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Calibration of the Quantum/Classical Hamiltonian in Semiempirical QM/MM AM1 and PM3 Methods

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We report a theoretical study on the calibration of the semiempirical quantum mechanical/molecular mechanical (QM/MM) Hamiltonian for the interaction of a series of functional groups with a TIP3P water molecule. Both AM1 and PM3 methods are employed to describe the quantum mechanical groups, which include neutral and charged molecules. Following most of the current QM/MM formalisms, the QM/MM Hamiltonian is built up by combining an electrostatic term and a van der Waals 6−12 potential. Owing to the lack of a precise definition of the electrostatic potential in semiempirical methods, various expressions for determining such an electrostatic energy between QM and MM subsystems have been considered. Likewise, the van der Waals parameters have been optimized to reproduce equilibrium geometries and interaction energies for selected complexes computed at the B3LYP level. Comparison is made with other sets of van der Waals parameters reported in the literature. The results reveal the extreme sensitivity of the van der Waals parameters to the QM/MM formalism and parametrization details, which makes it necessary to verify their transferability between different semiempirical QM/MM methods.

Introduction

In the past years, quantum mechanical/molecular mechanical (QM/MM) methods have allowed the study of reactive processes in very large systems containing hundreds or thousands of atoms.[1] The basic idea is to treat quantum mechanically the reactive part of the system, which is a priori quite localized, while keeping a classical description of the surrounding environment.[2] Accordingly, the Hamiltonian of the whole system is expressed as noted in eq 1, where the first two terms stand for the standard Hamiltonian of the QM and MM systems and the last one holds for the interaction between QM and MM regions. When the QM/MM frontier lies in a chemical bond, an ad hoc SCF calculation is needed.[3] Though implementations using ab initio and density functional theory methods have been reported,[4] a large number of studies in the literature deals with semiempirical methods,[5] particularly the AM1[6] and PM3[7] ones. For the classical subsystem, a variety of force fields have been used, like AMBER,[8] CHARMM,[9] GROMOS,[10] or MM3,[11] for instance. The reliability of the results depends on the level of theory used for the QM system, the force field for the MM part, and the QM/MM interaction potential.

$$\hat{H} = \hat{H}_{\mathrm{QM}} + \hat{H}_{\mathrm{MM}} + \hat{H}_{\mathrm{QM/MM}} \qquad (1)$$

The QM/MM Hamiltonian is generally expressed as the addition of electrostatic and nonelectrostatic contributions. When classical sites are described by using a set of point charges $\{q_{\mathrm{m}}\}$, the electrostatic term is given by eq 2, where $V_{\mathrm{QM}}(R_{\mathrm{m}})$ is the potential created by electrons and nuclei in the QM system (eq 3, where m represents sites in the MM subsystem located at position R_{m}). The nonelectrostatic component is generally expressed using a 6−12 Lennard-Jones term (eq 4, where q holds for nuclei in the QM subsystem). Energy derivatives are obtained straightforward, so that geometry optimization or molecular dynamics simulations may be envisaged.

$$\hat{H}^{\mathrm{elec}}_{\mathrm{QM/MM}} = \sum_m q_{\mathrm{m}} V_{\mathrm{QM}}(R_{\mathrm{m}}) \qquad (2)$$

$$V_{\mathrm{QM}}(R_{\mathrm{m}}) = V^{\mathrm{el}}_{\mathrm{QM}}(R_{\mathrm{m}}) + V^{\mathrm{nuc}}_{\mathrm{QM}}(R_{\mathrm{m}}) \qquad (3)$$

$$\hat{H}^{\mathrm{vdW}}_{\mathrm{QM/MM}} = \sum_q \sum_m \left(\frac{A_{\mathrm{qm}}}{R^{12}_{\mathrm{qm}}} - \frac{B_{\mathrm{qm}}}{R^{6}_{\mathrm{qm}}} \right) \qquad (4)$$

One of the major challenges for QM/MM methods is the realistic simulation of enzyme reactions. Generally, a large QM subsystem (50−100 atoms) has to be considered, which severely limits the possibility to perform QM/MM calculations using first principles methods, though approximate models such as the Empirical Valence Bond[12] have proved to be valuable. Therefore, semiempirical methods emerge as an alternative to treat the QM system. However, their limitations do not ensure an accurate description of the reactive process nor the interactions between QM and MM systems, and a careful analysis is necessary to validate the computational scheme. The suitability of semiempirical theory to treat QM/MM interactions has been examined in numerous studies,[3a,5c,e,f,13] mostly motivated by the

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lack of a precise definition of the electrostatic potential,[14] $V_{\mathrm{QM}}(R)$, in semiempirical methods.[15]

To gain further insight into the reliability of the semiempirical QM/MM Hamiltonian, this study (i) makes a comparison of different algorithms developed for the computation of the electrostatic QM/MM component, and (ii) examines the need to optimize parameters involved in the nonelectrostatic QM/MM term to derive, in fine, an accurate combined quantum/classical force field. The rest of the paper is as follows. First, we briefly review some of the expressions used to compute the electrostatic QM/MM interaction. Second, we report the details of the calculations performed to compare the algorithms selected to calculate the electrostatic component and to calibrate the nonelectrostatic term. Third, the results of the comparison between electrostatic QM/MM algorithms are presented. Finally, we discuss the results of the van der Waals (vdW) parametrization.

Definition of the QM/MM Electrostatic Potential

According to Field et al.,[3a] the electronic contribution to the interaction of the QM molecule with a point charge is determined using an expression (eq 5) based on the NDDO (neglect of differential atomic overlap) scheme adopted in semiempirical methods.

$$V_{\mathrm{QM}}^{\mathrm{el}}(R) = -\sum_{\mu,\nu} P_{\mu\nu}(\mu\nu|s^{\mathrm{m}}s^{\mathrm{m}}) \tag{5}$$

where s^{m} is a notional s orbital on m and μ, ν are atomic orbitals belonging to the same QM atom.

The two-center two-electron integrals in eq 5 are computed in terms of the interaction of a finite multipole expansion of charges about the relevant atoms (ss, sp, and pp distributions on QM atoms are treated as monopole, dipole, and quadrupole expansions with corresponding parameters $\rho^{\mathrm{q}}{}_0$, $\rho^{\mathrm{q}}{}_1$, and $\rho^{\mathrm{q}}{}_2$). For example, for an s-orbital distribution the multipole expansion is simply a point charge centered on the atom and the integral takes the form noted in eq 6.

$$(s^{\mathrm{q}}s^{\mathrm{q}}|s^{\mathrm{m}}s^{\mathrm{m}}) = [R_{\mathrm{qm}}{}^2 + (\rho_0^{\mathrm{q}} + \rho_0^{\mathrm{m}})^2]^{-1/2} \tag{6}$$

where R_{qm} is the distance between the centers q and m, and $(\rho_0{}^{\mathrm{q}} + \rho_0{}^{\mathrm{m}})^2$ is the Ohno−Kloppman factor that accounts for damping of classical Coulomb interactions due to overlapping electron densities.

