REGULAR ARTICLE

Can semi-empirical models describe HCl dissociation in water?

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Abstract We discuss the failure of commonly used AM1 and PM3 semiempirical methods to correctly describe acid dissociation. We focus our analysis on HCl because of its physicochemical importance and its relevance in atmospheric chemistry. The structure of non-dissociated and dissociated $HCl - (H_2O)_n$ clusters is accounted for. The very bad results obtained with PM3 (and also with AM1) are related to large errors in gas-phase proton affinity of water and gas-phase acidity of HCl. Indeed, estimation of pKa values shows that neither AM1 nor PM3 are able to predict HCl dissociation in liquid water since HCl is found to be a weaker acid than H_3O^+. We have proposed in previous works a modified PM3 approach (PM3-MAIS) adapted to intermolecular calculations. It is derived from PM3 by reparameterization of the core–core functions using ab initio data. Since parameters for H–Cl and O–Cl core–core interactions were not yet available, we have carried out the corresponding optimization. Application of the PM3-MAIS method to HCl dissociation in $HCl–(H_2O)_n$ clusters leads to a huge improvement over PM3 results. Though the method predicts a slightly overestimated HCl acidity in water environment, the overall agreement with ab initio calculations is very satisfying and justifies efforts to develop new semiempirical methods.

Keywords Semi-empirical · Acid dissociation · Proton

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1 Introduction

In the development of quantum chemistry and its applications, semiempirical methods have played a major role. Even if today most ab initio and density functional methods are widespread tools in chemistry, semiempirical approaches still represent a convenient choice for preliminary studies of complex chemical phenomena or for investigating very large systems such as enzymes, either by their own or in combination with other methodologies (QM/MM [1–3], ONIOM [4,5]).

However, commonly used AM1 and PM3 semiempirical methods suffer from several well-known limitations, among which one may quote: (1) a rough description of intermolecular interactions, in particular of hydrogen bonds [6–8], and (2) large errors in the intrinsic acidity and/or basicity of molecules [9–12]. These restrictions are particularly critical in enzymatic catalysis modeling, since hydrogen bonds and proton transfer processes often play a fundamental role in these biochemical reactions. Thus, developing new and more efficient methods is of utmost importance and not surprisingly a number of efforts have been made in this direction [5,13–18].

Owing to the relevance of interactions with water in chemistry and biochemistry, in the last years we have been interested in extending semiempirical models to describe hydration phenomena [7,8]. We have proposed a simple approach in which only the intermolecular core–core contribution to the total energy is modified. Specifically, we change the Gaussian Correction Function (GCF) proposed by Dewar [19] and Stewart [20] by a parameterized interaction function (PIF) aimed to reproduce ab initio data for the intermolecular potential energy surface. One of the main interests of this function is that the unphysical artifacts introduced by the GCFs in AM1 and PM3 are completely eliminated. Afterwards, one can derive a unique core–core function

incorporating the PIFs and the standard GCFs for dealing with long- and short-range interactions, respectively. A convenient procedure to achieve this has been reported [21]. The so-called PM3-MAIS method (MAIS= method adapted for intermolecular studies) has provided excellent results for the potential energy surface of the $H_5O_2^+$ system [21] and has suggested a way to improve PM3 results in chemical reactivity studies. PM3-MAIS is therefore expected to improve the description of proton transfer reactions with respect to standard PM3. The aim of the present work is to explore and analyze this hypothesis focusing on a fundamental physico-chemical process: HCl dissociation in water clusters.

The properties of $HCl - (H_2O)_n$ systems are particularly relevant in the context of atmospheric chemistry. Indeed, ozone depletion processes occurring in the stratosphere are thought to be initialized by HCl dissociation on ice surface or in small water clusters [22–38]. Furthermore, recent diffraction studies by Botti et al. [36,39] raise interesting questions regarding the incomplete dissociation of this acid in concentrated solutions. Both spectroscopy experiments and theoretical studies have provided detailed information about the molecular mechanisms involved in HCl hydration, dissociation and ion stabilization in small water and mixed clusters or in model surfaces. The structure of the 1:1 complex is clearly that of an hydrogen-bonded species, as ab initio studies have confirmed [38]. The interaction produces an elongation of the HCl bond length and a significant increase in the ionic character with respect to the isolated molecule [30]. If further solvation occurs, the bond length is still increased [35]. This has been experimentally observed because acid–water clusters have a unique stretch band coming from the acid that does not overlap any of pure water bands [30]. Rotational spectroscopy has been able not only to confirm structural parameters coming from calculations, but also to identify many features indicative of the cooperative nature of this interaction [40] that might be responsible for dissociation. Ab initio calculations [24,27,34,38,41] and infrared spectroscopy studies [35,40] of acid clusters with up to three water molecules coincide in describing these systems as nonionic. Situation changes when going to four water molecules where both ionic and non-ionic structures were found [29,34,42]. Dissociation is complete for most isomers of larger clusters [34,37,38]. A comparative study of zwitterionic clusters of different hydrogen halides found that the stability of HX–water clusters follows closely the strength of the acid [34].

Semiempirical calculations on ion dissociation in $HCl–(H_2O)_n$ clusters has been investigated by Buesnel et al. [23] at the AM1 level. The authors showed that this method is not able to predict dissociation as a consequence of the considerable underestimation of gas-phase water proton affinity. We have shown in a previous work [21] that PM3 also underestimates this property while the PM3-MAIS value is

very close to the experiment. However, description of proton transfer in $HCl–(H_2O)_n$ clusters also requires a correct prediction of HCl gas-phase acidity. We report here a detailed analysis of PM3 and PM3-MAIS results for a series of $HCl–(H_2O)_n$ clusters and discuss the suitability of the methods to describe proton transfer. More generally, this study is aimed to critically evaluate the limits of current semiempirical theories to describe acid dissociation processes in water. Since PM3-MAIS parameters for some core–core interactions (Cl–H and Cl–O) were not yet available, they have been optimized in the present work following the previously proposed strategy [21].

