

Molecular Mechanics Calculations on Aliphatic Amines<sup>1</sup>S. Profeta, Jr.,\*<sup>†</sup> and N. L. Allinger\*

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**Abstract:** The MM2 force field has been extended to cover aliphatic amines. Dipole moments and geometries of the simple alkyl amines were fit, and the calculations were then applied to a variety of more complicated molecules. A heat of formation scheme was developed based on a group of 18 compounds. For these, the standard deviation between the experimentally determined heats of formation and the calculated values was 0.46 kcal/mol. A number of systems containing piperidine, pyrrolidine and other fragments, and many methylated derivatives were examined. In general the results are quite good with respect to structures, conformational energies, dipole moments, and heats of formation.

Over the past 15 years or so, molecular mechanics has developed into a powerful tool for the calculation of structures, energies, and sometimes other properties of molecules.<sup>2-4</sup> The MM2 program<sup>3</sup> does a rather good job of such calculations with hydrocarbons,<sup>3,4</sup> and it has subsequently been extended to many other functionalized kinds of molecules. The present description concerns the extension of the MM2 program to the amines. The parameters developed herein are already included in all publicly available versions of MM2.

In earlier work on alcohols and ethers,<sup>5a</sup> it was found expedient to include lone pairs specifically in the parameterization. These lone pairs exerted van der Waals characteristics which allowed us to better reproduce the structures of these compounds than we otherwise found possible. Burkert<sup>5b</sup> and independently Rasmussen<sup>5c</sup> have suggested that the use of charges can reproduce these geometries equally as well, without the use of lone pairs. Certainly, there is one obvious disadvantage to the lone pair construction, in that ammonia, for example, does not invert through a symmetrical transition state in the present formalism. However, apart from this one shortcoming, it seems that the lone pair formalism reproduces well the desired structures and other characteristics of alcohols, ethers, and amines. In any event, it is the scheme used in the present work.

## Acyclic Amines

We began with ammonia and the methylamines and established the necessary values for the natural bond lengths, angles, and torsional angles so as to reproduce the observed structures, rotational barriers, and dipole moments. The data utilized are given in Table I. One discrepancy in the results was immediately noted. Namely, as we go through the series of amines primary, secondary, tertiary, the C-N bond length becomes shorter. It was not possible to derive a parameterization that would permit this, within the context of the present force field.<sup>6</sup> Hence the error was averaged out as well as possible.

The stretching and bending force constants were taken from studies on vibrational spectra with use of valence force fields. The stretching constants were used unchanged, while the bending constants were reduced to one-half the spectroscopic value, consistent with earlier practice. A complete listing of the amine force field parameters appears in Table II.

Looking specifically at the structure, MM2 reproduces that of methylamine about as well as the ab initio study.<sup>7</sup> The most glaring error in the MM2 fit is the large difference between the calculated and observed methyl group tilt, which the ab initio method reproduces quite well.<sup>7,8</sup>

The structure of dimethylamine has been investigated by McKean<sup>9,10</sup> using infrared (IR), by Wollrab and Laurie<sup>11</sup> using microwave spectroscopy (MW), and by Beagley and Hewitt<sup>12</sup> using electron diffraction (ED). Using the FORCE method of Pulay,<sup>13</sup> Skaarup et al.<sup>14</sup> carried out ab initio calculations on

dimethylamine. The experimental and ab initio results are detailed in Table I along with our calculated geometry (Figure 1). Some time after this work was completed, Schäfer reported 4-21G optimized geometries for CH<sub>3</sub>NH<sub>2</sub> and CH<sub>3</sub>NHCH<sub>3</sub>.<sup>15a</sup> These results show a slight improvement over the previous<sup>14</sup> ones; however, the problems of C-N bond lengthening and exaggerated bond angles at nitrogen remain.<sup>15b</sup>

Four discrepancies between the present calculations and experiment are apparent: (1) The C-H bond lengths are not cal-

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(3) (a) N. L. Allinger, *J. Am. Chem. Soc.* **99**, 8127 (1977); (b) N. L. Allinger and Y. Yuh, *QCPE*, **12**, 395 (1980); Profeta, S., Jr., *QCPE Bull.*, **1**, 57 (1981); (c) The original version of the MM2 program [MM2-77: N. L. Allinger and Y. Yuh, *ibid.*, **12**, 395 (1980)] is available from the Quantum Chemistry Program Exchange, University of Indiana, Bloomington, Indiana 47401. A later version (which contains only additions and improvements, but gives identical results for any molecules that could be treated by the original version), MM2-82, together with the companion program designed to deal with conjugated systems, MMP2-82, are available from the Molecular Design, Ltd., 2132 Farallon Dr., San Leandro, CA 94577. The amine parameters discussed herein are present in all versions of MM2.

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(5) (a) N. L. Allinger and D. Chung, *J. Am. Chem. Soc.* **98**, 6798 (1976); N. L. Allinger, S. H.-M. Chang, D. H. Glaser, and H. Höning, *Isr. J. Chem.* **20**, 51 (1980); (b) U. Burkert, *Tetrahedron*, **33**, 2237 (1977); (c) S. Melberg and K. Rasmussen, *J. Mol. Struct.*, **57**, 215 (1979), and earlier papers.

(6) Subsequent to the completion of this work, it was recognized that this problem stemmed from what we have called the "electronegativity effect", and it is now evident what steps must be taken to correct for it. These corrections will not, however, be made in MM2 for practical reasons, but they will be included in MM3 in due course. See: L. Norskov-Lauritsen and N. L. Allinger, *J. Comput. Chem.*, **5**, 326 (1984), for further discussion.

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Table I. Experimental and Calculated Data on Small Amines

parameter	MM2	ab initio	MW <sup>c</sup>	ED <sup>c</sup>
Ammonia				
N-H, Å	1.013	(see ref 89)	1.0144 ± 0.0020 <sup>90</sup>	
H-N-H, deg	107.6		107.1 ± 0.9	
Methylamine				
C-H, Å	1.114	1.095 (a) <sup>7</sup> 1.086 (s)	1.093 ± 0.006 <sup>90,91</sup>	
C-N, Å	1.454	1.484	1.474 ± 0.005	1.467 ± 0.002 <sup>92</sup>
N-H, Å	1.015	1.010	1.014	
H-C-H, deg	109.0 (a) <sup>b</sup> 109.1 (s) <sup>b</sup>	107.5 (s) 108.4 (a)	109.47 ± 0.8	
C-N-H, deg	111.3	111.0	112.1 ± 0.8	
H-N-H, deg	105.4	105.9	105.85 ± 0.6	
CH <sub>3</sub> tilt, deg	0.19	3.9	3.5	
Trimethylamine				
C-N, Å	1.465		1.454 ± 0.003 <sup>93</sup>	1.454 ± 0.002 <sup>92</sup>
C-N-C, deg	110.9		110.9 ± 0.6	
Dimethylamine (Figure 1)				
N-H, Å	1.017	0.999 <sup>14</sup> (1.021) <sup>97</sup>	1.019 ± 0.007 <sup>9,11</sup>	1.00 ± 0.2 <sup>12</sup>
N-C, Å	1.460	1.461 (1.393) <sup>a</sup>	1.463 ± 0.005	1.455 ± 0.002
C-H, Å	1.115	1.080 (1.122) <sup>a</sup>	1.084 ± 0.005	1.106 ± 0.003
C-H, Å	1.115	1.081	1.098 ± 0.004	1.106 ± 0.003
C-H, Å	1.115	1.090	1.098 ± 0.004	1.106 ± 0.003
C-N-H, deg	109.5	112.3	108.9 ± 0.3	107 ± 2.0
C-N-C, deg	112.1	115.1 (129.4) <sup>a</sup>	112.2 ± 0.2	111.8 ± 0.6
N-C-H, deg	109.4	109.4	109.7 ± 0.3	
N-C-H', deg	110.7	109.2	108.2 ± 0.3	112.0 ± 0.8
N-C-H'', deg	110.7	114.0	113.8 ± 0.3	
H-C-H', deg	108.2	108.0	109.0 ± 0.2	106.8 ± 0.8
H-C-H'', deg	108.3	108.5	109.0 ± 0.2	106.8 ± 0.8
H'-C-H'', deg	109.4	107.6	107.2 ± 0.3	106.8 ± 0.8
CH <sub>3</sub> tilt, deg	0.9	3.2	3.4	

<sup>a</sup> Values in parentheses are MINDO/3 values, see ref 94. <sup>b</sup> (a) = anti; (s) = synclinal. <sup>c</sup> MW = microwave; ED = electron diffraction.

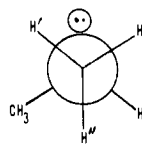


Figure 1. Designation of atoms in dimethylamine ( $\omega$ H-C-N-C = 180°) (from Boggs<sup>14</sup>).

culated by MM2 to be as different as the ab initio method predicts, or as deduced from IR studies (i.e., these show two short C-H bonds and one long one, trans to the lone pair). (2) The MM2 C-N-H angle is considerably closer to the microwave value of 108.9°; whereas the ab initio value is opened by 3°. (3) The C-N-C angle is off by 3° in the ab initio calculation, whereas the MM2 result is excellent. (4) The H'-C-H'' angles is approximately tetrahedral by the MM2 method; conversely, both the ab initio and microwave results show a 2° shrinkage (107.4 ± 0.2).

Further discussion on the topic of tilt and asymmetry of methyl groups in asymmetric environments, giving ab initio results and caveats concerning the interpretation of the same, is given by Flood, Pulay, and Boggs.<sup>8</sup>

The calculated and experimental geometries for trimethylamine are also given in Table I. Except for the aforementioned problem with the C-N bond length, there is little discrepancy between the two.

Torsional barriers are usually a major problem in the development of a force field. For methylamine fragments the torsional coefficients involving the lone pair were all set equal to zero. A value for the  $V_3$  term of 0.25 kcal/mol for the H-C-N-H dihedral angle was chosen (see Figure 1 for staggered dimethylamine). The calculated values of 1.90, 3.04, and 4.22 kcal/mol for methyl-, dimethyl-, and trimethylamine are then in good agreement with the experimental values of 1.98, 3.28, and 4.35 kcal, respectively. The calculated values were deliberately set a bit low as discussed elsewhere.<sup>3,4,16</sup>

Some difficulties arose in developing torsional potentials for the C-C-N-H and C-C-N-Lp fragments. In contrast to the potentials for methyl rotations in the methylamines which have been determined with high accuracy, the torsional potentials in "ethylamine"-type fragments have not been unequivocally evaluated. These values are crucial to the accuracy of the force field for torsions in alkyl amines larger than ethylamine.

