Toward Improved Force Fields. 2. Effective Distributed Multipoles

György G. Ferenczy,*,† Peter J. Winn,‡ and Christopher A. Reynolds‡

*Research Laboratory for Inorganic Chemistry, Hungarian Academy of Sciences, P.O. Box 132,
H-1518 Budapest, Hungary, Gedeon Richter Ltd., P.O. Box 27, H-1475 Budapest, Hungary, and
Department of Biological and Chemical Sciences, University of Essex, Wivenhoe Park, Colchester,
Essex CO4 3SQ, United Kingdom*

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This is the second of a series of papers discussing the possibility of separating and accurately calculating electrostatic and polarization energies in simulations using classical force fields. A method is described for determining a set of effective distributed multipoles which have significantly improved convergence properties in evaluating the electrostatic interaction energy between molecules. These fitted multipoles are derived to reproduce the electrostatic potential and its derivatives as calculated from a full distributed multipole analysis. The method is based on previous work on the determination of multipole-fitted charges (Ferenczy, G. G. *J. Comput. Chem.* **1991**, *12*, 913; Chipot et al. *J. Phys. Chem.* **1993**, *97*, 6628) and does not involve the use of a numerical grid. In applications on model systems, fitted charges and dipoles are able to reproduce both the interaction energy and the optimized geometry obtained from a full distributed multipole analysis. Potential-derived charges, however, result in significant errors when the molecules are in close proximity to each other. The method was also used to investigate a possible reason why norepinephrine has a higher affinity than epinephrine in the β_1-adrenergic receptor subtype, while the specificity is reversed in the β_2- and β_3-adrenergic receptor subtypes. This new method offers much potential in the development of new force fields, particularly those involving polarization through induced dipoles, because only fitted charges and dipoles are required to reproduce quantitatively electrostatic interactions.

Introduction

The design of molecular force fields is complicated by the need to balance the conflicting requirements of accuracy and ease of computation while retaining desirable properties such as transferability. Practical force fields usually employ atomic charges for ease of computation. However, a more in-depth consideration of the underlying physics would suggest that distributed multipolar expansions up to quadrupole are necessary to give an adequate description of intermolecular interactions. Here we present work on effective multipoles which have significantly improved convergence properties over distributed multipole expansions. This therefore represents a step toward reconciling these two disparate approaches within a single practical framework.

Since these new effective multipoles (typically charges plus dipoles) are derived from the wave function expressed as a distributed multipole analysis[1] (DMA) by a fitting procedure, they have the desirable property of reproducing the electrostatic component of an energy decomposition scheme. (This may not necessarily be the case if the force field parameters are derived from experimental data by a fitting process.) The key role played by electrostatics has been illustrated by DMA-based studies on the equilibrium geometries of van der Waals complexes.[2−4] In many cases, electrostatics was soley responsible for a correct description of the orientation. Indeed, various other multicenter multipolar expansions have been proposed[5−7] in an attempt to give an improved electrostatic representation of the wave function. Unfortunately, these invariably require expansions at least up to the quadrupole level to give good results.[7,8] Consequently, the use of distributed multipoles in molecular dynamics studies is usually too expensive in terms of CPU time. Most force fields, therefore, use distributed charge models for the evaluation of electrostatic interaction energies. These charges can be chosen to include the effect of some higher moments. Potential-derived charges[9] and multipole-fitted charges[10−12] have this property,[13] but they are still unable to describe electrostatic interaction energies correctly.

In an attempt to achieve the accuracy of distributed multipoles, an extension of the multipole-fitting procedure has been formulated to generate higher rank fitted moments. These fitted moments have considerably improved convergence properties since accurate electrostatic energies can be obtained using lower rank multipoles than required for similar accuracy with a DMA. In particular, it can be shown that multipole-fitted charges and dipoles are sufficient for the correct description of intermolecular electrostatic interactions of molecules in close proximity to each other. This offers distinct advantages in force field development. Firstly, it offers much improved accuracy at a reasonable cost. Secondly, since the multipole-derived charges are more transferable than potential-derived charges, similar advantages are to be expected over potential-derived multipoles.[14,15] Thirdly, both electrostatics and polarization can be handled on an equal footing, since polarization is normally treated through interactions involving induced dipoles. Moreover, we will show that the errors involved in ignoring dipoles and higher moments are comparable to those involved in ignoring polarization.[12,16] This implies that advances must be made in both areas simultaneously and our approach will facilitate this, particularly as many current force fields already have code to handle dipole−dipole interactions.

In the following sections, we outline the method and illustrate its effectiveness through calculations on the interaction energy between small molecules and also through calculations on the interaction energy between two agonists and the key binding

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† Hungarian Academy of Sciences and Gedeon Richter Ltd.
‡ University of Essex.
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residues in the agonist binding site of a model of the β-adrenergic receptor.

Methods

Calculation of Effective Multipoles. Effective multipoles are effective in the sense that a set of multipoles of rank M, obtained from a fitting procedure, approximates the effect of a set of multipoles of rank N, obtained from a multipolar expansion, with $M < N$. The derivation of effective multipoles is an extension of our earlier fitting method for calculating charges to reproduce the effect of DMA multipoles.[10-12] Here we present an extension of the method to derive a set of fitted multipole moments, FMs, from a set of DMA multipoles otherwise referred to as reference multipole moments, RMs.[17] Since the FM set consists of lower rank moments than the RM set, the replacement of the RM set by the FM set results in faster evaluation of the electrostatic energy.

Let us suppose that we have a set of RM series and a set of sites for the FMs. For a quantitative description of electrostatics, a DMA up to rank 2−3 is considered necessary, but for the present purposes moments up to rank 6−8 are more appropriate as RM series. The rank of the FM series is considerably lower, being 0 or 1 (that is, charges or charges plus dipoles). The procedure to calculate the FMs is outlined below; a more quantitative description is given in the Appendix. First we choose a particular RM series and a set of sites for the FMs which are within a sphere centered on the reference site. We want to choose the fitted multipole moments, FMs, so that they reproduce the effect of the RM series outside the sphere. This is perfectly realized if the FMs create multipole moments with respect to the reference site which are equal to the RMs. In our method, a least squares-like equation is set up so that the sum of the squares of the differences between the RMs and moments created at the same site by the fitted moments is minimal. Since the FMs are calculated using a fitting procedure, the reproduction is approximate rather than exact. Nevertheless, FMs reproducing the effect of the particular RM series can be calculated. The same procedure is performed for all reference series to obtain several sets of FMs. Since the site of an FM series can be included into the fitting procedure of several RM series, the final FM set is obtained as the sum of FMs calculated in separate fits. (The limitations of the separate fitting to each set of RMs are discussed in ref 11.) For example, in a hydrogen fluoride molecule having an RM series and an FM series at both atomic sites, an FM set is obtained for both atoms when fitted to the hydrogen RM series. Another FM set is created when fitted to the fluorine RM series. For both atoms, the final FMs are the sums of the contributions obtained in the two fits.

The number of FM centers involved in the fit of an RM series is determined by the radius of a sphere. A larger radius increases the number of sites and thus improves the reproduction of the RM series. On the other hand, the FMs reproduce the effect of the RMs outside the sphere. Consequently, the radius must not be larger than the separation of atoms in intermolecular interactions. A radius of about 2 Å seems to be a reasonable compromise. This corresponds to a value of $r_{\mathrm{incl}} \simeq 0.0$ Å (see Figure 1 of ref 12.) The use of such a radius ensures that RMs on an atom are fitted by multipoles centered on the atom itself, on the nearest neighbors, and in some cases, also on the next nearest neighbors. The use of $r_{\mathrm{incl}} = 2.0$ Å will generate FMs on more atomic sites.

The effectiveness of the fit can be predicted by considering that lower rank multipoles appear with considerably higher weights in the fitting procedure (the weights, W, are given by eq 8 in the Appendix), as illustrated by the data in Table 1. Thus, the description of the lower moments exceeds that of the higher moments. We can therefore expect that the fitting of n FMs results in a very good approximation to the n lowest rank reference moments.