The nuclear contribution follows the expression adopted for core−core interactions, as noted in eqs 7−9, where α, K, L, and M depend on atom type and Z_{q} is the core charge of the q atom. The exponential terms in $f(q,m)$ (eq 8) were introduced in MNDO[16] to correct the lack of penetration effects in the electronic component (the negative sign for the exponential terms holds for negative charges q_{m} so that such terms always represent a repulsive contribution). The function $g(q,m)$ is an additional term in AM1 and PM3 introduced to correct deficiencies of the MNDO method in hydrogen-bonded interactions.

$$V_{\mathrm{QM}}^{\mathrm{nuc}}(R) = \sum_q Z_{\mathrm{q}}\left[(s^{\mathrm{q}}s^{\mathrm{q}}|s^{\mathrm{m}}s^{\mathrm{m}})f(q,m) + \frac{1}{R_{\mathrm{qm}}}g(q,m)\right] \tag{7}$$

where the sum runs over all the q atoms in the QM system.

$$f(q,m) = 1 \pm \mathrm{e}^{-\alpha_{\mathrm{q}}R_{\mathrm{qm}}} \pm \mathrm{e}^{-\alpha_m R_{\mathrm{qm}}} \tag{8}$$

$$g(q,m) = \sum_i K_{\mathrm{q,i}}\, \mathrm{e}^{-L_{\mathrm{q},i}(R_{\mathrm{qm}}-M_{\mathrm{q},i})^2} + \sum_j K_{m,j}\mathrm{e}^{-L_{m,j}(R_{\mathrm{qm}}-M_{m,j})^2} \tag{9}$$

Field et al.[3a] left unchanged the semiempirical parameters on QM atoms and optimized those on MM sites. In the final expression, $\rho_0{}^{\mathrm{m}}$ adopted a value of zero, the terms corresponding to MM atoms in the function $g(q,m)$ were omitted, and only one parameter per MM atom type, α_{m}, was used and set to 5.0 (au^{-1}) in order to get the best fit to ab initio data.

Most of the alternative algorithms formulated to compute $V_{\mathrm{QM}}(R)$ are related at some extent to the preceding equations. Thompson[5c] uses a similar approach to that reported by Field et al.,[3a] the main difference being the exclusion of the Gaussian expansion terms in the function $g(q,m)$ for both QM an MM atoms. Bakowies and Thiel also assume $\rho_0{}^{\mathrm{q}} = 0$ and neglect the function $g(q,m)$.[5e] However, following the semiempirical scheme previously introduced by Ford and Wang,[13a] they introduce in the exponential function $f(q,m)$ different adjustable parameters which are optimized to reproduce the HF/6-31G(d) electrostatic potential and field. The difference between the procedures adopted by Bakowies and Thiel[5e] and Ford and Wang[13a] mostly concern the parametrization of such adjustable parameters. In the approach employed by Vasilyev et al.,[5f] a scaling parameter (0.095 for MNDO and AM1, 0.097 for PM3) is introduced to correct the magnitude of the Ohno−Kloppman factor $(\rho_0{}^{\mathrm{q}} + \rho_0{}^{\mathrm{m}})^2$, and the extra terms in the core−core energies are omitted.

Other authors[13b,c,17] have used expressions where both $\rho_l{}^{\mathrm{q}}$ ($l = 0, 1, 2$) and $\rho_0{}^{\mathrm{m}}$ are set to zero. Indeed, there are some differences in the treatment of the additional correction terms. Thus, Cummins and Gready[13b,c] neglect both $f(q,m)$ and $g(q,m)$ functions and the core−charge interaction follows a simple Coulombic expression. A similar formalism has been adopted by Luque et al.[17a] and Chudinov et al.[17b] to compute the solute−solvent electrostatic interaction in the framework of semiempirical self-consistent reaction field methods.

Finally, Théry et al.[13d] adopted a procedure to compute $V_{\mathrm{QM}}(R)$ that presents some notable differences compared to the preceding ones. In this procedure the electronic contribution follows the usual semiempirical expression (eq 5) without making any simplification, and the standard parameters of the semiempirical method are used for both QM and MM atoms. However, the core−charge interaction energy is split in two terms as noted in eq 10, which represents the interaction of the QM core with the core of a classical pseudo-atom bearing an "implicit electronic population" given by $P_{\mathrm{m}} = Z_{\mathrm{m}} - q_{\mathrm{m}}$. Then, the first term in eq 10 corresponds to the semiempirical core−core repulsion for two atoms of core charge Z_{q} and Z_{m}, and the second one represents the interaction of the quantum core Z_{q} with the electron population of the classical atom, P_{m}.

$$q_{\mathrm{m}}V_{\mathrm{QM}}^{\mathrm{nuc}}(R) = \sum_q Z_{\mathrm{q}}Z_m\left[(s^{\mathrm{q}}s^{\mathrm{q}}|s^{\mathrm{m}}s^{\mathrm{m}})f(q,m) + \frac{1}{R_{\mathrm{qm}}}g(q,m)\right] - \sum_q Z_{\mathrm{q}}P_{\mathrm{m}}(s^{\mathrm{q}}s^{\mathrm{q}}|s^{\mathrm{m}}s^{\mathrm{m}}) \tag{10}$$

On the basis of the preceding review, in this work we have analyzed three formalisms to compute $V_{\mathrm{QM}}(R)$, which were chosen to encompass the algorithms mentioned above (see Table 1). The method I[18] neglects all the parameters assigned to both QM and MM atoms in eqs 6−9. Therefore, electron-charge integrals are expressed in terms of the interactions of monopole, dipole, and quadrupole expansions of the electron distribution