If one examines the N-H equilibrium in piperidine, one can see where the "ethylamine" torsions are critical. The crux of the ethylamine problem deals with the gauche/trans free energy difference around the C-N bond with the lone pair used as the terminal "atom" in the C-C-N-Lp dihedral angle. (This angle appears preferable as a reference angle in aliphatic amines, because the lone pair is unique.) The experimental data available on the conformational preferences of ethylamine present a contradictory picture. We wished to fit the experimental data for piperidine and the ethylamine equilibria simultaneously with the same sets of torsional parameters ( $V_1, V_2, V_3$ ). The numerical data to be fit come from Durig and Li<sup>17</sup> for ethylamine and from Anet<sup>18</sup> for the piperidine equilibrium, and they are mutually inconsistent. Either one (or both) set of data must involve an error of measurement or interpretation or else a transferable torsional potential function does not exist in this case within the present formalism. Since the previously established existence of accurate transferable potential functions forms the basis for molecular mechanics and has not been shown to really fail in any other case until this point, we do not feel this is the problem. The preferred equatorial position for the proton in piperidine seems quite well established, with a gas-phase preference of 0.25–0.74 kcal/mol (vide infra). We have chosen to fit to this molecule and let the ethylamine results come out as they may.

The problem with the experimental determination of the gauche/trans free energies in ethylamine lies in the difficulty of interpreting the data unequivocally. As a result of their infrared

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(18) F. A. L. Anet and I. Yavari, *J. Am. Chem. Soc.*, **99**, 2794 (1977).

Table II. Force-Field Parameters for Amines

van der Waals					
atom	radius, Å		$\epsilon^d$		
N	1.820		0.055		
H (attached to N)	1.325		0.034		
Lp (lone pair on N)	1.200		0.016		
Bond Dipole					
$\mu^e$					
C-N			+0.04		
N-H			-0.76		
N-Lp			+0.60		
Stretching					
Bond	$l_0$	$K_s^a$	$K_s^a$ (lit. value)	ref	
C-H	1.113	4.60 <sup>e</sup>	4.40-4.60	95	
C-C	1.523	4.40 <sup>e</sup>	(various, see ref 100)		
C-N	1.450	5.10	5.10; 3.01	95, 96	
N-H	1.015	6.10	5.90, 6.29; 6.44	95, 96	
N-Lp	0.600	6.10			
Bending					
angle	$\theta_0$	type <sup>g</sup>	$K_\theta^b$	$K_\theta^b$ (lit. value)	ref
H-C-H	109.40	1			97
	109.00	2	0.32 <sup>e</sup>	0.32	
	109.47	3			
C-C-H	109.39	1			97
	109.41	2	0.36 <sup>e</sup>	0.55	
	110.00	3			
C-C-C	109.47	1			97
	109.51	2	0.45 (0.34) <sup>f</sup>	0.8, 0.9	
	109.50	3			
H-N-H	104.50		0.50	0.587, 0.566	
C-N-H	109.47		0.50	0.457	95, 96
C-N-C	107.70		0.63 (0.47) <sup>f</sup>	1.0, 0.567, 1.045	95, 96, 98
C-N-Lp	109.20		0.50		
N-H-Lp	108.00		0.50		
H-C-N	108.80		0.50	0.48	95
C-C-N	109.50	1			
	108.80	2	0.57 (0.32) <sup>f</sup>		
	109.47	3			
Torsional Parameters <sup>d</sup>					
dihedral angle	$V_1$	$V_2$	$V_3$		
C-C-C-C <sup>e</sup>	0.20	0.27	0.093		
C-C-C-H <sup>e</sup>	0.0	0.0	0.267		
H-C-C-H <sup>e</sup>	0.0	0.0	0.237		
H-C-C-N	-0.15	0.0	0.15		
C-C-C-N	0.10	0.40	0.50 (2.50) <sup>h</sup>		
C-C-N-Lp	0.20	-0.22	0.10		
C-C-N-H	0.0	0.12	0.10		
C-C-N-C	-0.20	0.73	0.80 (2.50) <sup>h</sup>		
H-C-N-C	0.0	0.0	0.52		
H-C-N-Lp	0.0	0.0	0.0		
H-C-N-H	0.0	0.0	0.25		
N-C-C-N	-0.4	-0.9	1.50		
(O=C)-C-C-N	0.0	0.40	0.50		

<sup>a</sup> Values in mdyn/Å. <sup>b</sup> Values in mdynÅ/rad<sup>2</sup>. <sup>c</sup> Values in debyes; for a molecule X-Y the sign of the moment is positive if X is the positive end of the dipole and negative if it is the negative end. <sup>d</sup>  $\epsilon$  is a measure of the "hardness" of an atom. It is also proportional to the depth of the well at the van der Waals' minimum. Values in kcal/mol. <sup>e</sup> These values were previously chosen as described in ref 5. <sup>f</sup> Value of  $K_\theta$  with angle is within a four-membered ring. <sup>g</sup> Type refers to the substitution at the center carbon: 1, X-CR<sub>2</sub>-Y; 2, X-CHR-Y; 3, X-CH<sub>2</sub>-Y. <sup>h</sup>  $V_3$  term used when angle is within a four-membered ring.

studies on ethylamine, Fateley and co-workers<sup>19</sup> state that "...the *trans* minimum is predicted to be lower than the *gauche* minima by about 230 cm<sup>-1</sup> (0.66 kcal/mol) ... however, (the data we are now using) are not very appropriate for determining this aspect

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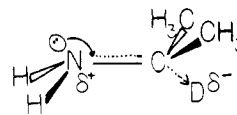


Figure 2. Electron delocalization in the gg form of isopropylamine.

of the potential function". Fateley's group<sup>20</sup> had previously interpreted similar studies as favoring the *gauche* conformation. Durig and Li<sup>17</sup> examined the gas-phase Raman spectrum of ethylamine and concluded that the *trans* conformer was lower in energy by 0.59 kcal/mol. These studies suffered from a lack of information about the *trans* conformer since it does not belong to a totally symmetric species and shows torsional overtones that are difficult to decipher.<sup>17</sup> Additionally, there remains the possibility that the one-dimensional model used treats the data inadequately.

In an effort to resolve the contradictions concerning ethylamine and piperidine, we turned to *ab initio* methods. Unfortunately, we found the energy differences we were examining to be within the noise level of the computational technique, as then available, and have seen significant input geometry and basis set dependence in the calculations.<sup>21,22</sup>

By electing to fit the N-H equilibrium in piperidine, we found that the results of our calculations for other molecules incorporating the C-C-N-Lp fragment were reasonably good, despite the discrepancy with ethylamine. Experimentally there are three major items which weight against the C-C-N-Lp *trans* preference. In isopropylamine, the gg form is favored over the gt form  $\Delta H = 0.12$  kcal/mol<sup>23</sup> (where gg refers to each C-C-N-Lp dihedral angle orientation) by temperature-dependent infrared band analysis of dilute solutions of deuterated isopropylamine. The conformationally heterogeneous quinolizidine alkaloids have been examined<sup>24</sup> and show the lone pair/*trans*-CH(D) phenomenon (Bohlmann bands) in the 2600-2900 cm<sup>-1</sup> region on the IR. Briefly, one sees a decrease in the C-D stretching frequency when there is some delocalization of the lone pair into the C-N bond, resulting in a partial C-N double bond and a "partial-negative" charge on the antiperiplanar D (or H). Figure 2 shows this graphically.

This argument has been used to explain the decrease in  $\nu_{CH}$  in the IR and the increased shielding of the  $\alpha$ -proton in the NMR spectra.<sup>24-27</sup> From IR and NMR work, it was concluded that an  $\alpha$ -CH bond *trans* to the lone pair is a thermodynamically favored situation. Furthermore, the hybridization of nitrogen in this conformation may differ from that in conformations where no  $\alpha$ -CH bond(s) bears this geometrical relationship to the lone pair. This argument as well as the "gauche effect" concept of Wolfe<sup>28</sup> have been considered by Durig et al.<sup>29</sup> in their Raman and infrared investigation of isopropylamine-*d*<sub>0</sub> and -*d*<sub>2</sub>. They examined the gaseous, liquid and solid phases of isopropylamine and gave a complete vibrational assignment for the *s-trans* (gg) conformer. An asymmetric potential function was fit to the observed transitions, and an enthalpy difference (gas phase) of 0.45 kcal/mol was found, with the *s-trans* (gg) conformer of lower energy. This value is in qualitative agreement with the previous  $\Delta H$  determined by Krueger and Jan<sup>23</sup> (0.12 kcal/mol) and our calculated value, 0.15 kcal/mol. Durig notes, however, that their rotational potential function of isopropylamine may be influenced

(20) A. S. Manocha, E. C. Tuazon, and W. G. Fateley, *J. Phys. Chem.*, **78**, 803 (1974).

(21) S. Profeta, Jr., P. A. Kollman, and N. L. Allinger, unpublished results.

(22) S. Profeta, Jr., to be submitted.

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(25) J. Skolik, P. J. Krueger, and M. Wiewiorski, *Tetrahedron*, **24**, 5439 (1968).

(26) See, for example: H. P. Hamlow, S. Okada, and N. Nakagawa, *Tetrahedron Lett.*, 2553, (1964); F. Bohlmann, *Ber.*, **91**, 2157 (1958).

(27) P. J. Krueger and J. Jan, *Can. J. Chem.*, **48**, 3226 (1970).

(28) S. Wolfe, *Acc. Chem. Res.*, **5**, 102 (1972).

(29) J. R. Durig, G. A. Guirgis, and D. A. C. Compton, *J. Phys. Chem.*, **83**, 1313 (1979).

by various sources of error. Hydrogen bonding may affect the vibrational intensities in the condensed phases, although the extent of such is apparently low because the hydrogen-bonded N-H stretches are relatively weak. Additionally, the asymmetric torsions have been approximated by harmonic oscillators and only a partial assignment could be made for the gt conformer. From a careful scrutiny of the available data,<sup>29</sup> we conclude that, allowing for errors in the function derived by Durig, the agreement between our calculated value and experiment is acceptable. An examination of the  $\Delta E$  values in Table V will show that MM2 does better than other calculational methods in predicting torsional barriers in small amines. The ab initio values are consistently too high, whereas these from the modified CNDO technique are consistently too low.