2 Parameterization procedure

In order to obtain the PM3-MAIS parameters for Cl–H and Cl–O interactions, we follow the protocol reported in our original paper [21]. Accordingly, the corresponding GCFs for intermolecular interactions in the $HCl–H_2O$ complex were replaced by PIFs, the functional form of which is a sum of atom–atom contributions similar to those used in classical interaction models:

$$PIF = \sum_{A,B}^{inter} g_{PIF}(A, B)$$

$$= \sum_{A,B}^{inter} \alpha_{(AB)} e^{-\beta_{(AB)} R_{(AB)}} + \frac{\chi_{(AB)}}{R_{(AB)}^6} + \frac{\delta_{(AB)}}{R_{(AB)}^8} + \frac{\varepsilon_{(AB)}}{R_{(AB)}^{10}} \tag{1}$$

Here α_{AB}, β_{AB}, χ_{AB}, δ_{AB} and ε_{AB} are adjustable parameters depending on (A,B) atom types. They are optimized in order to obtain the best agreement possible between the computed potential energy surface (PES) and reference MP2/aug-ccPVTZ calculations (for details see the original work). The PES consists of 700 conformations of the complex[1]. The internal parameters of each molecule correspond to the experimental geometries in gas-phase. In Table 1, we present the optimized parameters and Fig. 1 shows the shape of the PIF function for each atom pair. As shown, Cl–O and Cl–H have a small contribution to the total energy at typical distance values of intermolecular interactions.

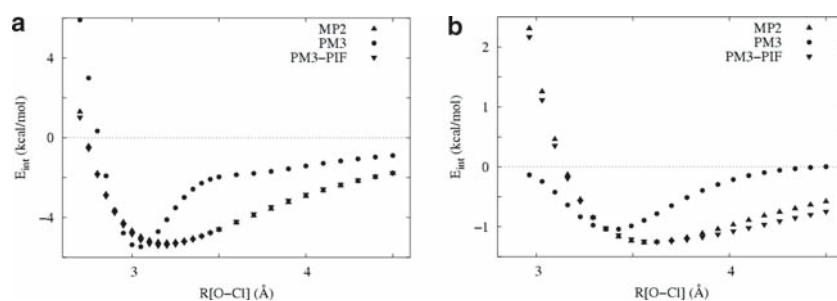Table 1 Optimized PIF parameters (in hartrees and bohr) for core-core intermolecular interactions

A–B	α	β	χ	δ	ε
Cl–O	35.27732	1.292906	−680.9553	19.13535	57189.97
Cl–H	27.42530	2.521105	−19.93522	29.06138	280.3394

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[1] The PES calculated is provided as Supporting Information.
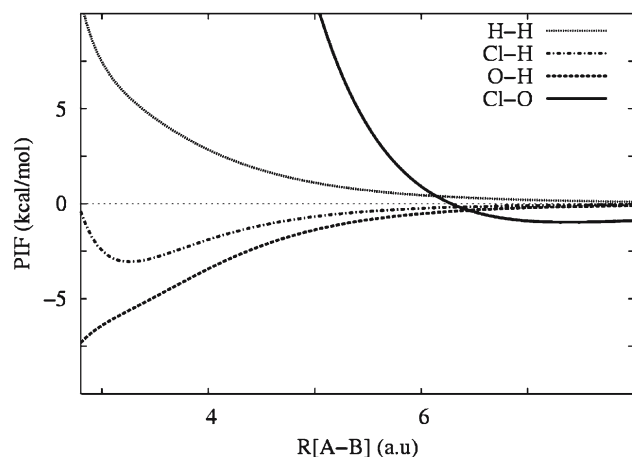
Fig. 1 Energy contribution of $g_{PIF}(A,B)$ functions (in kcal/mol) for the atomic pairs present in HCl–H$_2$O system. H–H and O–H curves from Ref. [7]

In Fig. 2, we show the H-bond donor and acceptor interaction energy curves resulting from the implementation of the new Cl–O and Cl–H functions and using for O–H and H–H the previously obtained PIF parameters [7]. Standard PM3 underestimates the minima position and predicts a considerably less attractive potential for distances beyond the energy

minimum. Clearly the replacement of GCF by PIF results in a much better agreement with MP2 data. Inspection of a vast section of the PES confirms this result, as shown in Fig. 3. The improvement is particularly noticeable in the attractive region. The correlation coefficient between MP2 and PM3-PIF results is 0.874, whereas it is only 0.674 for standard PM3.

The second step in the parameterization procedure consists of obtaining a unique function (MAIS) that fits the standard PM3 GCF behavior at short distances (typically at the bonded region) and the PIF at larger lengths [21]. At short distances, an energy shift with respect to GCFs may be necessary [21]. The MAIS function is conveniently defined as a set of Gaussian atomic pair functions:

$$g_{MAIS}(A,B) = \sum_{n=1}^{3} \alpha_{n_{AB}} e^{-\beta_{n_{AB}} (\gamma_{n_{AB}} - R_{AB})^2} \qquad (2)$$

MAIS functions for O–O and H–H were taken from our previous publication [21]. The O–H, Cl–O and Cl–H functions have been optimized here. An O–H MAIS function was reported in Ref. [22] but we found it important to perform further reoptimization here. Nevertheless, methodical tests were carried out in order to verify that such a modification

Fig. 2 Interaction energy curves for HCl–H$_2$O dimer as a function of O–Cl distance. **a** HCl as H-bond donor, **b** HCl as H-bond acceptor. Internal geometries of HCl and H$_2$O were kept constant at the experimental gas-phase geometry. The relative orientation of the molecules

corresponds to that obtained in the MP2 optimized complexes **a** Cs geometry with an angle of 113.7° between the HCl and H$_2$O molecular axes, **b** C$_1$ geometry with an angle of 107.3° between H–Cl–H) MP2 interaction energies are BSSE corrected