TABLE 1: Comparison of the Weights, $W_{l_M l_t m_M m'_M m_t p_M p_t}(r_1,r_2)$, of the Reference Multipole Moments in Eq 8. All Indices Are 0, Except l_M, the Rank of the Reference Moments, Whose Value Is Shown in the First Column

l_M	$r_1 = 3.2$ Å $r_2 = 5.0$ Å weight	$r_1 = 3.2$ Å $r_2 = 10.0$ Å weight
0	$3.4015 \times 10^{+0}$	$1.2850 \times 10^{+1}$
1	1.9844×10^{-2}	3.7483×10^{-2}
2	2.2225×10^{-4}	2.9160×10^{-4}
3	3.1540×10^{-6}	3.5215×10^{-6}
4	5.1320×10^{-8}	5.3662×10^{-8}
5	9.1734×10^{-10}	9.3413×10^{-10}
6	1.7555×10^{-11}	1.7686×10^{-11}

As an example, let us consider an HF molecule with one charge, one dipole, and two quadrupole and two octopole moments on each atom. (The other dipole, quadrupole, and octopole moments are not independent for symmetry reasons; higher rank moments are presented in Table 2 but are not discussed in the present analysis.) The calculation of the fitted moments of two fitting procedures, one for each atomic reference series. When only charges are fitted, then the charges (two parameters, since there is one fitted charge on each atom) calculated in the first fit effectively reproduce the charge and the only independent dipole moment of the reference series on one atom. The other pair of fitted charges calculated in the second fit reproduce the charge and the dipole of the other reference series (compare the RM column with the FM^0 columns in Table 2). In this way, two charges are calculated for each atom. Fitted charges belonging to the same atom are summed to give the final fitted charge. Likewise, fitted charges and dipoles (four parameters on the two atoms) effectively reproduce the charge, the only dipole, and the two independent quadrupole moments of the reference series on one of the atoms (compare the RM column with the OFM^1 and CFM^1 columns in Table 2). Indeed the OFM^1 fitted octopoles are also in reasonable agreement with the RMs. Thus, we can expect that the interaction energy between HF molecules calculated with a set of fitted charges approximates the energy calculated with a DMA up to dipoles. Similarly, the interaction energy calculated with a set of fitted charges and dipoles approximates the energy calculated with a DMA up to quadrupoles.

In large molecules it is less straightforward to predict the goodness of the fit, but we can make an estimate in the following way. Let us supporse that both the RMs and the FMs are at atomic sites and that when fitting to an RM series, the number of centers of FMs, p, is between 2 and 5. (This corresponds to the assumption that the fitting involves the atom on which the RM series is based, its nearest neighbors, and in some cases, e.g. for an H atom or a carbonyl O, the next nearest neighbors.) Since the number of spherical multipole moments of an RM up to rank N is $(N + 1)^2$ on one center, then using p FM centers and fitted moments up to rank M, there are $p(M + 1)^2$ independent parameters to reproduce the $(N + 1)^2$ lowest reference moments. This argument was used to obtain the data presented in Table 3. These data suggest that with an appropriate number of FM centers, fitted charges approximate the effect of a DMA up to dipoles, while fitted charges plus dipoles can replace a DMA up to quadrupoles or even to octopoles. This conclusion is in line with the results presented in Tables 4−13 and illustrates the usefulness of a fitted charge + dipole set in calculating electrostatic interaction energies. It would therefore appear that larger molecules may be described better than small molecules because of the increase in the proportion of adjacent

TABLE 2: Reference Multipole Moments (RM) and Moments Created by the Fitted Moments at the Site of the Reference Moments: FM^0_{app} Is Obtained by Fitting Charges; OFM^1_{app} Is Obtained by a Fit of Both Charges and Dipoles in an Overall Fitting Procedure; CFM^1_{app} Is Obtained by a Fit of Charges and Dipoles in a Cumulative Fitting Procedure

multipole index (*lmc*)[a]	F atom				H atom			
	RM	FM^0	OFM^1	CFM^1	RM	FM^0	OFM^1	CFM^1
00	−0.5103	−0.5103	−0.5103	−0.5103	0.5103	0.5103	0.5103	0.5103
11*c*	−0.1320	−0.1275	−0.1320	−0.1320	0.0278	0.0266	0.0278	0.0278
20	−0.6536	0.1105	−0.6505	−0.5304	−0.0218	0.0231	−0.0218	−0.0203
22*c*	0.1132	−0.1914	0.1127	0.0919	0.0377	−0.0400	0.0377	0.0352
31*c*	0.1646	0.2345	0.1303	−0.2861	0.0388	−0.0490	0.0380	0.0891
33*c*	−0.2125	−0.3027	−0.1683	0.3693	−0.0501	0.0633	−0.0491	−0.1151
40	−0.0834	−0.2488	−0.4231	0.4877	0.0232	−0.0520	0.0316	0.1435
42*c*	0.1244	0.3709	0.6308	−0.7271	−0.0345	0.0775	−0.0471	−0.0345
44*c*	−0.1645	−0.1645	−0.8344	0.9618	0.0457	−0.1025	0.0623	0.2829

[a] Multipole moments are labeled according to ref 28.

TABLE 3: Predicted Reproduction of RMs as a Function of the Number and Maximum Rank of FMs[a]

number of fitted centers	number of RMs reproduced using fitted:	
	charges	charges and dipoles
2	2 charge+	8 dipole+
3	3 charge+	12 quadrupole+
4	4 dipole	16 octopole
5	5 dipole+	20 octopole+

[a] Entries in the second and fourth columns are the number of reproduced RMs and are calculated as $p(M + 1)^2$, where p is the number of centers (first column) and M is the maximum rank of FMs (in this case 0 and 1, respectively). The name of the multipole moment beside the numbers refers to the highest rank reproduced RM. Thus, "dipole" appears when the charge and three dipoles (4 moments) are reproduced, and "charge+" appears when the number of the parameters is 2 or 3, i.e. more than required for reproducing the charge (1 parameter) and less than required for charge+dipole (4 parameters).

TABLE 4: Electrostatic Interaction Energy Calculated Using Various Multipoles for an HF Dimer Near to Its Equilibrium Geometry (Figure 1): All Quantities Are in Atomic Units

maximum multipole rank	DMA[a]	OFM[b]	CFM[c]	ESP[d]
0	−0.006 418	−0.005 036	−0.005 036	−0.004 947
1	−0.005 896	−0.006 529	−0.006 378	
2	−0.006 658			
3	−0.006 731			
4	−0.006 786			

[a] Multipole moments are calculated from a distributed multipole analysis. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure. [d] Charges are fitted to electrostatic potentials.

TABLE 5: Electrostatic Interaction Energy Calculated Using Various Multipoles for a Water Dimer Near to Its Equilibrium Geometry (Figure 1): All Quantities Are in Atomic Units

maximum multipole rank	DMA[a]	OFM[b]	CFM[c]	ESP[d]
0	−0.009 177	−0.008 147	−0.008 147	−0.008 271
1	−0.008 826	−0.009 498	−0.009 678	
2	−0.010 161			
3	−0.010 305			
4	−0.010 299			

[a] Multipole moments are calculated from a distributed multipole analysis. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure. [d] Charges are fitted to electrostatic potentials.

sites. Indeed, because the fitting procedure is size-independent, the method should be appropriate for any molecule for which an accurate DMA can be obtained. (Whether this is true for MEP-derived multipoles[14,15] remains to be seen, since the related MEP-derived charges are known to exhibit problems on buried atoms because there is no link between the MEP grid point and the atomic center contributing to its potential[18−20].)