We also examined three cycloalkylamines related to isopropylamine, cyclobutyl-, cyclopentyl-, and cyclohexylamine. In these systems, as in isopropylamine, we calculate a gg preference over gt for the C-C-N-Lp fragments of 0.05, 0.15, and 0.16 kcal/mol for C4-C6, respectively. For cyclobutylamine, infrared data<sup>30</sup> were used to evaluate the amino torsions and the ring-puckering modes. The potential function governing the amino group rotation was derived and shows the gg isomer (H-C-N-Lp trans) favored over the gt by 0.15 kcal/mol, in excellent agreement with the  $\Delta H$  for isopropylamine (0.12 kcal/mol). The calculated gg/gt energy difference for cyclobutylamine (0.15 kcal/mol) is in good agreement with experiment. For cyclopentylamine, only qualitative evidence exists concerning its conformational preferences. Kalasinsky<sup>31</sup> has reported Raman and infrared spectra of gaseous, liquid, and solid cyclopentylamine. The data have been interpreted in terms of an envelope conformation of the cyclopentane ring, from precedents from other monosubstituted cyclopentanes,<sup>32</sup> with an equatorial NH<sub>2</sub> group. However, since a variable-temperature study of band intensities was not possible to determine a  $\Delta H$  value, only "very rough" estimates of conformer populations were given. These suggest a 1.6 kcal/mol energy difference for the axial-equatorial equilibrium, in good agreement with the calculated value of 1.5 kcal/mol (relative to 1-*eq*-NH<sub>2</sub>(envelope)). However, Kalasinsky<sup>31</sup> suggests  $\Delta H$  values of 2.0 or 1.2 kcal/mol for the gg-gt equilibrium depending on which conformer is more stable, far in excess of the calculated value of 0.15 kcal/mol. From the far-IR spectra, however, it is clear that a gg-gt equilibrium exists, and we suggest that the calculated  $\Delta E$  is a better assessment of this equilibrium. An axial-equatorial equilibrium complicates the spectral interpretation considerably.

In the case of cyclohexylamine, it has been established<sup>33</sup> that the amino group has a preference for the equatorial position, with the  $\Delta G$  dependent on solvent polarity and hydrogen-bonding strength. Free energies in the range of 1.1-1.8 kcal/mol have been reported.<sup>33</sup> Our calculated value, 1.37 kcal/mol (with a gg orientation around the C-N bond), was fixed by fitting to a  $\Delta G$  of 1.5 for cyclohexylamine and a gauche-trans difference of 0.65 kcal/mol for propylamine. We have previously evaluated the conformational preferences of propylamine using ab initio techniques in conjunction with our force-field calculations.<sup>34</sup> The calculated free energies of cyclohexylamines (vide infra) follow directly from the gauche-trans free energy difference in propylamine.

At this point, let us return to our discussion of propylamine. The propylamine molecule contains the azabutane moiety (C-C-N) which is important to the conformational analysis of cyclic and acyclic amines. No direct quantitative measurements are available for this system.<sup>35</sup> Pople<sup>36</sup> has reported ab initio

**Table III.** Conformational Energies (in kcal/mol) of Acyclic Amines<sup>a</sup>

compd/conformation	min energy	$\Delta E$ (calcd)	$\Delta E$ (exptl)	ref		
CH <sub>3</sub> NH <sub>2</sub>	CH <sub>3</sub> stg	1.90	1.98 ± 0.01	99		
		2.13		100		
		1.00		37		
(CH <sub>3</sub> ) <sub>2</sub> NH	CH <sub>3</sub> stg	3.04	3.25	101		
		3.62		36		
		1.41		37		
(CH <sub>3</sub> ) <sub>3</sub> N:	all CH <sub>3</sub> stg	4.22	4.35	99		
CH <sub>3</sub> CH <sub>2</sub> NH <sub>2</sub>	0°	2.00	2.20	17, 19		
		60°			0.0	0.6 ± 0.1
		120°			1.78	1.65
		180°			0.13	0.0
(CH <sub>3</sub> ) <sub>2</sub> CHNH <sub>2</sub>	gg	0.15	0.12 ± 0.02	23		
		0.67		101		
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	Tg*	0.0		34, 35		
		Tt			0.13	
		Gg			0.88	
		Gg'			0.65	
		Gt			1.00	
CH <sub>3</sub> NHCH <sub>2</sub> CH <sub>3</sub>	Gt	0.0	≥ 1.3	39		
		Gg			1.14	
(CH <sub>3</sub> CH <sub>2</sub> ) <sub>3</sub> N:	ggg	0.0		40		
		gtg			0.21	

<sup>a</sup>In systems with more than one degree of torsional freedom the upper case letter refers to the orientation of C-C-X-X, where X = C, N; the lower case letter refers to C-C-N-Lp.

calculations on a standard geometry for propylamine. The quantitative discrepancies between Pople's values and our values for the higher energy forms point out the problem associated with rigid rotation calculations on standard geometries. These problems have been discussed previously.<sup>34</sup> Clearly the enthalpy of *gauche*-azabutane with either a *gauche* or *trans* orientation around the C-N bond (Gg, Gg', Gt) should be higher than that of the *trans*. Pople's values of 1.78 and 2.50 are indicative of artificially high energies due to non-relaxed geometries for these forms. The MM2 geometries give rise to reasonable values for the higher energy conformers in the range of 0.6-1.2 kcal/mol (Table IV).

The MM2 calculated potential function for rotation around the C-C bond of propylamine is distinctly butane-like with maxima at 0° (4.44 kcal) and 120° (3.65 kcal) and minima near 60° (0.65 kcal) and 180° (0.0 kcal) (Table V).

The semiempirical calculations of Kao and Chung-Phillips<sup>37</sup> illustrate the general inadequacies of ZDO-type techniques in dealing with conformational equilibria of this kind. However, the MCNDO/1 technique does show some promise (Table IV).

A related system is the *sec*-butylamine molecule, which was calculated to have a similar rotational potential function (Table V). Once again there exists only indirect information on the rotational potential function, with the most exhaustive examination being a <sup>13</sup>C study by Eggert and Djerassi.<sup>38</sup> This molecule was examined as part of an FT-NMR study of over 100 aliphatic amines. Despite the overwhelming amount of data, there was sufficient scatter in the shift values, particularly for the branched amines, that the confidence level for the interpretation is not very high. However, Djerassi did obtain enough data to develop a set of linear correlations between the carbon chemical shifts of amines and the corresponding hydrocarbons. From these data, he concluded that the *gauche* methyl/methyl interaction and the *gauche* methyl/amine interaction for *sec*-butylamine are roughly similar,

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Table IV. Relative Energies (in kcal/mol) Calculated for Propylamine by Various Methods

conformer	MM2	STO-3G/MM1 <sup>a2</sup>	STO-3G/MM2 <sup>34</sup>	4-31G <sup>36</sup>	4-31G/MM1 <sup>2</sup>	4-31G/MM2 <sup>34</sup>	MCNDO/1 <sup>37</sup>
Tg	0.0	0.34	0.38	0.0	0.0	0.26	0.18
Tt	0.13	0.0	0.0	0.50	0.11	0.0	0.69
Gg	0.88	1.20		1.78	0.66		0.00
Gg'	0.65	0.64		0.11	0.30		0.61
Gt	1.00	0.84		2.50	0.61		1.15

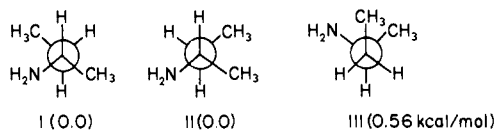
<sup>a</sup>This notation is similar to that of Pople: STO-3G single calculation performed on MM1 optimized geometries.

Table V. Conformational Energies (in kcal/mol) Calculated for Some Simple Amines by MM2

conformer	butane	propylamine <sup>34</sup>	sec-butyl-amine	methyl-ethyl-amine <sup>34</sup>
0°	4.73	4.44	4.49	5.01
G* <sup>a</sup>	0.87 (65)	0.65 (63)	0.56 (62)	1.14 (63)
120°	3.34	3.65	3.89	3.73
180°	0.00	0.00	0.00	0.00

<sup>a</sup>G\* = energy difference at "gauche" minimum (angle value in degrees).

due to the small change in the chemical shift of the  $\beta$ -carbon. Additionally, the  $\gamma$ -methyl group is found to be only 0.7 ppm more shielded than the corresponding methyl group in isopentane. From this, Djerassi concludes that the 1,4 nonbonded interactions for the molecule differ little from those in isopentane. The calculations support this interpretation, showing that there is little difference between conformers I and II below, while the third conformer (III) shows unfavorable van der Waals interactions between the three gauche hydrogens and the *gauche-gauche*/butane-azabutane segments.



We have previously discussed the conformational equilibrium in ethylmethylamine.<sup>34</sup> At the 4-31G level (using MM2 geometries), a significant preference is found for the trans conformer ( $\Delta E = 1.44$  kcal/mol), in reasonable agreement with the MM2 value, 1.14 kcal/mol.

Penn and Boggs<sup>39</sup> investigated the conformations of ethylmethylamine by microwave spectroscopy. They determined that the observed spectrum could be assigned to the trans rotamer (C-C-N-C), and since they were unable to find absorptions due to the gauche isomers, they assumed their abundance to be less than 10% and thus >1.3 kcal/mol higher in free energy. By using a suitable  $V_2$  term for C-C-N-C, we were able to calculate a trans-gauche energy difference of 1.14 kcal/mol, close to the limit they observed. We found that this term also allows us to fit the experimental  $\Delta G$  values of *N*-methylpiperidines, where the C-C-N-C angle is trans in the equatorial methyl and gauche (twice) in the axial methyl conformer. These systems will be discussed further below. The calculated torsional potential for rotation around the central C-N bond in ethylmethylamine is summarized in Table V. Additional discussion is given in ref 34.