Fig. 3 Comparison of the MP2 vs PM3 and vs PM3-PIF interaction energy (in kcal/mol) for 700 geometries of the HCl–H$_2$O complex. The correlation coefficient is 0.674 for standard PM3 and 0.874 for PM3 with PIF parameters
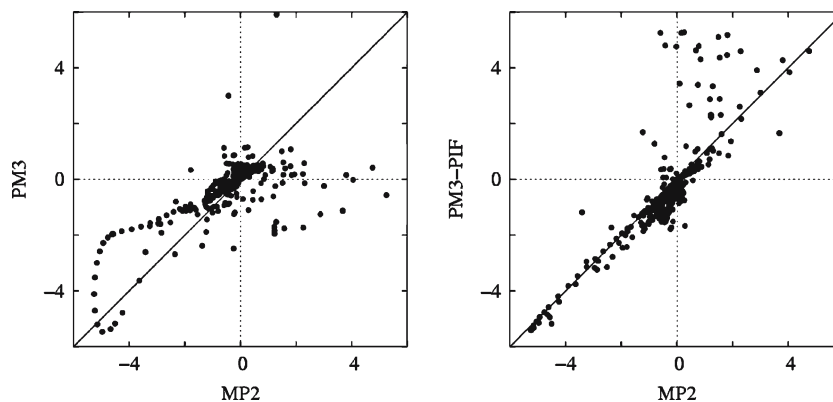
Table 2 MAIS parameters for H–O, Cl–O and Cl–H core–core function

| A–B	i	α	β	γ
O–H	1	0.038146	0.564949	4.128030
	2	−0.042715	0.518414	4.058190
	3	−0.039872	0.342029	0.529303
Cl–O	1	0.017759	1.022950	4.543160
	2	−0.001574	0.369802	7.538830
	3	−0.065971	0.591341	1.989830
Cl–H	1	−0.247371	1.520440	2.176850
	2	0.245420	1.649960	2.223590
	3	−0.009203	0.121566	0.841882

Values in bohr and hartrees

does not alter significantly the results of the previous one for neutral and protonated water clusters. The final set appears in Table 2 and Fig. 4 compares the shape of standard GCF, PIF and MAIS energy functions. Using MAIS, we obtain a correlation coefficient for the PES of the 1:1 complex of 0.846, just slightly smaller than the value obtained above with the PIF parameters.

3 Results and discussion

3.1 HCl gas-phase acidity

A necessary condition a method must fulfill in order to describe ionic dissociation in condensed phases, is the correct prediction of gas-phase proton affinities. Table 3 summarizes the computed and experimental values for water and chloride anion as well as the reaction enthalpy for the gas-phase process:

$$HCl + H_2O \rightarrow H_3O^+ + Cl^-$$
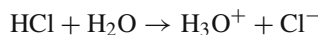
The proton affinity of water is not well reproduced by standard semiempirical models [9]. It is underestimated and the errors are extremely large: about 54 kcal/mol with AM1 and 25 kcal/mol for PM3. For the chloride anion, the proton affinity is also underestimated by these models [10], but the errors are a little smaller: 31 kcal/mol with AM1, 10 kcal/mol with PM3. When the proton exchange reaction above is considered, there is partial error compensation but the reaction enthalpy at either the AM1 or the PM3 levels is considerably overestimated. In contrast to standard AM1 or PM3, PM3-MAIS leads to excellent results.

To complete this analysis, let us consider the activation energy required for proton transfer in the 1:1 complex. Obviously, there is no true energy minimum for the ion pair $Cl^- \cdots H_3O^+$ and therefore, strictly speaking, one cannot talk about an energy barrier for proton transfer. However,
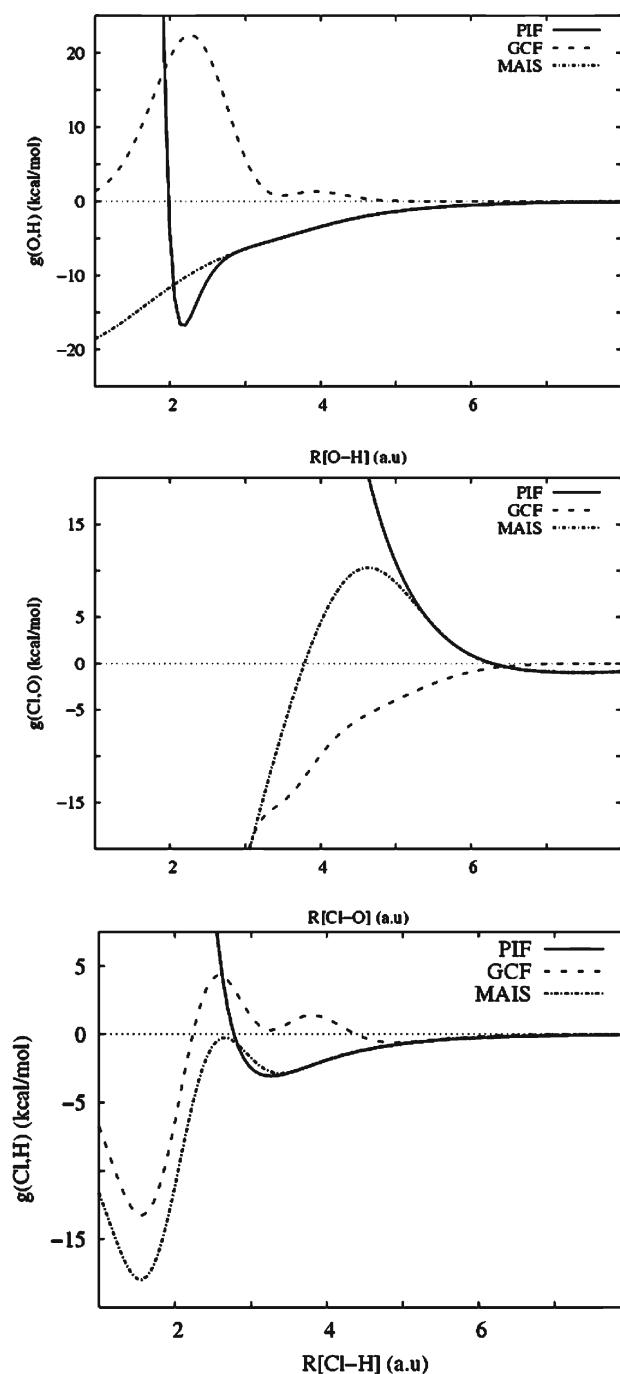
**Fig. 4** Energy contribution of MAIS to H–O, Cl–O and Cl–H core–core functions