TABLE 6: Electrostatic Interaction Energy Calculated Using Various Multipoles for Antiparallel HF Dimer (Figure 2a) at Several Intermolecular Separations (R): All Quantities Are in Atomic Units

maximum multipole rank	DMA[a]	OFM[b]	CFM[c]	ESP[d]
		$R = 5$		
0	−0.005 742	−0.004 506	−0.004 506	−0.004 427
1	−0.004 524	−0.004 768	−0.004 372	
2	−0.004 610			
3	−0.004 792			
4	−0.004 824			
5	−0.004 820			
		$R = 6$		
0	−0.003 408	−0.002 674	−0.002 674	−0.002 627
1	−0.002 675	−0.002 773	−0.002 611	
2	−0.002 709			
3	−0.002 791			
4	−0.002 801			
5	−0.002 799			
		$R = 7$		
0	−0.002 180	−0.001 710	−0.001 710	−0.001 680
1	−0.001 707	−0.001 751	−0.001 677	
2	−0.001 723			
3	−0.001 763			
4	−0.001 766			
5	−0.001 766			
		$R = 8$		
0	−0.001 475	−0.001 158	−0.001 158	−0.001 137
1	−0.001 154	−0.001 175	−0.001 138	
2	−0.001 162			
3	−0.001 183			
4	−0.001 184			
5	−0.001 184			

[a] Multipole moments are calculated from a distributed multipole analysis. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure. [d] Charges are fitted to electrostatic potentials.

At this point, it is worth stressing again that the FM centers involved in the fit are limited to those centers within a sphere of a given radius. Since the effect of the FMs approximates that of the RMs outside the sphere only, the extension of the radius of the sphere pushes apart the smallest intermolecular separation for which the replacement of the RMs by FMs is possible.

It is important to realize that the calculation of the interaction energy of fitted moments requires the inclusion of all terms containing the interaction of any of the fitted moments. This means that when fitted charges and dipoles are used, then the charge−charge, charge−dipole, and dipole−dipole interactions need to be evaluated. On the other hand, the interaction energy of DMA moments is an expansion according the

TABLE 7: Electrostatic Interaction Energy Calculated Using Various Multipoles for C_2H_2···HCN (Figure 2b) at Several Intermolecular Separations (R): All Quantities Are in Atomic Units

maximum multipole rank	DMA[a]	OFM[b]	CFM[c]	ESP[d]
		$R = 4$		
0	−0.003 745	−0.004 393	−0.004 393	−0.006 042
1	−0.010 762	−0.007 494	−0.007 039	
2	−0.006 877			
3	−0.007 500			
4	−0.007 492			
		$R = 5$		
0	−0.002 184	−0.002 532	−0.002 532	−0.003 411
1	−0.005 813	−0.003 920	−0.003 798	
2	−0.003 719			
3	−0.003 908			
4	−0.003 891			
		$R = 6$		
0	−0.001 354	−0.001 555	−0.001 555	−0.002 057
1	−0.003 404	−0.002 267	−0.002 226	
2	−0.002 191			
3	−0.002 259			
4	−0.002 249			
		$R = 7$		
0	−0.000 882	−0.001 005	−0.001 005	−0.001 310
1	−0.002 121	−0.001 407	−0.001 391	
2	−0.001 375			
3	−0.001 403			
4	−0.001 398			
		$R = 8$		
0	−0.000 598	−0.000 677	−0.000 677	−0.000 872
1	−0.001 388	−0.000 921	−0.000 914	
2	−0.000 906			
3	−0.000 919			
4	−0.000 916			

[a] Multipole moments are calculated from a distributed multipole analysis. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure. [d] Charges are fitted to electrostatic potentials.

TABLE 8: Electrostatic Interaction Energy Calculated Using Various Multipoles for C_6H_6···NH_3 (Figure 2c) at Several Intermolecular Separations (R): All Quantities Are in Atomic Units

maximum multipole rank	DMA[a]	OFM[b]	CFM[c]	ESP[d]
		$R = 6$		
0	−0.002 201	−0.002 703	−0.002 703	−0.003 628
1	−0.001 298	−0.002 180	−0.002 241	
2	−0.002 022			
3	−0.002 572			
4	−0.002 063			
5	−0.001 738			
6	−0.001 831			
7	−0.002 028			
8	−0.002 090			
		$R = 7$		
0	−0.001 387	−0.001 703	−0.001 703	−0.002 286
1	−0.001 188	−0.001 725	−0.001 547	
2	−0.001 570			
3	−0.001 976			
4	−0.001 734			
5	−0.001 636			
6	−0.001 690			
7	−0.001 727			
8	−0.001 720			
		$R = 8$		
0	−0.000 886	−0.001 087	−0.001 087	−0.001 459
1	−0.000 924	−0.001 232	−0.001 052	
2	−0.001 136			
3	−0.001 351			
4	−0.001 236			
5	−0.001 203			
6	−0.001 223			
7	−0.001 229			
8	−0.001 225			

[a] Multipole moments are calculated from a distributed multipole analysis. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure. [d] Charges are fitted to electrostatic potentials.

TABLE 9: Structure and Energy of the HF Dimer in the Minimum Energy Configuration As Obtained with Different Multipoles: The Angles Are Defined in Figure 1; Energies are in Atomic Units

multipole		angles		
type	max rank	Θ_1	Θ_2	energy
DMA[a]	2	122°	186°	−0.008 536
OFM[b]	0	180°	180°	−0.009 228
OFM[b]	1	118°	188°	−0.008 191
CFM[c]	0	180°	180°	−0.009 228
CFM[c]	1	121°	188°	−0.008 518
ESP[d]	0	180°	180°	−0.009 066

[a] Multipole moments are calculated from a distributed multipole analysis. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure. [d] Charges are fitted to electrostatic potentials.

intersite separation R, which requires truncation at a given power of R. This means that the energy up to R^{-3} requires the evaluation of the charge−quadrupoles terms in addition to those listed above. Nevertheless, for the model systems the interaction energies of DMA multipoles presented below are calculated with a truncation according to the multipole moment ranks in order to be consistent with the calculations using fitted moments.

Overall *versus* Cumulative Fitting. The fitting procedure considered so far includes the calculation of fitted moments of all ranks in one step. Thus, fitted charges and dipoles designed to reproduce a given series of reference moments are obtained as the solution of one least squares-like system of equations. Multipole moments obtained from such an overall fitting procedure will be referred to as OFMs; the OFMs share some similarities to the fitted moments of Williams.[14] An alternative approach involves obtaining fitted charges as the first step. These fitted charges create multipole moments at the reference site. The difference between the reference moments and those created by the fitted charges is then fitted by a set of dipoles. This cumulative fitting procedure can be continued to higher ranks, and the resulting moments will be referred to as CFMs; the CFMs share some similarities to the fitted moments of Kong.[15] The goodness of a cumulative fit can be qualitatively predicted in the same way as that of an overall fit, as described in the preceding section. Thus, in the case of HF, charges (two parameters) fitted in the first step effectively reproduce the reference charge and dipole (two parameters), while dipoles (two parameters) fitted in the second step effectively reproduce the reference quadrupoles (two parameters). Obviously, an overall fit is more flexible and is expected to result in a better description of the reference moments than a cumulative fit, as can be seen by comparing the OFM^1 and CFM^1 columns in Table 2. However, cumulative moments have advantages which will be discussed later.

Electrostatic Interaction Energies. *Small Model Systems.* Calculations on small model systems were undertaken to investigate the convergence of the interaction energy as a function of the DMA rank and to investigate whether DMA multipoles may be replaced by fitted ones. Three types of calculations were performed. The interaction energies between molecules in close proximity were evaluated with different rank DMA and fitted multipoles to investigate the effect of truncation. Then, similar calculations at several intermolecular separations

TABLE 10: Electrostatic Interaction Energy Calculated Using Various Multipoles for H_2O···HCl at $\Theta_1 = 37°$ and $\Theta_2 = 175°$ (Minimum Energy Configuration of DMA Octopoles): The Angles Are Defined in Figure 3; Energies Are in Atomic Units

maximum multipole rank	DMA[a]	OFM[b]	CFM[c]	ESP[d]
0	−0.006 548	−0.008 405	−0.008 405	−0.008 973
1	−0.006 901	−0.009 662	−0.012 807	
2	−0.012 421	−0.011 388	−0.009 716	
3	−0.010 818			
4	−0.011 750			
5	−0.011 320			
6	−0.011 490			
7	−0.011 428			
8	−0.011 447			

[a] Multipole moments are calculated from a distributed multipole analysis. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure. [d] Charges are fitted to electrostatic potentials.