An interesting calculational result, which has yet to be confirmed experimentally, is the small free energy difference between two low-energy conformers of triethylamine. Upon examination of a Drieding model of the molecule, one might initially guess that the  $C_3$  form, with all C-C-N-Lp gauche, is the lowest energy conformation. Indeed, we find that the  $C_3$  form is 0.21 kcal/mol lower in energy than a  $C_1$  form, which is a deformed gtg. The C-C-N-Lp dihedral angles of the  $C_1$  form are 60°, 179°, and 45°. In the  $C_3$  form, the methyl groups interact somewhat more than in the  $C_1$  form, giving rise to higher van der Waals energies. However, there is considerably more bending and torsion energy in the  $C_1$  form, and these bias the equilibrium toward the  $C_3$  form.

(39) R. E. Penn and J. E. Boggs, *J. Mol. Spectrosc.* **47**, 340 (1973).

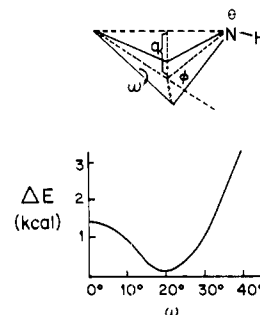


Figure 3. Calculated function of puckering in azetidine.

Bushweller<sup>40</sup> has recently reported a thorough NMR investigation of triethylamine and of methyldiethylamine, and he has compared the experimental results with calculations carried out with the MM2 program (using the parameters developed in the present work). His general conclusion is that the MM2 predictions are well borne out by experiment.<sup>40</sup>

Table V summarizes the calculated and observed conformational energies of several acyclic amines.

Next we would like to consider 1-methyl-1-aminocyclohexane. Here one faces the following question: Is a methyl group sterically "larger" than an amino group? If so, how do their  $\Delta G^\circ$  values counterbalance? We calculate that the methyl-equatorial conformer predominates with  $\Delta G^\circ = 0.69$  kcal/mol. This value is considerably lower than that of either methylcyclohexane (1.7–1.9 kcal) or cyclohexylamine (1.1–1.8 kcal),<sup>33</sup> but similar to the differences between them, as expected if the energies are additive.

We also examined the conformational equilibrium in 1-amino-2-methylcyclohexane. As was expected, the eq-eq conformer is lowest in energy. We find that the  $\Delta G_{Me}$  is reduced by 0.40 kcal/mol whereas the  $\Delta G_{NH_2}$  is reduced by only 0.09 kcal/mol. Thus the amino group vicinal to the methyl alters the free energy difference between the axial and equatorial methyl orientation more than the methyl lowers this same quantity for the amine.

### Cyclic Amines

The nitrogen analogue of cyclopropane, aziridine, was not dealt with as part of this study. The four-membered ring, azetidine, or azetane, was handled with reasonable success.

Far-infrared work by Carreira and Lord<sup>41</sup> showed the azetidine molecule to be puckered, with a planar barrier height of 1.26 kcal, and an equatorial hydrogen preference of 0.27 kcal (Figure 3). An electron-diffraction study<sup>42,43</sup> confirmed the nonplanarity of the ring with an observed pucker ( $\beta$ ) of 33°. Calculated values are 1.09 kcal/mol, 0.05 kcal/mol, and 36.2°.

Catalan et al.<sup>44</sup> carried out ab initio calculations on azetidine at several levels to examine its structure. They did a partial optimization (at the STO-3G level) starting with a  $C_3$  symmetry. They also examined ring inversion, nitrogen inversion, and ring-

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(42) V. S. Mastryukov, O. V. Dorofeeva, L. V. Vilkov, and I. Hargittai, *J. Mol. Struct.*, **34**, 99 (1976).

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(44) J. Catalan, D. Mo, and M. Yañez, *J. Mol. Struct.*, **43**, 252 (1978).

Table VI. Calculated and Observed Structure of Azetidine

structural feature	calcd MM2	exp ED <sup>42</sup>
C-N, Å	1.471	1.482 ± 0.006
C-C, Å	1.549	1.553 ± 0.009
C-H, Å	1.116	1.107 ± 0.003
N-H, Å	1.014	1.002 ± 0.014
∠C-C-C, deg	92.5	92.2 ± 0.4
C-C-C, deg	86.6	86.9 ± 0.4
C-C-N, deg	86.4	85.8 ± 0.4
H-C-H, deg	114.3	110.0 ± 0.7
Φ, <sup>a</sup> deg	36.2	33.1 ± 2.4
q, <sup>a</sup> Å	0.311	
ω, <sup>a</sup> deg	10.7	

<sup>a</sup> See Figure 3 for an explanation.

puckering with the small basis set and then recalculated ring-inversion energies with the 6-31G basis, with similar results. However, all of these results have been questioned by recent investigations, both experimental<sup>45,46</sup> and theoretical.<sup>47,48</sup>

Carreira<sup>41</sup> had assigned the far-infrared spectrum of azetidine (also referred to as trimethyleneimine (TMI)) in terms of a slightly asymmetric double-minimum potential well (see Figure 1, ref 45). However, Strauss et al.<sup>45</sup> showed that the three intense bands at 207, 184, and 148 cm<sup>-1</sup> from the Δν = 2 overtones could equally well be assigned to the lowest Δν = 1 transitions in a highly asymmetric single minimum potential well. Additionally, Bocian et al.<sup>46</sup> have calculated the Raman intensities for ring-puckering transitions for both the single- and double-welled potential functions and found the calculated intensities to be in better agreement with experiment when the highly asymmetric single well potential was used. These results are consistent with ab initio calculations on TMI<sup>47,48</sup> which predict a single puckered equilibrium conformation with the N-H in an equatorial position. The MM2 calculated and observed geometries of azetidine are listed in Table VI. The MM2 treatment does a good job reproducing the gross skeletal features with respect to bond lengths, torsional angles, and bond angles. The puckering function is shown in Figure 3.

We utilized separate bending and torsional constants for this four-membered ring as we had done with other four-membered rings previously, with considerable success.<sup>3,4</sup> In the case of azetidine, a reduction of the endocyclic bending constants by 25% and a 3-5-fold increase in the endocyclic threefold torsion terms were necessary to fit the observed geometry and barrier to planarity. While there remains some doubt regarding the equilibrium value of φ, the MM2 calculations clearly show a significant population of the N-H axial conformer. The bending and torsional parameters which govern this value were taken from the regular amine force field. It may be that the MM2 prediction is incorrect here. The physical situation is clearly that the "axial" hydrogen on the nitrogen is destabilized by van der Waals repulsion from the C<sub>3</sub>-methylene group. If this repulsion is sufficient, since the barrier to nitrogen inversion is not very large, the minimum in the potential energy corresponding to this conformation could be lifted above the barrier, and the conformation would disappear as a stable entity. Because of the effect of the lone pair in the MM2 model, which appears unrealistic in the present application, this result cannot be obtained, and a stable conformation is necessarily found. But this is a result which is built into the model, and it does not have any necessary physical significance.

Pitzer<sup>49</sup> in 1959, predicted pyrrolidine to be a pseudorotor with an estimated barrier of about 1.3 kcal. Very little other information about the parent molecule exists.<sup>107</sup> Our calculations show that the 2-half-chair form is preferred over a host of other conformations by an average of 0.30 kcal and that the height of the

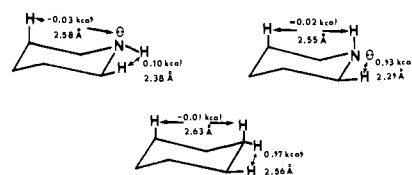


Figure 4. Important van der Waals interactions in piperidine conformers and cyclohexane.

barrier to planarity is 4.37 kcal/mol, very similar to cyclopentane itself. In the lowest energy conformer, the lone pair adopts a pseudoaxial position with the hydrogen pseudo-equatorial. It appears that the envelope forms with N on the flap or adjacent to it are also energy minima. Unfortunately, the molecule gives rise to an uninformative far-infrared spectrum,<sup>50</sup> and neither Raman nor microwave studies have been reported.

An infrared study<sup>23</sup> of the Bohlmann bands of pyrrolidine shows evidence for appreciable amounts of both "axial" and "equatorial" populations for the lone pair. Also available from this work was a ΔH° = 0.20 kcal/mol for the N-H equilibrium which favors the proton "equatorial".

Of all the cyclic amines, the piperidines are the most commonly encountered by organic and medicinal chemists, and the structures and conformational equilibria in these compounds have long been topics of heated debate among heterocyclic chemists and spectroscopists. Previous work by our group has presented conflicting ideas on the position of the equilibrium in piperidine itself. Work published in 1965 detailed both experimental<sup>51</sup> and theoretical<sup>52</sup> investigations which suggested that the hydrogen was equatorial. From dipole measurements on N-alkylpiperazines it was concluded<sup>51</sup> that the N-H equatorial preference was ca. 0.4 kcal. Semiempirical calculations were in complete agreement with the experimental findings.<sup>52</sup> Quantum mechanical methods (HF-SCF) used in further studies on the approach of a helium atom to ammonia supported the idea that at distances of less than 3 Å a hydrogen on nitrogen is "bigger" than a lone pair. In 1967 calculations were reported<sup>53</sup> which showed the axial hydrogen preferred by 0.6 kcal, but this conclusion hinged upon the explicit assumption that the lone pair on nitrogen could be omitted in the calculations. Much has been published since the appearance of the above-mentioned papers concerning both the "size" of the lone pair and its orientation in piperidine. Lambert's<sup>54</sup> and Katritzky's<sup>55</sup> articles provide excellent overviews of the arguments.

To accommodate the lone pair/hydrogen equilibrium in the piperidine molecule, it was desirable to make adjustments in the van der Waals characteristics of the hydrogen attached to nitrogen. Additionally, we varied the torsional terms involving the C-C-N-H and C-C-N-Lp angles such that we had a reasonable agreement with the observed value for the conformational free energy.

It has been widely assumed that the syn-diaxial hydrogen-hydrogen repulsions across the piperidine ring were responsible for the bias in the conformational equilibrium. Implicit in this assumption was the idea that the hydrogen on nitrogen is roughly the same as one on carbon in its van der Waals characteristics. This does not seem intuitively reasonable, from the standpoint of the relative electronegativity differences between nitrogen and hydrogen and from the viewpoint of relative polarizability of the hydrogen attached to nitrogen. Therefore, the arguments for the syn-diaxial theory have been based on questionable premises. According to our calculations on piperidine, the H/H axial and the Lp/H axial interactions are attractive in nature, with values

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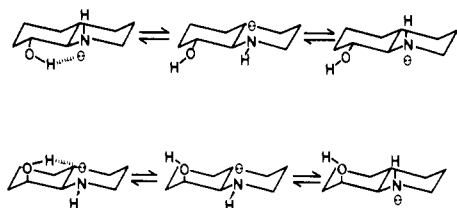


Figure 5. Conformations involved in the 8-perhydroquinolinol equilibria (from Aaron<sup>56</sup>).