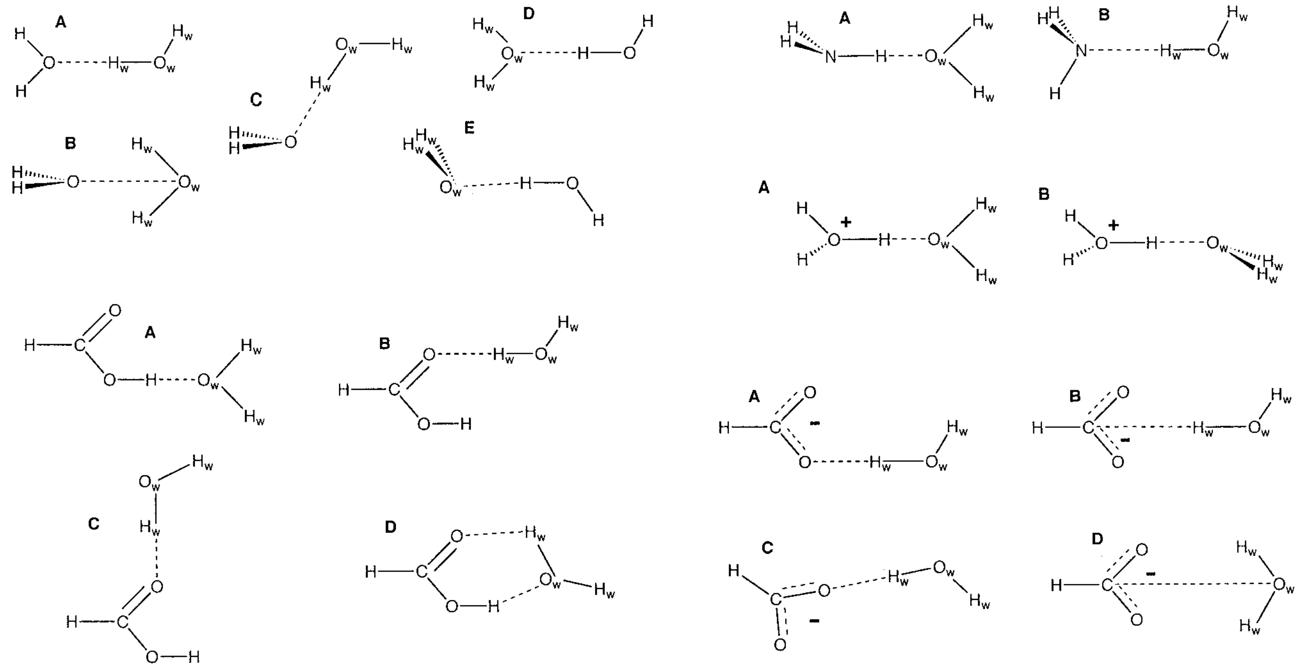

Figure 1. Schematic representation of the complexes between the QM monomer (H_2O, NH_3, HCOOH, H_3O^+, $HCOO^-$) and a TIP3P water molecule.

TABLE 1: Methods Considered in This Study To Compute the Electrostatic QM/MM Interaction Energy

method	electronic part	nuclear part
I	$\rho_0^m = 0$ $\rho_0^q = \rho_1^q = \rho_2^q = 0$	$(s^q s^q \vert s^m s^m) = 1/R_{qm}$ $f(q,m) = 1$ $g(q,m) = 0$ i.e. $E_{QM/MM}{}^{core} = Z_q q_m/R_{qm}$
II	$\rho_0^m = 0$	$f(q,m) = 1 \pm e^{-\alpha_q R_{qm}}$[a] $g(q,m) = \sum_i K_{q,i} e^{-L_{q,i}(R_{qm}-M_{q,i})^2}$
III	standard parameters for ρ_i^q and ρ_0^m	eq 10

[a] Following the MNDO formulation, when $q = (N,O)$ and $m = H$, $f(q,m) = 1 \pm R_{qm}e^{-\alpha_q R_{qm}}$. The negative sign holds for negative q_m charges so that the exponential term always represents a repulsive contribution.

with the point charge, whereas the core−charge interaction is simply given by a Coulomb term. The method II[18] follows closely the treatment adopted in AM1 and PM3 methods for the electron−core and core−core expressions, but omitting all those terms concerning the MM site, i.e., the factor ρ^m in the two-center two-electron integrals (see eq 6), the exponential factor $\exp(-\alpha_m R_{qm})$ in $f(q,m)$ (eq 8), and the Gaussian functions $K_{m,j} \exp(-L_{m,j}(R_{qm} - M_{m,j})^2)$ in $g(q,m)$ (eq 9). Finally, the method III follows exactly the definition made by Théry et al.,[13d] and the classical particle is treated as a core and an electron distribution having an s-type distribution (see above).

Computational Details

This section presents the computational strategy followed to calibrate the semiempirical QM/MM Hamiltonian. To this end, calculations were performed for a series of bimolecular hydrogen-bonded complexes involving a water molecule. Following other QM/MM parametrization studies,[1b,3a,4d,5a,f,19] the structural and energetic properties of the QM/MM interaction were adjusted to reproduce the reference values computed at a given QM level of theory. The series of QM molecules include prototypical neutral polar groups (H_2O, NH_3, HCOOH), a cation (H_3O^+), and an anion ($HCOO^-$). The TIP3P[20] water model was used for the MM water molecule. Finally, the level of theory used for comparison was the B3LYP density functional method[21] with the 6-31G(d)[22] basis, which gives a reliable description of electrostatic properties[23] and of structural and energetic features of hydrogen-bonded complexes.[24]

The reference energy profiles were obtained as follows. First, the geometry of each monomer was optimized at the AM1 and PM3 levels of theory, and was subsequently kept frozen. Complexes with a TIP3P water molecule were built up in selected orientations (see Figure 1). A partial AM1 or PM3 geometry optimization of the complexes was carried out with all degrees of freedom fixed except the intermolecular distance. Afterwards, the QM monomer−TIP3P water molecule distance was scanned (keeping the relative intermolecular orientation) and single-point calculations were carried out at the B3LYP level to obtain the interaction energy, which was corrected for the basis set superposition error using the counterpoise method.[25] The electrostatic AM1/TIP3P and PM3/TIP3P energy was then computed at each point along the profile using the same geometries. For comparison, B3LYP/TIP3P electrostatic energies were also calculated. The residual energy was then determined as the difference between the full B3LYP interaction energy and the electrostatic AM1/TIP3P or PM3/TIP3P energy. Finally, the vdW parameters of the QM atoms were optimized fitting the residual energy profiles (see below).

Results and Discussion

Electrostatic Energy Profiles. As noted before, the electrostatic interaction energy in QM/MM methods can be determined using a variety of expressions, which follow more or less closely the treatment adopted in NDDO-based methods, where a series of empirical terms are considered to properly deal with electrostatic interactions between atoms. The terms ρ_l ($l = 0, 1, 2$) were included to ensure the proper behavior of semiempirical repulsion integrals in the limits $R_{AB} \to \infty$ and $R_{AB} \to 0$.[26] The exponential term in the function $f(q,m)$ was included to account for the increase in the net electrostatic repulsion between neutral atoms with decreasing interatomic distance.[26] Finally, the Gaussian functions in $g(q,m)$ were added to the AM1

