regression analysis using $y = mx + c$ showed that the constant, c, was not significant because scaling relationships are most useful in the form $y = mx$.)

Finally, the effects of electron correlation (and hence implicit ad hoc polarization models) were quantified for a number of biologically relevant molecules by calculating the free energy of hydration for the process where one charge set was mutated to another. The Hartree−Fock charges do not include the effects of electron correlation, and consequently they fortuitously include polarization effects in an average way.[15] (This link between Hartree−Fock charges and implicit polarization has been pointed out many times[15] but has rarely been quantified.) Scaling relationships exist between Hartree−Fock and other more accurate charges (see Figure 3, Table 5, and ref 9). Consequently, scaled charges were also used in the free energy difference simulations to investigate whether scaling can compensate for ignoring electron correlation. (Hartree−Fock charges were scaled by a factor of 0.894 to mimic MP2 charges, and BLYP charges were scaled by a factor of 1.066 to mimic MP2 charges.) For selected molecules, simulations involving MP3/6-31G* and also an extended 6-31G basis set[17] (denoted 6-31GE) were also performed to test the convergence of both the MP2 method and the basis set. (The 6-31GE basis set has an extra set of diffuse functions and two sets of polarization



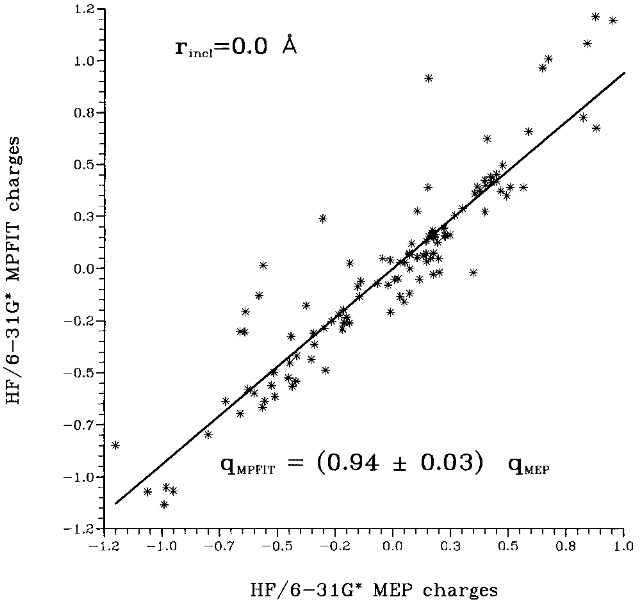


Figure 2. Comparison between the HF/6-31G* multipole-fitted and MEP-derived charges. The multipole-fitted charges were derived using integration radii of 2.0 and 15.0 Å. The top graph used r_{incl} = 2.0 Å; the bottom graph used r_{incl} = 0.0 Å. The molecules used were $HCONH_2$, C_2H_2, H_2O, C_2H_4, C_6H_6, C_4H_4O, CH_3CHO, CH_3CN, CH_3COCH_3, CH_3NH_2, CH_3OH, CO_2, COF_2, CH_4, H_2CCO, H_2CO, H_2NNO_2, HCl, HCN, $HCONH_2$, HCOOH, HF, CO, HOOH, NH_3, and PH_3.

functions; diffuse functions and polarization functions are believed to be important for describing higher multipoles[13]).

TABLE 2: Methyl Group Charges for Methyl Derivatives. The MPFIT Charges Were Determined from the HF/6-31G* DMA at the HF/6-31G* Geometry, with r_{up} = 15.0 Å; The Methyl Charges Are Expected To Increase As We Go Down the Table

	MPFIT		
compound	r_{incl} = 0.0 Å[a]	r_{incl} = 2.0 Å[b]	MEP[6]
methyl lithium	−0.769	−0.846	−0.767
methyl berylium hydride	−0.318	−0.228	−0.305
methyl borane	−0.218	−0.284	−0.205
ethane	+0.000	+0.000	+0.000
methylamine	+0.307	+0.370	+0.281
methanol	+0.267	+0.291	+0.264
methyl fluoride	+0.329	+0.349	+0.277

[a] Fitting to nearest neighbors. [b] Fitting over all atoms.

