Articles

Ab Initio and Molecular Mechanics (MM3) Calculations of Protonated–Neutral Diamine Hydrogen Bonds

Jennifer B. Sorensen,[†] Anita H. Lewin,[‡] and J. Phillip Bowen*,[†]

The Computational Center for Molecular Structure and Design, Department of Chemistry, University of Georgia, Athens, Georgia 30602, and Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina 27709

bowen@ccmsd.chem.uga.edu

Received April 20, 2000

Ab initio calculations of cation–neutral diamine complexes have been carried out at the MP2/6-311+G** level. The geometry and energetics of the charge-reinforced hydrogen bond are analyzed with respect to the alkyl substitution of both the protonated and neutral nitrogen atoms, and these results have been used to improve the quality of the MM3(2000) force field. In addition, specialized hydrogen bond parameters optimized for MM3(2000) are presented. These parameters allow very accurate gas-phase modeling of the charge–neutral diamine environment. Molecular mechanics calculations can model effectively protonated amine–neutral amine hydrogen bonds in the gas phase and solution (continuum dielectric) through a combination of charge–dipole interactions and explicit hydrogen-bonding terms.

Introduction

Our interest in hydrogen bonding of polyamine species is the result of ongoing work in our laboratories in which the roles of polyamines as ligands at the *N*-methyl-D-aspartate (NMDA) receptor site are being studied. The NMDA receptor is one of the major glutamate receptor subtypes, and it is known to exist throughout the central nervous system. Malfunction within the NMDA receptor complex has been linked to a variety of disorders, including brain ischemia, epilepsy, and neurodegenerative diseases.[1] Therapeutic agents targeting the NMDA receptor have been proposed to treat anxiety, trauma to the head and spinal cord, and numerous neurological diseases.[1] Polyamines have been proposed to act at two distinct sites within the NMDA receptor-ion channel complex, variously as agonists, inverse agonists, or antagonists. These compounds are therefore potentially very important in the treatment of a host of neurological disorders.[2]

In previously reported work, we performed a conformational analysis of 3α- and 3β-aminotropanes, 1,3-unsymmetrical diamines, with a variety of computational methods.[3] It was determined that the MM3 force field, where a dielectric continuum of 80 was use to mimic water solvent, did a superior job of reproducing the NMR-

* To whom correspondence should be addressed. Phone: (706) 542-2054. Fax: (706) 542-2673.
  † University of Georgia.
  ‡ Research Triangle Institute.
  (1) Ornstein, P. L.; Schoepp, D. D. *Current CNS Patents* **1990**, *1*, 413.

(2) Romano, C.; Williams, K. Modulation of NMDA Receptors by Polyamines. In *Neuropharmacology of Polyamines*; Carter, C., Ed.; Academic Press Limited: New York, 1994.
  (3) Lewin, A. H.; Sorensen, J. B.; Dustman, J. A.; Bowen, J. P. *J. Comput. Chem.* **1999**, *20*, 1371.

determined conformational stabilities[4] of these molecules in dilute aqueous media. It was recognized, however, that the molecular mechanics force field required improvement in order to describe accurately the charge-reinforced hydrogen bond that is possible in a protonated polyamine system, as would be found in a physiologic environment.

Hydrogen bonding is known to be an important mediating factor in protein–ligand binding, and charge-reinforced hydrogen bonds can be especially significant contributors to the binding energy of a host–guest complex.[5] Additionally, internal hydrogen bonding within a ligand can dictate the geometric features of a molecule. Molecular shape recognition is appreciated as an important mediator of interactions, potentially altering the ability of a guest to bind to a receptor. Polyamines, which contain several possible hydrogen bond donors and acceptors within one molecule, are a particularly appropriate class of compounds for these considerations.

Recent developments in the MM3 force field have refined the parameters for protonated amines,[6] specifically addressing electrostatic effects such as induction, charge–dipole, and dipole–dipole interactions. Although charge-reinforced hydrogen bonding is in part due to the previous terms, the MM3-calculated interaction energies between protonated and neutral amines did not match the ab initio calculated well depths. This suggested updating the explicit hydrogen bonding term to improve the quality of the molecular mechanics results. We have performed a series of ab initio calculations to obtain additional theoretical information about the effects that control the charged–neutral diamine interaction. These data have been used to parametrize the MM3(2000) force field for protonated diamine hydrogen bonds.

Theory and Methods

Several simple alkylamine complexes were studied to assess charged–neutral diamine interaction energies (E_{int}). Although it has been discovered via experiment[7] and theory[8] that amine basicity increases as the size of the alkyl group increases, the effect is assumed constant when comparing amines with the same alkyl group; therefore, methyl-, dimethyl-, and trimethylamine were complexed with each of the analogous protonated alkylamines, theoretically resulting in nine diamine complexes. In each case when the proton is initially located on the less substituted nitrogen, optimization of the complex causes the proton to migrate to the more substituted nitrogen, in accord with expectations as to the basicity of amines, and gas-phase experimental and theoretical data.[7–15] Therefore, six complexes result: methylammonium methylamine (**1**), dimethylammo-

(4) Lewin, A. H.; Burgess, J. P.; Sun, G.; Fudala, L. D. *Magn. Reson. Chem.* **1999**, *37*, 903.

(5) Teague, S. J.; Davis, A. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 736.

(6) Sorensen, J. B.; Lewin, A. H.; Bowen, J. P. *THEOCHEM*, submitted.

(7) Brauman, J. I.; Riveros, J. M.; Blair, L. K. *J. Am. Chem. Soc.* **1971**, *93*, 3914.

(8) Safi, B.; Choho, K.; De Proft, F.; Geerlings, P. *Chem. Phys. Lett.* **1999**, *300*, 85.

(9) Munson, M. S. B. *J. Am. Chem. Soc.* **1965**, *87*, 2332.

(10) Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1968**, *90*, 6561.

(11) Arnett, E. M.; Jones, F. M.; Taagepera, M.; Henderson, W. G.; Beauchamp, J. L.; Holtz, D.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 4724.
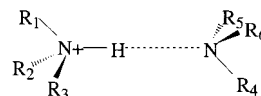
(12) Henderson, W. G.; Taagepera, M.; Holtz, D.; McIver, R. T.; Beauchamp, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 4728.

(13) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 311.

(14) Umeyama, H.; Morokuma, K. *J. Am. Chem. Soc.* **1976**, *98*, 4400.

(15) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695.

Table 1. Protonated Amine–Neutral Amine Complexes Studied in This Work

com-plex	name	R1	R2	R3	R4	R5	R6
1	methylammonium methylamine	CH_3	H	H	CH_3	H	H
2	dimethylammonium methylamine	H	CH_3	CH_3	CH_3	H	H
3	dimethylammonium dimethylamine	H	CH_3	CH_3	H	CH_3	CH_3
4	trimethylammonium methylamine	CH_3	CH_3	CH_3	CH_3	H	H
5	trimethylammonium dimethylamine	CH_3	CH_3	CH_3	H	CH_3	CH_3
6	trimethylammonium trimethylamine	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3

nium methylamine (**2**), dimethylammonium dimethylamine (**3**), trimethylammonium methylamine (**4**), trimethylammonium dimethylamine (**5**), and trimethylammonium trimethylamine (**6**). The complexes are shown in Table 1.

