

The Ability of the Semiempirical PM3 Method to Model Proton Transfer Reactions in Symmetric Hydrogen Bonded Systems

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Abstract

Geometries and energies of small proton-bound symmetric dimers and minimum energy pathways for the proton transfer from one subunit to the other were calculated both at the semiempirical MNDO/PM3 and at *ab initio* HF and post HF levels. Except for systems, in which carbon atoms are involved or oxygen atoms are part of acceptor molecules, PM3 can be used for a good quantitative description of hydrogen bonds near the equilibrium geometry. If the subunits are separated by more than 2.5 Å, attractive forces will be lost quickly. Proton transfer reactions are modeled in a qualitative acceptable manner. If proton transfer occurs between nitrogen acid/base pairs, PM3 barriers of activation are about 5 - 10 kcal/mol higher than *ab initio* results.

Keywords: hydrogen bond, proton transfer reaction, potential energy hypersurface, MO calculation, PM3

Introduction

The proton transfer between hydrogen bonded molecules is one of the simplest chemical reactions. In the last few years, such reactions were extensively studied with high level *ab initio* methods. So the general behavior of a system during formation of hydrogen bonds and proton transfer is well known. But the application of these methods in modeling large systems like biomolecules is still limited by computational resources [1,2]. In general, semiempirical molecular orbital methods are useful in this field. The MNDO methods AM1 and PM3 were used in the past to model complex reaction pathways for the serine protease trypsin [3], carboxypeptidase A [4] or carbonic anhydrase [1,5], where proton transfers are involved in rate limiting processes [6,7]. If we agree with the assumption of Pauling [8], that the main source of enzymatic catalytic power is the stabilization of transition states, then the knowledge of properties of ground and transition states is necessary to discuss every enzymatic

reaction. The ability of the used computational method to reproduce features of these states should be known.

If one wants to find a method to calculate proton transfer reactions, a first look must be taken on the ability of quantum mechanical methods to handle hydrogen bonds, because this reaction is preceded by aggregation of the proton donor with an acceptor molecule by a H-bond. The formation of a hydrogen bond can be described by a partial shift of electron density from the H-bond acceptor to the donor molecule [9], yielding a weak chemical bond between the two monomers. The amount of transferred charge and the strength of the formed bond depend both upon the excess of electron density at the electron donor site and upon the ability of the electron accepting site to consume additional electron density. This description can be reduced to the properties of the donor and acceptor atoms in a first approximation. If the participating molecules are larger, the molecular environment of these atoms is involved in the charge transfer process, too. Beside formation of a weak chemical bond, non bonding interactions play a key role. Electrostatic interactions are responsible for

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the conformation of the whole aggregate. Dispersion forces can not be neglected. If proton transfer takes place, the properties of the subunits change drastically. During a proton transfer reaction the electron density fluxes in the direction opposite to that of the proton movement [10]. The proton acceptor molecule loses electron density, which is transferred via the moving proton to the proton donor site. The interaction between the species at every point of the reaction pathway is different from the starting point of the reaction. So the chosen method for calculating proton transfer reactions must be able to describe hydrogen bonds over a wide range of participating species.

Critical reviews of the modeling of hydrogen bonds by *ab initio* quantum mechanical methods [11] show the usefulness of different levels of theory to reproduce the described effects. The usage of basis sets with diffuse and polarization functions is recommended. Dispersion forces must be modeled by inclusion of effects from correlated electron motion by configuration interaction or the Møller-Plesset treatment [12-15]. Errors of calculated energies become important, if the interaction energies or energy barriers are small. So the thermal correction of the calculated potential energy is unalterable, if one wants to reproduce experimental data of weak hydrogen bonds. By using standard basis sets, corrections due to the basis set superposition error (BSSE) should be made [16,17].

So the question of the ability of semiempirical methods to reproduce the effects described above is not trivial. It is widely accepted, that AM1 and PM3 are able to reproduce experimental heats of formation, geometries or dipole moments of stable molecules [18]. Effects of electron correlation, that must be calculated by extended *ab initio* methods, could be imitated by the method of parametrization. By calculating weak interatomic interactions PM3 results agree better with experimental data than those from AM1. In [19-21] it was shown, that AM1 is not able to reproduce conformations of several asymmetric hydrogen-

bonded aggregates, obtained with less restricted methods. So PM3 should be the current semiempirical method of choice for modeling hydrogen bonded molecules and proton transfer reactions.

In this work we present some tests of the usefulness of PM3 for those reactions. In order to test a given computational method, two ways are possible. First, a large amount of systems could be studied. The results can be evaluated by statistical methods. The second way includes the selection of representative systems, which are studied in detail. To obtain generalizable statements, the methodical sources of a computed behavior must be detected. In this work we do the second. We compare results from semiempirical and *ab initio* calculations on small symmetric hydrogen bonded systems. They are formed by aggregation of two equal anions or neutral molecules over a bridging proton. Compared with usual hydrogen bonds the interaction in such systems is very strong. Here errors of different levels of theory are more visible than in weakly interacting systems. The second advantage of sym-

metric models is the existence of symmetric double-well potential energy surfaces of proton transfer, whereas asymmetric neutral systems often show barrierless proton transfers, if the subunits are near their equilibrium distances. Within our models barriers of activation can be compared over a wide range of conformations, including the minimum energy pathway. The results obtained with different methods will be interpreted in terms of the parametrization of semiempirical methods and of the appropriate level of *ab initio* methods used for comparison.

