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are quite good, and one should be able to rely on heats of formation calculated by MM3 for compounds of this class.

All of the heat of formation input and output data are given in Table XXXI. The meaning of the terms is as usual.[3,8] The nine parameters to be evaluated are listed under "best values" in footnote *a*. These include bond energies for the CO and OH bond and structural terms when an oxygen is attached to a methyl, a secondary carbon, or a tertiary carbon. (If attached to a primary carbon, this is zero.) If two oxygens are simultaneously attached to a carbon along with zero, one, or two hydrogens, these terms are respectively OCO, OC1O, and OC2O. When two oxygens are attached to adjacent carbons, we have the term OCCO. These are the parameters used in this work. In Table XXXI are given the number of times each of these parameters appears in a given compound. sumh is the contribution to the heat of formation from the hydrocarbon portion of the molecule which is not being evaluated here but utilizes parameters carried over from the hydrocarbon work.[3]

Looking at the results in Table XXXI, a problem occurs at line 29, isopropyl *tert*-butyl ether. We believe this is an experimental error, since the more hindered compound di-*tert*-butyl ether (line 31) and also diisopropyl ether (line 28) show much smaller errors.

3-Oxabicyclo[3.2.2]nonane (line 36) shows a large error, and since there is nothing exceptional about this compound that we can see, we believe this is an experimental error also. The experimental value for 1-heptanol (line 13) is also clearly in error, and we also suspect the value for 1,3-propanediol (line 19), as this appears to be a rather ordinary structure. We have included 39 compounds in the heat of formation calculations, so the set is well over-determined, and the results should be reliable. Parameters necessary for calculating strainless heats of formation and strain energies were derived and are shown in Table XXXII.

Concluding Remarks

An MM3 parameter set has been derived which permits one to calculate with experimental accuracy various structures, conformational energies, heats of formation, and other properties for a series of alcohols and ethers. The studies have been sufficiently extensive that we believe these parameters will be applicable to compounds of this class in general. Vibrational spectra may also be calculated, although with more limited accuracy. As with the hydrocarbons, we believe that the addition of some selected cross terms into the force field will permit vibrational spectra to be calculated with considerably higher accuracy, but these are expected to have little effect on structures and energies.

The complete set of structural parameters (Table XXXIII), together with the heats of formation parameters are included in MM3(90). A copy of the full MM3 parameter set may also be obtained from the author upon request.

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Molecular Mechanics Calculations (MM3) on Aliphatic Amines

Lawrence R. Schmitz[†] **and Norman L. Allinger***

Contribution from the Departments of Chemistry, School of Chemical Science, University of Georgia, Athens, Georgia 30602, and Marshall University, Huntington, West Virginia 25755.
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Abstract: The MM3 force field has been extended to cover aliphatic amines. The structures of eight compounds have been examined and are generally fit to approximately within experimental error, including dipole moments and conformational equilibria. The heats of formation available (20 compounds) have been fit by a heat of formation parameterization. The vibrational spectra for four simple compounds have also been examined and, excluding the Bohlmann bands, fit to an rms error of 35 cm^{-1}. Hydrogen bonding has been examined in the ammonia dimer and in ethylenediamine.

Introduction

Molecular mechanics calculations have become increasingly convenient for the determination of molecular structures and many other properties in recent years.[1] The MM2 force field[2] has been widely used for such calculations and in general does a creditable job of giving structures and energies for a wide variety of molecules, including aliphatic amines.[4] However, over the years various flaws were found in MM2,[5] and it was decided some time ago to develop a new force field (MM3), by going back to the beginning and correcting these known significant errors in the original formulation. The MM3 force field for aliphatic hydrocarbons has been published.[6] Several other common functional groups have been and are now being examined by using MM3, and this paper is concerned specifically with the aliphatic amines.

The MM2 force field handled aliphatic amines reasonably well.[4] One dissatisfying feature of that force field stemmed from the fact that lone pairs were explicitly introduced into various compounds, including amines, in order to fit experimental data that

Table I. Methylamine (Å/deg)

	MM3	MW[13]	ED[8]	MW[11]
C-H	1.110 1.110	1.093		1.099
C-N	1.463	1.474	1.4652	1.471
N-H	1.016	1.014		1.010
H-C-H	108.71 107.79	109.47		108.0
C-N-H	112.29	112.1		
H-N-H	106.42	105.85		107.1
N-C-H	111.01 110.27			110.3
dipole (D)	1.29	1.336		

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* Address correspondence to this author at the University of Georgia.

[†] Current address: University of West Virginia.