for comparative purposes, it is possible to compute the energy profile for a fixed Cl–O distance, that here we arbitrarily chose to be 4.4 Å.

Results are shown in Fig. 5. They confirm the superiority of PM3-MAIS with respect to PM3 calculations. The original PM3 method predicts a very high proton transfer barrier (by 21.6 kcal/mol). The PM3-MAIS barrier is also overestimated but to a lesser extent (13.16 kcal/mol). The energy difference

Table 3 Computed and experimental [48] proton affinities of water and chloride anion and reaction enthalpies for the process: $HCl + H_2O \rightarrow H_3O^+ + Cl^-$ MP2 results do not include zero-point energy nor thermal corrections

	H_2O	Cl^-	Reaction
AM1	−112.2	−301.9	189.7
PM3	−141.1	−322.8	181.8
PM3-MAIS	−164.8	−327.9	163.1
MP2/aug-ccpVTZ	−170.2	−335.3	165.1
Experimental	−166.6	−333.4	166.8

All values are in kcal/mol
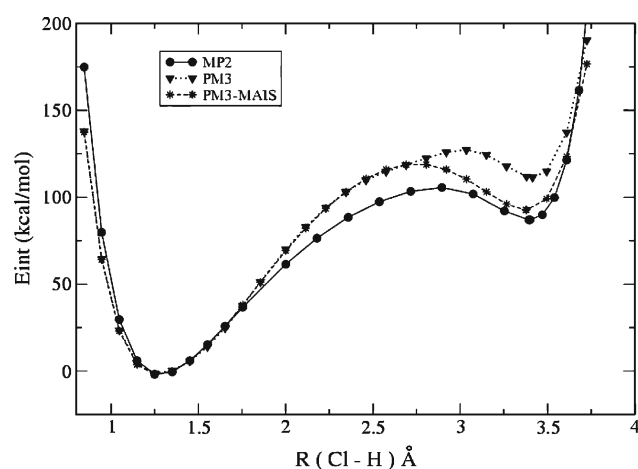
Fig. 5 Calculated proton transfer barrier with no structure relaxation between HCl and H_2O for a dimer in the C_{2v} geometry with a constant distance between Cl and O of 4.4 Å. MP2 data obtained using the aug-cc-pVTZ basis set

between reactants and products displays similar characteristics to the reaction energies in Table 2.

3.2 Hydrogen-bonding and ionic dissociation in HCl–$(H_2O)_n$ clusters

We now compare the ability of PM3 and PM3-MAIS to predict ion dissociation in HCl–$(H_2O)_n$ clusters with increasing number of molecules (AM1 calculations were reported before [23,43]). We have already underlined in the introduction that the experimental and ab initio data support the following facts: (1) neutral complexes are possible for $n \leq 4$ only and (2) ionized complexes are formed for $n \geq 4$. Buesnel et al. [23,43] showed that AM1 is unable to predict ionized complexes for values of n as large as 15. To the best of our knowledge a systematic study for PM3 has not yet been reported in the literature. We have therefore decided to analyze the number of water molecules that are required in PM3 and PM3-MAIS models in order to (1) stabilize an

ionized structure and (2) produce spontaneous dissociation of HCl.

HCl–$(H_2O)_n$ clusters with $n = 1$–4 have been fully optimized at the MP2/aug-ccpVTZ level. For a detailed analysis of ab initio calculations on these clusters, see Ref. [35,38,39]. We limit our study here to the following structures. For $n = 1$, only the HCl donor species is considered. For $n = 2$, there is only one possible structure, a cyclic one. For $n = 3$, there are two possible structures, a cyclic (the most stable one) and a non-cyclic, which are both considered. For $n = 4$, there are three non-dissociated and two dissociated structures; we have considered the most stable one for each structure type, that is, a non-dissociated cyclic structure and a dissociated pyramidal structure. All the structures and main geometrical parameters are presented in Fig. 6. The computed geometries are in good agreement with previous refined ab initio studies [24,29,30,38].

Using these structures, single point energy computations have been carried out with standard PM3 and PM3-MAIS. The results for interaction energies are compared in Fig. 7. Clearly, PM3-MAIS present a much better agreement with MP2 than standard PM3. In particular, the interaction energy for the pyramidal (dissociated) structure for $n = 4$ is correctly predicted with PM3-MAIS whereas the PM3 result is completely wrong. The reason lies on the errors obtained by this method for proton affinities (see Table 2).