TABLE 3: MPFIT RHF/6-31G* Charges for Methane, Ethane, and Acetylene, Determined Using r_{up} = 15.0 Å

		MPFIT			
compound		r_{incl} = 0.0 Å[a]	r_{incl} = 2.0 Å[b]	MEP[6]	expt[6]
methane	C	−1.00	+0.08	−	+
	H	+0.25	−0.02	+	−
ethane	C	+0.30	+0.15	+	+
	H	−0.10	−0.05	−	−
acetylene	C	−0.26	−0.28	−	−
	H	+0.26	+0.28	+	+

[a] Fitting to nearest neighbors. [b] Fitting to all atoms.

It is difficult to determine absolute free energies from molecular dynamics simulations, but free energy differences can be evaluated more readily. Here these were calculated using thermodynamic integration,[29] as implemented in AMBER 4.0.[30] The nonbonded parameters were taken from the AMBER all-atom force field,[31] and additional parameters were obtained by analogy to the existing parameters. Halogen nonbonded parameters were obtained by comparing the work of Mayo *et al.*[32] with the AMBER parameters. Errors arising from these approximations are unlikely to be significant since the parameters are the same for both the initial and final states of the perturbation. The HF and BLYP charges were perturbed to MP2 charges. Nitrous oxide, water, and ethanal were initially perturbed for 42 ps with a nonbonded interaction cutoff of 8 Å and a box of about 450 TIP3P waters, 12 Å in all directions. These calculations were performed quickly and are useful as a guide to convergence for the longer simulations. All the molecules were then run for 100 ps with a nonbonded cutoff at 8 Å and a large box of about 1500 TIP3P waters.[33] This choice of box size is not the most cost effective choice, as it is considerably larger than is normally employed with an 8 Å cutoff, but it does ensure that artifacts arising from the use of periodic boundary conditions are minimized. All the simulations were initially equilibrated for 10 ps at 298 K using the minmd routine of AMBER.

Results

The results of the tests to see how the multipole-fitted charges varied with the rank of the DMA are shown in Table 1. Figure 2 shows the relationship between multipole-fitted and MEP-derived charges. The results from the calculations to determine the chemical sense of multipole-fitted charges, based on electronegativity, are shown in Table 2, along with the MEP results of Wiberg and Rablen.[7] The calculations examining the dipole direction are shown in Table 3, and the results of the investigation of the conformational dependence of multipole-fitted charges are shown in Table 4. The scaling relationships between the different charge sets are reported in Table 5 and are displayed in Figure 3. Table 6 shows the results of the free energy difference simulations.

Discussion

Characterization of the MPFIT Method. Table 1 shows the convergence of the multipole-fitted charges with the rank of the DMA. When r_{incl} is set to 2.0 Å so that each distributed multipole is reproduced by point charges at almost every center, the smaller molecules tend to show convergence at around rank 5 in the DMA. As the number of atoms increases, we find that the charge set becomes less likely to converge, as shown for example by $CH_3CH_2OCH_3$. The most likely explanation for this is that a large number of charge centers allows too much leeway in the fitting procedure, and thus the charges do not

TABLE 4: Comparison of the Quantum Mechanical Dipole for Propanol with That Calculated from 6-31G* MPFIT Derived Charges Determined at a Number of Different Conformations[a]