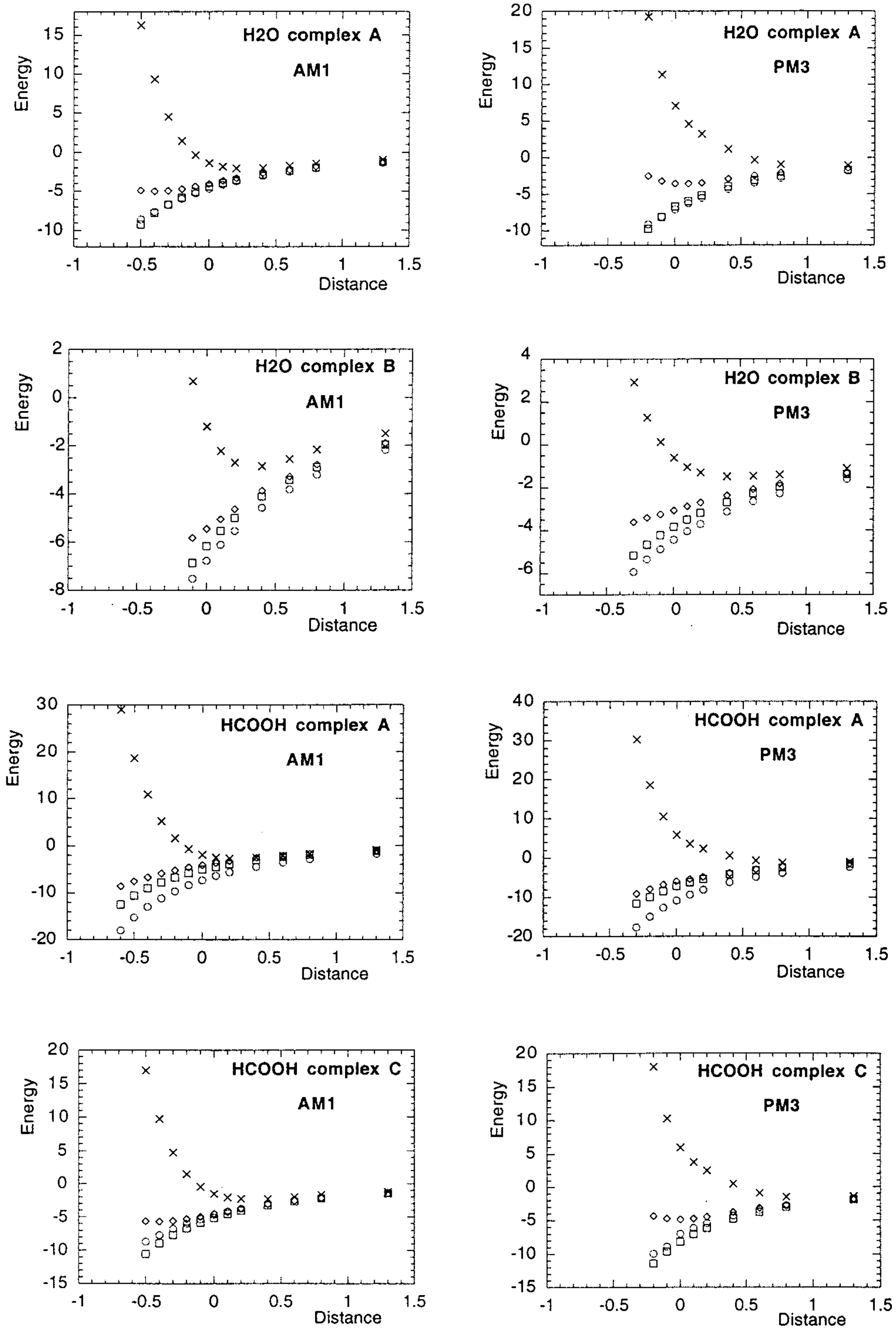

Figure 2. Electrostatic energy profiles (kcal/mol) for the interaction between water or formic acid with a TIP3P water molecule computed at the reference B3LYP (○) and semiempirical (AM1 and PM3) levels using formalisms I (□), II (◇), and III (×) to compute the electrostatic energy. The origin of distances (Å) in the *x*-axis is the equilibrium intermolecular separation determined at the semiempirical level (H_2O complex A: 3.10 (AM1) and 2.77 (PM3); H_2O complex B: 2.61 (AM1) and 3.05 (PM3); HCOOH complex A: 3.06 (AM1) and 2.75 (PM3); HCOOH complex C: 3.09 (AM1) and 2.77 (PM3)).

and PM3 Hamiltonians to correct excessive interatomic repulsions at large separations found in MNDO.[16] Whether or not those empirical terms are necessary to describe the interaction between QM and MM systems at intermolecular distances typical of molecular aggregates is, nevertheless, unclear.

In order to calibrate the performance of the three electrostatic formalisms (see Table 1), we determined the QM/MM electrostatic energy profiles for the complexes shown in Figure 1. The semiempirical AM1/TIP3P and PM3/TIP3P profiles were then compared with those obtained treating the QM monomer at the B3LYP level. Though calculations were carried out for all the complexes in Figure 1, the global trends are discussed on the basis of some representative results for selected complexes.

The AM1/TIP3P and PM3/TIP3P electrostatic profiles for the water dimer (complexes A and B) and formic acid−water pair (complexes A and C) are shown in Figure 2. The profiles determined using the method I exhibit the expected shape for the Coulombic interaction energy and, in fact, they roughly follow the shape of the reference B3LYP/TIP3P electrostatic energy profile. Thus, the semiempirical profile slightly under-

TABLE 2: Optimized van der Waals Parameters[a] for the Combined AM1/TIP3P and PM3/TIP3P Potential Using Method I for the Electrostatic Energy and B3LYP Equilibrium Energies and Distances as Reference Data

		AM1		PM3	
monomer	atom	ϵ	r	ϵ	r
H_2O	O	0.50	1.70	0.35	1.70
	H	0.34	0.40	0.20	0.40
NH_3	N	2.30	1.75	4.70	1.55
HCOOH	C	0.70	1.85	0.70	1.80
	O	1.15	1.80	1.15	1.80
	O(H)	1.00	1.50	0.90	1.55
	H(O)	0.80	0.15	0.90	0.01
H_3O^+	O	40.0	1.00	45.0	0.95
	H	0.1	0.10	0.05	0.05
$HCOO^-$	C	0.70	1.80	0.75	1.85
	O	0.65	1.70	0.65	1.75

[a] ϵ, kcal/mol; r, Å.

estimates or overestimates the B3LYP/TIP3P one in some cases, but there is general agreement between AM1(PM3)/TIP3P and B3LYP/TIP3P profiles when the formalism I is used. The regression equations obtained when the B3LYP/TIP3P values are compared with the AM1/TIP3P and PM3/TIP3P ones using the data determined for all the complexes are $E_{B3LYP} = 1.050E_{AM1}$ ($r = 0.98$) and $E_{B3LYP} = 1.022E_{AM1}$ ($r = 0.98$), respectively.

The results determined using method II are very similar to those computed with method I at large intermolecular distances. Nevertheless, the electrostatic energies are clearly less stabilizing as the intermolecular distance decreases, and in some cases (see complex A of H_2O and complex C of HCOOH in Figure 2) the electrostatic energy curve reaches a minimum and then tends to decrease (in absolute value) as the intermolecular distance is shortened. This behavior occurs in complexes of the type O···Hw−Ow or N···Hw−Ow (complex B of NH_3 in Figure 1; data not shown), but it is not found in interactions of the type O−H···Ow or N−H···Ow. Test calculations showed that the Gaussian functions in $g(q,m)$ make a negligible contribution and that the screening of electrostatic potential is due to the Ohno−Klopman factors and to the exponential term in the core−charge expression, whose contribution increase with larger penetration of the interacting atoms. This also explains why this effect is more relevant in the PM3 profiles, where such a behavior occurs even at the equilibrium intermolecular distances, than in the AM1 ones, since the fomer method tends to give equilibrium distances shorter (around 0.2 Å; see below and Table 3) than the latter.