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Table II. Dimethylamine (Å/deg)

	MM3	ED[9]	MW[12]
N–H	1.018	1.000	1.019
N–C	1.462	1.455	1.462
C–H	1.110	1.106	1.084
	1.110	1.106	1.098
	1.110	1.106	1.098
C–N–H	109.83	107	108.9
C–N–C	112.42	111.8	112.2
N–C–H	110.28	112.0	109.7
	110.47	112.0	108.2
	110.22		113.8
H–C–H	107.65	106.8	109
	108.48	106.8	109
	109.64	106.8	107.2
dipole (D)	1.07		1.03

Table III. Trimethylamine (Å/deg)

	MM3	ED[9]	MW[15]	ED[16]
C–N	1.460	1.454	1.451	1.458
C–N–C	111.20		110.9	110.9
N–C–H	111.37			110.2
N–C–H	110.54			110.2
N–C–H	110.30			110.2
dipole (D)	0.62		0.63	

Table IV. Diisopropylamine (Å/deg)

	MM3	ED[14]		MM3	ED[14]
C–N	1.472	1.47	C–N–C	117.36	120.1
	1.471		N–C–C	108.46	108.9
C–C	1.536	1.532		110.41	111.3
	1.535			108.04	
	1.534			111.39	
	1.534				

Table V. Di-*tert*-butylamine

	MM3	ED[17]	
N–C	1.480	1.467	
	1.479		
C–N–C	128.39	135	
N–C–C	110.66	111.3	av
	106.87–113.51		range
C···C(C–N–C)	2.665	2.71	

Table VI. Methylamine Frequencies[a]

sym	mode	exp[20a]	MM3	dif
A″	NH_2 str	3427	3422	−5
A′	NH_2 str	3361	3361	0
A″	CH_3 str	2985	2970	−15
A′	CH_3 str	2961	2969	8
A′	CH_3 str	2820	2872	52
A′	NH_2 sci	1623	1617	−6
A′		1473	1486	−13
A′		1430	1460	30
A″		1485	1446	−39
A″		na	1180	na
A′		1130	1133	3
A′	CN str	1044	1047	3
A″		na	1039	na
A′	NH_2 wag.	780	815	38
A″	NH_2 tor	264	264	−0
		rms error (23.1)		
		no Bohlmann 19.2		

[a] Not applicable is denoted by na.

otherwise could not be dealt with adequately. These lone pairs are somewhat artifactual and complicate the treatment of the vibrational spectrum.[7] They prevent a realistic inversion of the amine hydrogen, a process that one would like to be able to represent. We have found with MM3 that the various reasons for inserting lone pairs into the calculation in MM2 are no longer pertinent. The lone pairs do not require explicit treatment in MM3, and hence they are omitted. This solves the previously mentioned amine inversion problem, as far as MM3 is concerned.

The structures of the three methylamines (methylamine, dimethylamine, and trimethylamine) are known and were used to determine many of the amine parameters. The structures of these compounds are reported in Tables I–III.

Bond Lengths. The CN bond lengths for these compounds are reported as 1.465 (r_g),[8] 1.457 ($r_a + 0.002$),[9] and 1.458 Å (r_α)[16] for the methyl-, dimethyl-, and trimethylamines, respectively. It was not possible to reproduce this trend in the original MM2 force field. We now know that the shortening of the bond with increasing carbon substitution is due to an electronegativity effect,[10] and we have introduced such a correction into the later MM2 force fields.[2] By using a natural bond length (l_0) of 1.4480 Å and an electronegativity correction of 0.006 Å to the natural CN bond length when a hydrogen (rather than a carbon) is attached to the nitrogen, we now calculate these lengths to be 1.463, 1.462, and 1.460 Å, respectively. For methylamine, the NH bond length found by experiment was 1.010 ± 0.005 (r_0)[11] and for dimethylamine 1.00 ± 0.02 (r_a),[9] 1.019 (r_s).[12] We calculate these to be 1.016 and 1.018 Å, respectively.

Bond Angles. Many of the θ_0 parameters required in the force field were found by fitting to the methylamines. The HNH angle in methylamine was reported to be 105.85° [13] and subsequently as 107.1° [11] in two microwave studies. We calculate this angle to be 106.4°. To fit the CNC angle, dimethylamine, trimethylamine, diisopropylamine, and di-*tert*-butylamine were considered as models (see Tables IV and V). Initially, only the two methylamines were considered. That parameterization resulted in too small of a CNC angle in the bulky amines. In order to improve the MM3 structures of the bulky amines, the CNC angle in the methylamines was compromised slightly. We now calculate the following values for the CNC angles: dimethylamine, 112.33° (111.8° θ_a);[9] trimethylamine, 111.20° (110.9° θ_α);[16] diisopropylamine, 117.36° (120.1° [14]); and di-*tert*-butylamine, 128.38°, (135°),[17] and (128.5).[18] The natural angles (θ_0) involving

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(2) The MM2 force field for hydrocarbons was first described in ref 3. Extensions to functionalized molecules and other special problems were described in subsequent papers, which are summarized in ref 1. The original version of the program (MM2(77)) is available from Quantum Chemistry Program Exchange, University of Indiana, Bloomington, Indiana 47405, Program 395. The latest version of the MM2 program, which is referred to as MM2(87), is available to academic users from the Quantum Chemistry Program Exchange, and to commercial users from Molecular Design Limited, 2132 Farallon Drive, San Leandro, CA 94577.