Table VII. Calculated Structures of Piperidine and *N*-Methylpiperidine Conformers

	piperidine		<i>N</i> -methylpiperidine	
	<i>eq</i> -H	<i>ax</i> -H	<i>eq</i> -CH <sub>3</sub>	<i>ax</i> -CH <sub>3</sub>
bond lengths				
1-2	1.461	1.462	1.468	1.468
1-7 (CH <sub>3</sub> )			1.467	1.466
2-3	1.535	1.535	1.534	1.535
3-4	1.534	1.534	1.533	1.534
bond angles				
6-1-2	112.1	111.8	111.1	110.4
1-2-3	111.7	111.7	111.7	114.0
2-3-4	110.5	110.4	110.5	110.4
3-4-5	109.6	109.8	109.4	110.2
2-1-7(CH <sub>3</sub> )			110.9	112.1
dihedral angles				
1-2-3-4	56.2	56.3	56.8	55.2
2-3-4-5	54.6	54.3	54.7	53.4
6-1-2-3	57.5	57.9	58.0	54.8
3-2-1-7(CH <sub>3</sub> )			178.2	71.0
$\Delta E$ , kcal/mol	0.0	0.30	0.0	2.50

of  $-0.02$  and  $-0.03$  kcal/mol per interaction, respectively (compare with cyclohexane, Figure 4). The difference between the van der Waals energies of the two conformers is but  $0.06$  kcal/mol. Clearly, we have adjusted several parameters involving nitrogen which will affect the outcome of the calculations, but in the case of piperidine, our force field indicates that except for torsion both conformers are essentially the same structurally and energetically.

As part of the detailed study of hydrogen bonding in amino alcohols, Aaron and Ferguson<sup>56</sup> examined the *N*-H equilibrium in the *trans*-8-decahydroquinolinol systems utilizing dilute-solution IR measurements (Figure 5). They recorded the IR spectra of the  $\alpha$ - and  $\beta$ -epimeric alcohols and assigned the free and hydrogen-bonded hydroxyl absorptions in each. From the mole fractions of the observed species, a  $\Delta G^\circ_{\text{NH}}$  of  $0.5 \pm 0.1$  kcal/mol was calculated with an equatorial *N*-H preference. We have examined the equilibrium in the parent decahydroquinoline and find a  $\Delta G^\circ = 0.30$  kcal/mol, in good agreement with those of Aaron, and also Katritzky<sup>55</sup> ( $0.4 \pm 0.2$  kcal/mol for gas phase and nonpolar solutions).

Anet and Yavari<sup>18</sup> examined the *N*-H equilibrium in piperidine with <sup>1</sup>H and <sup>13</sup>C NMR techniques at very low temperatures. By freezing out nitrogen inversion and using appropriate deuteration, Anet deduced a  $\Delta G^\circ = 0.36$  kcal/mol for piperidine. This value agrees well with the initial microwave estimate,<sup>57</sup>  $\Delta G^\circ = 0.25 \pm 0.15$  kcal/mol based on the relative intensities of absorptions in the spectrum due to the axial and equatorial orientations of the imino hydrogen. However, from the more recent and extensive update of their work, Costain reports<sup>58</sup>  $\Delta E$  at  $0.74 \pm 0.07$  kcal/mol, a value more in line with that of Scott<sup>59</sup> ( $0.60$  kcal) from the vapor-phase infrared spectrum. From the spectra of *N*-H and *N*-D piperidine, Costain et al. conclude that an equatorial-axial ratio of 3:1 best fits the data.

The structures of the piperidine conformers as listed in Table VII are virtually identical. Katritzky<sup>60</sup> has also examined the

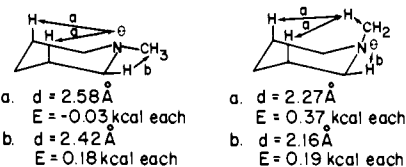


Figure 6. Pertinent van der Waals interactions in *N*-methylpiperidine conformers.

structure of piperidine using the GEOMIN program; however, this study used a primitive force field and yielded little insight into conformer structural differences.

*N*-Methylpiperidine was considered next. The literature abounds with papers debating the magnitude and nature of the *N*-methyl preference. Eliel<sup>61</sup> lists a small, but representative, table of values of the  $\Delta G^\circ_{\text{Me}}$  for the equilibrium, which ranges from  $0.4$  to  $2.7$  kcal/mol, all favoring the equatorial *N*-methyl. The best earlier estimates placed the value near  $1.8$  kcal/mol. Most workers now agree that the value lies near  $2.7$  kcal.<sup>61-65</sup> The most recent work of Robinson<sup>62</sup> claims a still larger value for the gas phase,  $3.15$  kcal/mol. Our compromise value is  $2.50$  kcal, obtained by optimizing the C-C-N-C torsional terms for *N*-methylpiperidine concurrently with about ten other structures (quinolizidine, *cis*-perhydroquinoline, 1,2,2,6-tetramethylpiperidine, tropane, 2-methylpiperidine, etc.). The two dominating terms in the steric energies are the bending and torsional terms. These terms account for  $2.4$  kcal of the difference between the axial and equatorial conformers. The torsional energy is easily understood by examining the dihedral angles around nitrogen. Clearly, the gauche CCNCH<sub>3</sub> orientation raises the energy of the axial form substantially over the corresponding trans orientation in the equatorial methyl form (at least  $2.3$  kcal based on the ethylmethylamine gauche effect<sup>34</sup>). For the dihedral angle of  $71^\circ$ , each gauche interaction actually costs  $0.59$  kcal in torsion alone. As one can see in Figure 6, there are also two syn-diaxial hydrogen-(methyl)-hydrogen interactions costing  $0.34$  kcal each. These interactions, coupled with the opening of the C-C-N angles to  $114.0^\circ$  (at  $0.25$  kcal per angle), combine to give an overwhelming bias toward the equatorial *N*-methyl conformer. Additionally, when one compares the geometries of the two conformers to the geometry of trimethylamine, the angle distortions are particularly evident. In trimethylamine, the C-N-C angles are  $110.8^\circ$ . In the equatorial *N*-methyl conformer, they are similar, in  $110.9^\circ$  for the  $-\text{CH}_2-\text{N}-\text{CH}_3$  angle and  $111.1^\circ$  for the internal angles. However, for the axial conformer, these same values are  $112.1^\circ$  and  $110.4^\circ$ , indicating some distorting force at work. The repulsion between the syn-axial hydrogens and the methyl is mainly responsible for this distortion. The methyl retreats from the hydrogens, quite analogous to what is found in *ax*-methylcyclohexane.<sup>3,4</sup> The C-N bonds are shorter than the C-C bonds, so the energy of the axial methyl is somewhat higher here than in the hydrocarbon.

Anet and co-workers<sup>63</sup> examined the *N*-methyl conformational equilibrium in the congested 1,2,2,6-tetramethylpiperidine system. They found by DNMR and fast acid quenching techniques that there is a lower  $\Delta G^\circ_{\text{NMe}}$  here than in the parent compound. Indeed, they report a  $\Delta G^\circ = 1.90 \pm 0.2$  kcal/mol for this highly hindered piperidine. The calculations bear this out also, with an equatorial preference of  $1.70$  kcal/mol.

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(58) J. E. Parkin, P. J. Buckley, and C. C. Costain, *J. Mol. Spectrosc.*, **89**, 465 (1981).

(59) D. W. Scott, *J. Chem. Thermodyn.*, **3**, 649 (1979).

Table VIII. Calculated and Observed Conformation Energies (in kcal/mol) in Simple Monocyclic Amines

system	stable conf	$\Delta E$ (calcd)	$\Delta E$ (exptl)	ref
azetidine	puckered, N-H eq	0.05	0.27	41
pyrrolidine	2-env. or half-chair	0.24	0.20 $\pm$ 0.04	107
cyclobutylamine	NH <sub>2</sub> eq(gg) <sup>a</sup>	0.15	0.16	102
cyclohexylamine	NH <sub>2</sub> eq(gg) <sup>a</sup>	1.37	1.1-1.8	33
1-amino-1-methylcyclohexane	Me eq	0.64		
eq-1-amino-2-methylcyclohexane	Me eq	1.45		
1-amino- <i>eq</i> -2-methylcyclohexane	NH <sub>2</sub> eq	1.28		
1-amino-2,2-dimethylcyclohexane	NH <sub>2</sub> eq	1.12		
piperidine	N-H eq	0.30	0.3-0.8	54, 55, 58
eq-2-methylpiperidine	N-H eq	0.29		
ax-2-methylpiperidine	N-H eq	0.23		
3-methylpiperidine	CH <sub>3</sub> eq	1.62	1.6, 1.65	65, 66
eq-3-methylpiperidine	N-H eq	0.30		
ax-3-methylpiperidine	N-H eq	0.49		
4-methylpiperidine	CH <sub>3</sub> eq	1.75	1.9, 1.93	66, 103
2,2,6,6-tetramethylpiperidine	N-H eq	0.40		
cis-2,6-di- <i>tert</i> -butylpiperidine	N-H ax	-0.65	0.65	67, 69
N-methylpiperidine	CH <sub>3</sub> eq	2.50	0.4-3.15	60, 104
2-methylpiperidine (N-H eq)	CH <sub>3</sub> eq	2.11	2.5 <sup>b</sup>	65, 66
eq-2-methyl-N-methylpiperidine	N-CH <sub>3</sub> eq	1.68	2.5 <sup>b</sup>	
eq-3-methyl-N-methylpiperidine	N-CH <sub>3</sub> eq	2.57	2.5 <sup>b</sup>	
eq-4-methyl-N-methylpiperidine	N-CH <sub>3</sub> eq	2.47	2.5 <sup>b</sup>	
eq-4- <i>tert</i> -butyl-N-methylpiperidine	N-CH <sub>3</sub> eq	2.52	2.5 <sup>b</sup>	
1,2,2,6-tetramethylpiperidine	N-CH <sub>3</sub> eq	1.70	1.95 $\pm$ 0.2	63
1- <i>eq</i> ,2-dimethylpiperidine	2-CH <sub>3</sub> eq	1.68	1.5, 1.9, 1.7	65, 66
1- <i>eq</i> ,3-dimethylpiperidine	3-CH <sub>3</sub> eq	1.62	1.5, 1.77, 1.6	64, 66
1- <i>eq</i> ,4-dimethylpiperidine	4-CH <sub>3</sub> eq	1.72	1.98, 1.8	64, 66
2,3,3-trimethylpiperidine	2-CH <sub>3</sub> eq	1.24		
2,2,3-trimethylpiperidine	3-CH <sub>3</sub> eq	1.13		
1- <i>eq</i> ,2,3,3-tetramethylpiperidine	2-CH <sub>3</sub> eq	0.60		

<sup>a</sup> Each C-C-N-Lp dihedral is gauche. <sup>b</sup> This approximate value was taken as an average from analogous systems in ref 60-66 and 103.