The next step in this comparative study must be, of course, the full optimization of the clusters at the semiempirical level in order to verify the presence or absence of minima for neutral and ionized structures for the different values of n and their relative stability. We now include clusters for $n = 1$–6. Geometry optimization is started at the MP2 geometry when available. The criteria used for deciding if an optimized structure corresponds to a ionic or neutral cluster followed what other authors [29] have suggested; $r_{H-Cl} \leq 1.43$ Å. For some initial structures corresponding to non-dissociated situations, geometry optimization led to proton transfer (see details below). We verified in those cases that there is no energy minimum corresponding to a non-dissociated structure of the same type by carrying out further calculations with slightly different initial geometries. A summary of computed interaction energies is presented in Table 4 and geometrical structures are presented in Fig. 8a, b. MP2 energy values for n = 5, 6 are taken from the literature (see references in the table).

Fundamental differences between PM3 and PM3-MAIS are evident. With the standard PM3 method, neutral structures are located for all clusters whereas ionized structures are found for $n \geq 3$. The latter are always less stable than the former (except for $n = 5$ where the energies are very close). PM3 predicts a dissociated structure for the non-cyclic $n = 3$ cluster, in contradiction with MP2 results. PM3-MAIS predicts neutral structures for $n \leq 3$ and ionized structures for

Fig. 6 Optimized structures for
HCl–$(H_2O)_{n=1-4}$ complexes
obtained using
MP2/aug-cc-pVTZ
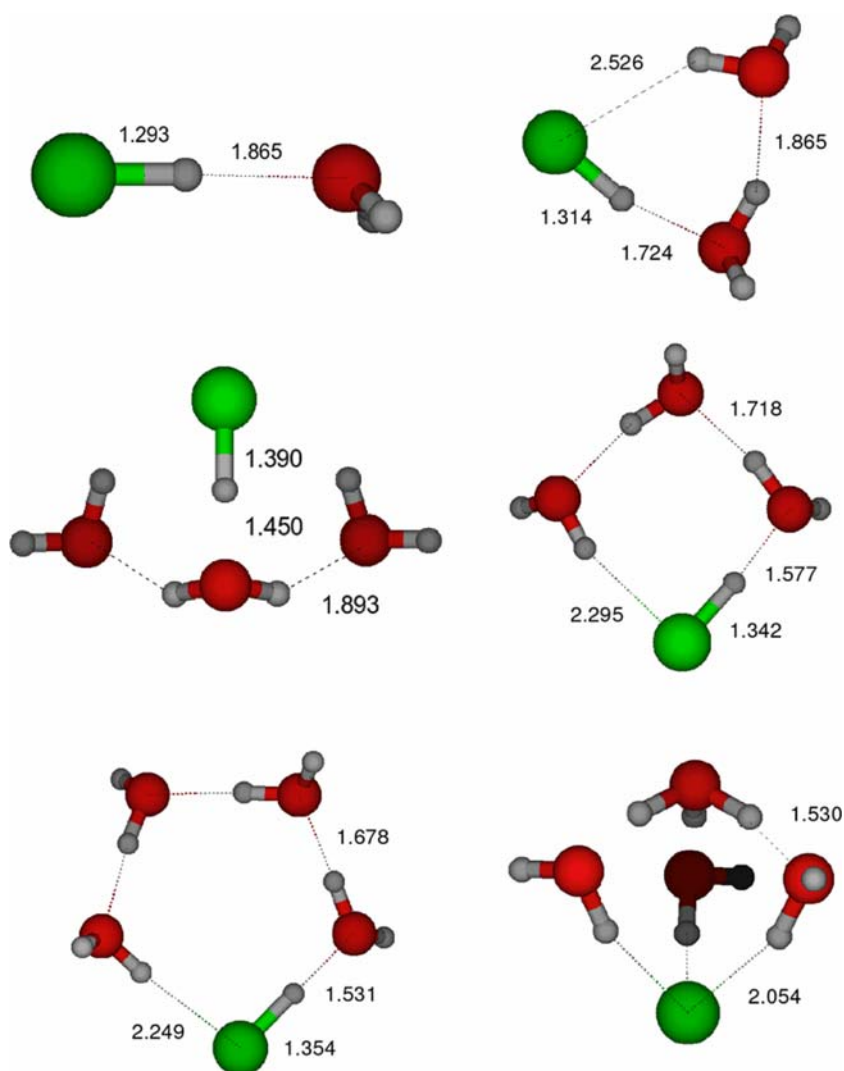
n ≥ 3. Overall, PM3-MAIS stabilization energies are much closer to MP2 than standard PM3. The main fault of the reparameterized method lies on the prediction of $n = 3$ (instead of $n = 4$) for the smallest dissociated cluster.

Standard PM3 results incorrectly suggest that HCl–$(H_2O)_n$ clusters would not be exclusively ionized with increasing values of n. A systematic configurational search of stable clusters with n larger than 6 is not practical due to the increasing number of degrees of freedom. In these cases, a molecular dynamics investigation is very helpful (work in this direction is currently in progress). However, exploratory calculations have allowed us to locate neutral structures for n as large as 10 and in most cases they are more stable than the ionic minima found for the same stochiometry. Thus, the underlying question is whether PM3 is able to predict HCl dissociation in liquid water. To this aim, it is instructive to estimate pK_a values at different computational levels. We do not compute entropy and solvation contributions but rather

we take them from experiment, so that for a given process:

$$AH \rightarrow A + H^+$$

the PM3 free energy in aqueous solution of HCl or H_2O can be simply obtained from the expression:

$$\Delta G_{aq}^{PM3} = \Delta G_{aq}^{exp} - \Delta H_{gas}^{exp} + \Delta H_{gas}^{PM3} \quad (3)$$

where ΔH_{gas} is obtained from the proton affinity of each species. Similar expressions are used for AM1, PM3-MAIS and MP2 methods. The resulting pK_a values:

$$pK_a^{PM3} = \frac{\Delta G_{aq}^{PM3}}{2.303RT} \quad (4)$$

are summarized in Table 5 and they are compared to experimental data. While PM3-MAIS leads to reasonable values of pKa compared to the ab initio or experimental quantities, AM1 and PM3 predict too negative values. Even worse,
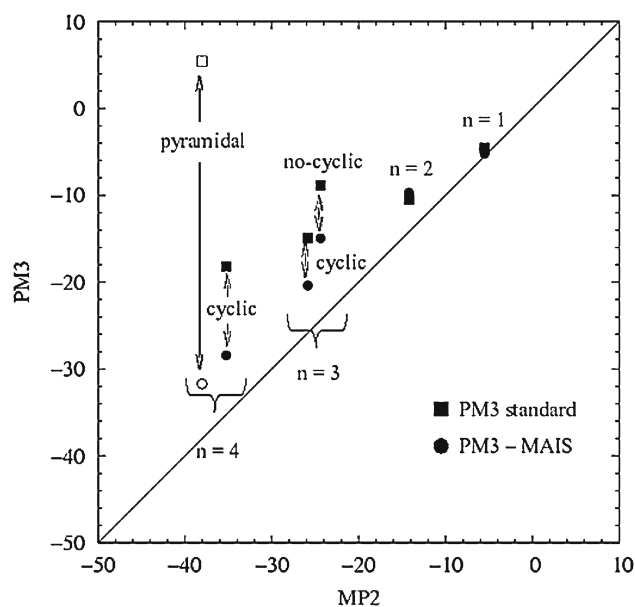
Fig. 7 Comparison of PM3 and PM3-MAIS interaction energies for HCl–(H₂O)$_n$ clusters with MP2/aug-cc-pVTZ (BSSE corrected) values. Symbols are aligned at each corresponding MP2 value. *Open symbols* correspond to ionic structures at the MP2 level

their relative pKa has the wrong sign, which means that HCl should be non-dissociated in aqueous solution.

3.3 Non-additive energy contributions

We have previously reported that non-additive energy contributions are underestimated with semiempirical methods probably due to the use of minimal basis sets [7]. In order to check their role in the present case, we have computed many-body terms within the non-canonical scheme (Eq. 5) where the relaxation energy of the monomers is a zero-order term [44]. Thus,

$$E_{i,j,...,n}^{\text{int}} = \sum V_{ij} + \sum \delta_i + \eta_3 + \cdots + \eta_n \tag{5}$$

where δ_i corresponds to the relaxation energy of the monomers calculated as $\delta_i = E_i - E_0$, and the two body terms as $V_{ij} = E_{ij} - (E_i - E_j)$. Larger contributions, for example the three body non-additivities, are obtained in the usual form as:

$$\eta_3 = E_{ijk}^{\text{int}} - \sum_{ij} V_{ij} - \sum \delta_i \tag{6}$$

In Table 6, we report the three- and four-body non-additive contributions to the total interaction energies of some of the clusters. For comparative purposes we use the MP2 optimized geometries. Note that the difference between standard PM3 and PM3-MAIS approaches lies on the core–core energy, which is a typical additive term. In other words, non-additivity should play an equivalent role in both methods. Thus the discussion below is limited to PM3-MAIS energy computations. Not surprisingly, the main term in the many body expansion comes from the pairwise energy, V_{ij}. PM3-MAIS many-body terms are systematically smaller than MP2 ones. Nonetheless, their relative contribution to the total interaction energy is in reasonable agreement with ab initio data. It is worth mentioning that this agreement is far better than the one obtained for pure water clusters [7]. The reason for this is that, for the HCl–water case, the largest component to the three body non-additive term comes from the interaction of permanent dipoles in the molecules whereas for water–water interaction the higher order terms (dipole–quadrupole and quadrupole–quadrupole) are also important. Thus, the HCl–water case is less sensitive to the induction–dispersion energies, as Milet et al. [29] found using the SAPT expansion. This feature might be of some importance for the study of larger systems and condensed phase phenomena simulation. Besides, it might be interesting to test the recently

Table 4 Interaction energies for optimized structures of HCl − (H₂O)$_n$ clusters (in kcal/mol, calculated using the neutral monomers as reference)

N		MP2		PM3		PM3-MAIS	
		nd	d	nd	d	nd	d
1		−5.51		−5.61		−5.79	
2		−14.21		−12.05		−12.24	
3	Cyclic	−25.86		−19.30			−27.89
	non-cyclic	−24.38			−8.91	−21.66	
4	Cyclic	−35.25		−24.84			−38.87
	non-cyclic		−38.04		−18.28		−38.05
5			−51.34[a]	−29.88	−30.50		−52.42
6			−61.80[a]	−36.35	−35.14		−59.45

[a] From Ref. [39], obtained at the MP2/aug-cc-pVDZ+(2s2p/2s) level

MP2 interaction energies (except for $n = 5$–6, see footnote) were calculated using aug-cc-pVTZ and are BSSE corrected. Non-dissociated (nd) and dissociated (d) clusters are indicated