Finally, the method III appears to be rather poor for the present TIP3P water complexes. Clearly, the repulsive term is largely overestimated and the electrostatic energy is clearly destabilizing even at geometries close to the equilibrium intermolecular distances. For instance, the PM3/TIP3P energy predicted by the method III at the equilibrium geometry is +7 kcal/mol for complex A of H_2O, whereas the corresponding value in the reference B3LYP/TIP3P electrostatic energy profile is −7 kcal/mol (Figure 2). Such a large difference has no physical justification and must be attributed to an inappropriate balance of the two terms in the right-hand side of eq 10. Thus, even though the underlying assumption of method III (i.e., treating the classical particle as a core plus an implicit electron population) is appealing, a careful calibration is required to balance the attractive and repulsive terms in eq 10.

Parametrization of the Nonelectrostatic Term. There is not a priori a rigorous physical justification to discriminate between methods I and II to compute the semiempirical QM/MM electrostatic energy. In the framework of method II, the contribution of the $g(q,m)$ function to the electrostatic energy is negligible (see above) and this term can be eliminated. However, both the Ohno−Klopman factor and the exponential term have an important contribution to the interaction energy and their screening effect cannot be omitted. Compared to the computationally simpler method I, which includes only the pure Coulombic contribution, method II adds short-range repulsions between the QM core and the classical charge, which otherwise should be handled by the vdW component of the QM/MM Hamiltonian. According to Cummins and Gready,[13c] the Ohno−Klopman factor may be essential for a realistic choice of van der Waals parameters and for a proper description of solute−solvent H-bonding in the case of ionic solutes. The damping parameter factor is likely to be more important for describing interactions involving ionic species than for neutral species due

TABLE 3: Equilibrium Distances (d, Å) and Interaction Energies (E, kcal/mol) Computed at the AM1 and PM3 QM/MM Level[a] for the Different Complexes

		B3LYP		AM1		AM1/TIP3P		PM3		PM3/TIP3P	
monomer	complex	E	d	E	d	E	d	E	d	E	d
H_2O	A	−4.7	2.92	−2.7	3.10	−5.2	2.85	−2.7	2.77	−5.2	2.87
	B	−3.1	2.91	−5.0	2.61	−3.9	3.01	−2.1	3.05	−3.9	2.95
	C	−5.4	2.89	−3.3	3.03	−5.3	2.83	−3.5	2.78	−5.7	2.79
	D	−4.7	2.91	−2.7	3.09	−4.3	3.03	−2.7	2.77	−4.1	2.93
	E	−5.4	2.88	−3.2	2.61	−4.5	2.97	−3.5	2.77	−4.0	2.91
NH_3	A	−2.4	3.19	−1.0	3.17	−2.5	3.23	−0.3	2.86	−2.0	3.16
	B	−7.1	2.94	−0.9	3.50	−6.7	2.98	−2.9	2.78	−6.7	2.86
HCOOH	A	−8.3	2.74	−3.4	3.06	−7.7	2.73	−3.8	2.75	−6.9	2.70
	B	−4.3	2.90	−3.6	3.05	−5.5	2.98	−3.4	2.78	−5.7	2.93
	C	−4.0	2.97	−3.0	3.09	−5.1	3.12	−3.2	2.77	−5.3	2.97
	D	−9.6	3.08	−5.5	3.40	−7.0	3.52	−4.1	3.06	−7.3	3.46
H_3O^+	A	−33.9	2.47	−17.4	2.82	−33.8	2.53	−21.9	2.65	−34.4	2.44
	B	−34.4	2.47	−17.5	2.80	−33.5	2.49	−22.3	2.64	−32.9	2.43
$HCOO^-$	A	−16.3	2.72	−10.9	2.92	−15.6	2.78	−14.8	2.69	−17.3	2.77
	B	−14.0	3.04	−11.2	3.01	−14.9	2.97	−10.2	2.76	−15.0	3.02
	C	−14.1	2.71	−8.6	3.00	−14.6	2.77	−10.9	2.72	−14.5	2.77
	D	−17.1	3.12	−15.9	3.19	−20.5	3.22	−16.2	2.98	−20.3	3.27
msd[b]				+4.3	+0.15	−0.1	+0.07	+3.5	−0.08	−0.1	+0.02
rms[c]				6.6	0.26	1.2	0.13	4.9	0.16	1.3	0.11
c[d]				1.62		0.99		1.41		0.98	
r[e]				0.92		0.99		0.96		0.99	

[a] Values computed using the formalism I for the electrostatic term and the optimized parameters given in Table 2 for the van der Waals component. [b] Mean signed deviation. [c] Root-mean-square deviation. [d] Coefficient of the linear regression E(B3LYP) = cE(other method). [e] Correlation coefficient.

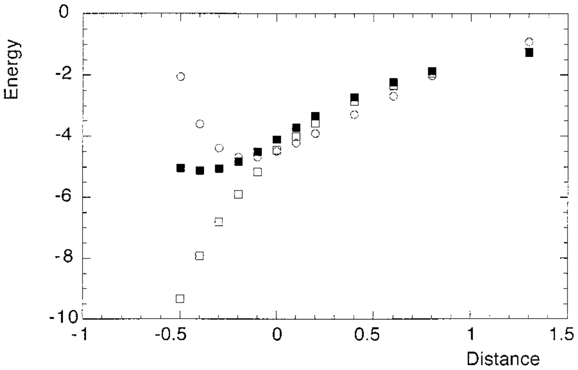

Figure 3. Total (electrostatic + van der Waals) interaction energy (kcal/mol) corresponding to complex A of water computed at the reference B3LYP level (○) or at the semiempirical AM1 QM/MM level. In this latter case, values were determined by adding the electrostatic energy calculated with either method I (unfilled symbols) or II (filled symbols) to the van der Waals energy computed using parameters taken from data compiled by Gao (□; ref 1b). The origin of distances (Å) in the *x*-axis is the equilibrium intermolecular separation determined at the AM1 level (3.10 Å).

to larger diatomic overlap in the former. Because of the need to keep a proper balance between electrostatic and nonelectrostatic terms in the QM/MM Hamiltonian (eqs 2−4), the preceding discussion strongly argues against the transferability of vdW parameters when different electrostatic formalisms are used in semiempirical QM/MM calculations.