		conformation about $O{-}C_\alpha$ and $C_\alpha{-}C_\beta$ bonds				
method	source of dipole	aa	ag	ga	g+g-	g+g+
RHF/6-31G*	μ_{quantal}	*1.65*	*1.68*	*1.84*	*1.89*	*1.80*
	μ_q(aa)	**1.65**	1.77	2.62	2.71	2.56
	μ_q(ag)	1.97	**1.68**	2.58	2.59	2.54
	μ_q(ga)	1.78	1.65	**1.87**	1.95	2.15
	μ_q(g+g−)	1.75	1.78	2.06	**1.83**	2.28
	μ_q(g+g+)	2.00	1.87	2.20	2.51	**1.91**
MP2/6-31G*	μ_{quantal}	*1.55*	*1.57*	*1.73*	*1.70*	*1.69*
	μ_q(aa)	**1.57**	1.69	2.61	2.63	2.43
	μ_q(ag)	1.86	**1.58**	2.58	2.55	2.48
	μ_q(ga)	1.74	1.64	**1.87**	1.87	2.04
	μ_q(g+g−)	1.94	1.73	2.06	**1.74**	1.73
	μ_q(g+g+)	1.62	1.71	2.20	1.74	**1.73**
BLYP/6-31G*	μ_{quantal}	*1.37*	*1.40*	*1.54*	*1.50*	*1.50*
	μ_q(aa)	**1.38**	1.51	2.39	2.48	2.27
	μ_q(ag)	1.66	**1.43**	2.38	2.41	2.35
	μ_q(ga)	1.56	1.51	**1.60**	1.71	1.89
	μ_q(g+g−)	1.75	1.55	1.74	**1.56**	2.05
	μ_q(g+g+)	1.45	1.55	2.00	2.10	**1.54**

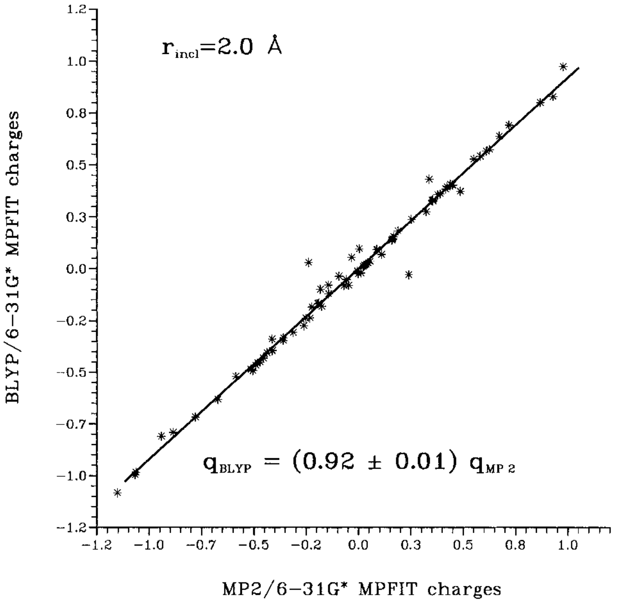
[a] Where the classical dipole moment (μ_q) is calculated for the same conformation as the one used to determine the multipole-fitted charges, the value is boldface. The symbols a and g represent antiperiplanar and gauche conformations, respectively.

TABLE 5: Regression Analysis Using $y = mx$ between Various Multipole-Fitted Charges Evaluated with $r_{\text{up}} = 15.0$ Å. The 6-31G* Basis Set Was Used Unless Otherwise Stated; R Is the Correlation Coefficient, and δm Is the Error on the Gradient

		$r_{\text{incl}} = 0.0$ Å			$r_{\text{incl}} = 2.0$ Å		
charge set *y*	charge set *x*	*m*	δm	*R*	*m*	δm	*R*
BLYP/STO-3G	HF	0.60	0.02	0.89	0.67	0.02	0.93
BLYP/3-21G	HF	0.80	0.02	0.95	0.86	0.01	0.97
BLYP	MP2	0.93	0.01	0.98	0.92	0.01	0.99
MP2	HF	0.89	0.01	0.99	0.92	0.01	0.99
BLYP	HF	0.84	0.01	0.98	0.87	0.01	0.97
LDA	HF	0.85	0.01	0.96	0.87	0.01	0.97

converge to a definitive set. With r_{incl} set to zero, so that the distributed multipole series was reproduced by charges on neighboring atoms, convergence is observed at rank 4 even for large molecules (rank 4 corresponds to hexadecapoles). It should be noted also that limiting the number of charge centers to the neighboring atoms has the important advantage that fitted charges reflect the electron distribution of their close environment. This is likely to give charges that are more chemically meaningful and more transferable from one molecular environment to another; both of these qualities are highly desirable in force fields.