Fig. 8 Optimized geometries
for HCl–(H2O)$_n$ complexes
a with PM3 and **b** with
PM3-MAIS. All distance values
are in Å
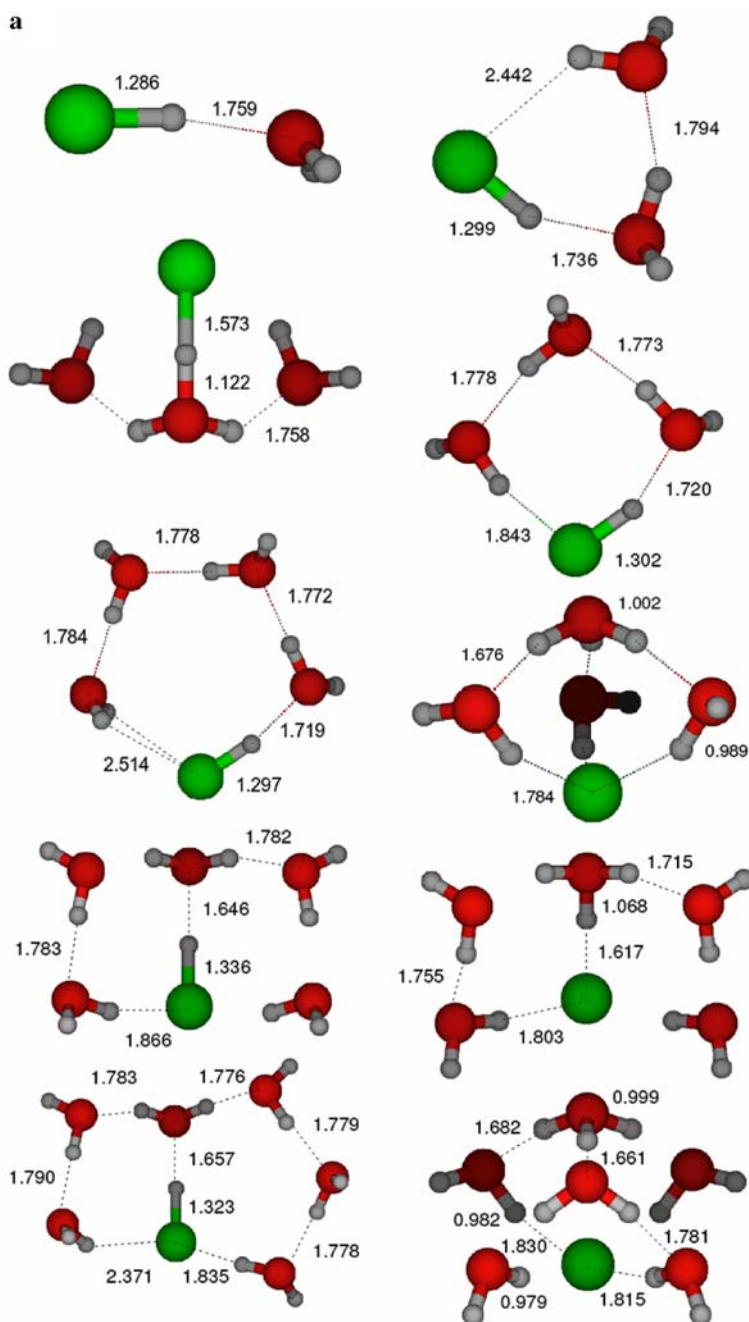
proposed method by Giese and York [45] for treatment of
charge-dependent polarizability in semiempirical quantum
models.

3.4 Frequency analysis

The nature of H-bonded systems can be looked into by means
of spectroscopic analysis where the frequency shift of the
proton donor in hydrogen-bonded complexes reflects the
simultaneous change of several properties upon coordination.

Experimental and computed data for the H–Cl stretching
frequency in $n = 1, 2$ complexes reflect the simultaneous
change of several properties upon coordination.

In Table 7, a summary of experimental and theoretical re-
sults [30,46,47] is made. Standard PM3 predicts a wrong
shift in the $n = 1$ complex and a too low shift for the
$n = 2$ complex. Analysis of the H–Cl force constant shows
that PM3 erroneously predicts an increase of this property
under complexation of HCl with one water molecule. The
PM3-MAIS results provides the right sign in both cases. The

Fig. 8 continued
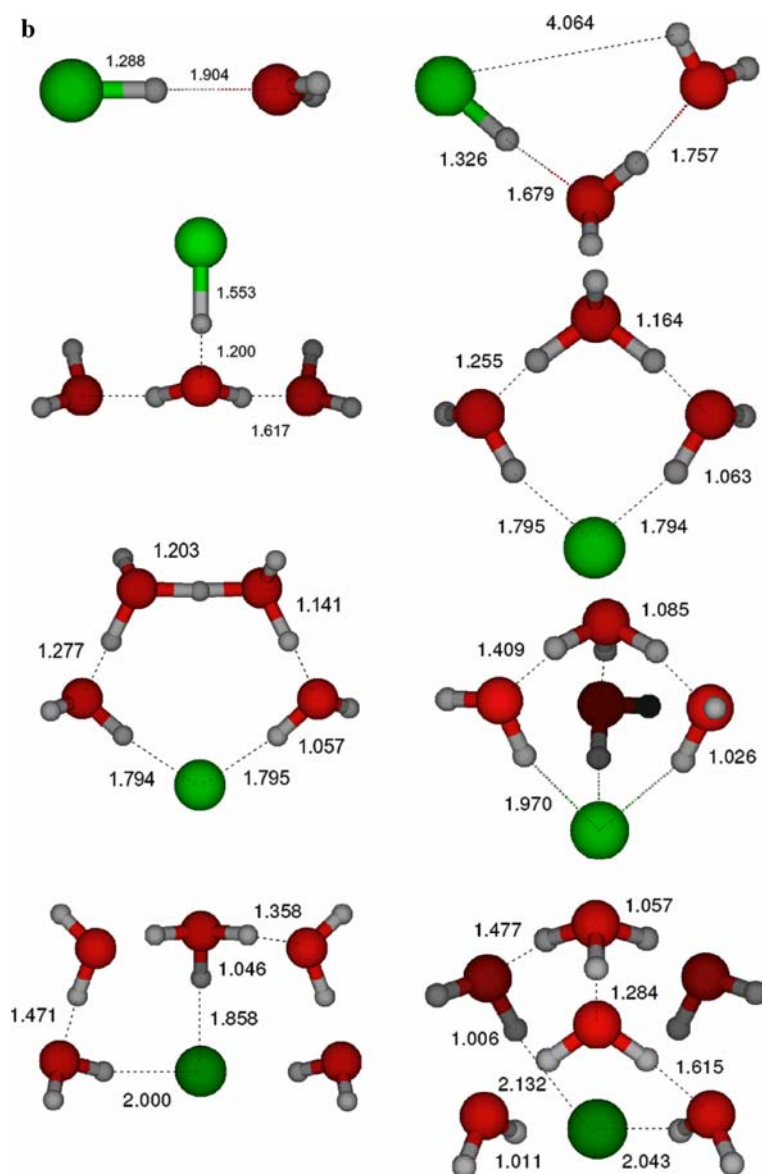
Table 5 Computed absolute and relative pKa values for HCl and H$_3$O$^+$ (ΔpKa = pKa$_{HCl}$ − pKa$_{H_3O^+}$)