To calculate E_{int} of each complex with the molecular mechanics method, the energy difference is found between the complex, optimized to its minimum energy geometry (AB_{opt}), and the sum of the two free optimized components (A_{opt} and B_{opt}). Although a small amount of strain energy is induced by the geometry changes between the components in their free state and in the complex, this is a sufficiently small difference that it may be neglected when determining E_{int}. Therefore, the interaction energy is computed from the MM3 final steric energies as

$$AB_{opt} - (A_{opt} + B_{opt}) = E_{int\text{-}MM3} \qquad (1)$$

To develop a model of the ion–neutral interaction for each of the complexes, frozen-core second-order Møller–Plesset perturbation theory was used with the 6-311+G** basis set. This method is standard for MM3 parametrization, and the inclusion of electron correlation is especially important when considering nonbonded effects. The basis set was chosen to adequately model hydrogen bonding, yet maintain consistency with the commonly used basis sets in MM3 parametrization efforts. It is essential to compute the interaction energy in such a way that it is equivalent to the MM3 equation described above. Equation 1 may not be used directly, because AB_{opt} is artificially low in the ab initio calculation due to basis set superposition error[16] (BSSE). This phenomenon leads to excessive stabilization of each component due to virtual orbital sharing. It may be subtracted out using a counterpoise correction, which calculates the difference between the energy of a monomer at fixed geometry within its own basis set (A_{sp}, B_{sp}) and the energy of the same species within the complex basis set (A_{cp}, B_{cp}). Thus, the magnitude of the correction for each monomer is $A_{cp} - A_{sp}$ and $B_{cp} - B_{sp}$. Subtracting out these energy differences results in a corrected optimized complex energy gives

$$AB_{opt} - (A_{cp} - A_{sp}) - (B_{cp} - B_{sp}) =$$
$$AB_{opt} - A_{cp} + A_{sp} - B_{cp} + B_{sp} \quad (2)$$

The extent of interaction between the components, then, is the difference between the corrected complex and the optimized monomers;[17] this is equivalent to the equation formulated for the molecular mechanics E_{int}:

(16) Liu, B.; McLean, A. D. *J. Chem. Phys.* **1973**, *59*, 4557.

(17) Mayer, I.; Surjan, P. R. *Chem. Phys. Lett.* **1992**, *191*, 497.

$$AB_{opt} - A_{cp} + A_{sp} - B_{cp} + B_{sp} - A_{opt} - B_{opt} = E_{int\text{-}MP2} \quad (3)$$

It would be ideal to use either an ab initio method that a priori avoids BSSE or a complete (approaching infinite) basis set. Since neither option was compatible with our goals of calculating with both efficiency and accuracy, a suitable compromise was selected: utilization of an adequate basis set and counterpoise correction. Polarization and diffuse functions were added to the basis set in order to improve the treatment of nonbonded interactions, particularly those involving hydrogen. Gaussian94[18] was used for all of the quantum chemical calculations reported herein.

Each complex was optimized at the MP2/6-311+G** level of theory to determine its minimum energy geometry. From that point on the potential energy surface, an energy curve was calculated along a linear $N^+−H\cdots N$ trajectory, optimizing the complex in all degrees of freedom with the exception of the N^+- - -N internuclear distance, which was fixed in small (0.2−0.5 Å) increments[19] from approximately 2.2 Å-6.5 Å. The seven-term BSSE formula (eq 3) was applied at each point of the trajectory to establish a counterpoise-corrected curve and interaction energy; this is important since not only the well depth, but also the position of the minima may be affected by BSSE. On average, however, the position of the minimum was not affected significantly enough to warrant extrapolation of new data from the corrected curve. To confirm that the interaction energy does fall off to a zero value, calculations were also carried out with the components spaced 50, 100, and 500 Å apart. As anticipated, E_{int} at the furthest point is effectively zero (<0.0001 kcal/mol); therefore, this small correction was not subtracted from each curve.

Given the ab initio interaction energy and the MM3 energies for the two components, we can solve for the "target" MM3 complex energy necessary to reproduce the model E_{int}:

$$E_{int\text{-}MP2} + A_{opt\text{-}MM3} + B_{opt\text{-}MM3} = AB_{opt\text{-}MM3}(target) \quad (4)$$

In charged complexes, the nonbonded energy terms (dipole−dipole, charge−dipole, and van der Waals) are particularly important in calculating the energy of the complex; these terms are already well determined in the MM3 program. Any remaining interaction energy falls into the hydrogen-bonding term, which needed to be updated for ion−neutral diamines due to the new ammonium ion parameters.[6] Therefore, any difference between the MM3 calculated complex energy and the "target" energy was treated as a deficiency in the hydrogen-bonding term.

MM3 uses a direction-dependent hydrogen-bonding equation[20] with two parameters; the geometry parameter, r (Å), determines the equilibrium internuclear distance of the hydrogen bond pair (hydrogen to acceptor), and the energy parameter, ϵ (kcal/mol), is a hardness factor that determines the strength of the interaction. The equation that determines the extent of the hydrogen bond interaction is

$$E_{HB} = \frac{\epsilon}{D}\left(1.84 \times 10^5 \exp\left(\frac{-12}{P}\right) - 2.25P^6\right) \times \cos\theta \times \frac{l}{l_0} \quad (5)$$

In this equation, D is the dielectric constant, P is the ratio between the equilibrium (r) and calculated hydrogen bond distances, θ is the hydrogen bond angle, l and l_0, respectively, are the actual and equilibrium X−H bond lengths, in angstroms. Because the two parameters are not independent (adjusting r will change not only the hydrogen bond distance, but also the depth of the well), a balanced combination of ϵ and r is necessary to model the energy and the geometry of the hydrogen bonding interaction. The molecular mechanics hydrogen-bonding parameters were iteratively optimized to reproduce E_{int} and geometric characteristics (specifically the N^+- - -N distance) of the ab initio calculated complexes.