This is well illustrated in Figure 3, which shows the interaction energy profile for complex A of H_2O at the B3LYP and AM1 QM/MM levels. The AM1 QM/MM values were determined by adding the electrostatic energy calculated with either method I or II to the vdW energy computed using the vdW parameters reported by Gao.[1b] When method II is used in conjunction with vdW parameters optimized for closely related formalisms,[18] the energy profile (see Figure 3) shows a minimum at an intermolecular distance around 0.2 Å shorter than the B3LYP value (2.92 Å) and the well depth is close to the B3LYP interaction energy (−4.7 kcal/mol). In contrast, when method I is used, no minimum appears in the energy profile for the range of distances examined. Clearly, in this latter case the balance between electrostatic and vdW components of the QM/MM Hamiltonian is not maintained.

In order to examine the suitability of the vdW parameters for a given electrostatic formalism and Hamiltonian, the vdW parameters of the QM monomer were optimized to reproduce the difference between the total B3LYP interaction energy and the electrostatic energy calculated using the "pure" Coulombic approach (method I) for all the complexes in a given dimer.[27] To this end, an AMBER-like 6−12 expression was chosen for the nonelectrostatic QM/MM component (eq 11), since this work fits into a project to combine QM calculations with the MM AMBER program.[28] The initial set of vdW parameters of the QM solutes was selected from the AMBER force field.[8] The final parameters are given in Table 2 and the computed interaction distances and energies are given in Table 3.

$$E_{\mathrm{vdW}} = \epsilon_{\mathrm{qm}}\left[\left(\frac{r_{\mathrm{qm}}}{R_{\mathrm{qm}}}\right)^{12} - 2\left(\frac{r_{\mathrm{qm}}}{R_{\mathrm{qm}}}\right)^{6}\right] \qquad (11)$$

$$\epsilon_{\mathrm{qm}} = (\epsilon_{\mathrm{q}}\epsilon_{\mathrm{m}})^{1/2}$$

$$r_{\mathrm{qm}} = r_{\mathrm{q}}^{*} + r_{\mathrm{m}}$$

where ϵ is the atomic hardness, r^* is the atomic van der Waals radius, and R is the interatomic distance.

Throughout the parametrization process, we attempted to assign vdW parameters only to heavy atoms and, in order to limit the numerical solutions, we tried to maintain the vdW radii close to the AMBER values. In this process, the energy profiles for ammonia were satisfactorily reproduced, assigning vdW parameters only to the nitrogen atom. Nevertheless, vdW parameters for hydrogen atoms were necessary to improve the fitting for water. In fact, this finding was not unexpected on the basis of previous studies that revealed the need to include vdW parameters in both oxygen and hydrogen atoms to obtain radial distribution functions close to the experimental one.[29] Attempts to retain a single set of parameters for the OH group were unsuccessful, and different parameters were considered for water, formic acid, and particularly protonated water. Different parameters were also required for the sp^2 and sp^3 oxygen atoms in formic acid. Indeed, the parameters for the sp^2 oxygen in formic acid had to be reoptimized to improve the fitting to the reference energy profiles for the formate anion.

Overall, the ability of the vdW parameters to reproduce the B3LYP energy profiles can be assessed in Figure 4, which shows the B3LYP and AM1/TIP3P profiles for selected complexes (PM3/TIP3P plots are available upon request). The shapes of the B3LYP and AM1/TIP3P profiles show in general close agreement. Considering all the points lying 3 kcal/mol above the energy minimum, the average deviation from the B3LYP values is 0.5 (0.6) and 0.8 (0.5) kcal/mol for neutral and ionic compounds at the AM1/TIP3P (PM3/TIP3P) level. Particularly, the marked deviation in the energy profile observed when vdW parameters adapted to the electrostatic formalism II are used (see above and Figure 3) is satisfactorily corrected.

Table 3 reports the interaction energies and distances for the equilibrium structures of the complexes computed at the B3LYP, AM1, PM3, AM1/TIP3P, and PM3/TIP3P levels. The QM/MM interaction energies reproduce closely the reference B3LYP values, as noted in the average deviation and root mean square error, which are close to 0.1 and 1.2 kcal/mol, respectively. It is worth noting that such statistical parameters for the pure AM1 and PM3 methods are at least 3.5 and 4.9 kcal/mol. The agreement in the interaction energies is also noted in the regression equations E(B3LYP) = cE(other method), since the scaling coefficient c is close to unity for both AM1/TIP3P and PM3/TIP3P methods, whereas deviations larger than 40% are found for the pure QM methods. The QM/MM methods also improves the description of intermolecular distances compared to the AM1 and PM3 methods. This improvement is not as relevant as for the interaction energies owing to the less uniform deviation of AM1 and PM3 equilibrium distances compared to the B3LYP values. Overall, these results point out that the QM/MM method not only reproduces satisfactorily the reference interaction energies but also corrects energetic and geometrical deviations in QM AM1 or PM3 calculations.

An interesting aspect is the equivalence between QM and MM monomers for the same compound; that is, the geometrical and energetic features should be the same irrespective of whether monomer is treated quantum mechanically or classically. This can be checked for the dimer of water comparing the results for complexes A−D and C−E (see Figure 1). Clearly, the results are identical for each couple of complexes when B3LYP, AM1, or PM3 methods are used (the slight differences obey to the use of the TIP3P geometry for the QM monomer when reversing QM and MM monomers). However, the QM monomer acting as hydrogen-bond acceptor leads to shorter distances and larger (in absolute values) interaction energies than when it acts as hydrogen-bond donor. This difference can be attributed to the