Table IX. Steric Energy Components of the 2-Methylpiperidines

energy, kcal/mol	N-H		N-CH <sub>3</sub>	
	eq	ax	eq	ax
compression	0.40	0.42	0.82	0.76
bending	0.73	1.50	1.64	2.55
stretch-bend	0.12	0.18	0.30	0.35
1,4-VDW	5.36	5.26	7.18	7.00
other VDW	-1.46	-1.21	-0.96	-1.01
torsion	1.82	2.92	2.35	3.35
total	6.96	9.07	11.34	13.02
$\Delta E$ (calcd)	0.0	2.11	0.0	1.68
$\Delta E$ (exptl) <sup>65,66</sup>	0.0	2.52	0.0	1.5, 1.8

Similarly, we investigated an analogous effect with a methyl attached at carbon in 1,2,3,3-tetramethylpiperidine. Here the calculations show a drastic reduction in the free energy difference, with the equatorial C(2) methyl preferred over the axial by only 0.67 kcal/mol. This predicts a sizable population of the axial C(2) methyl conformer which is yet to be verified experimentally.

Laser Raman studies by Day<sup>67,68</sup> prompted us to examine *cis*-2,6-di-*tert*-butylpiperidine. In the Raman spectrum of this compound, two intense bands are seen at 3376 and 3308 cm<sup>-1</sup> in a 3:1 ratio. Day interpreted these as due to the equatorial and axial orientations of the N-H, respectively. In light of the presence of Bohlmann bands in the 2774-2715 cm<sup>-1</sup> region, there is some population of the N-H equatorial conformer. We suggest, however, that the axial N-H conformer predominates, since we calculate  $\Delta E = 0.65$  kcal/mol, corresponding to exactly a 3:1 axial:equatorial ratio. The calculated repulsions between the two nearest methyl hydrogens and the equatorial imino hydrogen are 1.05 kcal/mol each. No such large repulsions are seen in the *ax*-H conformer. Additional spectroscopic work on this system is in progress.<sup>68</sup>

The next group of compounds we examined were various alkyl-substituted piperidines. Table VIII lists the conformational

Table X. Conformational Energies (in kcal/mol) for C-Methyl Groups in Piperidine Systems

	calcd	exptl
Piperidines		
2-Me	2.11	2.52 <sup>65,66</sup>
3-Me	1.62	1.6-1.65 <sup>65,66</sup>
4-Me	1.75	1.9, <sup>66</sup> 1.93 <sup>103</sup>
N-Methylpiperidines		
2-Me	1.68	1.89, <sup>65</sup> 1.5, <sup>65</sup> 1.8 <sup>66</sup>
3-Me	1.62	1.77, 1.5, <sup>64</sup> 1.6 <sup>66</sup>
4-Me	1.72	1.98, <sup>64</sup> 1.8 <sup>66</sup>

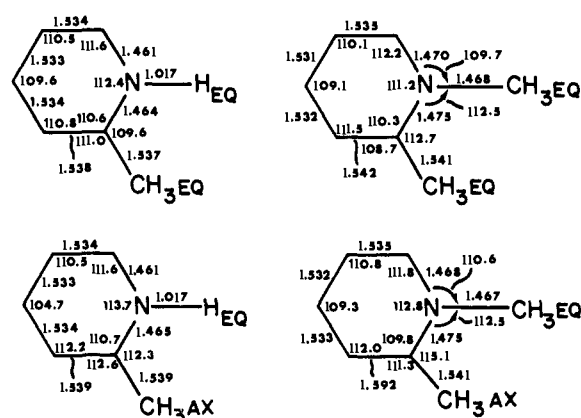


Figure 7. Calculated structures for 2-methylpiperidines.

energies we calculated for several representative amines. Our primary objective was an examination of the trends in the conformational equilibria reflecting the increased structural complexity of each system. We examined the geometries and energies of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -methyl groups in both the axial and equatorial positions, in the parent piperidine and in the N-methyl derivative.

As noted by Eliel,<sup>65,66</sup> the conformational energy of the methyl group in 2-methylpiperidine is unusually large (Tables VIII-X). Although the calculated value (2.11 kcal/mol) is smaller than

(66) E. L. Eliel, D. Kandasamy, C.-Y. Yen, and K. D. Hargrave, *J. Am. Chem. Soc.*, **102**, 3698 (1980).

(67) J. C. Day, *J. Org. Chem.*, **43**, 3646 (1978).

(68) J. C. Day, personal communication.



Eliel's, it is still apparent that this energy is larger than that for all the other piperidines. Booth finds a similar effect in the methyldecahydroquinolines. Both Eliel<sup>65,66</sup> and Booth<sup>69</sup> feel that the shorter C–N bond length and the ring puckering around nitrogen cause an increase in the 2,6-syn-diaxial repulsions across the ring. This explanation is only partly borne out by the calculations. The calculated energies (Table IX) and structures (Figure 7) for the conformers show that one must consider the opening of the C–N–C internal angle (112.4° in equatorial conformer, 113.7° in axial conformer) which exerts a flattening effect at the nitrogen (compare cyclohexane, 111.4° and piperidine, 112.1°). Angle bending in the *ax*-2-methylpiperidine conformer at C-2 is greater than one might expect with an external (N–C–CH<sub>3</sub>) angle expansion to 115.1°. In the case of *N*,2-dimethylpiperidine, the elongated methyl–N and methyl–C bonds do not cost much energy, and accordingly, the strain at C(2) is not as great. Yet, there is a sizable difference in the bending energies of the two *N*,2-dimethylpiperidine conformers. The similarity in the torsion energies of the two narrows the overall energy difference to 1.68 kcal, favoring both methyls equatorial, a result very similar to 1,2-dimethylcyclohexane where the  $\Delta E$  is 1.62 kcal/mol favoring the diequatorial conformer.<sup>3,4</sup>

Rozeboom and Houk have proposed<sup>70</sup> a possible explanation for the large  $\Delta E$  in the 2-methylpiperidine system based on their photoelectron spectral investigations. In their studies of methylated piperidines, they found that axial methyl groups at the C-3 or C-4 position showed a very small effect on the ionization potentials (IPs), whereas an *ax*-2- or -6-methyl group caused a very large lone pair IP decrease. This effect was the same for both *N*-H and *N*-Me piperidines where each *a*-axial methyl group lowered the IP by  $0.26 \pm 0.02$  eV. Houk proposed that only a CC hyperconjugative mechanism, in which the  $\sigma_{CC}$  orbital is a more potent hyperconjugative donor than a  $\sigma_{CH}$  orbital, could be compatible with the PES results. Indeed, the orbital contour plots (see Figure 2 in ref 70) show significant mixing of the amine lone pair and 2,6-axial bonds in piperidine. Such an effect would be incorporated into the torsional potential in molecular mechanics.

A caveat is in order concerning interpretation of the theoretical conformational studies of piperidines and the work of Rozeboom and Houk. Their study gives misleading relative energies for the substituents on piperidine rings. The calculations, done at the STO-3G level, suggest that in piperidine an equatorial *N*-H is favored by 1.0–1.9 kcal/mol while equatorial *N*-Me is favored by 5.4–10.8 kcal/mol. The authors make no comment regarding the accuracy of these values. However, they state that the geometries used were based on the *crystal structure* of piperidine·H<sub>2</sub>S.<sup>71</sup> Indeed, the geometries used differ greatly from those found in our studies: e.g., compare C–N = C–C = 1.49 Å, or C–H = 1.09 Å, or *N*-H = 1.00 Å and all bond angles = 109.5°, or all dihedral angles staggered or anti to the MM2 values in Table VII. It becomes clear that the energy differences are quite sensitive to the geometry used in the calculations. It is also worthwhile to note a significant basis set dependence of the relative energies, as can be seen in the following results on piperidines by using MM2 refined geometries: piperidine STO-3G  $\Delta E$  = –0.23 kcal, 6-31G  $\Delta E$  = 0.78 kcal; *N*-methylpiperidine STO-3G  $\Delta E$  = 2.36 kcal, 6-31G  $\Delta E$  = 3.77 kcal; 2-methylpiperidine (2-Me equilibrium) STO-3G  $\Delta E$  = 2.12 kcal, 6-31G  $\Delta E$  = 3.12 kcal. These results present a sample of the somewhat perplexing situation encountered when using ab initio techniques to evaluate conformation equilibria. The results in piperidine are acceptable at the 6-31G level, whereas the STO-3G results are more in line with experimental observations for *N*- and 2-methylpiperidine. The geometry/basis set dependence phenomenon has been explored by others; however,

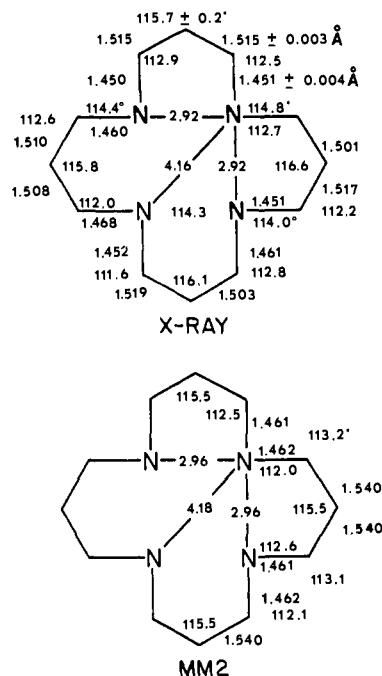


Figure 8. The observed and calculated structures for the macrocycle [16]aneN<sub>4</sub>.

we have examined amines systematically and preliminary results are available from one of the authors (S.P.). We conclude that one must make *very* judicious use of ab initio relative energy values and explore both basis set and geometry sensitivity of the results. Errors of  $\pm 1$ –1.5 kcal/mol are very common.