Results and Discussion

Ab Initio Calculated Complex Energies. MP2-calculated interaction energies for the six diamine complexes are shown in Table 2. The magnitude of E_{int} (well depth) varies approximately 15% among the complexes, depending upon the substitution around both the hydrogen bond donor and acceptor. In general, the symmetrical complexes, which have the same degree of substitution around both the protonated and the neutral amines (**1**, **3**, and **6**), have deeper wells than complexes with the substitution pattern R_n, R_{n-1} (**2** and **5**), followed by the R_n, R_{n-2} complex (**4**). The less substituted ammonium ions have larger interaction energies than the more highly substituted ones. This trend may be ascribed to the acidity of the alkylammoniums. On the basis of experimentally determined gas-phase proton affinities of the alkylamines,[7,9−13] the primary methylammonium is more acidic than its tertiary analogue, trimethylammonium. It has been suggested that this effect is due to the relative amounts of inductive stabilization.[7,10,11,21] Thus, the strength of the interactions of the primary ammonium ion with neutral amines may be enhanced by its being a better proton donor than the analogous tertiary ammonium ion. Previous investigation[22] of the ammonium-ammonia complex found that the interaction energy does not change significantly around the minimum of the interaction well. It was suggested that the electrostatic attraction and exchange repulsion both increase dramatically around the minimum yet cancel each other, resulting in little net change. Due to the smaller basis set and different method used in the earlier work, however, we are cautious about applying the previous conclusions to the current data.

There is a moderate amount of difference between the BSSE-corrected and uncorrected interaction energy curves for each complex. Figures 1−3 show the energy curves for complexes **1**, **2**, and **4**, respectively. In general, the uncorrected curves have attractive wells that are approximately 10−15% deeper, due to orbital sharing between the two components at close range. Therefore, the uncorrected curves only tend to have steeper slopes around the bottom of the well, beyond that the general shapes of the interaction curves are similar.

Ab Initio Calculated Complex Geometries. Although the hydrogen bond pair is usually defined in terms of the proton and its acceptor atom, the absolute position of the proton is difficult to determine from experiment. In addition, the hydrogen atom is not likely to be fixed in solution, rather experiencing some equilibrium motion between the donor and acceptor atoms. Therefore, measuring the distance between the two heavy atoms, in this case nitrogens, is a more appropriate means of assessing the complex geometry. The N^+- - -N

(18) Gaussian 94, Revision E.2: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; and Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.
(19) The smaller increment was used specifically on complexes **1**, **2**, and **4**. Fewer points were sampled on the PES of **3**, **5**, and **6**.
(20) (a) Lii, J.-H.; Allinger N. L *J. Phys. Org. Chem.* **1994**, *7*, 591. (b) Lii, J.-H.; Allinger, N. L *J. Comput. Chem.* **1998**, *19*, 1001.

(21) Baeten, A.; De Proft, F.; Langenaeker, W.; Geerlings, P. *THEOCHEM* **1994**, *306*, 203.
(22) Liebman, J. F.; Romm, M. J.; Meot-Ner, M.; Cybulski, S. M.; Scheiner, S. *J. Phys. Chem.* **1991**, *95*, 1112.

Table 2. Calculated Interaction Energies of the Six Complexes[a]

complex	MP2/6311+G**	MP2/CP[b]	MM3(2000)	ΔMP2(CP) − MM3(2000)	MM3(2000)*[c]	ΔMP2(CP) − MM3(2000)*[c]
1	26.4681	24.0201	23.8211	0.1990	24.0196	0.0005
2	24.4990	21.9829	23.3022	−1.3193	21.9861	−0.0032
3	25.9136	22.9603	21.8873	1.0730	22.9624	−0.0021
4	23.5435	20.7462	22.3855	−1.6393	20.7468	−0.0006
5	24.8773	21.6464	21.5489	0.0975	21.6525	−0.0061
6	25.8482	21.8884	20.5308	1.3576	21.8898	−0.0014

[a] kcal/mol. [b] Ab initio values corrected for BSSE using eq 3. [c] MM3(2000) with specialized 8···48 parameters read in.

Table 3. Hydrogen Bond Geometric Features of the Six Complexes

	N+- - - N[c]			N+EnDash−H[c]			H···N[c]			N+−H−N[d]		
complex	MP2	MM3*[a]	MM3[b]	MP2	MM3*[a]	MM3[b]	MP2	MM3*[a]	MM3[b]	MP2	MM3*[a]	MM3[b]
1	2.692	2.692	2.704	1.121	1.068	1.067	1.571	1.627	1.639	179.51	175.20	175.24
2	2.743	2.742	2.705	1.091	1.063	1.068	1.652	1.679	1.638	176.61	179.23	178.98
3	2.680	2.680	2.715	1.124	1.073	1.068	1.556	1.609	1.648	179.58	176.94	176.81
4	2.762	2.761	2.714	1.081	1.064	1.070	1.681	1.698	1.644	178.79	178.55	178.81
5	2.718	2.718	2.717	1.100	1.071	1.071	1.618	1.647	1.646	179.11	178.92	178.93
6	2.679	2.680	2.722	1.125	1.077	1.070	1.555	1.603	1.652	179.98	179.83	179.76

[a] MM3(2000) with specialized hydrogen bond parameters read in for each environment. [b] MM3(2000) with default (average) hydrogen bond parameters. [c] Angstrom, values calculated as r_e. [d] Degree.

pair distances and other significant geometric features of the six charged-neutral diamine complexes are listed in Table 3.

The shortest internuclear distances are observed in complexes of ammonium ions with their respective conjugate bases (symmetrical complexes). In addition, a greater degree of substitution results in a shorter internuclear distance. Although this may seem contradictory to steric arguments, it may in fact be the relative strength of the acid and base, as discussed for the trends in E_{int}, that govern the interaction between the amines. Slightly longer bond lengths are found in the complexes where the protonated amine has one greater degree of substitution than the neutral amine, and the most substituted ammonium ion has the shortest internuclear distance. The longest observed internuclear distance is in **4**, which is a tertiary ammonium−primary amine complex. This may be rationalized by the fact that the trimethylammonium donor is the weakest acid, and the methylamine acceptor is the weakest base,[15] out of all of the alkylamines studied in this work.

It is interesting to note that the shortest internuclear distance is observed in complex **6**, which has tertiary substitution on both the protonated and neutral components; however, it did not have the strongest interaction energy. The six proximate methyl groups do not appear to be a steric disadvantage; all of the methyls are gauche to each other, and any possible repulsion should be minimized.

The concepts of acidity and basicity of amines and ammonium ions are useful when explaining the observed trends in protonated diamine complexes. One indicator of ammonium acidity is its ability to share a proton. In geometric terms, one can measure the elongation of the N+−H bond as the cation changes from its free to complexed state, and use the difference as an indicator of how tightly the proton is being held by the cation (shown in Table 4). According to MP2 calculations, the greatest degree of elongation occurs in the symmetric complexes, each donor N+−H bond is approximately 0.1 Å longer than in the free ammonium. This result, as might be expected, correlates with interaction strength; the three symmetric complexes have the deepest interaction wells. In fact, the general trend holds for all six

Table 4. Change in Calculated Bond Length[a] **Due to Electron Transfer**

complex	MP2 complex	MP2 free	Δ	MM3(2000)[b] complex	MM3(2000)[b] free	Δ
1	1.1210	1.0245	0.0965	1.0672	1.0277	0.0395
2	1.0913	1.0242	0.0671	1.0678	1.0259	0.0419
3	1.1238	1.0242	0.0996	1.0680	1.0259	0.0421
4	1.0810	1.0244	0.0566	1.0703	1.0258	0.0445
5	1.1000	1.0244	0.0756	1.0705	1.0258	0.0447
6	1.1246	1.0244	0.1002	1.0704	1.0258	0.0446

[a] Angstrom. [b] MM3(2000) with average parameters as implemented in force field. Values are r_e.

complexes studied between the elongation of the hydrogen donor bond and the ammonium−amine well depth.