TABLE 11: Structure and the Energy of the H_2O···HCl System in the Minimum Energy Configuration As Obtained with Different Multipoles: The Angles Are Defined in Figure 3; Energies Are in Atomic Units

multipole		angles		
type	max rank	Θ_1	Θ_2	energy
DMA[a]	2	37°	179°	−0.012 542
DMA[a]	3	37°	175°	−0.010 818
OFM[b]	0	0°	180°	−0.008 949
OFM[b]	1	20°	178°	−0.009 657
OFM[b]	2	37°	178°	−0.011 433
CFM[c]	0	0°	180°	−0.008 949
CFM[c]	1	0°	180°	−0.013 138
CFM[c]	1	18°	178°	−0.013 071[e]
CFM[c]	2	19°	178°	−0.009 809
ESP[d]	0	0°	180°	−0.009 553

[a] Multipole moments are calculated from a distributed multipole analysis. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure. [d] Charges are fitted to electrostatic potentials. [e] Local minimum.

TABLE 12: Total Ligand Receptor Interaction Energies, in kJ mol^{-1}: Unless Otherwise Stated, $r_{incl} = 0.0$ Å Was Used

system	DMA[a]	OFM[b]	OFM[d]	CFM[c]	charge[e]	charge[f]
NOR−β_2, β_3-AR	−615.0	−614.4	−614.9	−609.5	−663.7	−659.7
EPI−β_2, β_3-AR	−503.3	−499.8	−499.9	−494.8	−528.3	−527.1
NOR−β_1-AR	−638.2	−641.4	−642.5	−631.9	−686.2	−680.8
EPI−β_1-AR	−499.5	−491.7	−495.0	−483.6	−509.2	−509.5

[a] Multipole moments are from a DMA at the hexadecapole level. [b] Charges plus dipoles are calculated from an overall fitting procedure. [c] Charges plus dipoles are calculated from a cumulative fitting procedure. [d] Charges plus dipoles were evaluated using $r_{incl} = 2.0$ Å. [e] Multipoles fitted charges. [f] Multipoles fitted charges evaluated using $r_{incl} = 2.0$ Å.

TABLE 13: Interaction Energy/kJ mol^{-1} between the Agonist (Norepinephrine, NOR, or Epinephrine, EPI) and ^{311}Leu and ^{311}Phe: The Residue Number Given Is for the β_2-AR

system	DMA[a]	OFM[b]	OFM[d]	CFM[c]	charge[e]	charge[f]
NOR−^{311}Leu	−98.2	−99.9	−98.8	−102.6	−107.4	−106.1
EPI−^{311}Leu	−99.7	−100.6	−100.2	−105.0	−113.9	−113.8
NOR−^{311}Phe	−119.5	−121.6	−122.8	−120.5	−120.2	−119.9
EPI−^{311}Phe	−113.6	−110.8	−112.9	−112.2	−124.1	−123.2

[a] Multipole moments are from a DMA at the hexadecapole level. [b] Charges plus dipoles are calculated from an overall fitting procedure. [c] Charges plus dipoles are calculated from a cumulative fitting procedure. [d] Charges plus dipoles were evaluated using $r_{incl} = 2.0$ Å. [e] Multipoles fitted charges. [f] Multipoles fitted charges evaluated using $r_{incl} = 2.0$ Å.

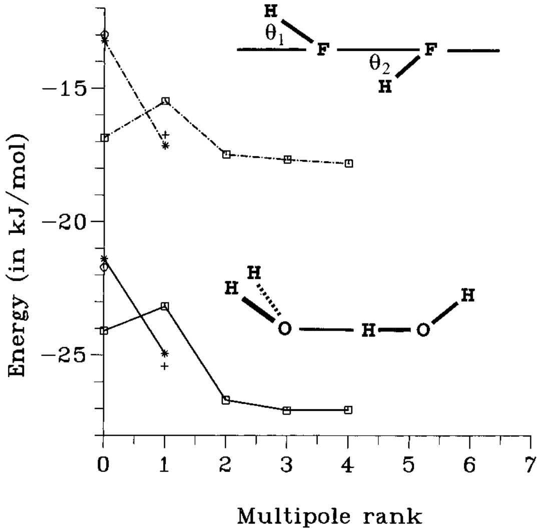

Figure 1. Schematic structures and the interaction energies of the HF dimer and water dimer calculated with various multipole sets. ☐ represents points calculated with DMA multipoles, * represents points calculated with fitted multipoles, + represents points calculated with CFMs, and ○ represents points calculated using ESP charges.

were performed to study how the importance of different rank moments varies with distance. Finally, the minimum energy configurations of some bimolecular systems were calculated, again with different rank DMA and fitted moments. Interaction energies were calculated using both OFMs and CFMs. In addition, interaction energies calculated with potential-derived (ESP) charges are presented; since ESP charges are widely used in classical force fields, a comparison of the performances of ESP charges with fitted moments is important in assessing the usefulness of the latter. In all cases, the wave functions were calculated with a 6-31G* basis set at their 6-31G* optimized geometry with the CADPAC[21] program. The interaction energies were calculated with the ORIENT program.[22] This program is able to evaluate the interaction energy of multipole sets with contributions up to R^{-5}. The program was modified in order to make it possible to evaluate contributions of any order.

Applications to Large Systems: The β-Adrenergic Receptor. Calculations on the essential agonist binding residues of a *model* of the heptahelical β_2-adrenergic receptor (β_2-AR) were carried out (a) to assess the potential performance of the fitted moments in real applications and (b) to investigate the molecular origin of the subtype specificity of epinephrine and norepinephrine in the β_1-, β_2-, and β_3-ARs. Molecular modeling and site-directed mutagenesis studies[23] have identified ^{113}Asp on helix three, ^{204}Ser and ^{207}Ser on helix five, ^{286}Trp and ^{290}Phe on helix six, and ^{311}Leu on helix seven as key residues in agonist binding. Consequently, these residues plus the docked agonist (epinephrine or norepinephrine) were taken from the minimized model receptor structure[23,24] and blocked with suitable end groups (either CH_3NH- or $-COCH_3$) where appropriate, and the DMA was determined using the CADPAC program with a 6-31G* basis set as above. The interaction energies were calculated using ORIENT.

Results and Discussion

Figure 1 and Tables 4 and 5 present the results for the HF dimer and the water dimer, respectively, near their equilibrium geometries. The four atoms of the HF dimer are in the same plane, while the planes of the water molecules are orthogonal to one another. Similar conclusions can be drawn from the interaction energies of both dimers. The inclusion of DMA