Models and Methods

Semiempirical calculations are done with the program MOPAC-6 [22] and the PM3 hamiltonian [23]. The geometry optimizing routines BFGS and EF (eigenvector following) were used. *Ab initio* calculations are performed with HONDO-8.4 [24], using the 6-31G* and 6-31+G* basis sets [25] at the RHF and MP2 levels. In correlation calculations, all electrons were included. Geometry optimizations were done with a gradient minimizing routine based upon the Newton-Raphson method. Force constant calculations use analytical second derivatives (RHF) or central differences

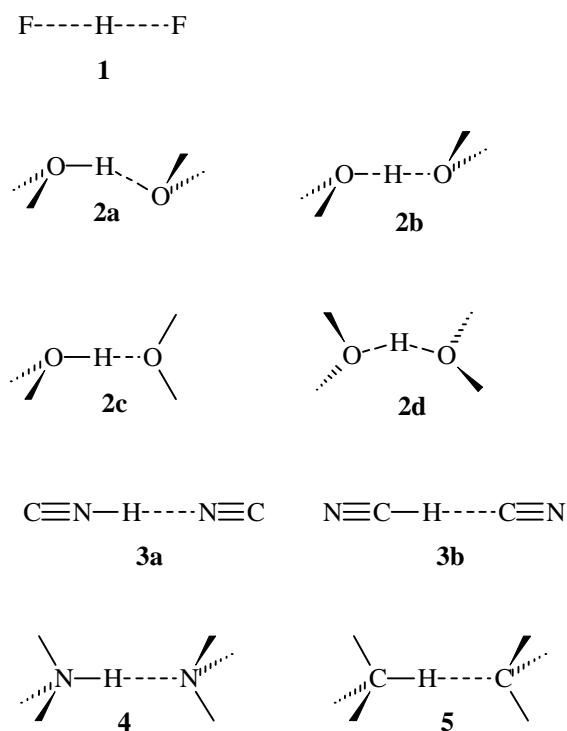


Figure 1: Schematic conformations of the described aggregates. Dotted lines represent a hydrogen bond. Structures 2a and 2b are the result of PM3. *Ab initio* RHF methods yield structure 2c, MP2 calculations indicate 2d.

of analytical gradients (PM3, MP2). Transition states were optimized by following the eigenvector corresponding to the largest negative eigenvalue of the hessian, starting at appropriate geometries. All calculations are done on IBM RS/6000 workstations. For computer graphics and the initial building of the molecular models we used SYBYL-6.01 [26].

The systems under study are summarized in figure 1. Geometry optimizations of the monomers were done with applied symmetries; they were completed after reaching a gradient norm of 0.01 kcal/(mol Å) with PM3 and 0.00005 Hartree/Å with *ab initio* methods.

The proton affinity of a compound is defined as the negative standard reaction enthalpy of protonation. Proton affinities of the monomers were calculated from PM3 heats of formation, including a calculated $\Delta_f H$ of 353.6 kcal/mol for one proton. *Ab initio* proton affinities result from standard enthalpies at 298.15 K:

$$PA_{A^-}^{PM3} = \Delta_f H_{A^-} + \Delta_f H_{H^+} - \Delta_f H_{AH} \quad (1a)$$

$$PA_{A^-}^{ab\ initio} = H_{A^-} + H_{H^+} - H_{AH} \quad (1b)$$

The thermal correction of the energy of a compound A uses translational, rotational and vibrational contributions at standard temperature [27]:

$$H_A = E_A + E_{A, tr} + E_{A, rot} + E_{A, vib} + RT \quad (2)$$

Hydrogen bonded aggregates were constructed with SYBYL, using an initial hydrogen bond angle of 180 degrees and an acceptor-hydrogen distance of 1.8 Å. The geometry optimizations are done as described above. Appropriate symmetry point groups were used when possible. The found equilibrium structures were characterized as true minima by force constant calculations. Energies of as-

sociation of the free monomers A and B which approach each other to the complex AB consist of the energy required for the deformation of the monomers and of the interaction energy between A and B in the complex. Enthalpies of association were calculated using differences of standard heats of formation in the case of PM3:

$$\Delta_{ass} H^{PM3} = \Delta_f H_{AB} (R) - \Delta_f H_A (\infty) - \Delta_f H_B (\infty) \quad (3a)$$

Association enthalpies were obtained from *ab initio* calculations using the following scheme:

$$\Delta_{ass} H^{ab\ initio} = \Delta_{int} H + \Delta_{def} H$$

$$\Delta_{int} H = E_{AB}^{(AB)} (R) - E_A^{(AB)} (R) - E_B^{(AB)} (R) + \delta H_{AB} (R) - \delta H_A (R) - \delta H_B (R)$$

$$\Delta_{def} H = E_A^{(A)} (R) - E_A^{(A)} (\infty) + E_B^{(B)} (R) - E_B^{(B)} (\infty) + \delta H_A (R) - \delta H_A (\infty) + \delta H_B (R) - \delta H_B (\infty)$$

where (R) symbolizes the optimized geometry of the complex AB and () stands for the optimized geometry of the compounds at infinite distance. $E_{AB}^{(AB)} (R)$, $E_A^{(AB)} (R)$ and $E_B^{(AB)} (R)$ are the energies of the dimer AB or the monomers A and B at the geometry of the complex in the basis set of the dimer, respectively. The differences between these energies is the error free interaction energy. δH_A is the thermal correction to the energy of a compound A at a particular geometry. Thus, the final equation for corrected association enthalpies from *ab initio* calculations is

$$\Delta_{ass} H^{ab\ initio} = H_{AB}^{(AB)} (R) - H_A^{(A)} (\infty) - H_B^{(B)} (\infty) - \Delta E_{CC} \quad (3b)$$

$$\Delta E_{CC} = E_A^{(AB)} (R) - E_A^{(A)} (R) + E_B^{(AB)} (R) - E_B^{(B)} (R)$$

	PM3[a]	RHF[b]	MP2[b]	exp.
CH ₃ ⁻ / CH ₄	418.1	424.6 (447.2)	417.8 (448.8)	416.6[c]
OH ⁻ / H ₂ O	389.5	394.9 (421.4)	383.1 (421.9)	390.8[c]
F ⁻ / HF	385.1	368.9 (404.1)	358.7 (406.5)	371.3[c]
CN ⁻ / HCN	348.3	347.3 (363.4)	346.8 (368.3)	349.3[c]
CN ⁻ / HNC	324.7	336.6 (351.3)	327.6 (347.3)	
NH ₃ / NH ₄ ⁺	197.1	205.7 (208.6)	204.0 (209.1)	205.0[d]
H ₂ O / H ₃ O ⁺	141.1	164.0 (167.6)	161.3 (167.9)	173.0[d]

Table 1.
Proton affinities in kcal/mol.

