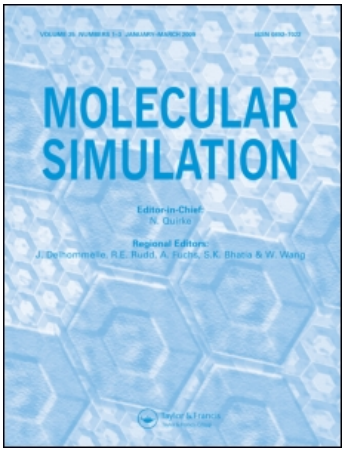

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Force Field Modelling of Conformational Energies

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Force Field Modelling of Conformational Energies

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The ability of five different force fields (MM2, MM3, AMBER, OPLS, MMFF) to calculate relative conformational energies of seven molecules is compared to results at the MP2/aug-cc-pVTZ level. It is found that the quality of the results deteriorates as the polarity of the molecules increases for all force fields, strongly indicating that the use of fixed partial charges for representing the electrostatic interaction limits the accuracy that can be obtained.

Keywords: Force field; Conformational energies

INTRODUCTION

Force field methods describe molecules by a classical ball-and-stick model, and use experimental results or quantum mechanical calculations to parameterize the model [1,2]. The force field energy is written as a sum of terms.

$$E_{\mathrm{FF}} = E_{\mathrm{str}} + E_{\mathrm{bend}} + E_{\mathrm{tors}} + E_{\mathrm{vdw}} + E_{\mathrm{el}} \qquad (1)$$

All force fields have the five elements in Eq. (1), and some also includes cross terms between these diagonal terms and/or special functions for, e.g. hydrogen bonds. The stretch and bend energies are typically written as low order Taylor expansions, with the parameters having a clear physical interpretation in terms of equilibrium distances and angles, and vibrational frequencies. The torsional energy is written as a low order Fourier series, with parameters chosen to reproduce rotational energy profiles. The most popular van der Waal energy function is a Lennard-Jones function, which contains a weak attractive dispersion term, and a strong repulsive part at short distances arising from the Pauli exclusion principle.

The electrostatic energy is the other component of the non-bonded energy, and is usually parameterized in terms of a Coulomb expression with partial charges for each atom.

$$E_{\mathrm{el}} = \sum_{i>j}^{N} \frac{Q_i Q_j}{\varepsilon R_{ij}} \qquad (2)$$

The dielectric constant ε has a value of one in vacuum, but is often given a slightly larger value to model the implicit screening by solvent or other molecules. In some cases, it is taken to be distant dependent, again to model the effect of screening.

While the first four terms in the force field expression (1) can be parameterized from experimental data, the partial charges in Eq. (2) are normally assigned by fitting to the electrostatic potential calculated by electronic structure methods. The electrostatic potential V_{esp} at a point $\mathbf{r}$ is given by the nuclear charges and electronic wave function as shown in Eq. (3).

$$V_{\mathrm{esp}}(\mathbf{r}) = \sum_{i}^{N_{\mathrm{nuc}}} \frac{Z_i}{|\mathrm{R}_i - \mathbf{r}|} - \int \frac{\Psi^2(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|}\, \mathrm{d}\mathbf{r}' \qquad (3)$$

The fitting is done by minimizing an error function of the form shown in the Eq. (4), under the constraint that the sum of the partial charges Q_i is equal to the total molecular charge [3]. The electrostatic potential is sampled at a number of points in the near vicinity of the molecule.

$$\mathrm{ErrF(Q)} = \sum_{r}^{N_{\mathrm{points}}} \left(V_{\mathrm{esp}}(\mathbf{r}) - \sum_{i}^{N_{\mathrm{atoms}}} \frac{Q_i}{|\mathrm{R}_i - \mathbf{r}|} \right)^2 \qquad (4)$$

It is well-known that the partial charge model gives a rather crude representation of the electrostatic

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potential surrounding a molecule [4]. The distributed multipole method developed by Stone [5,6] is a systematic method for improving the representation, and inclusion of electric moments up to quadrupole moments at nuclei and bond midpoints can yield a very accurate representation for a fixed geometry.