The intuitive idea that acidity/basicity is a function of substitution is also borne out by these measurements. Among complexes with the methylamine acceptor (**1**, **2**, and **4**) the percent elongation decreases with increasing substitution of the cation. Therefore, the primary methylammonium is a stronger acid than the secondary or tertiary ammonium ions. Conversely, the tertiary amine (trimethylamine) is the strongest base. These data are in direct agreement with the interpretation of acidity of ammonium ions (basicity of amines) as due to inductive stabilization. There is also a direct correlation between the basicity of the proton acceptor and the proton-acceptor distance. That is, shorter N···H distances are observed with the more basic (more substituted) amines. In addition, the symmetric complexes, in order from most to least highly substituted, have the shortest hydrogen bond pair distance.

One other important hydrogen bond geometric feature is the N+−H−N hydrogen bond angle. In all cases, the bond is fairly linear (Table 3). At the optimized geometry, the complex usually deviated from linearity by only a few degrees. In a trend similar to the one discussed above for hydrogen bond distances, the most symmetric complexes are also the most linear. The N+−H−N angle in **6** is 180.0°, followed by the other symmetric complexes **3** and **1**. The least linear complex is **2**, which has an N+−H−N angle of 176.6°. Interestingly, there is no obvious correlation between the linearity of the bond and the strength of the interaction. However, in previous work[22] a "trifurcated" ammonium−amine complex was also examined, where it was found that the interaction energy

was significantly less than for the linear species. This does support the notion that linear complexes are inherently more strongly interacting than nonlinear hydrogen bond arrangements.

Significant variations in bond lengths occur in both the cation and neutral species as they change between free and complexed states. For example, in every complex the N^+-H bond lengthens as the cation undergoes complexation. This phenomenon was previously discussed as a result of the acidic ammonium ion releasing its proton to the hydrogen bond acceptor in the complex, changing the bond length 0.06−0.10 Å. The lengths of the N^+-H bond that do not participate in hydrogen bonding systematically decrease, as do the lengths of the N^+-C bonds. On the other hand, the bond lengths of the neutral amine hydrogen bond acceptor (both N−H and N−C bonds) systematically increase upon complexation with a cation.

Parametrization of the MM3 Force Field. At the outset of this study, a comparison between the MP2 and MM3(96) interaction energies was made. At that time, the molecular mechanics well depths were significantly different from those calculated with ab initio methods, and, in some cases, the deviation was as much as 13 kcal/mol. Initially, it was contemplated that in order to adequately model the interaction between protonated and neutral amines with a variety of substitution patterns, individual parameter sets would be required for each hydrogen bond pair. Reparametrization of the ammonium ion environment for MM3(2000),[6] in particular the $C-N^+$ and N^+-H bond moments, provided a force field which was able to approximately reproduce the ammonium-amine electrostatic interactions. Since much of the charged-neutral interaction depends on charge-controlled terms (such as the charge−dipole term), these bond moments are an important component of calculating accurate interaction energies. Modifying the 8···48 hydrogen bond parameters in accord with the new bond moments has resulted in the current force field.

Much of the uncertainty in using molecular mechanics to model interactions of this type is due to a general inability to reproduce charge-controlled effects. Only in recent work[23] has a scheme been introduced to account for polarization effects in MM3. Therefore, investigations of how phenomena such as dipole−induced dipole and charge-induced dipole interactions affect the energetics of a system are novel. Since the hydrogen bond term is currently acting as a catch-all for the missing charge-driven interaction components, specific parameters for each electronic environment (substitution pattern) around the two nitrogen atoms have been developed to very accurately model gas-phase equilibrium interaction energies. The hydrogen bond parameters introduced in eq 5, ϵ and r, were adjusted iteratively for each complex in accord with the new dipole parameters[6] until the molecular mechanics minimized result best matched the MP2 calculated minimum geometry and energy. The specialized charge-neutral amine hydrogen bond parameters are listed in Table 5.

For the six amine−ammonium ion complexes **1**−**6** a direct correlation is observed between the N- - -N+ distance and the MM3 hydrogen bond parameter r. This correlation is to be expected, as r determines the hydro-

Table 5. MM3 Hydrogen Bond Parameters for the 8···48 Atom Type Pair

environment	e	r
MM3(2000)	22.422	1.687
1	22.718	1.675
2	20.555	1.730
3	24.065	1.649
4	20.010	1.7405
5	22.540	1.688
6	24.645	1.6395

gen bond pair length (H···N), just as the parameter l_0 determines the equilibrium bond length. Potentially, steric effects could lengthen the hydrogen bond from its equilibrium position. Conversely, attractive effects may shorten the distance between donor and acceptor. The hydrogen bond parameter, r, is seen to be inversely proportional to ϵ, consistent with the idea that a shorter H···N distance signals a greater interaction energy. However, it is difficult to discern a correlation between the magnitude of the energy parameter, ϵ, and the depth of the interaction well. In fact, the protonated amine − neutral amine interaction in MM3 is controlled by both the charge−dipole term and the explicit hydrogen bond term. Most of the charge−dipole attraction is attributable to interactions between the charged protonated nitrogen and neutral N−H bonds. To a lesser extent, interaction with N−C bonds is also stabilizing.

Evaluation of the ab initio results has established that the interaction energy is sensitive to the substitution of both donor and acceptor nitrogens. In MM3 there is only one atom type for the sp³ ammonium nitrogen (type 39) and (N⁺)H proton (type 48), and one standard sp³ amine nitrogen (type 8).[24] In keeping with the philosophy of transferability of parameters, ideally only one set of hydrogen bond parameters should be implemented to describe the 8···48 hydrogen bond pair, regardless of substitution. This results in somewhat of a compromise when choosing parameters to implement in the MM3-(2000) force field, since there is not a single pair of ϵ and r which exactly reproduces all of the interaction energies. The average values, which are utilized in the force field, provide satisfactory results based on the examples studied to date, where the desired limit of error is around one kcal/mol in E_{int}. The specialized parameters discussed in this work may be added to the force field at a user's discretion when more accurate results are sought.

Comparison of the Resulting MM3 Values with ab Initio Models: Energies. Morokuma[25] has performed decomposition analyses of hydrogen bonds, breaking down the energy into components attributed to electrostatic, polarization, exchange repulsion, charge transfer, and complex "mixed" interactions. Although we do not attempt to quantify the effect of each of these terms in a molecular mechanics calculation, it is certain that at least some of these factors do affect the well depths. Since MM3 is not an electronic structure method, it is inherently unable to reproduce certain effects, such as electron exchange. There has been some success in imitating phenomena such as delocalization, which may be achieved more readily in neutral, bonded systems. MM3 terms do address both steric (such as stretching

(23) Ma, B.; Lii, J.-H.; Allinger N. L *J. Comput. Chem.* **2000**, *21*, 813.