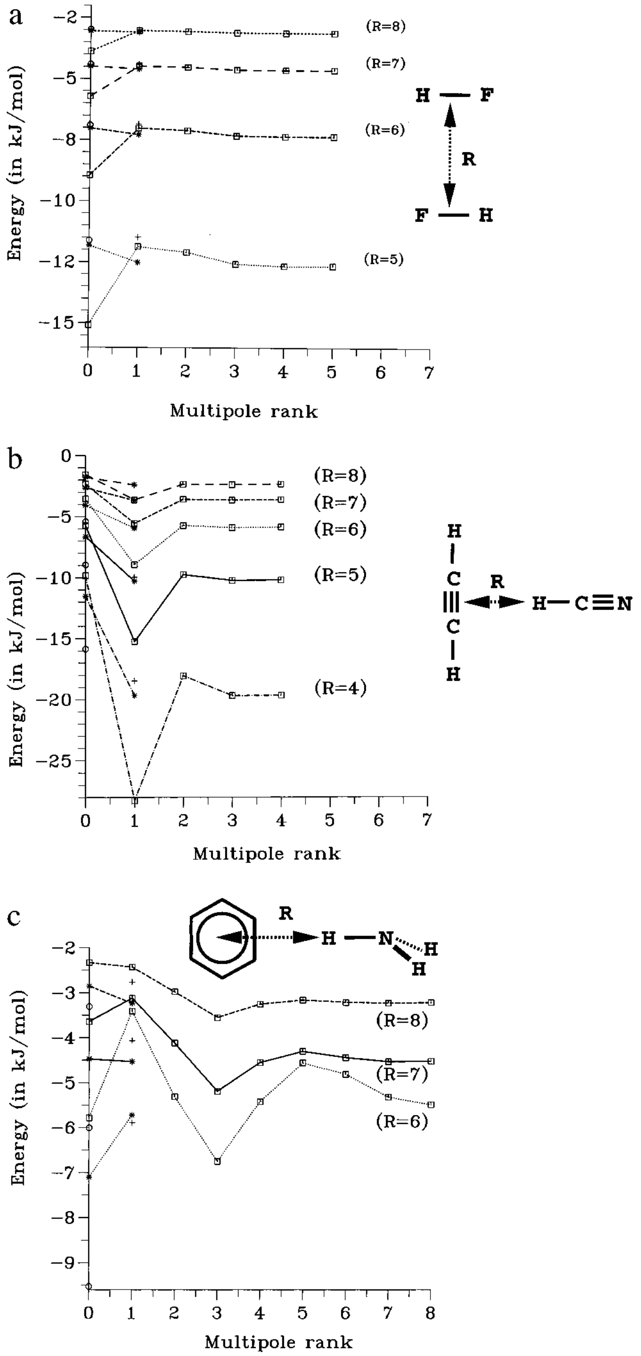

Figure 2. Schematic structures and the interaction energies of (a) an antiparallel HF dimer, (b) $C_2H_2\cdots HCN$, and (c) $C_6H_6\cdots NH_3$ as a function of the intermolecular separation calculated with various multipole sets. □ represents points calculated with DMA multipoles, * represents points calculated with fitted multipoles, + represents points calculated with CFMs, and ○ represents points calculated using ESP charges. Distances are in atomic units.

quadrupoles represents a significant improvement in reproducing the interaction energy. As for FMs, charges give poor results, while charges plus dipoles are considerably better. The poor energy of fitted charges is due to the fact that for both dimers the DMA charges give energies nearer to the converged limit than does the DMA up to dipoles. Thus fitted charges, which are designed to simulate a DMA up to dipoles, give energies worse than DMA charges or fitted charges plus dipoles. ESP charges give results very close to those of multipole-fitted charges. The OFM and CFM energies are also very similar.

Figure 2 and Tables 6, 7, and 8 contain energies for the antiparallel HF dimer and the $C_2H_2\cdots HCN$ and $C_6H_6\cdots NH_3$ systems, respectively. The same calculations were performed as before, except that several different intermolecular separations were considered. For the HF dimer (Table 6, Figure 2a), the energies of DMA multipoles show significant improvement when dipoles are included and modest improvement when quadrupoles and octopoles are included. Consequently, fitted charges (effectively reproducing DMA multipoles up to dipoles) reasonably approximate the converged DMA results. ESP charges and multipole-fitted charges perform similarly. OFM energies are better than CFM energies, as expected.

In the case of the $C_2H_2\cdots HCN$ system (Table 7, Figure 2b), the inclusion of DMA quadrupoles is fundamental and octopoles still have a significant effect at the smallest intermolecular separation. The increased importance of higher rank moments is the consequence of the lower polarity of the molecules considered. A set of fitted charges and dipoles seems to approximate the energies of a DMA up to octopoles. Multipole-fitted charges underestimate the interaction energy. The energies obtained from ESP charges are better than those from multipole-fitted charges but worse than those of the multipole-fitted charge+dipole set.

In the $C_6H_6\cdots NH_3$ system, one of H−N vectors is orthogonal to the benzene plane and points toward the center of the benzene ring (Figure 2c). The DMA interaction energy (Table 8) exhibits very poor convergence. Interestingly, fitted charges plus dipoles yield interaction energies near to the converged values, but taking into account the oscillatory nature of the DMA energies; this very good result may be fortuitous. OFM and CFM energies are very similar, while ESP charges give interaction energies far too negative.

In all three examples above, the relative error between energies obtained with different rank moments does not change significantly as the intermolecular separation increases. Nevertheless, the magnitude of the interaction energy and thus the magnitude of the difference between energies of different rank moments decrease with increasing separation. Considering the relative error in the energy, the importance of using fitted charges and dipoles rather than fitted charges alone is more pronounced and extends to larger intermolecular separations in the case of the less polar $C_2H_2\cdots HCN$ and $C_6H_6\cdots NH_3$ systems.

In the third type of calculation, the minimum energy configurations of the HF dimer and the $H_2O\cdots HCl$ system were optimized using the Buckingham−Fowler model.[2] This involved using multipoles of different source and rank with the following hard-sphere radii: H = 0.0 Å, F = 1.35 Å, O = 1.4 Å, Cl = 1.8 Å. The geometry of the HF dimer (Table 9, Figure 1), as obtained with a DMA up to quadrupoles, is close to that of ref 2. On the other hand, when electrostatics is represented by fitted charges (either multipole-fitted or ESP), then the energy is minimal at a linear arrangement of the molecules. Using fitted charges plus dipoles (either OFM or CFM) yields an energy and geometry similar to that obtained with a DMA up to quadrupoles.

The interaction energy of the $H_2O\cdots HCl$ system was calculated at the geometry shown in Figure 3. (The HCl molecule was placed in the plane orthogonal to that of the water molecule.) The energy converges slowly with increasing multipole rank at the geometry corresponding to the minimum energy of DMA octopoles (Table 10). The minimum energy configuration and energy of DMA quadrupoles are somewhat different from those of DMA octopoles (Table 11). Fitted charges (both multipole-fitted and ESP) give qualitatively poor minimum energy geometries. The geometry of the minimum energy configuration obtained with OFM charges and dipoles ($\theta_1 = 20°$, $\theta_2 = 178°$) is better but still deviates from that of a DMA up to octopoles ($\theta_1 = 37°$, $\theta_2 = 175°$). With the inclusion of fitted quadrupoles, the minimum energy geometry is well reproduced ($\theta_1 = 37°$,

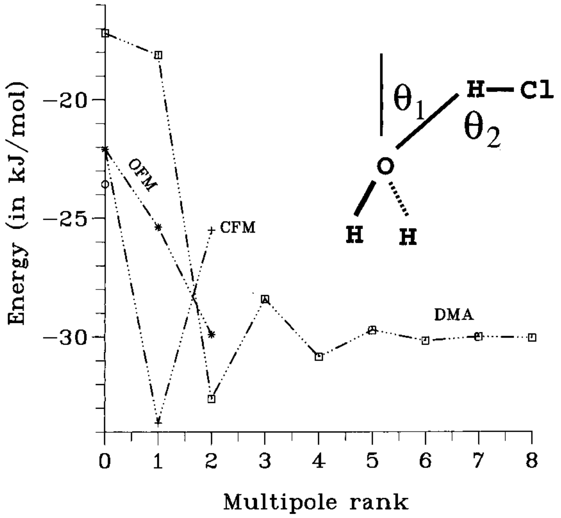

Figure 3. Schematic structure and the interactions energies of the $H_2O\cdots HCl$ system at $\theta_1 = 32°$ and $\theta_2 = 178°$ (minimum energy geometry of DMA octopoles) as a function of DMA multipole ranks. □ represents points calculated with DMA multipoles, * represents points calculated with fitted multipoles, + represents points calculated with CFMs, and ○ represents points calculated using ESP charges.

$\theta_2 = 178°$). On the interaction energy surface of CFM charges+dipoles, the absolute minimum corresponds to the planar arrangement of the atoms. There are also two symmetrical local minima on the surface ($\theta_1 = 18°$, $\theta_2 = 178°$). Their energy is close to that of the global minimum. The inclusion of CFM quadrupoles results in a notable change in energy and predicts the off-planar arrangement ($\theta_1 = 19°$, $\theta_2 = 178°$) to be the energetically preferred one. This is in qualitative agreement with the results of DMA quadrupoles and octopoles. The difficulty in the description of the electrostatic and interaction energy surface of the $H_2O\cdots HCl$ dimer stems from the flatness of the surface and from the slow convergence of the interaction energy with increasing multipole rank (see Table 10). (During a molecular dynamics or Monte Carlo simulation at 298 K these effects may not be significant as all the very low energy structures will be sampled with a similar probability.)