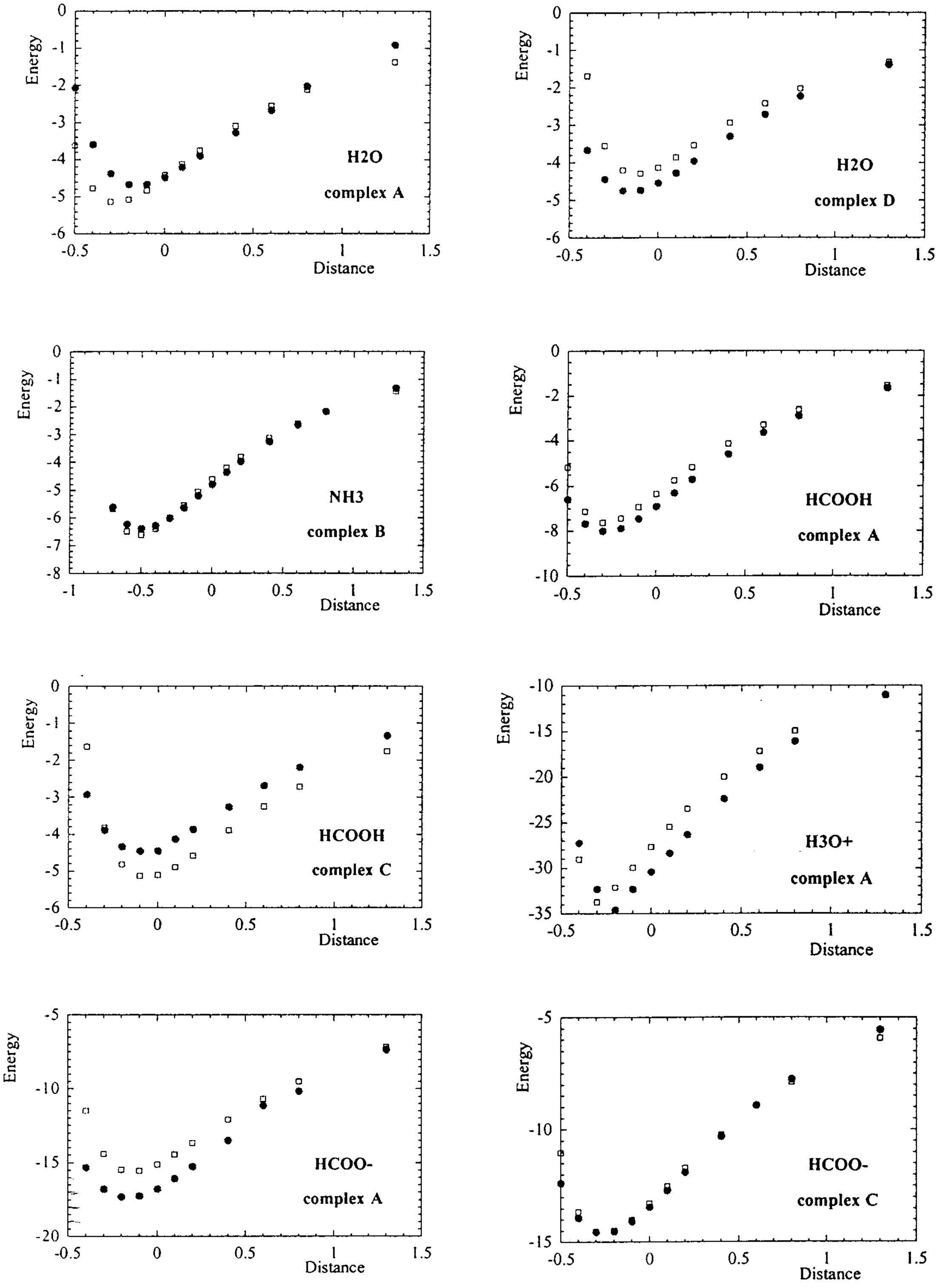

Figure 4. Representation of the total interaction energies (kcal/mol) computed for selected complexes at the B3LYP level (filled symbols) and from AM1/TIP3P calculations (unfilled symbols) performed using the approximation I for the electrostatic QM/MM term and the optimized parameters given in Table 2 for the van der Waals QM/MM term. The origin of distances (Å) in the *x*-axis is the equilibrium intermolecular separation determined at the AM1 level.

lack of Lennard-Jones parameters for the hydrogen atoms in the TIP3P water, which permits a closer contact between QM (acceptor) and MM (donor) water molecules than in the QM (donor) and MM (acceptor) pair. This finding, which has been found in other QM/MM parametrizations,[4d] reveals the difficulty to properly balance hydrogen-bond donor and acceptor properties in the QM monomer in QM/MM simulations in aqueous solutions.

Another point of concern is the transferability of vdW parameters between AM1 and PM3 QM/MM calculations, since the AM1 equilibrium distances may differ 0.2−0.3 Å from the PM3 ones for the series of complexes. The parameters optimized for AM1 and PM3 (Table 2) are generally quite similar, suggesting that they can be mostly transferable. This is confirmed in Table 4, which shows the equilibrium distances and energies obtained by computing the AM1/TIP3P values

TABLE 4: Equilibrium Distances (*d*, Å) and Interaction Energies (*E*, kcal/mol) Computed at the AM1/TIP3P (PM3/TIP3P) Level Using the van der Waals Parameters Optimized for PM3/TIP3P (AM1/TIP3P) Calculations for the Different Complexes[a]

		B3LYP		AM1/TIP3P		PM3/TIP3P	
monomer	complex	*E*	*d*	*E*	*d*	*E*	*d*
H_2O	A	−4.7	2.92	−5.4	2.80	−5.1	2.87
	B	−3.1	2.91	−4.0	3.09	−3.8	2.99
	C	−5.4	2.89	−5.6	2.76	−5.5	2.82
	D	−4.7	2.91	−4.3	2.95	−4.1	3.01
	E	−5.4	2.88	−4.5	2.94	−4.0	2.96
NH_3	A	−2.4	3.19	−3.1	3.07	−1.5	2.31
	B	−7.1	2.94	−8.4	2.80	−5.1	2.98
HCOOH	A	−8.3	2.74	−7.4	2.76	−7.1	2.79
	B	−4.3	2.90	−5.6	2.93	−5.6	3.01
	C	−4.0	2.97	−5.2	3.02	−5.3	3.05
	D	−9.6	3.08	−7.0	3.54	−7.4	3.46
H_3O^+	A	−33.9	2.47	−35.2	2.48	-32.4	2.47
	B	−34.4	2.47	−35.6	2.40	-31.0	2.48
$HCOO^-$	A	−16.3	2.72	−15.1	2.82	-18.0	2.69
	B	−14.0	3.04	−14.5	3.01	-15.4	3.02
	C	−14.1	2.71	−14.0	2.80	-15.1	2.72
	D	−17.1	3.12	−19.6	3.29	-21.2	3.26
msd[b]				−0.3	+0.04	+0.1	+0.06
rms[c]				1.2	0.15	1.8	0.12
c[d]				0.97		1.01	
r[e]				0.99		0.98	

[a] Values computed using the formalism I for the electrostatic term and the optimized parameters given in Table 2 for the van der Waals component. [b] Mean signed deviation. [c] Root-mean-square deviation. [d] Coefficient of the linear regression *E*(B3LYP) = *cE*(other method). [e] Correlation coefficient.

TABLE 5: Equilibrium Distances (*d*, Å) and Interaction Energies (*E*, kcal/mol) Computed at the AM1 and PM3 QM/MM Level for the Different Complexes Using the van der Waals Parameters Reported in by Cummins and Gready[a]

		B3LYP		AM1/TIP3P		PM3/TIP3P	
monomer	complex	*E*	*d*	*E*	*d*	*E*	*d*
H_2O	A	−4.7	2.92	−6.0	2.74	−6.9	2.57
	B	−3.1	2.91	−4.5	2.81	−4.3	2.75
	C	−5.4	2.89	−6.2	2.73	−7.5	2.53
	D	−4.7	2.91	−5.2	2.70	−4.9	2.71
	E	−5.4	2.88	−5.4	2.72	−5.1	2.66
NH_3	A	−2.4	3.19	−2.8	2.91	−1.5	2.96
	B	−7.1	2.94	−7.7	2.85	−8.7	−2.58
HCOOH	A	−8.3	2.74	−7.7	2.62	−7.0	2.65
	B	−4.3	2.90	−6.5	2.84	−6.4	2.88
	C	−4.0	2.97	−6.0	2.89	−6.1	2.87
	D	−9.6	3.08	−8.9	3.24	−9.0	3.21
H_3O^+	A	−33.9	2.47	−29.4	2.51	−28.1	2.46
	B	−34.4	2.47	−29.3	2.48	−26.8	2.44
$HCOO^-$	A	−16.3	2.72	−18.1	2.57	−22.6	2.39
	B	−14.0	3.04	−16.5	2.70	−17.1	2.76
	C	−14.1	2.71	−18.4	2.45	−19.2	2.42
	D	−17.1	3.12	−25.0	2.99	−26.5	2.98
msd[b]				−0.9	−0.13	−1.1	−0.18
rms[c]				3.0	0.17	4.1	0.23
c[d]				0.97		0.94	
r[e]				0.95		0.91	