Table X lists the conformational free energies for methyl groups in the piperidines as determined by experiment and by calculation. The value is somewhat large for 2-methyl and normal (cyclohexane like) for 3- and 4-methyl by experiment, and the calculations reproduce these values reasonably well.

The last monocyclic amine which we examined was an unusual system, a 16-membered ring with nitrogens at every fifth position. This tetraazacyclohexadecane, also referred to as [16]aneN<sub>4</sub>, was recently shown to have a highly symmetric structure, with nearly *D*<sub>2d</sub> symmetry apart from the *N*-H bonds.<sup>72</sup> The alternating *N*-H bonds lower the symmetry of the ring to *S*<sub>4</sub>. Most noteworthy in the comparison between the crystal structure and the calculated structure (Figure 8) is the high correlation of the C–N bond lengths and the overall trends of the bond angles. Despite the differences between the observed and calculated values for the angles, there are clearly observable trends inherent in both structures. The calculated structure shows very regular dihedral angles, with little deviation from skeletal angles of 60 or 180°. The X-ray structure shows values for the C–C bond lengths a bit on the short side (expected because the data were collected at room temperature and corrections for thermal motions were not made) while the calculated values are quite normal. The correlation between the X-ray and calculated nitrogen–nitrogen transannular distances is quite good.

### Heat of Formation Calculations

One of the salient features of the molecular mechanics method is its ability to be parameterized to yield accurate heats of formation. With the use of a small number of bond enthalpy increments, one can calculate the heats of formation of hydrocarbons and several other classes of compounds with experimental accuracy.<sup>4</sup> We expect similar results for amines.

Accurate gas phase heats of formation are known for only about 19 aliphatic amines. The experimental accuracy of these determinations is as good as that for any other functional group we have studied, with an average error of 0.20 kcal/mol.<sup>73</sup> Ac-

(69) H. Booth, D. V. Griffiths, and Josefowicz, *J. Chem. Soc., Perkin Trans. 2*, 751 (1976).

(70) M. D. Rozeboom and K. N. Houk, *J. Am. Chem. Soc.*, **104**, 1189 (1982). This study presents  $\Delta E$  values at wide variance with ours. We believe that the reason for these differences arises from the very approximate, non-optimized geometries used by Rozeboom.

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(72) W. L. Smith, J. D. Ekstrand, and K. N. Raymond, *J. Am. Chem. Soc.*, **100**, 3539 (1978).

**Table XI.** Data Necessary for Amine Heat Calculation

eq	wt	HF(0)	SUMH	STERIC <sup>a</sup>	POP <sup>a</sup>	TORS <sup>a</sup>	T/R <sup>a</sup>	ERR <sup>b</sup>	compound
1	9	-5.50	-9.61	0.54	0.0	0.0	2.40	0.12	methylamine
2	9	-4.43	-19.23	1.94	0.0	0.0	2.40	0.12	dimethylamine
3	8	-5.67	-28.84	4.52	0.0	0.0	2.40	0.18	trimethylamine
4	8	-11.35	-17.54	1.12	0.05	0.36	2.40	0.17	ethylamine
5	7	-17.16	-35.08	3.07	0.03	0.72	2.40	0.31	diethylamine
6	8	-22.06	-52.62	11.01	0.05	1.08	2.40	0.19	triethylamine, ggg
7	9	-16.77	-23.95	1.79	0.36	0.72	2.40	0.13	<i>n</i> -propylamine
8	8	-20.02	-25.46	1.55	0.04	0.36	2.40	0.17	isopropylamine, gg
9	5	-22.50	-30.37	2.44	0.71	1.08	2.40	0.40	<i>n</i> -butylamine
10	5	-25.20	-31.88	3.19	0.05	0.72	2.40	0.40	<i>sec</i> -butylamine
11	9	-23.57	-31.79	2.93	0.18	0.72	2.40	0.13	isobutylamine
12	9	-28.90	-33.39	1.94	0.0	0.36	2.40	0.15	<i>tert</i> -butylamine
13	9	-0.80	-25.65	10.95	0.25	0.36	2.40	0.19	pyrrolidine
14	8	-11.27	-32.07	6.58	0.10	0.0	2.40	0.15	piperidine
15	7	-20.19	-39.99	6.96	0.05	0.0	2.40	0.27	2-methylpiperidine
16	7	9.90	-22.45	29.67	0.03	0.72	2.40	0.20	cyclobutylamine, gg
17	8	-13.13	-28.86	11.54	0.15	0.36	2.40	0.22	cyclopentylamine, gg
18	8	-1.03	-41.60	21.80	0.0	0.0	2.40	0.19	quinuclidine
19	0	-10.44	-44.74	23.87	0.0	0.0	2.40	0.19	3-azabicyclo[3.2.2]nonane

<sup>a</sup> See text for definitions. <sup>b</sup> ERR = quoted experimental error.

**Table XII.** Results of the Least-Squares Fitting of Amine Enthalpy Increments<sup>a</sup>

structural features best values		C-N	N-H	N-Me	NISO	NSEC	NTER	TBUN
		6.117	-2.163	-0.217	-1.065	1.189	-1.929	-2.001
eq	wt	HF(0) calcd	HF(0) exptl	difference (calcd - exptl)		compound		
1	9	-5.10	-5.50	0.40		methylamine		
2	9	-4.06	-4.43	0.37		dimethylamine		
3	8	-6.15	-5.67	-0.48		trimethylamine		
4	8	-11.82	-11.35	-0.47		ethylamine		
5	7	-17.60	-17.16	-0.44		diethylamine		
6	8	-21.66	-22.06	0.40		triethylamine, ggg		
7	9	-16.89	-16.77	-0.12		<i>n</i> -propylamine		
8	8	-20.38	-20.02	-0.36		isopropylamine, gg		
9	5	-21.95	-22.50	0.55		<i>n</i> -butylamine		
10	5	-24.79	-25.20	0.41		<i>sec</i> -butylamine		
11	9	-23.77	-23.57	-0.20		isobutylamine		
12	9	-28.90	-28.90	0.00		<i>tert</i> -butylamine		
13	9	-0.43	-0.80	0.37		pyrrolidine		
14	8	-11.73	-11.27	-0.46		piperidine		
15	7	-20.39	-20.19	-0.20		2-methylpiperidine		
16	7	11.10	9.90	1.20		cyclobutylamine, gg		
17	8	-13.68	-13.13	-0.55		cyclopentylamine, gg		
18	8	-0.98	-1.03	0.05		quinuclidine		
19	0	-7.21	-10.44	3.23		3-azabicyclo[3.2.2]nonane		
20	0	-65.64	-65.34	-0.30		2,2,6,6-tetramethyl-4-piperidone		

<sup>a</sup> The standard deviation = 0.4644 on the basis of 18 equations.

**Table XIII.** Strainless Amines Heat Data and Calculated Results<sup>a</sup>

structural features best values		C-N	N-H	N-Me	NISO	SECN	TERN	TBUN
		6.839	-2.405	-0.149	-1.166	1.315	-0.490	-2.319
eq	wt	HF(0) calcd	HF(0) exptl	difference (calcd - exptl)		compound		
1	1	-5.10	-5.10	0.00		methylamine		
2	1	-4.06	-4.06	0.00		dimethylamine		
3	1	-6.15	-6.15	0.00		trimethylamine		
4	1	-11.87	-11.82	-0.05		ethylamine		
5	1	-16.95	-16.91	-0.04		propylamine		
6	1	-20.38	-20.38	0.00		isopropylamine		
7	1	-28.90	-28.90	0.00		<i>tert</i> -butylamine		

<sup>a</sup> The standard deviation = 0.0247 on the basis of 7 equations.

cordingly, we attempted to fit these values well, sometimes compromising a torsional barrier fit in certain key compounds (e.g., *N*-methylpiperidine, 2-methylpiperidine, and quinuclidine).

The method for the calculation of amine heat of formation parameters was as follows:<sup>4</sup> using bond enthalpies derived from the hydrocarbons (SUMH in the Table XI), one totals the hydrocarbon fragment contributions, the torsional increment (TORS)

necessary to compensate for torsional modes, the conformational population increment (POP) to compensate for any other conformers, and a translation-rotation increment (T/R). Added to the sum of the previous terms is the calculated steric energy (STERIC), and this total is then matched against the experimental (HF(0)) in a least-squares routine to derive the optimized values for each bond and structural feature involving nitrogen (Table XII). These values are then placed in our main program and used for subsequent heat of formation calculations on amines. We also derived "strainless" heat of formation parameters (Table

(73) J. D. Cox and G. Pitcher, "Thermochemistry of Organic and Organometallic Compounds", Academic Press, New York, 1970.

XIII), which were developed in the following fashion:<sup>4</sup> We take our calculated heat of formation of compounds which have each bond or structural unit as the values to be fitted. The hydrocarbon fragments contribute to a certain "strainless" value and this is summed with the POP, TOR, and T/R terms mentioned above. No steric energies are added. The least-squares fit then develops a set of parameters which yield a "strainless" parameter set which permits the calculation of relative strain energies between molecules, including those which are not isomers.

For aliphatic amines we have used the following parameter types for the heat calculations: C-N; N-CH<sub>3</sub>; N-CR<sub>3</sub> (TBUN); R<sub>2</sub>NH (SECN, NSEC); N-CHR<sub>2</sub> (NISO); R<sub>3</sub>N (TERN, NTER). These terms are analogous to terms used in the hydrocarbon<sup>3,4</sup> and oxygen force fields.<sup>5a</sup> Similarly, attachment of a nitrogen to an iso carbon or a tertiary carbon permits us to allow for enthalpy changes in these attached alkyl groups as a function of the local environment. Table XI details the component values for each molecule. Table XIII gives the results for the strainless parameters derived by the least-squares fitting by using the values from the previous table.

The overall MM2 fit to the experimental data is good, with a standard deviation of 0.46 kcal/mol, quite close to the hydrocarbon value (0.42 kcal/mol). There are two particular problems in the fitting, both of which may be largely experimental in origin.