(24) There are separate atom types for hydroxylamine (146) and hydrazine (150) nitrogen atoms. Parameters associated with these atom types have not been altered in this work.

(25) Umeyama, H.; Morokuma, K. *J. Am. Chem. Soc.* **1977**, *99*, 1316.
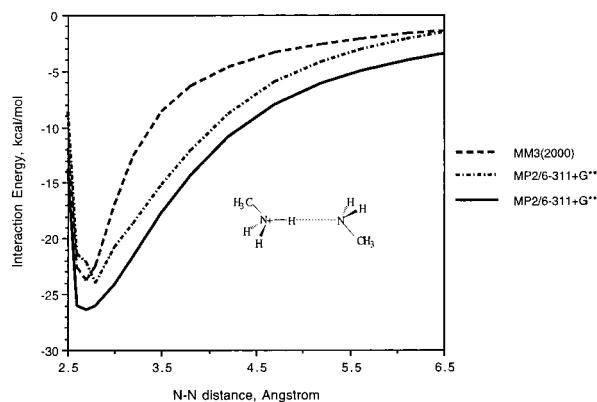
Figure 1. Calculated interaction energies of complex **1**: methylammonium methylamine.
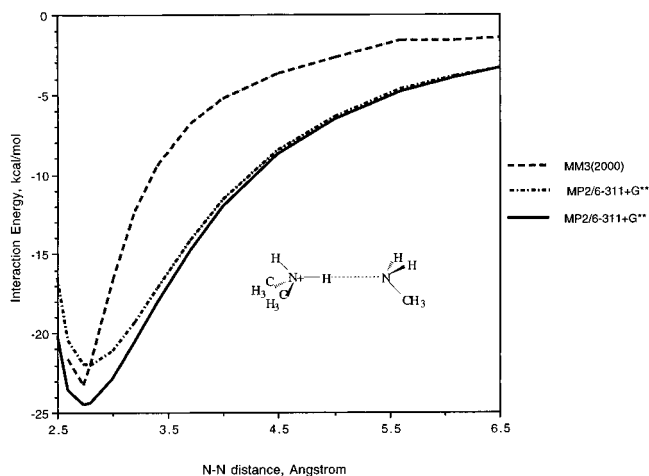

Figure 2. Calculated interaction energies of complex **2**: dimethylammonium methylamine.

Figure 3. Calculated interaction energies of complex **4**: trimethylammonium methylamine.

Comparison of the Resulting MM3(2000) Values with ab Initio Models: Geometries. To obtain bond lengths that were comparable to ab initio results, MM3 coordinates were converted to r_e values using the program's internal conversion algorithm.[26] The first geometric feature under consideration is the hydrogen bond length. For the six complexes, the average difference between the MM3(2000) and MP2 calculated N^+- - -N distances is 0.030 Å. This distance becomes negligible when the specialized parameters are utilized. In contrast, the difference between MM3 and MP2 calculated N^+—H bond distance averages 0.038 Å, with or without the specialized parameters. In part, the failure of MM3 to reproduce these bond lengths is due to its inability to properly model donor-bond elongation. In addition, the force field was parametrized specifically to match the N^+- - -N internuclear distance, not the complexed N^+—H bond length. In the free ammonium ion, however, the N^+—H bond length has been well parametrized.[6]

MM3(2000) (with and without the specialized parameters) and MP2 agree reasonably well with respect to the hydrogen bond angle, with an average difference of 1.6° for the six complexes. In particular, the tertiary ammonium complexes are in good agreement (approximately 0.2° difference), and the most significant deviation of 4.3° is seen in **1**. There is no parameter that directly determines the hydrogen bond angle, rather it is a combination of various steric/nonbonded factors. Since the hydrogen bond term in MM3 is direction-dependent, the (non)-linearity of the bond is explicitly taken into account in the molecular mechanics calculation. The MM3 hydrogen bond equation is designed to maximize the strength of a linear hydrogen bond, consequently the hydrogen bond angle is de facto determined by all of the parameters acting in concert to minimize the total energy of the system.

In addition to the hydrogen bond length and angle, it would be desirable to compare the MP2 and MM3 calculated values of other geometric features within the complexes (Tables 6 and 7). It was not possible to more closely reproduce some other geometric features of the components within the complexes, for example, N—C bonds, due to the fact that these parameters were

and bending) and electrostatic (including dipole—dipole, charge—dipole, hydrogen bond, van der Waals) factors that may be parametrized to provide accurate total hydrogen bond energies.

Agreement between MM3(2000) and the counterpoise-corrected MP2 values for optimum interaction energy is quite good. The signed average deviation between the two methods is 0.04 kcal/mol, and the absolute average is 0.95 kcal/mol over the six model complexes. When the environment-specific hydrogen bond parameters are used, the deviation is reduced to a negligible amount, about 0.002 kcal/mol. Away from the minimum, however, MM3 is unable to mimic MP2 energy curves (Figures 1−3). A more generalized treatment of inductive effects will likely improve the way in which molecular mechanics treats long-range interactions in charged species. For each complex, the MM3(2000) interaction falls off much more steeply than the ab initio curves indicate. In general, the molecular mechanics calculated interaction between the charged and neutral amine drops 50% from its maximum value when the two components are only 3.2 Å apart (N^+- - -N distance). On the other hand, the ab initio interaction energy does not fall to 50% of its maximum until the components are spaced approximately 4.0 Å. The shape of the MM3 curve is simply due to the mathematics of the distance-dependent hydrogen bond (a function of $[Ar]^6$ and $\exp[Br]$) and charge—dipole (a function of $1/r^2$) terms.
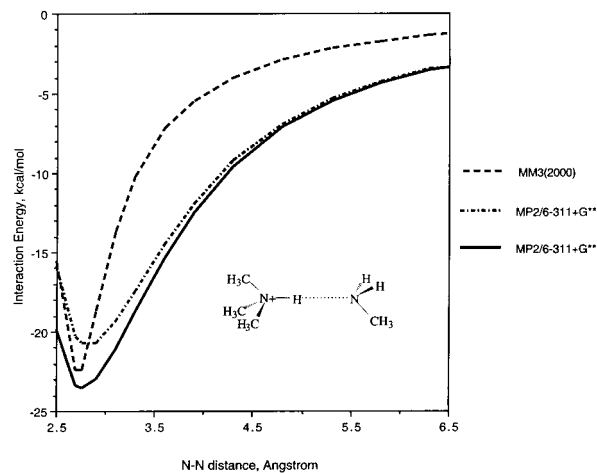
(26) Ma, B.; Lii, J.-H.; Schaefer, H. F.; Allinger, N. L. *J. Phys. Chem.* **1996**, *100*, 8763.