[a] Using a calculated $\Delta_f H = 353.6$ kcal/mol for H⁺;
[b] 6-31+G*, 6-31G* basis set values in parantheses;
[c] see ref. [41];
[d] see ref. [42].

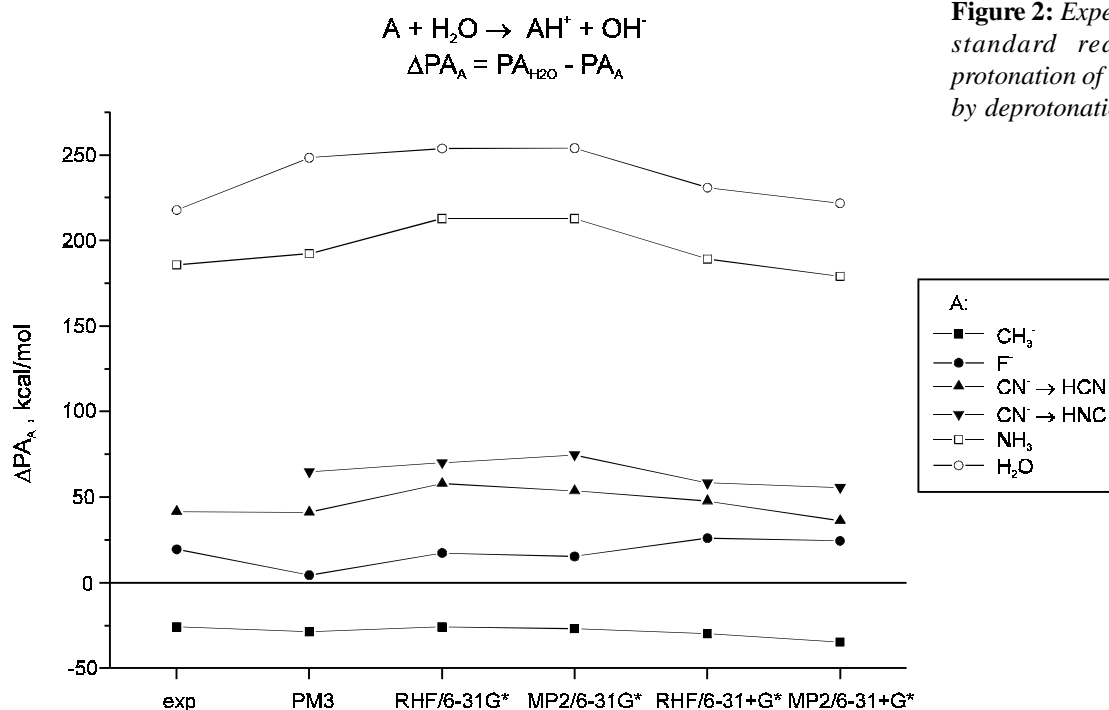


Figure 2: Experimental and calculated standard reaction enthalpies of protonation of the described monomers by deprotonation of water.

The energy difference given by the last formula is the BSSE of the uncorrected interaction energy of the distorted monomers, calculated by the counterpoise procedure [28].

Adiabatic proton transfer reactions were modeled by freezing the donor and acceptor atoms at selected distances and varying the acceptor-hydrogen distance. All other internal coordinates were fully optimized at each step. The molecular symmetry was turned off. PM3 calculations were terminated after reaching a gradient norm of 0.01 kcal/(mol Å), *ab initio* calculations terminated after a gradient norm of 0.0005 Hartree/Å. Equilibrium and transition configurations were optimized onto a gradient norm of 0.00005 Hartree/Å. Energies of activation from *ab initio* calculations were corrected for BSSE, treating the transition state in the same partitioning scheme like the optimized starting point of the reaction:

$$\Delta H^{\neq, PM3} = \Delta_f H_{TS} - \Delta_f H_{AB} \quad (4a)$$

$$\Delta E^{\neq, ab\ initio} = E_{TS} - E_{AB} - \delta E_{CC, TS} + \delta E_{CC, AB} \quad (4b)$$

Results and Discussion

Proton affinities

Proton affinities can be used as a first raw estimation of the behavior of an asymmetric system prior to proton transfer. The calculated enthalpies for protonation of the species considered are shown in table 1. Because protonation of a molecule is always coupled with deprotonation of another, proton affinities relative to a reference system are shown in figure 2.

They represent the reaction enthalpy of proton transfer from the reference molecule (usually water) to an acceptor molecule without contributions of a hydrogen bond. Errors in this property influence errors of barriers of activation, assuming a dependency like the Hammond-Postulate. The values agree well with many previous published results and are useful to determine the necessary level of theory.