Figure 2 shows that there is a distinct similarity between the multipole-fitted and MEP-derived charges. As r_{incl} is increased from 0.0 to 2.0 Å, the line appears to become more defined, although some points do however move further away from the line. Generally though, the correlation coefficients and regression coefficients are similar for both values of r_{incl}. The points off the line show some intrinsic differences between the methods (this is discussed in the next section). It should be noted also that MEP fitting procedures may not rigorously define all the charges in a molecule,[34−36] and this may explain both the points off the line and the deviation of the slope away from a value of 1.0. In general, the outliers belong to different molecules and invariably correspond to the most buried atom in the molecule, i.e. the ones furthest from the molecular surface. These are precisely that charges that tend to be ill-defined in MEP fitting procedures, and the phenomena is well-known.[34−36] It is also known that buried atoms may display a range of charge values without significantly affecting the reproduction of the MEP at the surface.[36] The deviation of the slope away from 1.0 may reflect the different treatment of electrostatic penetration in the two approaches. In general terms, however, the two sets of charges appear similar, with the multipole-fitted charges being just slightly less polar than the MEP ones. (The reduction in polarity is of a magnitude similar to that arising from the inclusion of electron correlation; see below.)



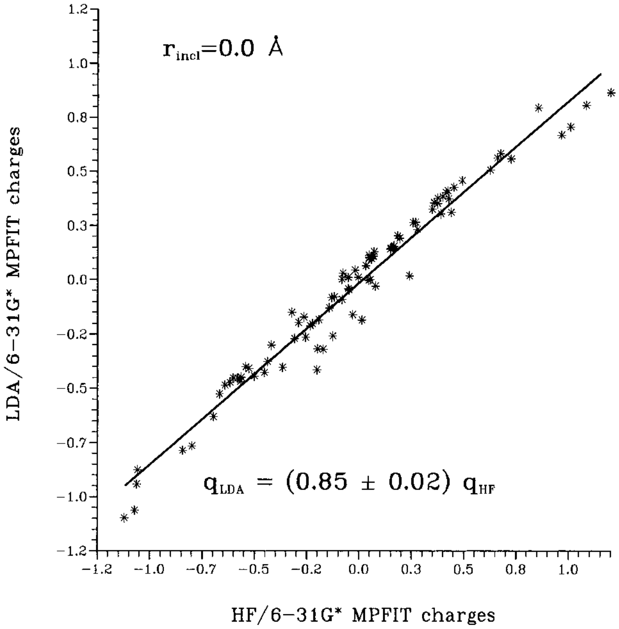


Figure 3. (Top) Comparison between BLYP/6-31G* charges and MP2/6-31G* charges for $r_{\text{incl}} = 2.0$ Å. (Bottom) Comparison between LDA/6-31G* charges and HF/6-31G* charges for $r_{\text{incl}} = 0.0$ Å. These two relationships were selected as showing the best correlation (top) and the worst correlation (bottom) of all the 6−31G* results in Table 5. CH_3SH and H_2S were included, in addition to those molecules listed for Figure 2.

The Chemical Sense of Multipole-Fitted Charges. In Tables 2 and 3 we have followed the method of Wiberg and

TABLE 6: Free Energy of Hydration Difference between MP2 and HF Derived MPFIT Charge Sets and the Free Energy of Hydration Difference between MP2 and BLYP MPFIT Charge Sets[d]