Table 6. Bond Lengths of the Six Model Complexes[a]

complex	N⁺−C		N⁺−H		N⁺−H[b]		N−C		N−H	
	MP2	MM3[c]	MP2	MM3[c]	MP2	MM3[c]	MP2	MM3[c]	MP2	MM3[c]
1	1.4938	1.5118	1.0214	1.0275	1.1210	1.0672	1.4865	1.4602	1.0195	0.9982
2	1.4893	1.5050	1.0222	1.0257	1.0913	1.0678	1.4849	1.4597	1.0191	0.9982
3	1.4876	1.5050	1.0214	1.0256	1.1239	1.0680	1.4782	1.4591	1.0191	0.9995
4	1.4875	1.5030			1.0810	1.0703	1.4844	1.4595	1.0190	0.9982
5	1.4861	1.5029			1.1000	1.0705	1.4775	1.4589	1.0194	0.9997
6	1.4852	1.5029			1.1246	1.0704	1.4745	1.4563		

[a] Angstrom. [b] Hydrogen bond donor proton. [c] MM3(2000) with average parameters as implemented in the force field. Values in r_e.
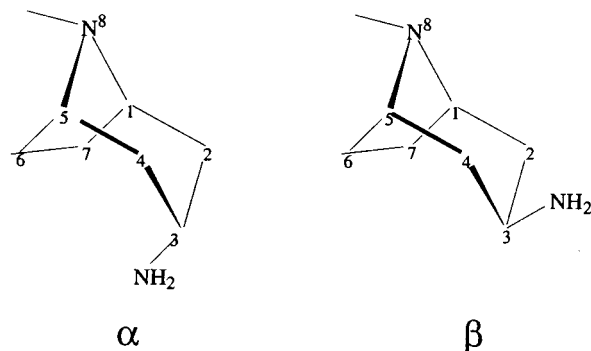
Table 7. Bond Angles of the Six Model Complexes[a]

complex	C−N⁺−C		C−N⁺−H[b]		H−N⁺−H[b]		C−N−C		C−N−H		H−N−H	
	MP2	MM3[c]	MP2	MM3[c]	MP2	MM3[c]	MP2	MM3[c]	MP2	MM3[c]	MP2	MM3[c]
1			110.7	111.6	108.9	106.7			110.8	107.0	111.7	114.2
2	113.3	114.5	113.3	114.5	106.9	105.4			108.7	107.4	104.5	103.4
3	113.1	114.6	108.6	109.0	108.2	105.0	111.4	110.1	107.8	106.9		
4	111.3	112.0	107.5	106.8					111.4	109.2	104.5	103.6
5	111.3	112.0	107.6	106.9			111.2	110.2	107.5	107.0		
6	111.2	111.9	107.7	106.9			109.8	109.5				

[a] Degree. [b] Hydrogen bond donor proton. [c] MM3(2000) with average parameters as implemented in the force field.

developed in other work.[27,28] In addition, there are differences between the calculated geometries of the free species which make direct comparison of ab initio and molecular mechanics values of the complexes difficult. For example, in free protonated amines, MM3 bond lengths are systematically longer than the ab initio values, and in the neutral amines the MM3 bond lengths are consistently shorter than the MP2 values. These differences will affect the resulting bond lengths in the complexes.

It is possible, on the other hand, to compare the differences between MP2 and MM3 structural trends as the amines go from free to complexed species. For the ab initio calculations, complexation shortens each of the bonds to the protonated nitrogen with the exception of the bond to the donated proton. The bond length decrease is fairly small in bonds to hydrogen, about 0.002−0.003 Å, while bonds to carbon shorten approximately 0.012 Å. Similarly, bond lengths decrease in MM3 upon complexation, but the changes are practically negligible (approximately 0.0002−0.0003 Å between N⁺ and hydrogen, and 0.0004 Å between N⁺ and carbon). In the neutral species, all of the MP2 calculated skeletal bond lengths increase upon complexation. Bonds to hydrogen lengthen approximately 0.005 Å, and bonds to carbon about 0.020 Å. Although the MM3 bond lengths also increase, MM3 is not able to reproduce the degree of elongation, only changing 0.002 Å and 0.005 Å for bonds to hydrogen and carbon, respectively. Due to the lack of authentic electron transfer in the molecular mechanics method, smaller geometry changes are observed. However, the trends are consistent between MP2 and MM3.

Despite the inherent differences in the methods, the differences between MP2 and MM3 calculated bond lengths are moderate (see Table 6). For N⁺−H bonds that are not hydrogen bond donors, the MP2 bond lengths are an average of 0.005 Å shorter than the MM3 values. This compares reasonably well with the ab initio/mechanics difference of 0.002 Å calculated for all N⁺−H bonds in the parameter training set.[6] For the N⁺−C bonds, MP2

(27) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551 and subsequent papers.
(28) Schmitz, L. R.; Allinger, N. L. *J. Am. Chem. Soc.* **1990**, *112*, 8307.

Figure 4. 3α- and 3β-aminotropane.

values are consistently shorter than MM3, by an average of 0.017 Å, and the larger errors are observed in the symmetrical complexes. This difference may be attributed in large part to donation of electron density into the N⁺−C bonds that occurs upon complexation, since the average difference between ab initio and MM3 N⁺−C bonds was only 0.005 Å in the free ammonium ion parametrization. Thus, even if MM3 bond lengths are close to the ab initio values calculated in the free species, some errors will remain when comparing the geometries of a complex. On the neutral side of each complex, the MP2 bond lengths are longer than the MM3 for both N−C and N−H bonds, by an average of 0.020 and 0.022 Å, respectively. This larger difference is to be expected, since the MM3 amine geometric parameters[28] were developed and validated against a different kind of experiment (electron diffraction and microwave) from ab initio calculations.