As widely accepted, PM3 is able to calculate such thermodynamic properties. Relative proton affinities compared with water as donor show a difference of 2 to 11 kcal/mol from experimental values. If asymmetric proton transfer occurs and if hydrogen bond energies are neglected, then the reaction would be more endothermic than expected. This error is due to the error in the heat of formation of the hydroxyl ion (exp.: -33.2 kcal/mol, PM3: -17.5 kcal/mol). It should be marked here, that this error influences the study of other phenomena, where hydroxyl ions are part of a reacting system (e. g. nucleophilic substitutions on carbonyl compounds).

Ab initio results show a somewhat larger deviation from experimental results. Inclusion of diffuse functions at heavy atoms improve *ab initio* results drastically, if anions are studied. In [14,21,29] it was assumed, that additional p and sp functions at hydrogens yield no further improvement. The majority of proton transfers takes place with water as donor. Here a hydroxyl ion will be formed. The proton affinity of the hydroxyl ion calculated with MP2/6-31+G* is somewhat too low. This effect is not surprising, because this basis set is fitted on RHF energies. Thermodynamic corrections of the total energy at 0 K reach magnitudes of 10 kcal/mol. They are not negligible and have to be taken into account, if one wants to reproduce experimental reaction enthalpies.

Table 2. Hydrogen bond geometries and energies.[a]

	PM3	RHF[b]		MP2[b]	
(F – H – F) ⁻	D _{∞h}	D _{∞h}		D _{∞h}	
F ... F	2.207	2.268	(2.253)	2.328	(2.298)
F ... H	1.1035	1.134	(1.1265)	1.164	(1.149)
Δ _{ass} H	-37.76	-43.68	(-49.60)	-44.17	(-51.06)
(H ₂ OH – OH ₂) ⁺	C ₁	C _s		C ₂	
O ... O	2.563	2.482	(2.456)	2.418	(2.415)
O ... H	1.661	1.444	(1.405)	1.211	(1.210)
∠ O ... H ... O	146.7	180.0	(180.0)	173.0	(173.0)
Δ _{ass} H	-23.77	-28.4	(-31.35)	-32.11	(-35.81)
(CNH – NC) ⁻	C _{∞v}	C _{∞v}		C _{∞v}	
N ... N	2.703	2.758	(2.717)	2.673	(2.615)
N ... H	1.662	1.718	(1.668)	1.586	(1.492)
Δ _{ass} H	-25.86	-23.38	(-26.20)	-27.06	(-31.45)
(H ₃ NH – NH ₃) ⁺	C _{3v}	C _{3v}		C _{3v}	
N ... N	2.769	2.845	(2.815)	2.770	(2.730)
N ... H	1.721	1.791	(1.755)	1.672	(1.615)
Δ _{ass} H	-17.30	-21.00	(-23.89)	-23.74	(-28.30)
(NCH – CN) ⁻	D _{∞h}	C _{∞v}		C _{∞v}	
C ... C	2.707	3.201	(3.100)	3.132	(3.006)
C ... H	1.3535	2.109	(1.998)	2.018	(1.870)
Δ _{ass} H	-38.42	-17.73	(-19.82)	-18.10	(-20.81)
(H ₃ CH – CH ₃) ⁻	C _{3v}	C _{3v}		C _{3v}	
C ... C	2.786	4.359	(3.702)	3.923	(3.491)
C ... H	1.483	3.274	(2.608)	2.825	(2.375)
Δ _{ass} H	-20.71	-0.57	(-1.79)	-0.42	(-2.52)

[a] Distances in Å, angles in degrees, association enthalpies in kcal/mol. [b] 6-31+G*, 6-31G* basis set values in parantheses.

Association enthalpies, hydrogen bond geometries

Geometries and association enthalpies are compared in table 2. They reflect the electrostatic nature of interaction within the used systems. The conformations are influenced by magnitude and direction of dipole moments, chemical bonding and additional interatomic forces. Results from all methods are comparable, except for systems (2), (3b) and (5).

Comparing association enthalpies, qualitative tendencies are reproduced by PM3 very well. The interaction rises, as well as the electron affinity of the donor site rises. Except systems (3b) and (5) the H-bond energy calculated with PM3 is weaker than uncorrected *ab initio* results.

In order to discuss the usefulness of corrections, the associated values are presented in table 3. Thermodynamic adaptation of the potential energies of the monomers and the dimer yields a reduction of the association energy by about 1 - 2 kcal/mol. That is negligible, if the interaction is in the range of a few tenth kcal/mol. If we come into the region of usual hydrogen bonds, this correction reaches about 25 to 50 % of the association enthalpy. The correctness of thermodynamic corrections depends on the accuracy of calculated vibrational frequencies. Intermolecular vibrational frequencies are found to be very sensitive to the quality of basis set [30]. They depend on the validity of the harmonic oscillator approximation, on the method used to calculate the Hessian matrices, and on the deviation of the assumed equilibrium geometry from a true minimum, too. So it should be appropriate to assign a methodical error of 2 kcal/mol to *ab initio* association energies. Corrections due to BSSE represent the usefulness of the cho-

sen basis. If one is able to use specially adapted basis sets, this error should become negligible [15]. But in most cases this procedure is not practicable, so the BSSE should be taken into account. If the molecular system contains negative ions, basis sets without diffuse functions produce BSSE of several kcal/mol. By using the 6-31+G* basis, this error becomes quite small. Interestingly, this basis set seems to produce poorer results than the 6-31G* basis by calculating systems without excess of electrons. The aggregates (2) and (4) are better described without diffuse functions. After implementation of electron correlation at the MP2 level, the BSSE calculated by the counterpoise method reaches magnitudes of about 1 - 4 kcal/mol. It should be marked here, that neither the correctness of the counterpoise procedure nor its usefulness for the evaluation of error-free energies is out of discussion [31]. Taking all these statements into account, association enthalpies calculated with PM3 are in good agreement with high level *ab initio* results. The PM3 results can be used to predict the general behavior of aggregates over a wide range of participating monomers, except for systems like (2), (3b) or (5). If we are able to explain, why these systems are mishandled, then our results could be generalized.