		difference in the free energy of hydration/kcal mol^{-1}						
molecule	note	$q_{MP2} \rightarrow q_{HF}$	$q_{MP2} \rightarrow q_{BLYP}$	$q_{MP2} \rightarrow$ scaled q_{HF}	$q_{MP2} \rightarrow$ scaled q_{BLYP}	$q_{MP2} \rightarrow q_{MP3}$	q_{MP2} (6-31G*) → q_{MP2} (6-31GE)	q_{MP2} (6-31G*) → q_{HF} (6-31GE)
NO	*a,b*	−0.225						
NO	*a,c*	−0.235						
NO	*b*	−0.0005	0.0404					
H_2O	*c*	−0.813						
H_2O	*b*	−0.816	1.357	1.513	**0.115**	0.576	0.451	−0.797
ethanal	*b*	−0.841	0.118	**0.112**	*0.271*	−0.392	0.623	2.4096
ethanal radical	*c*	5.021						
ethanal radical	*b*	5.078	6.229	5.759	5.935	2.709		
uracil	*b*	−2.714	2.378	*1.856*	−**0.04**			
5−fluorouracil	*b*	−2.433	1.826	*1.629*	−**0.393**			
1,1-dichloro-2,2-difluoroethylmethoxide	*b*	−0.464	0.555	**0.185**	*0.283*			
methylethoxide	*b*	0.295	0.682	*0.266*	**0.226**			
ethene	*b*	0.141	0.124	−**0.004**	*−0.080*	0.096	0.034	0.143

[a] Excited state. [b] Box = 36 Å, time = 100 ps. [c] Box = 24 Å, time = 42 ps. [d] The MP2−HF free energy difference gives an indication of the error arising through ignoring correlation effects. The difference is closely related to the error that may arise from an inappropriate treatment of polarization. The table also shows how this error may be moderated by scaling the charges. The scaling is considered effective if the error is more than halved (bold) or is reduced by about 1 kcal mol^{-1} or is negligible (italic). MP3 and large basis set (6-31GE) results are also recorded for selected molecules.

Rablen[7] to see whether the multipole-fitted charges carry more chemical meaning than conventional MEP-derived charges. In Table 2, it appears that both MEP-derived charges and multipole-fitted charges do not correctly follow the electronegativity trend of X, here defined by the charge on the methyl group in $MeXH_n$. Interestingly, in the case of the charges fitted with $r_{incl} = 0.0$ Å, the sequence is wrong only between methylamine and methanol, and here, the error is small. Moreover, it may not be correct to assume that the N−O electronegativity difference should necessarily govern the difference in charge on the methyl group, since the polar hydrogens will also influence this picture.

In Table 3, the experimentally determined sense of the C−H dipole is used as the test for chemical meaning. All three molecules are predicted correctly when $r_{incl} = 2.0$ Å. The failure on methane for $r_{incl} = 0.0$ Å probably arises because there are not enough sites to allow sufficient flexibility in the fitting. Methane therefore is a special case because it is so small, and overall we see that multipole-fitted charges give C−H dipoles similar to experimental methods.

From Tables 1−3 we conclude that it is preferable to use $r_{incl} = 0.0$ Å since this will generate well-converged transferable charges. There may be a few cases, such as methane, where the extra flexibility from the use of $r_{incl} = 2.0$ Å may be beneficial. However, in a subsequent article we show that the extra accuracy arising from the use of $r_{incl} = 2.0$ Å is minimal compared with the loss of accuracy that arises when higher rank multipoles are ignored. Thus we conclude that when higher accuracy is required, fitted charges and dipoles should be used in conjunction with $r_{incl} = 0.0$ Å.

Table 4 shows the results of tests on the conformational transferability of multipole-fitted charges. Our RHF/6-31G* results are very similar to previous work using MEP-derived charges.[8] For some columns, the multipole-fitted results show less dipole variation than the MEP-derived results; for some columns they show more. The MP2 dipole results are generally less polar than the RHF dipole results, and the density functional dipoles are less polar still. These differences arise because of the differential treatment of electron correlation, as mentioned above. Overall though, there appears to be the same amount of variation in dipole between the different methods. Thus, even for the more transferable multipole-fitted charges, it is necessary to use special techniques[8] to devise charges valid across a range of conformations. The errors apparent in Table 4 can lead to errors in the calculated free energy of hydration[8] of about 1−2 kcal mol^{-1}. The significance of such an inadequate treatment of the charge density deformation caused by conformational variation will be discussed below.