Application of MM3(2000) to the 3-Aminotropanes. Gas phase results (dielectric constant = 1.5) of our original diamine model, 3-aminotropane (Figure 4), using the newly parametrized MM3(2000) force field, compare well with the ab initio HF/6-31G* relative energies[3] of the conformations shown in Figures 5 and 6, with only a few discrepancies. The relative energies for α and β are shown in Tables 8 and 9, respectively. In particular, the unusual MM3(96) result for diprotonated 3β-aminotropane, where the conformation with an axial *N*-methyl group (β3c) was unexpectedly preferred to the
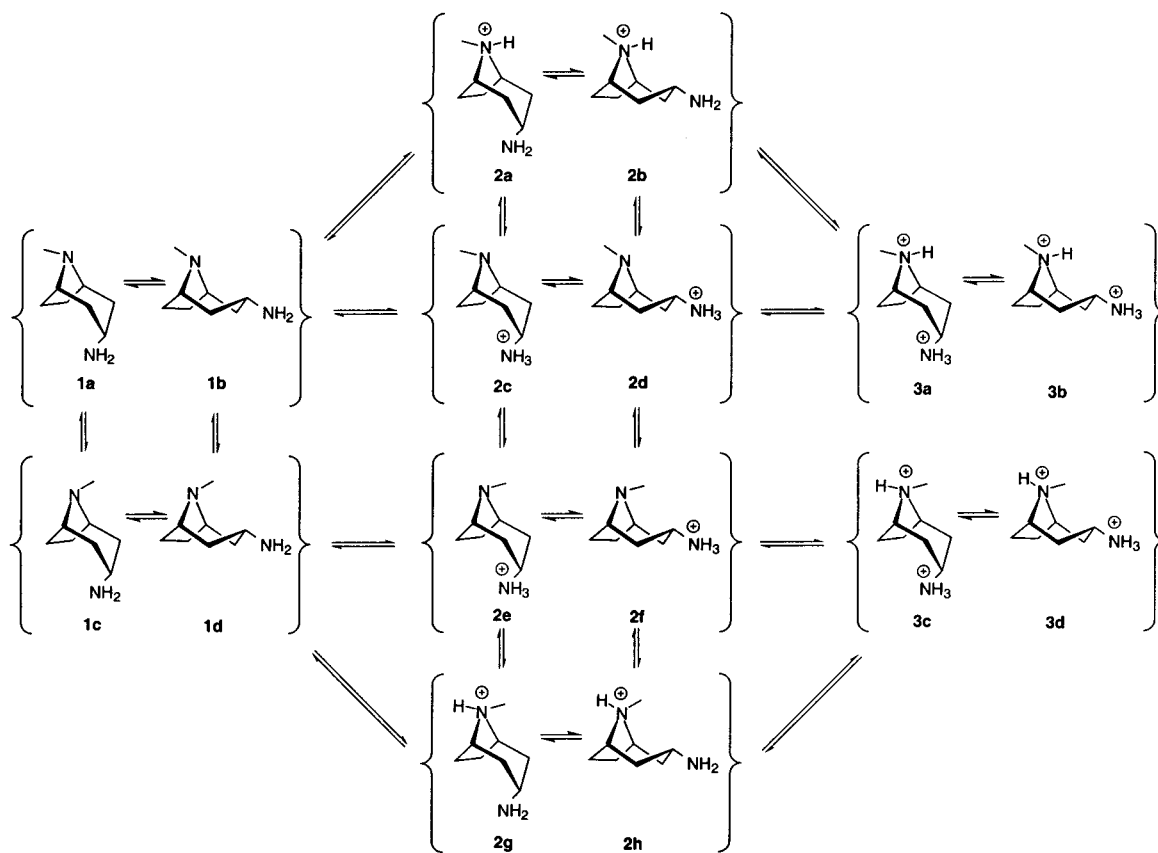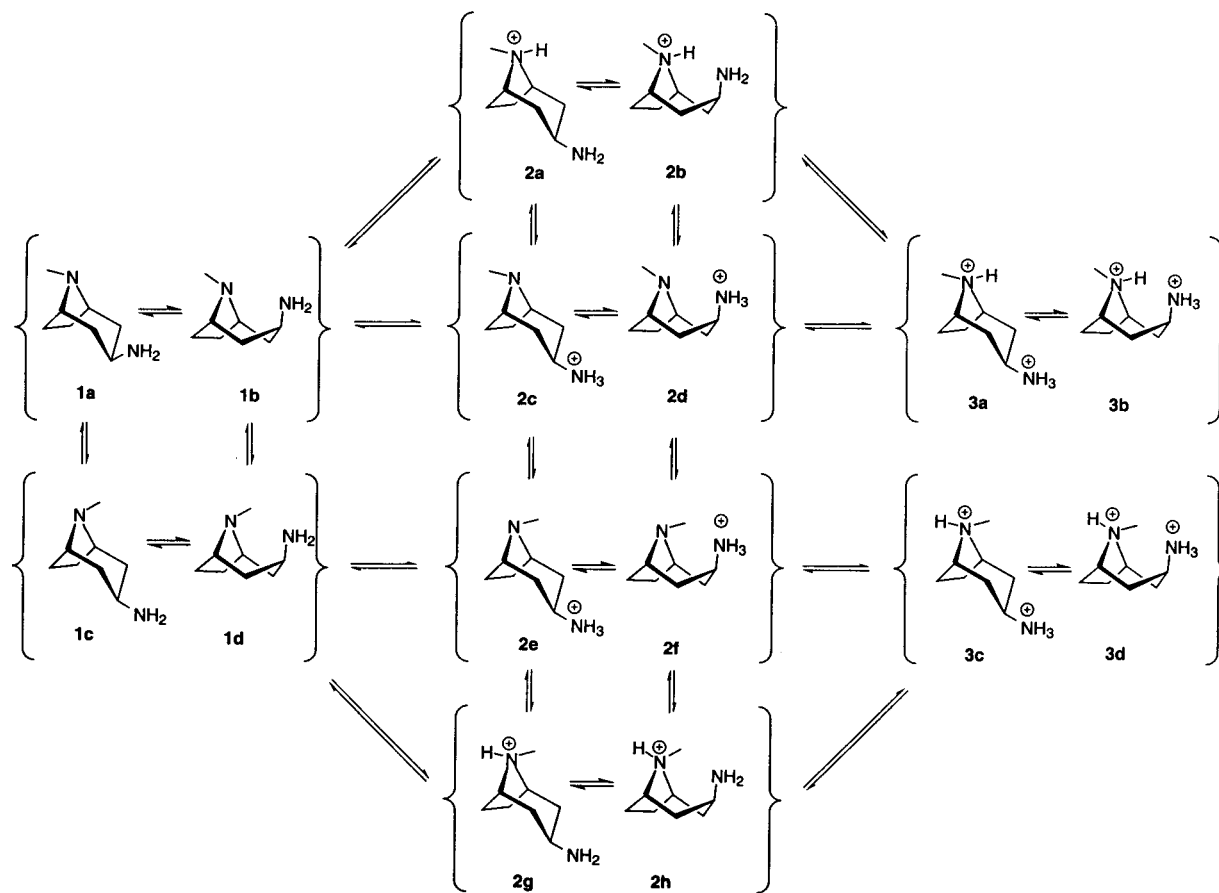
Figure 5. Interconversion of α species.

Figure 6. Interconversion of β species.

Table 8. Relative Energies of 3α-Aminotropanes[a,b]

structure	HF/6-31G*	MM3(96)	MM3(2000)	MM3(96)-80	MM3(2000)-80
1a	0.00	0.00	0.00	0.00	0.00
1b	3.63	2.07	2.07	2.03	2.03
1c	1.02	1.37	1.37	1.31	1.31
1d	6.40	6.33	6.33	6.25	6.25
2a	0.00	0.00	0.00	0.00	0.00
2b	7.78	6.44	7.00	4.61	4.64
2c	14.93	14.77	16.24	11.87	12.40
2d	15.82	14.70	15.66	12.87	13.37
2e	16.57	16.19	18.12	13.10	13.63
2f	20.72	19.73	21.36	17.00	17.51
2g	2.31	1.22	1.56	1.48	1.44
2h	X[c]	X[c]	X[c]	X[c]	X[c]
3a	0.00	0.00	0.00	0.00	0
3b	3.29	3.50	0.63	3.52	3.44
3c	1.87	0.05	2.08	1.40	1.41
3d	X[c]	2.27	4.94	6.63	X[c]

[a] kcal/mol. [b] See Figure 5. [c] Unstable, nonstationary points.