First let us resume general effects of the parametrization of PM3. The earlier NDDO methods were not able to model weak interatomic forces. Within AM1 and PM3 this became possible. There the MNDO core-core repulsion term was modified by introducing some spherical Gaussian functions [32]. This variant of parametrization leads to additional „van der Waals-like“ forces at distances outside the van der Waals

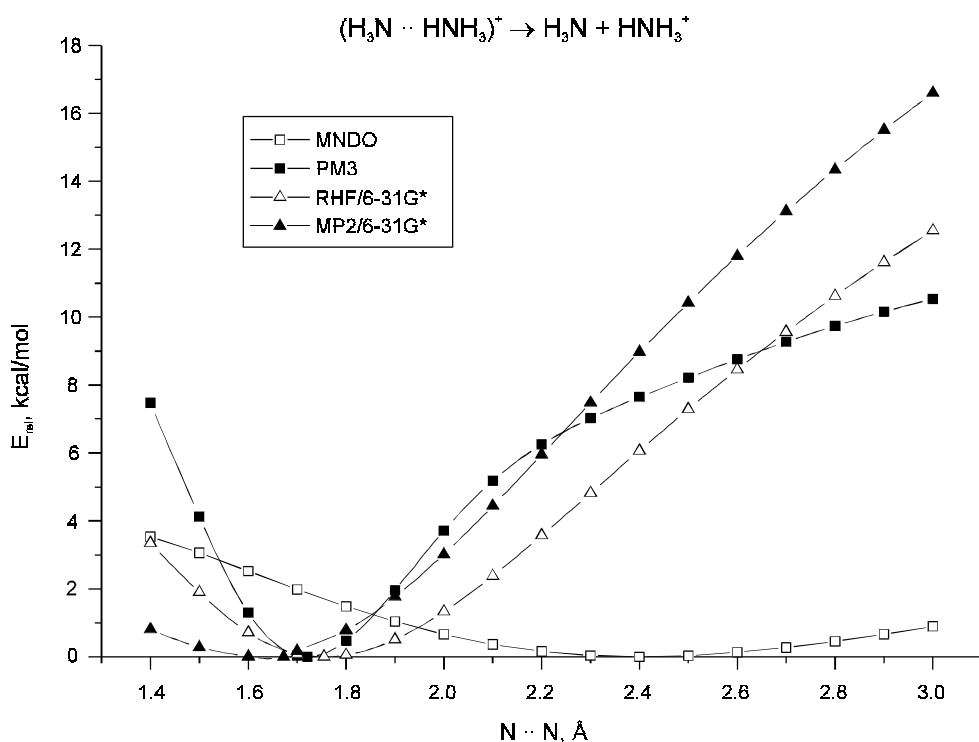


Figure 3: Potential energy curves for dissociation of aggregate (4) by fixing the C_{3v} symmetry.

Table 3. Corrections to *ab initio* association energies in kcal/mol.[a]

	RHF[b]		MP2[b]	
	δH	δE_{cc}	δH	δE_{cc}
(F – H – F) ⁻	-1.23 (-0.80)	0.65 (9.38)	-0.79 (-0.38)	2.21 (13.96)
(H ₂ OH – OH ₂) ⁺	0.73 (0.47)	1.71 (1.06)	-0.58 (-0.43)	3.58 (3.04)
(CNH – NC) ⁻	1.23 (1.09)	0.67 (2.19)	0.84 (0.18)	2.35 (4.82)
(H ₃ NH – NH ₃) ⁺	1.56 (1.50)	1.39 (0.89)	1.04 (0.87)	3.07 (2.13)
(NCH – CN) ⁻	1.17 (1.41)	0.40 (3.92)	1.16 (1.49)	1.16 (6.31)
(H ₃ CH – CH ₃) ⁻	0.48 (1.27)	0.24 (4.13)	0.35 (1.08)	1.33 (6.42)

[a] see eq. 3b;

[b] 6-31+G*, 6-31G* basis set values in parantheses.

radii; so dispersion forces can be simulated. As an example, the dissociation of system (4) into its components is shown in figure 3. Like assumed, *ab initio* MP2 calculations yield a stronger attraction and a shorter hydrogen bond than the RHF method. In comparison with simple MNDO, the PM3 curve shows an additional attractive force, if the components are in the range of a hydrogen bond. But if they are drawn apart, this force will decrease quickly.

Within AM1, not the whole parameter set was included in the overall optimization [32]. This was done during the development of PM3. In addition, two Gaussians per atom were used for the core-core term [23], whereas AM1 defines between two and four. The resulting improvement by calculating asymmetric hydrogen-bonded systems was shown in [19-21]. These tests suggested, that AM1 is the first method based on the NDDO approximation, that is able to simulate weak attractive intermolecular forces at all. But only PM3 has been shown to predict geometries of selected weak interacting complexes which are comparable with calculated *ab initio* structures. The published tests should be generalizable. That's why we do not present AM1 calculations here. On the other hand, an optimization procedure which adjusts the whole parameter set by minimizing the square of the difference between calculated and experimental data can undermine the theoretical framework of a semiempirical method. So the unusual results from PM3 calculations on systems (2), (3b) and (5), and tendencial differences between results from PM3 and *ab initio* calculations on the other systems, have to be explained both by approximations made in the theoretical background and by effects from the optimization of parameters.