The Importance of Electron Correlation. Table 5 and Figure 3 give information on the relationship between the charges derived using different quantum chemical methods. In particular, it is noticeable how small basis set (STO-3G) BLYP calculations give particularly poor results. Elsewhere we have noted that small basis set density functional calculations perform very badly compared to small basis set Hartree−Fock methods.[37] Understandably, we see in Figure 3 that the correlation is far better for charges derived using the same basis set. The best correlation is between the MP2 and BLYP methods (Figure 3, top), although the HF method compares well with both of the above. The gradients of the graphs give us extra information. We see clearly from the gradient of the MP2 vs HF graph that the HF charges are more polar than the MP2 charges. This effect has been observed many times before for potential-derived charges,[9,10] the underlying molecular electrostatic potential,[14,38] and the associated dipole moment.[12,13,39] The relationships between the charges are similar to those for MEP-derived charges reported by Wampler[9] and others, and so it is encouraging that the multipole-fitted charges behave similarly. The BLYP charges are the least polar, perhaps reflecting a good treatment of electron correlation; the LDA charges have a polarity similar to the BLYP charges but not surprisingly give the most scatter, as shown in Figure 3 (bottom). It is most important to note such relationships when deriving a force field from ab initio calculations when the clear intention is to separate and accurately calculate both the electrostatic and polarization energies. Additional scaling relationships are reported as Supporting Information.

The important question of how the extra polarity in the Hartree−Fock wave function relates to free energies is shown in Table 6. The table primarily shows the free energy of hydration differences resulting from the following:

(i) Changing an MP2 Charge Set to an HF Charge Set. This clearly indicates the error in the free energy of hydration which arises when electron correlation is ignored.

(ii) Changing an MP2 Charge Set to a BLYP Charge Set. These two charge sets show the best correlation in Table 5,

and so this enables us to assess the effect of scaling charge sets that are well correlated.

We are not aware of experimental free energies of hydration for most of these molecules, but the experimental values for ethene and water are +1.3 and −6.3 kcal mol^{-1}, respectively, and the value for ethanal is probably about −3.8 kcal mol^{-1} since the values for propanal and butanal are −3.5 and −3.2 kcal mol^{-1}, respectively.[40] The calculated absolute free energy of hydration of uracil[41] is about −18 kcal mol^{-1}. These values help to set the differences reported in Table 6 into context: in some cases they are minimal; in other cases they are quite significant.

From the $NO^•$, H_2O, and ethanal radical results, which do not change as the simulation time increases, we can be reasonably confident that the simulations have converged well. For this study though, it is sufficient to consider the magnitude of the changes. Generally, it might be expected that a more polar molecular charge distribution would be stabilized through interactions with water. This is indeed reflected in column 3 of Table 6, where the difference in free energy of hydration is mostly negative. The MP2 to BLYP results, in column 4 of Table 6, are of a magnitude similar to the MP2 to HF results, but positive. This is in keeping with our observation in Figure 3 that the BLYP charges are less polar than the MP2 charges.

Methylethoxide and the ethanal radical both require a little extra discussion. For the ethanal radical, the magnitude of the free energy difference is noticeably large (about 6 kcal mol^{-1}). Moreover, examination of its charges shows that they would lie well off the lines in Figures 3 and Table 5. The error is probably due to a lack of convergence in treating the electron correlation. Indeed, the free energy difference obtained by perturbing the MP2 charges to MP3 charges is 2.7 kcal mol^{-1}. In many cases it will not be possible to assess whether the MP2 charges provide an adequate description because MP3 calculations will be too expensive. However, reference to Figure 3 or perturbing the MP2 charges to BLYP charges should give an indication since in either case small differences may be indicative of convergence. (For all other perturbations from MP2 to MP3 charges, the free energy difference was well below 1 kcal mol^{-1}, although we believe that these simulations have converged; it is difficult to calculate free energy differences to an accuracy of 1 kcal mol^{-1} or better.) Methylethoxide also does not fit well with the overall pattern, and this is reflected by a positive energy for the perturbation of MP2 to HF charges. The significant result to emerge from these free energy calculations, however, is their magnitude. Even for closed shell molecules containing C, H, O, and N (such as uracil) the error for the process $q_{\mathrm{HF}} \rightarrow q_{\mathrm{MP2}}$ can be as high as 3 kcal mol^{-1}. This is a very significant error, which has profound implications both for the general practice of using free energy difference simulations and also for the development of force fields. One encouraging point though concerns the halogenated molecules, which are electron rich and frequently require a careful treatment of electron correlation in quantum chemical calculations. The simulation results shown here suggest that free energy difference simulations on halogenated molecules will not be subject to more severe errors than their hydrogenated counterparts.