A fundamental limitation of the energy expression in Eq. (1) is the neglect of coupling between the five diagonal terms. A coupling between the first three terms can be incorporated by adding stretch/bend, bend/torsional, etc. terms, and this is common practice in more sophisticated force fields. The coupling between the electrostatic energy and the bonded terms is usually generalized as the dependence of the atomic charges (or electric moments) on the geometry, and it is well-known that both atomic charges and higher order moments are sensitive to the geometry [7,8]. The fluctuating charge model attempts to model the geometry dependence by allowing the charges to adjust to changes in the geometry [9]. Although this represents an important first step, it is clear that higher order moments are also required to give a systematic approach for improving the representation of V_{esp}. Alternatively, or complementary, a polarizability tensor can be added to each nucleus, with the electric field at the nucleus inducing a dipole moment [10]. Since the induced dipole moment affects the electric field at other sites, this necessitates an iterative scheme. Fluctuating charge models and polarizable force fields are computationally more expensive than fixed charge models by a factor of 2–10, and have consequently only seen limited use so far. Force fields incorporating both higher order multipole moments and polarizabilities should be capable of yielding a much better description of the electrostatic energy, and such methods are currently at the development stage [11].

In connection with developing force field methods for modeling chemical reactivity [12–15], we noticed that the accuracy of conformational energies depended significantly on the nature of the system, especially the polarity of the molecules. In the present paper, we investigate this in a more systematic fashion. The ability to reproduce conformational energies should be an important test-ground for developing force fields with a better representation of the coupling between the geometry and the electrostatic energy.

COMPUTATIONAL DETAILS

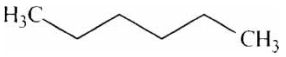
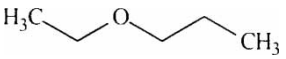
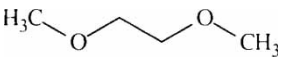
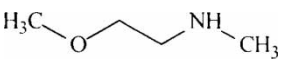
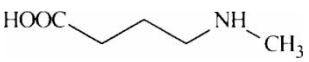
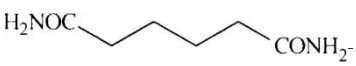
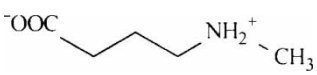
All force field calculations have been done using the MacroModel program [16]. Conformational searches have been done with a Monte Carlo approach [17], typically using a few thousand trial structures. The resulting statistics indicate that the searches are exhaustive. Electronic structure calculations have been performed with the Gaussian program package [18]. All calculations have been done in vacuum with a dielectric constant of one. The quality of the force field energies is evaluated based on single point MP2/aug-cc-pVTZ calculations [2] on the force field optimized geometries.

RESULTS

We have chosen the seven molecules shown in Table I as our test systems, representing a progression from non-polar to zwitterionic structures. The molecules are large enough to have a non-trivial set of conformations, but small enough that reasonably high level electronic structure calculations can be employed to establish a suitable set of reference data. We have chosen the MP2/aug-cc-pVTZ level [2] as our reference level. The root-mean-square deviations relative to this reference for some other methods are given in Table II. The semi-empirical methods AM1 and PM3 give quite poor results, and both HF and B3LYP calculations gives deviations of 5–10 kJ/mol, with no clear improvement upon enlarging the basis set from cc-pVDZ to aug-pVTZ. The use of diffuse functions at the MP2 level gives a rather large improvement for Mol7 due to the presence of the carboxylate group. Based on the differences between the cc-pVTZ and aug-cc-pVDZ results relative to those with the aug-cc-pVTZ basis set, we estimate that the latter gives relative conformational energies accurate to $\sim$1 kJ/mol, which is of sufficient accuracy for the present purpose. A similar level of theory has been used in related work on alanine tetrapeptide conformations [19].

The correlations between relative conformational energies for the seven target molecules for five different force fields are given in Table III, and Figs. 1–3 show the correlation for the MM3 force field and Mol1, Mol4 and Mol6, respectively. Table III lists the correlation coefficient (R^2) and slope of the least squares fitted line for each combination of molecule and force field. Both hexane and ethylpropyl ether (Mol1 and Mol2) give correlations coefficients and slopes close to one for all five force fields, showing that relative conformational energies are well reproduced. Dimethoxyethane (Mol3) is problematic for the AMBER and MMFF force fields, and the MM2 force field has a tendency of overestimating the high energy conformations. Mol4, Mol5 and Mol6 are problematic for all of the force fields, with the MMFF being the least poor. The zwitterionic Mol7 gives a very good correlation for all of the force field, although the slopes indicate that the high energy conformations are systematically overestimated.

TABLE I Systems used in the present work.

Notation	*Structure*	*AMBER*	*OPLSA*	*MM2*	*MM3*	*MMFF*
Mol1		12	12	12	12	12
Mol2		11	11	13	11	11
Mol3		10	10	12	9	10
Mol4		16	19	19	17	20
Mol5		52	46	52	49	55
Mol6		28	18	65	60	44
Mol7		9	6	10	7	12

The entry under each force field refers to the total number of conformations.

TABLE II Root mean square deviations for conformational energies calculated by different electronic structure methods, relative to MP2/aug-cc-pVTZ results.