System (2) is the only example presented with two lone pairs at the acceptor site. Like all ZDO methods, PM3 can not reproduce lone pairs. They simply produce a region of negative electrostatic potential. This situation is irrelevant, if acceptor atoms involved in hydrogen bonds contain only one accessible lone pair and if they are surrounded by a near symmetric environment. The best example is ammonia in system (4). In these cases the overall conformations are reproduced very well by all methods. All these models bear a linear hydrogen bond. Systems (4) [33-35] and (5) show C_{3v} symmetry, systems (1) [17] and (3) are linear. In the case of oxygen, interactions with lone pairs could be mishandled. System (2) can be used as an example. Within PM3 two possible geometries are found for the proton bridged water dimer. Normal mode analyses indicate both conformations as true minima. The properties of the global minimum conformation (see schematic structure 2a in figure 1) are presented in table 2. The formed hydrogen bond angle is far away from being linear. Here the conformation is simply determined by the direction of the water dipole, which points to the center of positive charge of the hydronium ion. The schematic drawing seems to present a C_s symmetry for this structure, but a system with this point group is indicated as a saddle point from force constant calculations. The unrestricted geometry optimization started at the symmetric structure converges to a geometry with C₁ symmetry, which has no imaginary vibrations. No other geometry with lower energy than this structure was found by scanning the potential energy hypersurface, varying several internal coordinates. The second minimum of system (2) (see structure 2b in figure 1, and point M2 in figure 4) has C_{2h} symmetry.

Table 4. Global barriers of proton transfer.[a]

	PM3	RHF[b]	MP2[b]
(F – H – F) ⁻	0.00	0.00	0.00
(H ₂ OH – OH ₂) ⁺	0.00 [c]	0.50	0.00
(CNH – NC) ⁻	7.11	4.33 (3.57)	1.72 (1.14)
(H ₃ NH – NH ₃) ⁺	9.53	5.06 (4.53)	2.30 (2.04)
(NCH – CN) ⁻	0.00	9.94 (8.84)	6.55 (5.23)
(H ₃ CH – CH ₃) ⁻	0.05	23.22 (16.78)	18.33 (12.56)

[a] Values in kcal/mol;
 [b] 6-31+G*, 6-31G* basis set values in parantheses. Values corrected for BSSE;
 [c] See text for discussion.