Considering the large errors (differences) reported in Table 6, we need to consider whether simply scaling the BLYP charges to resemble MP2 charges will greatly reduce the errors. Indeed, column 6 shows that scaling the charges does reduce the free energy difference for most of the molecules. We observe a similar effect for the HF-scaled charges (column 5). As expected, the scaling is more effective for the MP2 to BLYP results where there is a stronger underlying correlation; this is particularly noticeable for water, uracil, and 5-fluorouracil, and methylethoxide. Scaled BLYP charges have a greater similarity to MP2 charges because of the intrinsic inclusion of electron correlation. It is also not surprising that the ethanal radical results are barely improved at all; again this is due to the lack of correlation between charges for this molecule. Thus for molecules like the ethanal radical, we could never confidently state an equivalence between charge sets derived from such different calculations. The non-negligible error obtained for water reported in columns 5 and 6 must be noted since water is a fundamental component in most simulations of biological systems.

Other researchers have suggested that basis set truncation generates greater errors in the MEP and related properties than does electron correlation.[10,13] Consequently, methods that include electron correlation should not be used with small basis sets. Here the MP2/6-31G* to MP2/6-31GE perturbations generate smaller free energy changes than the HF to MP2 or HF to BLYP perturbations. Thus while the 6-31G* to 6-31GE free energy changes are positive, showing that the 6-31G* basis set may be the origin of some of the overestimation of polarity, the effects due to electron correlation are larger. The truncation of the basis set to 6-31G* appears to introduce an error of less than 1 kcal mol^{-1} for these molecules.

We believe that the magnitude of the polarization energy is likely to be comparable to the error arising from ignoring electron correlation effects. Evidence for this may be obtained from three sources: molecular dynamics calculations with explicit polarization,[42−46] hybrid quantum mechanical−molecular mechanics calculations,[47−52] and self-consistent reaction field studies of the polarizing effect of solvent.[53,54] As an overall guide, it appears that the reported polarization energy contributes around 10−30% of the total interaction energy, and so in many cases the polarization energy will indeed be on the order of 2−3 kcal mol^{-1}. Molecular dynamics studies on water clusters,[42] $(H_2O)_n$, $n = 3-8$, show that polarization contributes about 13% of the total energy (which ranges from about 15 kcal mol^{-1} for $n = 3$ to 70 kcal mol^{-1} for $n = 8$). For cations binding to crown ethers in aqueous solution, this contribution[43] can rise to about 30%. The polarization contribution to the total energy is far higher for bulk water than for water clusters, rising,[44,45] to about 30%, or 3−6 kcal mol^{-1}. These effects can be significant, even for hydrophobic solutes; thus inclusion of explicit polarization[46] raises the barrier between the methane−methane contact minimum and solvent-separated minimum from 1.0 to 1.5 kcal mol^{-1}. Combined quantum mechanics−molecular mechanics calculations have been used to determine the effect of solvent polarization on the molecular electrostatic potential and hence the charges and dipoles of a number of solutes.[47,48] It is found that the charges and dipoles are enhanced by about 30%. Using the Born equation,[49] it can be shown that polarization contributes about 40%, or 0.5−2.0 kcal mol^{-1}, to the free energy of hydration. For dimethyl ether polarized by K^+ in aqueous solution, the percentage increase is much larger,[50] but the magnitude of the effect is only about 0.1 kcal mol^{-1}. However, the author found much larger polarization effects (10−20%, 3−15 kcal mol^{-1}) in the crown ether 18-crown-6, even when polarized by solvent alone.[51,52] Luque has shown that the polarization contribution to the free energy of hydration of about 20 small neutral molecules can range from 1 to 2 kcal mol^{-1}, or about 10−20% of the total value;[53] a similar magnitude could be deduced from work by Parchment.[54] These energies[42−54] are comparable to those reported in Table 6, and this in part justifies the use of HF charges in force fields that do not include explicit polarization.[15] However, the errors caused by the neglect of polarization and the use of uncorrelated charges are expected to have opposite sign only in simulations performed in polar solvents, and in these cases we are not aware of any means of predicting the extent of error cancellation. On the other hand, the cited polarization energies and the results of Table 6 do support the idea that force fields including explicit polarization require charges evaluated using methods that include electron correlation.