Method	*Mol1*	*Mol2*	*Mol3*	*Mol4*	*Mol5*	*Mol6*	*Mol7*
AM1	6.67	12.92	5.57	15.08	7.15	31.13	33.08
PM3	3.88	16.06	7.07	20.16	10.82	14.91	16.99
HF/cc-pVDZ	6.97	4.18	3.15	2.71	5.96	8.67	5.76
HF/aug-cc-pVTZ	6.98	3.95	4.51	4.48	7.16	12.03	19.48
B3LYP/cc-pVDZ	3.99	1.83	2.61	1.05	1.93	3.23	13.69
B3LYP/aug-cc-pVTZ	4.36	2.02	2.70	2.42	3.37	6.55	8.23
MP2/cc-pVDZ	1.13	1.76	3.19	1.91	1.83	1.80	13.02
MP2/aug-cc-pVDZ	0.48	0.50	0.60	1.24	0.70	0.80	1.76
MP2/cc-pVTZ	0.32	0.72	0.90	0.64	0.76	0.70	5.83

TABLE III Correlation between force field and MP2/aug-cc-pVTZ conformational energies.

Force field	*Fit*	*Mol1*	*Mol2*	*Mol3*	*Mol4*	*Mol5*	*Mol6*	*Mol7*
AMBER	R^2	0.96	0.97	0.69	0.00	0.37	0.53	1.00
	Slope	1.00	1.07	0.59	− 0.15	0.44	0.80	1.12
OPLS	R^2	0.92	0.98	0.90	0.31	0.49	0.80	0.96
	Slope	0.96	0.95	1.01	0.93	0.86	0.91	1.22
MM2	R^2	0.95	0.92	0.95	0.78	0.65	0.62	0.89
	Slope	1.00	1.00	1.40	0.99	0.88	0.76	1.30
MM3	R^2	0.97	0.98	0.92	0.53	0.73	0.37	1.00
	Slope	1.12	0.87	1.10	0.83	0.82	0.49	1.79
MMFF	R^2	0.98	0.99	0.39	0.75	0.78	0.81	0.99
	Slope	1.20	1.00	0.92	1.14	1.05	0.95	1.07

R^2 and *Slope* refer to the correlation coefficient and slope of the best least squares line, neglecting the lowest energy point which is used for aligning the energy scales.

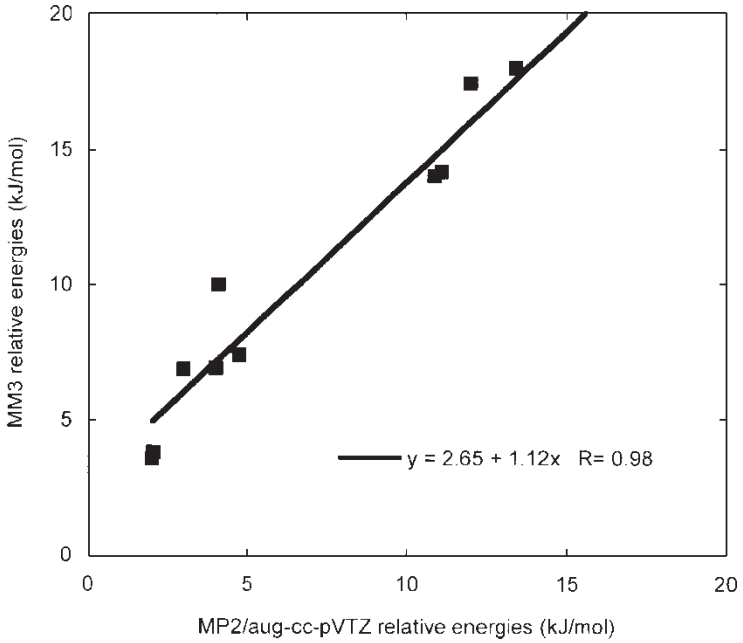


FIGURE 1 Correlation between MM3 and MP2/aug-cc-pVTZ relative energies for hexane (Mol 1).

Table IV shows the ratio of the absolute value of the electrostatic energy relative to the sum of the absolute values of all the energy terms in the force field, averaged over the conformations. Comparing Tables III and IV, it is clear that there is a strong connection between the performance of a force field for predicting conformational energies and importance of the electrostatic energy. For polar molecules, the latter contributes strongly to the total energy, and an accurate description is, therefore, necessary for achieving a good performance. The good results for the zwitterionic structure Mol7 are probably due to the highly localized charges, and the resulting dominance of the electrostatic energy in the force field function.