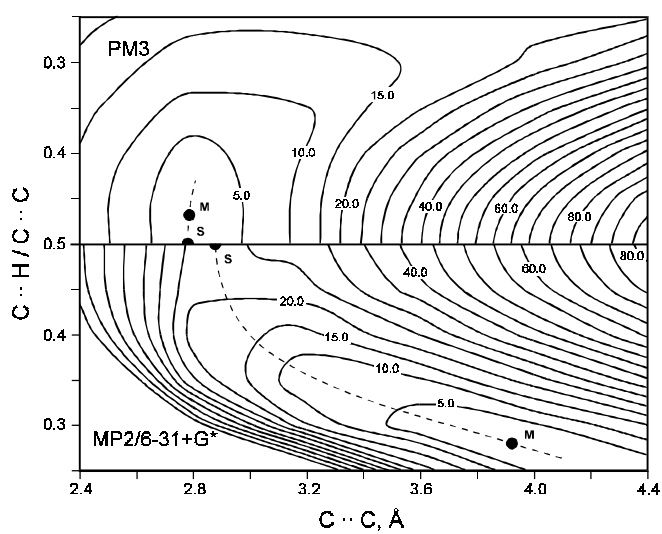
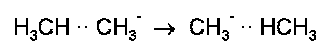
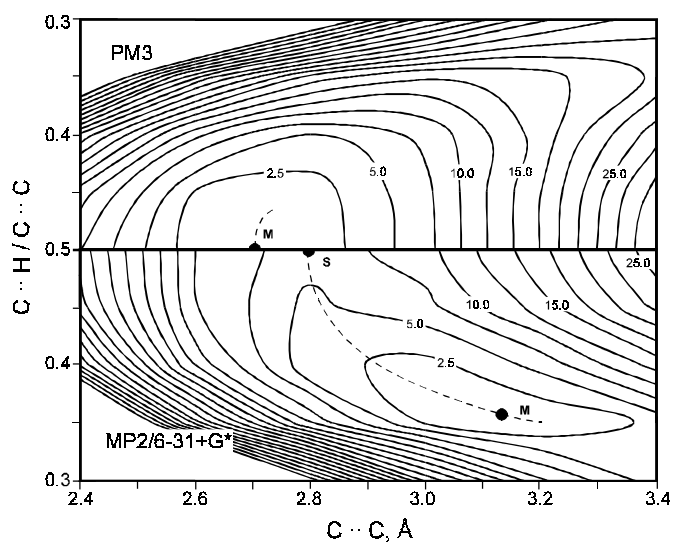
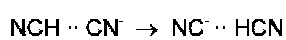
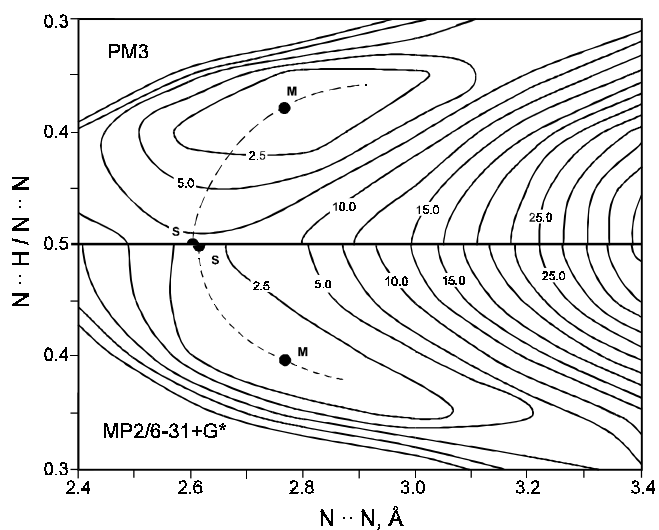
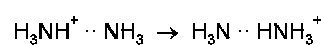
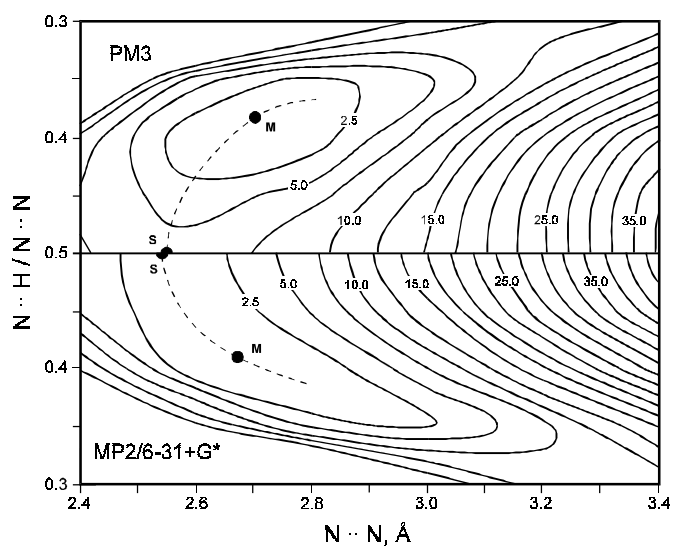
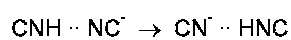
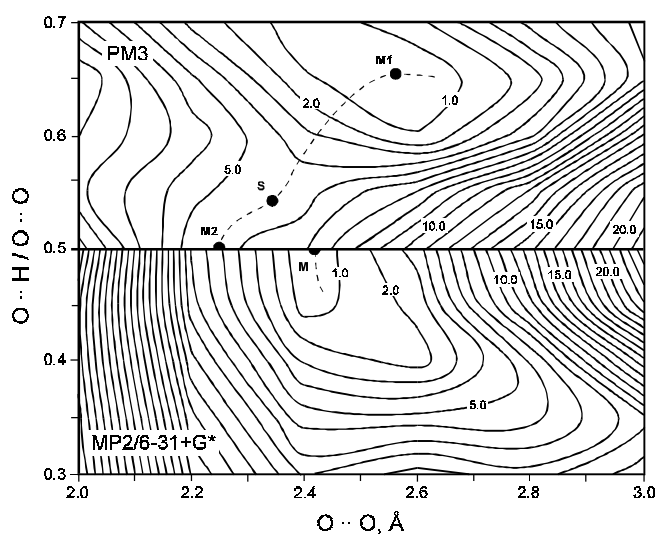
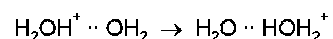
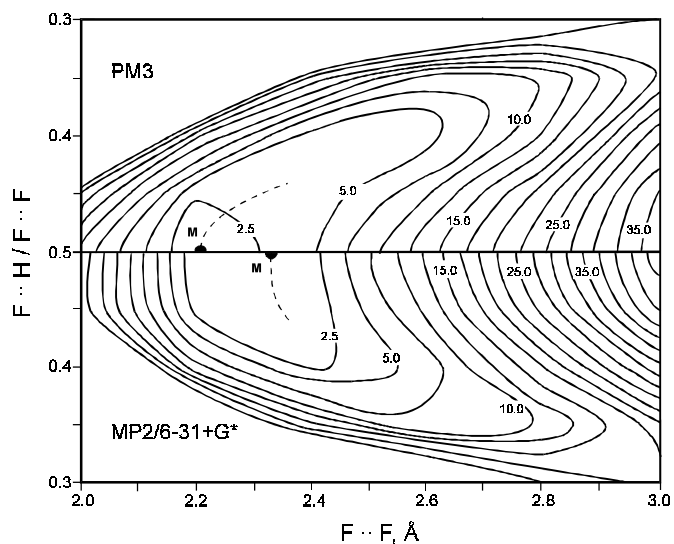
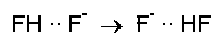
Ab initio methods of course take lone pairs into account. SCF calculations on system (2) yield a C_s conformation with one water molecule in the symmetry plane [33,34,36] (see structure **2c** in figure 1). No oxygen lone pair of the water molecule points directly to the bridging proton. After inclusion of electron correlation this situation is altered. Here one oxygen lone pair of the water molecule interacts with the H-bonding proton (see structure **2d** of figure 1). The resulting conformation has C₂ symmetry; the two fold axis includes the bridging proton and the midpoint of the O-O line. These results indicate difficulties of all used levels of theory to handle such systems. The PM3 result gives only an estimation of the magnitude of the interaction energy. A discussion of reasons for the unusual topologies of the potential energy hypersurfaces would expand this work. The cartesian coordinates of the found equilibrium structures of system (2) and results of force constant calculations are given as supplementary material.

The second error of PM3 seems to be related to hydrogen bond lengths and association energies. From the study of asymmetric uncharged hydrogen bonded aggregates [20] it is assumed, that PM3 in general produces hydrogen bonds that are about 0.2 Å shorter than *ab initio* values. Our results suggest, that this statement depends on the level of theory of the *ab initio* method used for comparison. Except for systems (1), (3b) and (5) with highly charged acceptor atoms the PM3 geometries are rather comparable with the MP2/6-31+G* results than with other. The PM3 variant of the simulation of effects from electron correlation works very well, if the system contains no excess of electrons. But in the case of the chemically unusual system (5) PM3 produces a close interaction between two proton bridged methyl anions, while *ab initio* methods separate methane and the methyl anion. The distance increases by introducing diffuse functions. The *ab initio* result is more reasonable, since saturated carbon atoms cannot accept additional electron density induced by a hydrogen bond, if they are not surrounded by an electron accepting environment. Within PM3 this seems to be possible. An example, which presents a possible electron donating or accepting back-

ground, is given by the symmetric complex between cyanic acid and a cyanide ion. All methods indicate a linear equilibrium structure with a genuine hydrogen bond. But PM3 calculations yield a strong interaction and a geometry with D_{∞h} symmetry. *Ab initio* methods separate the two monomers and produce a weak hydrogen bond.