The results presented confirm the widely held view[7,8] that a DMA, at least up to quadrupoles, is needed for calculating electrostatic interaction energies near the equilibrium geometry of interacting molecules. For some systems at smaller intermolecular separations, even higher rank moments may represent a marked improvement. However, the most significant result to emerge here is that fitted charges and dipole moments can effectively replace a DMA up to quadrupoles or even to octopoles.

As shown in the figures, the error incurred by using only fitted charges can be as high as 8 kJ mol^{-1}. This is comparable to the errors that can arise by neglecting the polarization energy.[12] Consequently, any improvements in electrostatics ought to be accompanied by corresponding improvements in the treatment of polarization. The strategy outlined here for deriving fitted charges and dipoles provides an ideal self-consistent framework for this because polarization is usually implemented through induced dipoles. Some of the issues that may arise in extending this work to include polarization were discussed in the provious article.[12] We also note that an improved electrostatic and polarization model has to take account of the variation of the atomic multipole set with conformation,[25,27] since ignoring this can easily give rise to errors to 9 kJ/mol or more in the free energy of hydration.[25,26]

Calculations on the *β*-Adrenergic Model Systems. The overall interaction energies of epinephrine and norepinephrine

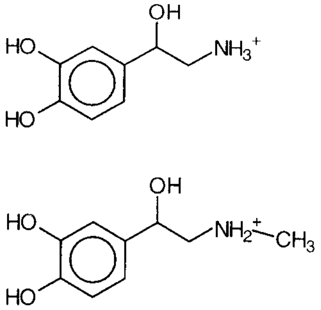

Figure 4. Structure of norepinephrine (top) and epinephrine (bottom).

(Figure 4) with the β-adrenergic receptors are reported in Table 12. Since these are gas phase calculations evaluated using a dielectric constant of 1.0, the calculated energies bear no resemblance to the experimental ligand binding affinities. However, they clearly show that charges plus dipoles generally reproduce the interaction energy evaluated using a DMA up to hexadecapoles. They also show that OFMs give better quantitative agreement than CFMs, while charges alone may give errors in the region of 50 kJ mol^{-1}. The results show that charges (or charges plus dipoles) evaluated using $r_{\text{incl}} = 2.0$ Å so that more fitting sites are included[12] generally give very slightly superior results to those evaluated using $r_{\text{incl}} = 0.0$ Å. However, since the difference in accuracy is minimal compared to the effect of including higher rank multipoles, we conclude that generally the number of fitting sites should be restricted through the use of $r_{\text{incl}} = 0.0$ Å; the additional benefits arising from the use of $r_{\text{incl}} = 0.0$ Å are discussed elsewhere.[12]

It is believed that ^{311}Leu may play an important role in determining subtype specificity in the β-AR receptors. The β_2 and β_3 receptors which contain Leu at position 311 have a higher affinity for epinephrine, while the β_1 receptors which contain Phe at position 311 have a higher affinity for norepinephrine. Molecular modeling studies[23] suggest that the change from Leu in the β_2 and β_3 receptor to Phe in β_1 receptor favors the smaller norepinephrine on steric grounds. In addition, the studies suggest that the $-NH_3^+$ group of norepinephrine will make better interactions with the π system[30] of the Phe (cf. Figure 2c) than with the σ-bonded Leu, while the additional methyl group of epinephrine will make better hydrophobic contacts with the hydrophobic leucine side chain. (There are other differences between the β_1-, β_2-, and β_3-ARs, but the residues concerned probably do not interact directly with the ligand; it is also important to note that the primary interaction of the charged quaternary nitrogen atom on the agonist is with ^{113}Asp.) Thus, in order to assess whether this hypothesis has any energetic basis, we have analyzed the interaction energy between the ligand and the residue at position 311. The results are reported in Table 13. The DMA hexadecapole interaction energies confirm that norepinephrine forms a stronger interaction with the Phe than with the Leu, while epinephrine forms a stronger interaction with the Leu than with the Phe. The OFM results are in good quantitative agreement with this (the CFM results are almost as good as the OFM results). The use of atomic charges however would lead one to conclude that epinephrine makes a stronger interaction with the Phe than does norepinephrine. Thus the use of atomic charges in this problem could lead to a qualitatively incorrect conclusion, while the use of effective multipoles would lead to the correct conclusion. The norepinephrine−Phe interaction is similar to the benzene−ammonia interaction; as Figure 2c shows, such interactions involving nonpolar systems are not well described by the use of point charges.

Fitted Multipole Moments for Sample Molecules. In this section, fitted moments for small molecules are presented. As

TABLE 14: Fitted Moments[a] of Some Molecules: All Quantities Are in Atomic Units

molecule atom	coordinates			OFM[b]				CFM[c]			
	x	y	z	Q_{00}	Q_{10}	Q_{11c}	Q_{11s}	Q_{00}	Q_{10}	Q_{11c}	Q_{11s}
C_2H_2											
H	0.000	0.000	0.000	−0.114	0.000	−0.269	0.000	0.262	0.000	0.041	0.000
C	2.003	0.000	0.000	0.114	0.000	−0.812	0.000	−0.262	0.000	−0.250	0.000
C	4.276	0.000	0.000	0.114	0.000	0.812	0.000	−0.262	0.000	0.250	0.000
H	6.279	0.000	0.000	−0.114	0.000	0.269	0.000	0.262	0.000	−0.041	0.000
H_2O											
H	0.000	0.000	0.000	0.789	0.000	0.214	−0.011	0.397	0.000	−0.114	−0.016
O	1.808	0.000	0.000	−1.578	0.000	0.362	−0.468	−0.794	0.000	0.073	−0.094
H	2.261	1.751	0.000	0.789	0.000	−0.043	−0.210	0.397	0.000	0.044	0.107
HF											
F	0.000	0.000	0.000	−0.702	0.000	−0.349	0.000	−0.452	0.000	−0.124	0.000
H	1.733	0.000	0.000	0.702	0.000	−0.088	0.000	0.452	0.000	0.121	0.000
NH_3											
N	0.000	0.000	0.216	−2.795	0.761	0.000	0.000	−1.069	0.128	0.000	0.007
H	0.000	1.772	−0.504	0.932	0.161	0.000	−0.357	0.356	−0.381	0.000	−0.000
H	1.534	−0.886	−0.504	0.932	0.161	−0.309	0.179	0.356	0.128	0.006	−0.004
H	−1.534	−0.886	−0.504	0.932	0.161	0.309	0.179	0.356	0.128	−0.006	−0.004
HCN											
H	0.000	0.000	0.000	0.049	0.000	−0.199	0.000	0.159	0.000	−0.097	0.000
C	2.009	0.000	0.000	0.072	0.000	−0.431	0.000	0.277	0.000	0.027	0.000
N	4.190	0.000	0.000	−0.121	0.000	−0.279	0.000	−0.437	0.000	0.071	0.000
CH_3CHO											
C	3.880	2.354	0.000	0.449	0.000	0.144	0.114	−0.161	0.000	−0.045	−0.070
H	2.619	3.992	0.000	−0.118	0.000	−0.143	0.148	0.056	0.000	−0.043	0.065
H	5.059	2.352	1.698	−0.155	0.189	0.113	−0.004	0.046	0.057	0.040	0.018
H	5.059	2.352	−1.698	−0.155	−0.189	0.113	−0.004	0.046	−0.057	0.040	0.018
C	2.298	0.000	0.000	0.543	0.000	−0.226	0.269	0.659	0.000	0.023	0.074
H	3.306	−1.848	0.000	0.099	0.000	−0.045	0.011	−0.082	0.000	0.027	−0.129
O	0.000	0.000	0.000	−0.661	0.000	−0.176	−0.042	−0.565	0.000	−0.063	−0.023