SUMMARY

We have shown that the quality of conformational energies degrades as the polarity of the molecule increases, although a zwitterionic structure with strongly localized charges gives a good correlation

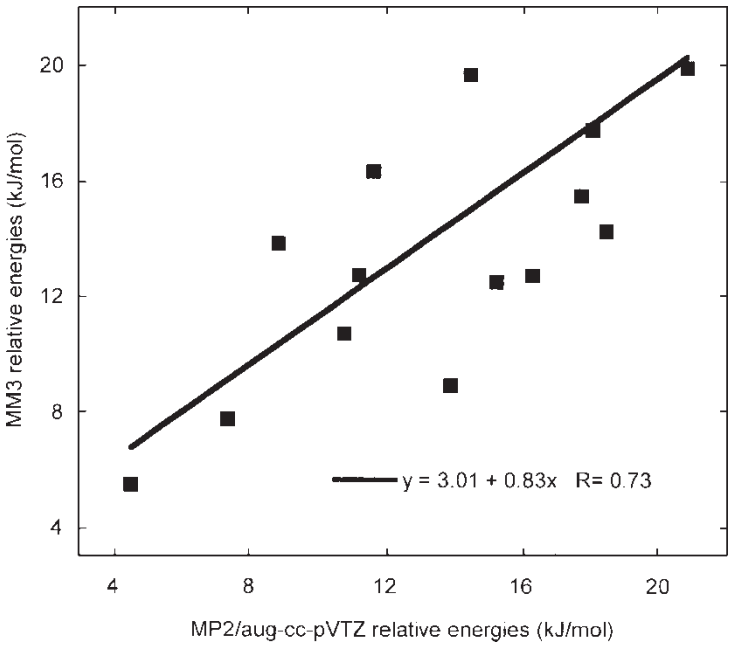


FIGURE 2 Correlation between MM3 and MP2/aug-cc-pVTZ relative energies for 2-methoxy N-methyl ethaneamine (Mol 4).

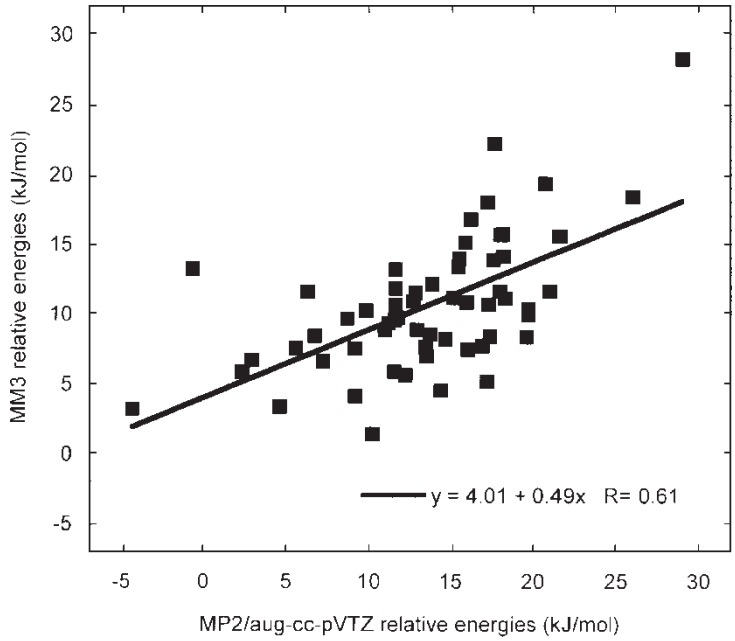


FIGURE 3 Correlation between MM3 and MP2/aug-cc-pVTZ relative energies for hexanediamide (Mol 6).

TABLE IV Fraction of electronic energy relative to the sum of all force field energy terms.

Force field	*Mol1*	*Mol2*	*Mol3*	*Mol4*	*Mol5*	*Mol6*	*Mol7*
AMBER	0.24	0.29	0.73	0.50	0.84	0.87	0.93
OPLS	0.41	0.50	0.59	0.66	0.77	0.92	0.91
MM2	0.00	0.00	0.45	0.10	0.38	0.84	0.70
MM3	0.00	0.00	0.58	0.55	0.37	0.72	0.84
MMFF	0.00	0.00	0.50	0.60	0.66	0.83	0.82

The fraction is defined as the absolute value of the electrostatic energy divided by the sum of the absolute value of all energy terms, averages over all conformations.

with high quality MP2 calculations. All of the tested force fields (AMBER, OPLS, MM2, MM3 and MMFF) display this trend. The analysis clearly suggest that the use of fixed partial charges for representing the electrostatic energy is the source of the poor correlation, and that more elaborate force fields incorporating higher order electric moments and polarizabilities is required to improve the performance.

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