[a] Values computed using the formalism I for the electrostatic term and the nonelectrostatic treatment reported in refs 13b,c (see text and ref 30). [b] Mean signed deviation. [c] Root-mean-square deviation. [d] Coefficient of the linear regression *E*(B3LYP) = *cE*(other method). [e] Correlation coefficient.

using the vdW parameters optimized for PM3/TIP3P and vice versa. The values in Table 4 closely agree with those reported in Table 3, and the statistical analyses indicate that they reproduce the B3LYP energies and distances with deviations slightly larger than those given in Table 3. These results suggests that a single set of vdW parameters can be parametrized for both AM1/TIP3P and PM3/TIP3P calculations.

A final aspect of this analysis is the comparison with the results obtained in other semiempirical QM/MM parametrizations. Compared with the vdW parameters reported by Gao in his AM1/TIP3P parametrization (ϵ in kcal/mol; r^* in Å) [(O(H): $\epsilon = 0.15$, $r^* = 1.18$; O(=C): $\epsilon = 0.20$, $r^* = 1.66$; N: $\epsilon = 0.15$, $r^* = 1.57$; C, $\epsilon = 0.08$, $r^* = 1.96$; H(O,N): $\epsilon = 0.10$, $r^* = 1.12$], σ was transformed to r^* using the relationship $r^* = 2^{1/6}\sigma/2$),[1b] the results in Table 2 mainly differ in the "hardness" values, which are sensibly larger than those reported by Gao. Clearly, this stems from the steepest variation (see Figure 2) in the electrostatic energy determined with the pure Coulombic approach (method I) relative to the profile obtained with method II (comparable to Gao's formalism), which already incorporates short-range repulsions between the QM core and the classical charge (see above). Accordingly, one cannot expect the vdW parameters to be directly transferable between methods based on different treatment of the electrostatic QM/MM Hamiltonian, as exemplified in Figure 3.

Cummins and Gready have recently reported an alternative set of vdW parameters optimized for semiempirical QM/TIP3P methods,[13b,c] which were also derived using the pure Coulombic formalism (method I) for electrostatic interactions. Indeed, the initial set of vdW parameters were taken from the AMBER force field. The optimized vdW parameters are (ϵ in kcal/mol; r^* in Å) O(H): $\epsilon = 0.15$, $r^* = 1.65$; O(=C): $\epsilon = 0.20$, $r^* = 1.60$; N: $\epsilon = 0.16$, $r^* = 1.75$(AM1)/1.70(PM3); C: $\epsilon = 0.12$, $r^* = 1.85$; H(O,N): $\epsilon = 0.02$, $r^* = 1.00$ Å. Compared to the values in Table 2, the vdW radii are rather similar, but surprisingly the hardness parameters are again sensibly lower than those given in Table 2. In fact, when these parameters are used to compute AM1/TIP3P and PM3/TIP3P energy profiles for the series of complexes,[30] the equilibrium distances are shorter by 0.1−0.2 Å and the interaction energies are larger (in absolute values) by around 1.0 kcal/mol (root mean square deviations of 3−4 kcal/mol) than the corresponding B3LYP values, as can be stated from inspection of Table 5.

There are relevant differences in the parametrization process adopted by Cummins and Gready and that followed in this study: (i) the vdW parameters were optimized by fitting the electrostatic component of the solvation free energy, which was determined by subtracting the nonelectrostatic component (computed from a linear relationship with the solvent-accessible surface) to the experimental free energy of solvation (for ionic compounds, the Born solvation correction term was also considered); (ii) a 10−12 pair potential function was considered for hydrogen-bond interactions; (iii) hydrogen atoms in the TIP3P water molecule were assigned nonzero van der Waals parameters ($\epsilon = 0.02$ kcal/mol; $r^* = 1$ Å), and (iv) a nonzero scaling parameter that multiplies the Ohno−Kloppman factor was used for ionic compounds. Clearly, this evidences the marked dependence of the vdW parameters on the choice of the parametrization model, in line with the conclusion of recent studies,[31] which have revealed marked differences in the coupling between QM and MM systems depending on the nature of the vdW parameters.

Conclusions

An accurate description of chemical processes by mixed QM/MM methods cannot be achieved without a proper balance between the electrostatic and nonelectrostatic energy terms in the QM/MM Hamiltonian. This is generally accomplished by fitting geometrical and energetic properties of selected complexes determined in the gas phase at a suitable level of theory. In semiempirical QM/MM methods, nevertheless, an additional difficulty arises from the lack of a precise definition of the electrostatic potential. The results presented in this study reveal that the electrostatic interaction energy is very sensitive to the formalism used for the electrostatic potential, which should in turn affect the suitability of the van der Waals parameters. Particularly, the adoption of an electrostatic formalism that retains some essential features of the NDDO scheme includes short-range repulsions between the QM core and the MM charge, which otherwise should be handled by the vdW component of the QM/MM Hamiltonian if a pure Coulombic treatment is used. The results also reveal that, for a given electrostatic formalism, both equilibrium distances and interaction energies computed at a suitable reference level of theory can be satisfactorily reproduced in the parametrization of the 6−12 van der Waals term. However, the magnitude of the parameters turns out to be very sensitive to the specific details of the parametrization model. Therefore, these results warn against the direct transferability of van der Waals parameters, which might lead to an incorrect coupling between QM and MM molecules.

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(18) The method I corresponds to the approach adopted by Cummins and Gready (ref 13b,c), and the method II roughly follows the formalism reported by Field et al. (ref 3a). In fact, Field et al. retain the parameter α_m in eq 8, which is set to 5.0. However, the inclusion of this term was found to lead to very small differences from the values computed using the method II for the complexes and intermolecular geometries examined here. Note that the Cummins and Gready model has also some elements of method II since for H-bonding interactions involving ions, the Ohno-Klopman factors are retained for some atom pairs directly involved in the H-bond.[13c]

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(27) BSSE-corrected B3LYP energies were determined using the AM1 or PM3 internal geometries for the QM monomer. Test calculations showed that the use of these geometries for the QM monomer instead of the B3LYP optimized ones affected very slightly both the location and depth of the minimum in the energy profile.

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