[a] Multipole moments are labeled according to ref 28. [b] Multipole moments are calculated from an overall fitting procedure. [c] Multipole moments are calculated from a cumulative fitting procedure.

demonstrated in ref 10 for semiempirical wave functions and in the previous article[12] for ab initio wave functions, fitted charges (Table 14, CFM Q_{00}) are similar to potential-derived charges. When a set of charges and dipoles are calculated in an overall fit, then the charges are significantly different from those obtained when only charges are fitted (Table 14). The sign of the charges of a set of fitted charges and dipoles is usually not against chemical intuition, but the magnitude of the charges is highly exaggerated in some cases. In C_2H_2, the fitted charge is negative on the carbon and positive on the hydrogen atom,[12] but the signs of the charges are inverted when charges plus dipoles are calculated in an overall fit. This inverted polarity of the C−H bond is modulated by the large dipoles appearing on both the carbon and the hydrogen atoms and pointing toward the negative hydrogens. A similar effect can be observed in the other molecules; the effect of the change in the magnitude of the charges caused by fitting both charges and dipoles rather than charges alone is compensated by the dipoles. This suggests that a set of charges and dipoles of an overall fit reflect the deformation of the electron density in a complex, less transparent way. Because of this, charges will continue to have many uses in explaining qualitative effects. In addition, appropriately chosen charges are able to describe quantitatively the electrostatic interactions of molecules at medium and large intermolecular separation at a low computational cost. For all these reasons, CFMs have advantages over OFMs. In the latter, the moments of all ranks have similar importance in reproducing the effect of the reference moments. On the other hand, CFMs are similar to multipole moments calculated from a multipolar expansion in the sense that the importance of the moments decreases with increasing rank. This is the reason why CFMs are chemically reasonable, and an important consequence is that a series of CFMs can be truncated when the interaction energy at large intersite separation is calculated.

Conclusions

It has been demonstrated in the literature that DMA multipoles of rank 2−3 are able to describe correctly intermolecular electrostatic interactions. Moreover, in the framework of the Buckingham−Fowler[2] or related models,[3,4] they are able to predict equilibrium geometries of van der Waals complexes. The present contribution provides several examples where multipole-fitted charges are insufficient for the correct description of intermolecular electrostatic interactions of close molecules. They fail to reproduce the electrostatic interaction energies calculated with DMA multipoles and predict qualitatively poor equilibrium geometries of van der Waals complexes. More importantly, we have found that a multipole-fitted charge and dipole set is able to replace DMA multipoles up to quadrupoles or even octopoles. This is significant because the use of the lower rank fitted moments in molecular modeling studies is computationally more economical than the use of DMA multipoles. Consequently, we propose the following strategy for the calculation of intermolecular electrostatic interaction energies with classical force fields. When the intermolecular separation is smaller than a given limit (say when the closest atoms are within 4 Å), then a fitted charge and dipole set is used to evaluate the electrostatic interaction energy. When the intermolecular separation is larger, then charge sets are appropriate for the calculation of electrostatics. (The latter charge set is the same as the charges in the charge+dipole set if cumulative fitted moments are used; this is a distinct advantage. On the other hand, when moments from an overall fitting procedure are used, then the charge+dipole set gives better interaction energies, but the charges used to evaluate the interaction energies of distant atoms are different from those in the charge+dipole set.) With this computational scheme, it is reasonable to find parameters that are able to reproduce quantitatively quantum mechanical electrostatic energies. This scheme may therefore be a significant step toward the separation of the energy components obtained with classical force fields. It therefore offers many advantages both in the development of force fields and in the interpretation of the results calculated with the force fields. A particularly important benefit of this scheme is that it allows polarization and electrostatics to be handled on an equal footing, since polarization is usually included through interactions involving induced dipoles.

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Appendix

The derivation of the equations to calculate fitted multipole moments that reproduce the effect of a reference multipole series is presented below.

The interaction energy (V) between two series of point multipoles is[28]

$$V = \sum_{l_A,m_A} \sum_{l_B,m_B} T_{l_A l_B m_A m_B} \hat{Q}_{l_A m_A}(\vec{R}_A)\, \hat{Q}_{l_B m_B}(\vec{R}_B)\, \hat{I}_{l_A+l_B,\bar{m}_A+\bar{m}_B}(\vec{R}_A - \vec{R}_B) \tag{1}$$

where $\hat{Q}$ is a complex multipole moment, $\hat{I}(\vec{R})$ is a complex irregular solid harmonic defined as in ref 28, $\bar{m} = -m$, and

$$T_{l_A l_B m_A m_B} = (-1)^{l_B+m_A+m_B}\left[\binom{l_A+l_B+m_A+m_B}{l_A+m_A}\binom{l_A+l_B-m_A-m_B}{l_A-m_A}\right]^{1/2} \tag{2}$$

Defining real multipole moments[28] as

$$Q_{lmc} = b_m Q_{lm} + b_{\bar{m}} Q_{l\bar{m}}, \quad \mathrm{i}Q_{lms} = b_m Q_{lm} - b_{\bar{m}} Q_{l\bar{m}} \tag{3}$$

with

$$\begin{aligned} b_m &= (-1)^m \sqrt{1/2}, & m &> 0 \\ &= 1/2, & m &= 0 \\ &= \sqrt{1/2}, & m &< 0 \end{aligned}$$

and real irregular solid harmonics I_{lmc} and I_{lms} similarly, eq 1 can be written with real quantities as

$$V = \sum_{l_A,m_A,p_A} \sum_{l_B,m_B,p_B} T_{l_A l_B m_A m_B} Q_{l_A m_A p_A}(\vec{R}_A)\, Q_{l_B m_B p_B}(\vec{R}_B) \times I_{l_A+l_B,\bar{m}_A+\bar{m}_B,p_A p_B}(\vec{R}_A - \vec{R}_B)(8 b_{m_A} b_{m_B} b_{\bar{m}_A+\bar{m}_B})^{-1} \min(p_A,p_B) \tag{4}$$

where p can take two values, $+1$ and -1, the former corresponding to the c index and the latter corresponding to the s index in eq 3. When $m = 0$, then only $p = 1$ is allowed. $\min(p_A,p_B)$ stands for the smaller of p_A and p_B. m runs from $-l$ to $+l$.

Now, let us suppose that we have a multipole series at $\vec{R}_M$ and we want to reproduce its effect by several series of multipoles at $\vec{R}_J$, $J = 1, 2, ...$ It is expected that the effect of a multipole series up to rank N_M at $\vec{R}_M$ can be well approximated by several multipole series up to rank N_J at $\vec{R}_J$, $J = 1, 2, ...,$ with $N_J < N_M$. To determine the multipoles at $\vec{R}_J$, $J = 1, 2, ...,$ we require, on the basis of eq 4, that

$$\int \mathrm{d}v_T \sum_{l_t,m_t,p_t} c_{l_t} \Big[\sum_{l_M,m_M,p_M} Q^R_{l_M m_M p_M}(\vec{R}_M) T_{l_M l_t m_M m_t} \times (8 b_{m_M} b_{m_t} b_{\bar{m}_M+\bar{m}_t})^{-1} \min(p_M,p_t)\, I_{l_M+l_t,\bar{m}_M+\bar{m}_t,p_M p_t}(\vec{R}_M - \vec{R}_T) - \sum_J \sum_{l_J,m_J,p_J} Q^F_{l_J m_J p_J}(\vec{R}_J) T_{l_J l_t m_J m_t} \times (8 b_{m_J} b_{m_t} b_{\bar{m}_J+\bar{m}_t})^{-1} \min(p_J,p_t)\, I_{l_J+l_t,\bar{m}_J+\bar{m}_t,p_J p_t}(\vec{R}_J - \vec{R}_T)\Big]^2 \tag{5}$$

be a minimum. The integration in eq 5 is taken over a spherical shell centered at $\vec{R}_M$. The selection of such a domain for the integration makes it possible to exploit the orthogonality of the spherical harmonics (see below). c_{l_t} is introduced to increase the flexibility of the method. In general, $c_{l_t} = 1$ is a reasonable choice. The R and F upper indices of the multipole moments refer to reference moments and fitted moments, respectively. The m index runs from $-l$ to $+l$. The Q_{lmp} and $Q_{l\bar{m}p}$ multipole moments are not independent, and this will be exploited toward the end of the derivation.