Since the interaction between monomers of a hydrogen bonded aggregate is closely related to a transfer of electron density, the source of errors of PM3 could be found in the parameters used for the one-electron one-center integrals for the donor and acceptor atoms. Within CNDO/2 and later methods these integrals are defined as average of the ionization potential and the electron affinity of an atomic orbital. The derived parameters U_{ss} and U_{pp} were taken from experimental data for MINDO/3 and earlier methods, within MNDO methods they were optimized [23,37]. A close look on published parameters indicates a continuous decrease of the amount of these values during the history of CNDO methods. In addition, the U_{ss} parameters of second row elements used in PM3 have an unusual discontinuity. All published tests of PM3 show significant improvements in reproducing

Figure 4 (next page): Two dimensional slices through potential energy hypersurfaces of proton transfer. The vertical axes measure the distance between the transferred proton relative to the donor-acceptor atom distances. The latter is measured on the horizontal axes. Since the surfaces are always symmetric, only one half is shown. Surfaces on the upper parts were calculated with PM3, the lower parts show results from the highest level of theory used. Grid points located on the horizontal line signed with 0.5 indicate transition states at fixed acceptor-donor distances. Points signed with **M** represent equilibrium structures, those signed with **S** are saddle points of first order. All values are in kcal/mol relative to the grid point with the lowest energy. *Ab initio* results are presented uncorrected, so activation barriers shown in table 4 differ from those taken from these surfaces.



experimental ground state properties of single molecules as a result of the addition of new parameters and the full parametrization [18,37]. So the Parametric Method yields a better description of molecules in general, but some parameters become underestimated. Some of them are essential in calculating systems like presented in this work. The small values of the U_{ss} and U_{pp} parameters make atomic orbitals able to accept or loose electron density. Other well known defects related to this error are the low electronegativity of nitrogen in PM3 and the lack of a rotational barrier of peptide bonds. From [38] it is assumed, that an improvement both of the theoretical framework of MNDO and of the adjustment of parameters might reduce the described errors. The PM3 results reported in this paper can be generalized to aggregates containing negative ions. If a „hydrogen bond“ is possible between methane and a methyl anion, then a close interaction between methyl groups and other anions should be calculated, too. The importance of this error depends on the problem to solve with PM3. If one wants to calculate the transition state for the nucleophilic attack of a hydroxyl ion on methyl acetate with full geometry optimization, this experiment would fail because of an unusual interaction between the methyl groups on both sides of the reaction centre with the nucleophile. If one calculates the same reaction with beta-lactam like structures, this error is negligible.

Proton transfer reactions

Slices through the potential hypersurfaces of proton transfers are shown in figure 4. Selected numerical values are presented in table 4. The transfer of a bridging proton between two equal subunits should produce double well shaped symmetric surfaces of the potential energy. If the equilibrium geometry contains the bridging proton in the middle between two equal heavy atoms, proton transfer occurs only at larger donor acceptor distances. If the hydrogen bond is stretched, the energy barrier rises [39]. The height of the barrier of proton transfer depends upon the strength of the initial and final hydrogen bond [40]. The minimum energy pathways include attraction of the subunits, until the transition state is reached. All methods indicate this well known behavior. The only example with different characterization is system (2), calculated with PM3. The schematic reaction path shown in figure 4 is not the path of proton transfer, it results from the change of the OHO angle by going from M1 with near C_s symmetry to M2 with C_{2h} symmetry.

Making the comparison of the behavior of well characterized systems more quantitative, methodical differences can be seen. Barriers of activation along the minimum energy pathway produced with PM3 are higher than any *ab initio* result. In the presented aggregates, only nitrogen acid - base pairs show this effect. The other systems have no global barrier of activation like (1) or show different conformations like (2), (3b) and (5). Inclusion of diffuse functions yields increased, MP2 lower barriers. Correction due to BSSE always raise the barrier by about 0.5 - 3 kcal/mol. That means, the

description of the binding region becomes poorer in the transition state than in the equilibrium geometry by using standard basis sets. When the subunits are divided, the barriers follow the dependence of the total energy on acceptor - donor distances, as shown in figure 3. The explanation of this effect was given above. The calculation of barriers of activation that are too high is a well known behavior of all methods based on the HF-level. Standard methods of quantum chemistry use stable molecules to fit basis set exponents or semiempirical parameters. By applying standard methods on transition states, errors of the HF-energy are still visible.

Summary

Our results show the usefulness and the errors of PM3 by investigating proton transfer reactions, and the level of *ab initio* calculations necessary for comparison. The general characteristics of hydrogen bonded aggregates and proton transfer reactions are reproduced by this method in a qualitative acceptable manner. In the case of negatively charged hydrogen bond acceptor molecules aggregated with unusual hydrogen bond donor molecules like C-H acids, a high amount of charge transfer will be calculated, yielding unusual close interactions and small barriers of proton transfer. Conformations of hydrogen bonded aggregates could be mishandled, if oxygen lonepairs are responsible to the geometry. Within most biological systems nitrogen containing residues like histidine sidechains act as proton acceptors. Except large barriers of activation, proton transfers in such systems are described very well. So results from PM3 calculations must be handled with care and with respect to the questions to answer with the aid of a quantum mechanical experiment.

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