Table 9. Relative Energies of 3β-aminotropanes[a,b]

structure	HF/6-31G*	MM3(96)	MM3(2000)	MM3(96)-80	MM3(2000)-80
1a	0.00	0.00	0.00	0.00	0.00
1b	8.71	6.15	6.15	6.65	6.77
1c	0.25	1.15	1.15	1.31	1.31
1d	X[c]	X[c]	X[c]	X[c]	X[c]
2a	2.15	0.00	9.05	0.00	0.00
2b	0.00	1.68	0.00	9.76	8.00
2c	13.77	12.78	21.44	10.86	11.32
2d	9.59	15.08	12.70	16.76	15.78
2e	15.68	14.99	23.73	12.13	12.58
2f	X[c]	X[c]	X[c]	X[c]	X[c]
2g	4.33	2.30	10.30	1.49	1.41
2h	X	12.82	20.97	X	X
3a	0.00	2.37	0.00	0.00	0.00
3b	X[c]	X[c]	X[c]	X[c]	X[c]
3c	2.29	0.00	2.59	1.32	1.42
3d	X[c]	X[c]	X[c]	X[c]	X[c]

[a] kcal/mol. [b] See Figure 6. [c] Unstable, nonstationary points.

conformation in which the *N*-methyl group was equatorial (β**3a**) has been corrected in MM3(2000), and now the molecular mechanics relative energies are in line with the Hartree−Fock result. The equatorial *N*-methyl group is now favored by 2.3 and 2.6 kcal/mol in the ab initio and MM3 calculations, respectively.

On the other hand, the difference between the ab initio and MM3 relative energies of a few structures has increased as a result of the reparametrization. For the most part these involve unstable, high-energy conformations in which whether the relative energy is 15 or 16 kcal/mol higher than the minimum conformation is a moot point. There are, however, two cases where the MM3(2000) results are in conflict with the ab initio data for low-energy conformations, and these merit discussion.

The first discrepancy is observed in diprotonated 3α-aminotropane. According to the Hartree−Fock calculation, the boat (α**3b**) is destabilized approximately 3.3 kcal/mol relative to the corresponding chair conformer (α**3a**). On the other hand, the MM3(2000) result suggests that the boat/chair difference is only around 0.6 kcal/mol. The small MM3-calculated relative energy difference is striking, especially considering that there is no opportunity for internal hydrogen bonding.[3] The result may be due to a difference in the charge−dipole term of the chair and boat energies; this term is actually about 1 kcal/mol lower in the boat form. Specifically, chair destabilization is caused by repulsion between the $^+N^3$ point charge and each of the two ring $^+N^8$−C bond dipoles. The positive carbon end of each bond is oriented toward the

positively charged nitrogen in the chair form, and the effect is magnified by the full positive formal charge residing on N^3. Previous work[6] has shown that maintaining the entire formal charge on each protonated nitrogen is a substantial approximation. In the corresponding boat interactions, the charge and the bond dipoles are separated by a greater distance, reducing the interaction (the charge−dipole term is a function of r^2). In addition, the angle between each bond vector and point charge in the boat conformation is slightly larger than is observed in the chair conformation. Thus, the charge−dipole interaction is minimized by perpendicular arrangement of the charge and bond dipole (this interaction is also a function of $\cos\theta$, where θ is the angle between the bond vector and a vector from the point charge to the midpoint of the bond).

The charge−charge term is also affecting the relative energy difference between the chair and boat conformations, in addition to charge−dipole repulsion. In the boat form, the two protonated nitrogen atoms are farther apart than in the chair form, and thus the charge−charge repulsion is higher in the chair by approximately 1 kcal/mol. A charge−charge chair destabilization (1.8 kcal/mol) is also observed in the chair-boat pair α**3c** and α**3d**. That the through-space interaction is a contributor to the energy despite physical hindrance of the chair carbon atoms is questionable. Thus, although some of the charge−dipole destabilization observed in the chair appears reasonable, the charge−charge effect may be

inaccurate. This anomaly is specifically observed in the diprotonated α species because of the unique position of N^3.

The second situation in which we see a notable difference between the Hartree−Fock and MM3(2000) results is in the relative energies of β**2a** and β**2b**. Hartree−Fock calculations favor the boat conformer by approximately 2 kcal/mol, while MM3 favors the boat by 9 kcal/mol. In the MM3 energy breakdown, a significant portion of the boat stabilization is due to internal hydrogen bonding. As discussed in previous work,[3] however, the Hartree−Fock structural data are inconsistent with an internal hydrogen bond, leading to speculation why the boat was favored in ab initio calculations. In addition to the hydrogen bond, the boat is stabilized approximately 8 kcal/mol in the charge−dipole term. This significant energy component is caused by favorable interactions between the tertiary protonated nitrogen and each of two primary N−H bonds. Since the charge and bond dipole are much closer to each other in the boat form than in the chair form, the r^2 term has a significant impact (the cos θ term is similar in both conformations). Thus, the hydrogen bond and charge−dipole terms overwhelm unfavorable steric interactions and torsional terms, leading to a significantly preferred boat structure.

As a result of the considerable energy lowering of β**2b**, all of the other monoprotonated β species have significantly higher relative energies according to MM3. However, their energies are still accurate when compared against each other. For example, consider the relative energies of β**2g** and β**2a**, where the structural difference is simply between an axial or equatorial *N*-methyl group.

The energy of the axial *N*-methyl conformation is approximately 1 kcal/mol greater than the equatorial conformation, which is precisely in line with other observations.[3]

MM3(2000) optimization of the 3-aminotropanes was also carried out with a dielectric constant of 80, to reproduce dilute aqueous solution conditions. The relative energies of diprotonated α and β compare well against relative energies extrapolated from NMR data.[4] The experimentally determined *A* value is 1.2 and 1.3 kcal/mol for α and β, respectively. In MM3, this value is 1.4 kcal/mol.

Conclusions

The molecular mechanics force field MM3(2000) has been updated to include parameters that model the nonbonded interaction (a charge-reinforced hydrogen bond) between a variety of ammonium ions and amines. Agreement between ab initio MP2/6-311+G** and molecular mechanics results are overall improved with the inclusion of specialized parameter sets. Application of the new force field to the rigid diamine 3α- and 3β-aminotropane provides relative energies that match both ab initio and NMR data well. MM3(2000) will be used in future efforts to model polyamine systems in physiological environments.