The expressions appearing between square brackets in eq 5 are the interaction energies of a unit multipole moment at $\vec{R}_T$ with the set of multipoles at $\vec{R}_M$ (sums over l_M, m_M, and p_M) and with the sets of multipoles at $\vec{R}_J$ (sums over J, l_J, m_J, and p_J). This becomes more transparent after making use of the addition theorem of irregular solid harmonics[29] adapted for the real case

$$I_{l_1 m_1 p_1}(\vec{R}_1 + \vec{R}_2) = \sum_{l_2 m_2 p_2} (-1)^{m_1} T_{l_1 l_2 m_1 m_2} \frac{b_{m_1}}{2 b_{m_2} b_{m_1+\bar{m}_2}} R_{l_2 m_2 p_2}(\vec{R}_1) \times I_{l_1+l_2,m_1+\bar{m}_2,p_1 p_2}(\vec{R}_2) \max(p_2 - p_1) \qquad |\vec{R}_1| < |\vec{R}_2| \tag{6}$$

where $R_{l_2 m_2 p_2}(\vec{R}_1)$ is a regular solid harmonic, and invoking the orthogonality of spherical harmonics

$$\int \mathrm{d}v_T\, I_{l_1 m_1 p_1}(\vec{R}_T)\, I_{l_2 m_2 p_2}(\vec{R}_T) \neq 0 \tag{7}$$

if $l_1 = l_2$, $m_1 = m_2$, $p_1 = p_2$ or $l_1 = l_2$, $m_1 = -m_2$, $p_1 = p_2$. Then eq 5 can be written, after some algebraic manipulations, as

$$\sum_{l_t,m_t,p_t} c_{l_t} \sum_{l_M,m_M,m'_M,p_M} W_{l_M l_t m_M m'_M m_t p_M p_t}(r_1,r_2) \times \Big(Q^R_{l_M m_M p_M}(\vec{R}_M) - \sum_J \sum_{l_J,m_J,p_J} P_{l_M l_J m_M m_J p_M p_J}(\vec{R}_J - \vec{R}_M)\, Q^F_{l_J m_J p_J}(\vec{R}_J)\Big) \times \Big(Q^R_{l_M m'_M p_M}(\vec{R}_M) - \sum_J \sum_{l_J,m_J,p_J} P_{l_M l_J m'_M m_J p_M p_J}(\vec{R}_J - \vec{R}_M)\, Q^F_{l_J m_J p_J}(\vec{R}_J)\Big) \tag{8}$$

The new symbols appearing in eq 8 are defined as

$$P_{l_M l_J m_M m_J p_M p_J}(\vec{R}_J - \vec{R}_M) = (-1)^{l_J+m_M} T_{l_M-l_J,l_J,m_M-m_J,m_J} \times \frac{b_{m_M}}{2 b_{m_M-m_J} b_{m_J}} R_{l_M-l_J,m_M-m_J,p_M p_J}(\vec{R}_J - \vec{R}_M) \max(-p_M,p_J)$$

and

$$W_{l_M l_t m_M m'_M m_t p_M p_t}(r_1,r_2) = T_{l_M l_t m_M m_t} T_{l_M l_t m'_M m_t} \times (64 b_{m_M} b_{m_t} b_{\bar{m}_M+\bar{m}_t} b_{m'_M} b_{m_t} b_{\bar{m}'_M+\bar{m}_t})^{-1} \times [\delta_{m_M,m'_M} + \delta_{2m_t,\bar{m}_M+\bar{m}'_M}(1 - \delta_{m_M+m_t,0}) p_M p_t] \times \frac{4\Pi}{[2(l_M + l_t) + 1][2(l_M + l_t) - 1]}(r_1^{1-2l_M-2l_t} - r_2^{1-2l_M-2l_t})$$

where r_1 and r_2 are the radii of a smaller and a larger sphere, respectively, and they define the spherical shell of the integration (r_1 and r_2 are related to r_{low} and r_{high} in ref 12).

A multipole moment at $\vec{R}_M$ can be expressed by a set of moments at $\vec{R}_J$.[28]

$$Q_{l_M m_M p_M}(\vec{R}_M) = \sum_{l_J,m_J,p_J} Q_{lJm_Jp_J}(\vec{R}_J)\, P_{l_M l_J m_M m_J p_M p_J}(\vec{R}_J - \vec{R}_M) \quad (9)$$

Thus in the second and third row of eq 8 differences between reference multipole moments at $\vec{R}_M$ and those created by fitted multipoles of $\vec{R}_J$ at $\vec{R}_M$ appear.

Since $Q_{lmp} = pQ_{l\bar{m}p}$, eq 8 can be further manipulated to include sums over only nonnegative m_t, m_M, m'_M, and m_j. Then taking the derivative of the equation with respect to $Q^F_{l_N m_N p_N}(\vec{R}_N)$ and equating the derivative with zero result in the following equation:

$$\sum_{l_t,m_t,p_t} c_{l_t} \sum_{l_M,m_M,m'_M,p_M} \tilde{W}_{l_M l_t m_M m_t m'_M} \tilde{P}_{l_M l_N m'_M m_N p_M p_N}(\vec{R}_N - \vec{R}_M) \times \Big[Q^R_{l_M m_M p_M}(\vec{R}_M) - \sum_J \sum_{l_J,m_J,p_j} \tilde{P}_{l_M l_J m_M m_J p_M p_J}(\vec{R}_J - \vec{R}_M) \times Q^F_{l_J m_J p_J}(\vec{R}_J)\Big] = 0 \quad (10)$$

In this equation m_t, m_M, m'_M, and m_J can take only nonnegative values. Note that m'_M runs from 0 to l_M, but due to the restriction imposed by eq 7, one of the following equations has to hold for m'_M.

$$m'_M = m_M$$

$$m'_M = m_M + 2m_t$$

$$m'_M = m_M - 2m_t$$

$$m'_M = -m_M + 2m_t$$

$\tilde{W}_{l_M l_t m_M m_t m'_M}$ and $\tilde{P}_{l_M l_J m_M m_J p_M p_J}(\vec{R}_J - \vec{R}_M)$ are defined as

$$\begin{aligned}\tilde{W}_{l_M l_t m_M m_t m'_M} = {} & W_{l_M l_t m_M m_t m'_M p_M p_t}[(1 + (1 - \delta_{m_M,0})(1 - \delta_{m_t,0})(1 - \delta_{m'_M,0})] + \\ & W_{l_M l_t m_M m_t \bar{m}'_M p_M p_t}[(1 - \delta_{m'_M,0}) + (1 - \delta_{m_M,0})(1 - \delta_{m_t})]p_M + \\ & W_{l_M l_t m_M \bar{m}_t m'_M p_M p_t}[(1 - \delta_{m_t,0}) + (1 - \delta_{m_M,0})(1 - \delta_{m'_M})] + \\ & W_{l_M l_t \bar{m}_M m_t m'_M p_M p_t}[(1 - \delta_{m_M,0}) + (1 - \delta_{m_t,0})(1 - \delta_{m'_M})]p_M\end{aligned}$$

and

$$\tilde{P}_{l_M l_J m_M m_J p_M p_J}(\vec{R}_J - \vec{R}_M) = P_{l_M l_J m_M m_J p_M p_J}(\vec{R}_J - \vec{R}_M) + (1 - \delta_{m_J,0})p_J P_{l_M l_J m_M \bar{m}_J p_M p_J}(\vec{R}_J - \vec{R}_M)$$

Then the $Q^F_{l_J m_J p_J}(\vec{R}_J)$'s can be calculated from a linear equation system defined by eq 10.

Supporting Information Available: Equilibrium geometries of the HF and H_2O dimers (1 page). Ordering information is given on any current masthead page.

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