Conclusions

MPFIT is a method for fitting charges directly to a wave function that has been expanded as a distributed multipole expansion. It involves integration over space rather than a summation over a set of arbitrarily chosen grid points. The method therefore possesses a number of advantages over conventional approaches. Each atom-centered multipole series is reproduced by charges on the surrounding atoms. The number of atom centers to which each multipole series is fitted should normally be limited to ensure transferability and convergence of the charge set. This can be done by varying the r_{incl} parameter so that the fitting only involves neighboring atoms. Overall, there appears to be a good correlation between multipole-fitted and conventional MEP-derived charges, although the former are slightly less polar. The multipole-fitted charges do not necessarily possess more chemical sense than charges derived by alternative methods such as those of Bader[55] or Hirshfeld.[56] The charges do, however, contain more chemical sense than conventional potential-derived charges. Finally, while multipole-fitted charges are more transferable than MEP-derived charges, like all charges derived from a single conformation, they appear to be highly conformationally dependent. Failure to allow for this particular form of polarization could give rise to errors of a few kcal mol^{-1} in free energy perturbation calculations.

Regression analysis shows that multipole-fitted Hartree−Fock charges are more polar than those derived from methods that include electron correlation, an effect which may result in errors as high as 2−3 kcal mol^{-1} for the free energies of hydration of neutral molecules. (The error may even be as high as 4−5 kcal mol^{-1} for molecules where the Hartree−Fock method is not appropriate.) Scaling the charges will generally reduce the error to 1−2 kcal mol^{-1}, but if the Hartree−Fock method is not appropriate, e.g. the ethanal radical, then scaling may actually increase the error. Our quantitative results, which are in line with the qualitative ideas of others,[15] show that ignoring electron correlation effects can give rise to an error that is comparable to ignoring polarization effects. Since these two effects are closely linked, more accurate versions of current force fields that include explicit polarization should probably base their charges on methods that include electron correlation. The results presented here suggest that nonlocal density functional methods are particularly appropriate. Indeed, such a move would represent a positive step toward basing the potentials on a quantum mechanical interaction energy decomposition scheme.[57] Since this new multipole-fitting method is fast, gives charges similar to conventional MEP-derived charges, and has more chemical meaning, it would make sense to determine the charges by this new method. Naturally, if the new force fields use only charges, then much information is inevitably lost. However, if the full distributed multipole analysis is used, the calculations become too expensive for use in molecular dynamics computer simulations. Consequently, the following article develops this theme further by suggesting a computationally feasible method of taking these ideas beyond the point charge model to include both charges and dipoles (and higher orders if necessary). Because explicit polarization is often handled in molecular mechanics force fields through the use of induced dipoles, the following article offers an attractive strategy for including both explicit polarization and higher order electrostatic effects within the same unified framework. Such an approach may offer improved accuracy in molecular mechanics simulations provided that the issues raised in this article are considered thoughtfully. Alternatively, this scheme may have many applications where it is necessary to describe both electrostatics and polarization using atomic multipoles.

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Supporting Information Available: Scaling relationships involving CI, MP2, and DFT MPFIT and MEP derived charges (1 page). Ordering information is given on any current masthead page.

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