	pKa		ΔpKa
	H$_3$O$^+$	HCl	
AM1	−41,7	−30,2	11,5
PM3	−20,5	−14,8	5,7
PM3-MAIS	−3,0	−11,1	−8,1
MP2	0,9	−5,6	−6,6
Exp	−1,70	−7,02	−5,32

shifts are overestimated (in absolute value) if one compares with experimental data but one must stress that ab initio investigations for these systems [30,46] have shown that: (1) anharmonic effects are substantial and (2) accurate computation of H–Cl vibrational frequencies needs to take into account correlation energy beyond MP2. It is therefore preferable to compare PM3-MAIS with non-corrected MP2 values in Table 7. Errors in PM3-MAIS frequencies represent an overestimation of 7% for HCl, 9% for the monohydrated complex and 21% for the dehydrated one. The larger magnitude of the latter is obviously connected with the results presented above for the neutral vs ionized cluster energies. Nonetheless, the tendency in frequency shift at the PM3-MAIS may be considered as satisfying at this approximated theoretical level and this is a very interesting feature in view of elucidating and interpreting the spectra of larger systems of atmospheric importance.

Table 6 Non-additive contributions to the total interaction energy of HCl–(H$_2$O)$_n$ clusters in kcal/mol calculated using MP2 optimized structure

	HCl–(H$_2$O)$_2$		HCl–(H$_2$O)$_3$		HCl–(H$_2$O)$_4^a$	
	Ab initio [b]	PM3-MAIS// MP2	Ab initio [b]	PM3-MAIS // MP2	Ab initio [b]	PM3-MAIS // MP2
$\Sigma\delta_i$	−0.68	0.92	−0.21	2.10	1.24	2.48
ΣV_{ij}	−11.50	−9.18	−18.07	−17.63	−225.51	−210.56
$\Sigma\eta_3$	−2.71 (18%)	−1.44 (15%)	−7.04 (27%)	−4.23 (19%)	20.74 (10%)	12.06 (6%)
$\Sigma\eta_4$			−0.74	−0.62	−1.10	1.21
					0.24	0.03
E_{int}	**−14.89**	**−9.70**	**−26.07**	**−20.38**	**−204.39**	**−194.78**

[a] This cluster corresponds to [H$_3$O$^+$(H$_2$O)$_3$Cl$^-$] and pairwise contributions considered the ionic monomers as reference and $E_{int} = E_{(H_9O_4Cl)} - 3E_{H_2O} - E_{H_3O^+} - E_{Cl^-}$
[b] All terms were calculated at the MP2/aug-cc-pVTZ level with BSSE correction
Numbers in parentheses correspond to the percentual contribution to the total interaction energy

Table 7 H–Cl stretching frequencies in cm^{-1} and absolute shifts upon water coordination

	HCl	HCl–(H$_2$O)		HCl–(H$_2$O)$_2$	
	ν_s	ν_s	$\Delta\nu_s^a$	ν_s	$\Delta\nu_s$
FTIR spectroscopy [47]	2886	2724	−162	2464	−422
PM3	2704	2724	+20	2512	−192
PM3-MAIS	2828	2534	−294	2036	−793
MP2 [b]	3044	2789	−255	2593	−451
MP2 corrected [c]	2995	2703	−202	n. a.	n. a.
MP3 corrected [c]	2886	2728	−158	2467	−418

[a] $\Delta\nu_s = $ HCl$\nu_s - $ HCl–(H$_2$O)$_n$ ν_s
[b] Calculated at the MP2/aug-cc-pVTZ level with BSSE correction with the Cs structure for the dimer
[c] Calculated with the 6-311++G(2d,2p) basis set by Alikhani and Silvi [46] with the C2v structure for the dimer using the mechanical anharmonicity and BSSE corrections

error of the PM3-MAIS approach seems to be the prediction of HCl dissociation in clusters with three water molecules (at least four molecules are required at the MP2 level and experimentally). However, bearing in mind the much larger errors are present in the standard PM3 calculations, PM3-MAIS results can be considered as satisfying. They represent the best improvement of PM3 that can be achieved by reoptimizing core–core functions. Better results will need a reparameterization of electronic terms as well as revision of some basic approximations (for instance the use of minimal basis sets) that limits the accuracy of non-additive effects, which are of crucial importance in both condensed phases and biomolecular systems.

4 Conclusions

In this study, the limitations to describe acid dissociation with customary semiempirical methods, AM1 and PM3, have been clearly established. This is a very serious problem as these methods are widely used to describe biochemical reactions in enzymatic environments where proton transfer processes often play a key role. In the case of a very strong acid such as HCl, dissociation in water is not predicted by AM1 or PM3 since huge errors in the gas-phase proton affinities predicted by these methods lead to the wrong sign of the relative pK_a: H$_3$O$^+$ is predicted to be stronger acid than HCl. The correct prediction of this fundamental property might be achieved either by a different reparameterization of semiempirical models or the implementation of different core–core functions able to reproduce high quality data. PM3-MAIS is an example of this latter option. Indeed, the resulting PM3-MAIS method reproduces the main trends in hydrogen-bonded clusters, namely the interaction energies. The main

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