First, the experimental heat of formation of cyclobutylamine has been arrived at by using an estimated heat of vaporization.<sup>74</sup> This procedure probably incorporates an experimental uncertainty of at least 0.5 kcal/mol. We calculate the heat of formation of cyclobutane to within less than 0.10 kcal/mol, thus, we cannot blame the hydrocarbon fragment of the compound for the large difference seen in the amine. By the same token, we do a decent job with most of the other amines. However, there remains the fact that the steric energy, and hence the calculated heat, of this molecule depends quite directly on torsional terms which have not been established with high accuracy at the point in the function where they are most critical in cyclobutylamine. The torsional parameters for the C-C-C-N angle, which is nearly 135° in the compound, have been derived from less strained compounds. We do not fit the equilibria in these compounds as well as we might wish; however, we cannot lower the steric energy of cyclobutylamine further without severely altering the compromise fits to other experimental quantities.

The second large discrepancy occurs in the 3-azabicyclo-[3.2.2]nonane (3-ABN) system. We feel that this is an outright error experimentally. There is simply no way we can fit other data for secondary amines and structurally similar hydrocarbons and yet be so far off in this case. Our confidence in the calculated steric energy is stimulated also by crystallographic<sup>75</sup> and NMR data<sup>76</sup> on 3-ABN. Conformational processes in 3-ABN have been examined by Yavari,<sup>77</sup> who recorded low-temperature <sup>1</sup>H spectra. It appears that the compound can undergo rapid pseudorotation and ring inversion due to the flexible -CH<sub>2</sub>NHCH<sub>2</sub>- bridge. We examined several geometries and found that the most stable conformation is indeed an equienergetic *dl* pair. Additionally, the crystal structure<sup>75</sup> and the calculated structure are very similar. The crystallographic study revealed that at 323 K crystals of 3-ABN are "closepacked fcc (face centered cubic)" while at 291° or 7° below the *T*<sub>1</sub> (transition temperature) the crystals, when grown slowly, were orthorhombic. As Westrum notes in his paper on the heats of compounds like this one and quinuclidine,<sup>77</sup> these compounds are difficult to handle, requiring an inert atmosphere, and the plastic nature of these crystals may lead to *hidden* phase transitions for which no allowance has been made. We also note that the heat of sublimation of the compound was not determined by Westrum's group.

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Table XIV. Dipole Moments of Various Simple Amines (Values in Debyes)

compounds	MM2	calcd ab initio <sup>c</sup>	exptl <sup>86</sup>
ammonia	1.43	1.66 (STO-3G) <sup>103</sup> 2.11 (4-31G) <sup>104</sup>	1.47
methylamine	1.33	1.41, <sup>103</sup> 1.77 <sup>7,8</sup>	1.30
dimethylamine	1.10	1.15, <sup>14</sup> 1.14, <sup>105</sup> 1.19 <sup>101</sup>	1.03
trimethylamine	0.64	0.95 <sup>101</sup>	0.63, 0.79-0.91
<i>n</i> -propylamine	1.33	1.45 (STO-3G) <sup>a</sup> 1.77 (6-31G) <sup>a</sup>	1.17, 1.25
isopropylamine	1.33		1.20, 1.45
ethylamine	1.33	1.41, <sup>a</sup> 1.43 <sup>b</sup> (STO-3G) 1.76 <sup>a,b</sup> (4-31G), 1.495 (g) (6-316*) <sup>105</sup> 1.75 (6-31G), <sup>a</sup> 1.459 (g) (6-31G*) <sup>105</sup>	1.23 1.08 (t) <sup>106</sup> 1.21 (g) <sup>106</sup>
diethylamine	1.10	1.098 (STO-3G) <sup>b</sup> 1.265 (6-31G) <sup>b</sup>	1.04-1.27
triethylamine	0.64	0.894 (STO-3G) <sup>b</sup> 0.939 (6-31G) <sup>b</sup>	0.67-1.02
<i>n</i> -butylamine	1.33		1.33-1.45
pyrrolidine	1.11		1.34, 1.44
<i>N</i> -methylpyrrolidine	0.64		0.80-1.34
piperidine	1.10	1.22, <sup>a</sup> 1.20 <sup>b</sup> (STO-3G) 1.42, <sup>a</sup> 1.318 <sup>b</sup> (6-31G)	1.05-1.35
<i>N</i> -methylpiperidine	0.64	0.904 (STO-3G) <sup>b</sup> 0.902 (6-31G) <sup>b</sup>	0.65-0.95
2-methylpiperidine	1.10	1.032 (STO-3G) <sup>b</sup> 1.171 (6-31G) <sup>b</sup>	
quinuclidine	0.64		1.17, 1.22, 1.57

<sup>a</sup> This work; calculated from MM1 optimized structures. <sup>b</sup> This work; calculated from MM2 optimized structures. <sup>c</sup> For compounds which are conformationally heterogeneous, the calculated moment is for the conformational mixture at room temperature.

Sometime after our work on heats of formation of amines was completed, we belatedly discovered the enthalpy of formation for 2,2,6,6-tetramethyl-4-piperidone.<sup>78</sup> The agreement between the calculated and observed structure is good.<sup>79</sup> While the quoted uncertainty in the enthalpy is large (1.05 kcal/mol), our calculated value (-65.64 calcd, -65.34 obsd) is in agreement with the experiment. This compound tests four sets of parameters, namely, hydrocarbon, ketone, amine, and electrostatic, and was a good test of the total MM2 force field.

### Dipole Moment Calculations<sup>3,4,80</sup>

An important part of calculations on molecules with polar linkages involves the dipole-dipole and dipole-charge interactions and their associated energies. The present calculations neglect dipole-charge interactions and utilize a simple dipole-dipole approach. The effect of the solvent is allowed for by dividing the gas-phase electrostatic energy by the dielectric constant of the solvent. Induced dipole moments are neglected. While this method allows for only superficial analysis of these interactions, it suffices for the bulk of the calculations detailed herein.

In cases where there is substantial dipole interaction energy, as in the piperidones, the experimental data on their conformational equilibria can best be reproduced by using different effective dielectric constants for different solvents. In most cases the dielectric constants used are the experimental bulk dielectric constants; however, in some special cases, e.g., benzene, there is a known effective dielectric constant which differs substantially from the bulk constant.<sup>81-85</sup> It must be pointed out also that this

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treatment is applied to interacting dipoles in a special way, and if the two bonds are bound to the same atom, the energy from the interaction is neglected, while the contribution of these individual moments is included in the dipole moment calculation. Additionally,  $C_{sp^2}-C_{sp^2}$  and C-H bonds are assigned moments of zero, so  $E_{\mu_{ab}}$  is calculated only in molecules having two or more polar groups.

In Table XIV are listed the moments of compounds used in our least-squares fitting for the N-Lp, N-H, and C-N moments. The experimental moments come mainly from the compendia by McClelland.<sup>86</sup> In selected cases, such as ammonia and methyl-, dimethyl-, and trimethylamine, the weights of these values were doubled or tripled in the fitting procedure to better reproduce these more accurately determined (by microwave techniques) gas-phase values at the cost of a less satisfactory fit to some of the solution-phase data. With the exception of quinuclidine, our fit to the experimental values is quite good. Quinuclidine is a molecule in which the induced moments in the ring structure would add to the permanent moment, rather than subtract from it. Thus the value calculated in the present scheme is expected to be too small. (The same qualitative situation applies in the other cyclic amines, but to only a minor extent, since in these cases the dipole does not point directly away from the ring from a structurally constrained, peripheral location). Indeed, the MM2 values are significantly better than those obtained so far by ab initio techniques, as the data clearly indicate.

### Conclusions

A force field has been developed which reproduces the structures, conformational properties, and enthalpies of formation of aliphatic amines with reasonable accuracy. We found that 1- and 2-fold torsional terms were necessary to reproduce the conformational energies of various simple amines like the methylamines, piperidine, and methylpiperidines. The calculated structures of several piperidines show the relationship of these systems to cyclohexane and help explain the relative  $\Delta G^\circ_{Me}$  for each. We find that the shorter C-N bond length along with the shorter C...C distance in the C-N-C angle contribute significantly in enhancing nonbonded repulsions in these simple amines.

This force field allows us to predict the relative energies of simple amine conformers with reasonable accuracy. Additionally, the force field has been independently tested by Weisman<sup>87</sup> in studies on orthoamides and various polyamines, by Froimowitz<sup>88</sup>

in investigations of structure-activity relationships in phenylpiperidines, morphinoids, and bicyclic analgesics, and by Bushweller,<sup>40</sup> who made measurements of several barriers and equilibria in a number of compounds. These workers have each reported that the amine force field gives reliable results.

Registry No.  $NH_3$ , 7664-41-7;  $CH_3NH_2$ , 74-89-5;  $(CH_3)_3N$ , 75-50-3;  $(CH_3)_2NH$ , 124-40-3;  $CH_3CH_2NH_2$ , 75-04-7;  $(CH_3)_2CHNH_2$ , 75-31-0;  $CH_3CH_2CH_2NH_2$ , 107-10-8;  $CH_3NHCH_2CH_3$ , 624-78-2;  $(CH_3CH_2)_3N$ , 121-44-8; *sec*-butylamine, 13952-84-6; azetidine, 503-29-7; piperidine, 110-89-4; *N*-methylpiperidine, 626-67-5; pyrrolidine, 123-75-1; cyclobutylamine, 2516-34-9; cyclohexylamine, 108-91-8; 1-amino-1-methylcyclohexane, 6526-78-9; 1-amino-2-methylcyclohexane, 7003-32-9; 1-amino-2,2-dimethylcyclohexane, 24247-77-6; 3-methylpiperidine, 626-56-2; 4-methylpiperidine, 626-58-4; 2,2,6,6-tetramethylpiperidine, 768-66-1; *cis*-2,6-di-*tert*-butylpiperidine, 66922-18-7; 2-methylpiperidine, 109-05-7; 4-*tert*-butyl-*N*-methylpiperidine, 7576-02-5; 1,2,2,6-tetramethylpiperidine, 60812-96-6; 1,2-dimethylpiperidine, 671-36-3; 1,3-dimethylpiperidine, 695-35-2; 1,4-dimethylpiperidine, 695-15-8; 2,3,3-trimethylpiperidine, 93474-52-3; 2,2,3-trimethylpiperidine, 93474-53-4; 1,2,3,3-tetramethylpiperidine, 93474-54-5; quinuclidine, 100-76-5; 3-azabicyclo[3.2.2]nonane, 283-24-9.

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