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(7) Because we use an extremely small mass for the electron, the usual formalism would give very high vibrational frequencies for vibrations which involve the lone pair. Certainly the stretching and bending frequencies would be sufficiently high that they would not couple with and distort the rest of the spectrum. The torsional frequencies would have to be examined individually. Of course, one would obtain very large contributions to the zero point energy from this artifact also. While these problems could be worked around, clearly it simplifies the problem to remove these lone pairs. The electron density is offset from the center of atoms like oxygen and nitrogen where lone pairs are present, and this offset is not allowed for in the present MM3 treatment. It could perhaps be better taken into account in other ways, should this be desirable (as is done with hydrogen, for example).

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Table VII. Dimethylamine Frequencies

sym	mode	exp[20b]	MM3	dif
A′	NH str	3374	3376	2
A′	CH_3 str	2986	2972	−14
A″	CH_3 str	2986	2970	−16
A′	CH_3 str	2960	2970	10
A″	CH_3 str	2955	2968	13
A″	CH_3 str	2795	2873	78
A′	CH_3 str	2795	2873	78
A″		1487	1535	48
A′		1469	1502	33
A′		1464	1478	14
A″		1466	1468	−2
A′		1446	1455	9
A″		1414	1449	35
A″	NH wag.	1443	1393	−50
A′		1240	1185	−55
A′		1151	1157	6
A″		1163	1145	−18
A″		1079	1090	11
A″		1027	1037	10
A′	CN str	933	918	−15
A′	NH wag.	738	753	15
A′	CNC bend	384	372	−12
A″	tor	256	270	14
A′	tor	230	206	−24

rms error (32.4)
no Bohlmann 24.4

Table VIII. Trimethylamine Frequencies[a]

sym	mode	exp[20c]	MM3	dif
E	CH_3 str	2978	2974	−4
A′	CH_3 str	2950	2971	21
A2	CH_3 str	na	2970	na
E	CH_3 str	na	2970	na
E	CH_3 str	na	2874	na
A′		2774	2874	100
A′		1466	1522	56
E		1478	1522	44
E		1459	1485	26
A′		na	1485	na
E		1444	1460	16
A2		na	1451	na
E		1272	1263	−9
A′		1183	1201	18
E		1102	1099	−3
A2		na	1093	na
E		1043	1010	−33
A′	CN str	825	830	5
E		425	397	−28
A′	CNC bend	366	356	−10
E		269	280	11
A2	CH_3 tor	261	241	−20

rms error (34.8)
no Bohlmann (25.0)

[a] Not applicable is denoted by na.

Table IX. Isopropylamine GG Frequencies

	exp mode	exp[28]	MM3	dif
A″	NH_2 str	3411	3422	11
A′	NH_2 str	3342	3362	20
A′	CH_3 str	2968	2966	−2
A″	CH_3 str	2965	2966	1
A′	CH_3 str	2945	2965	20
A″	CH_3 str	2950	2963	13
A″	CH_3 str	2860	2873	13
A′	CH_3 str	2878	2871	−7
A′	CH str	2752[a]	2896	144
A′	NH_2 scissor	1618	1635	17
A′	CH_3 def	1469	1494	25
A′	CH_3 def	1449	1470	21
A″	CH_3 def	1469	1464	−5
A″	CH_3 def	1460	1459	−1
A′	CH_3 def	1375	1451	76
A″	NH_2 twist (liq)	1360	1444	84
A′	CH def	1245	1400	155
A″	CH_3 def	1343	1345	2
A′	CH_3 rock	1130	1173	43
A″	CH def	1240	1156	−84
A′	CH_3 rock (liq)	942	1069	127
A″	CC str	1170	1016	−154
A″	CH_3 rock	1029	968	−61
A′	CC str (liq)	919	943	24
A″	CH_3 rock	976	931	−45
A′	CN str	819	865	46
A′	NH_2 wag.	785	768	−17
A′	CCN def	472	465	−7
A″	CCN def	369	394	25
A′	CCC def	404	370	−34
A″	NH_2 tor	267	268	1
A′	CH_3 tor	258	253	−5
A″	CH_3 tor	236	232	−4

rms error (55.1)
no Bohlmann 54.4

[a] A band at 2932 cm^{-1} is assigned to the C–H stretching vibration.[28] However, this region of the spectrum is complicated by overtones and Fermi resonance.[22] We believe the 2752 band is a more probable assignment.

hydrogen were adjusted to fit the molecules in Tables I–III. The N–C–C angle was fit to ethylamine. However, there is a problem. The two rotamers of ethylamine, trans and gauche Lp–N–C–C, have NCC angles of 115.0° and 109.7°, respectively.[19] Since this angle is strongly dependent on the orientation around the CN bond and since this cannot be well reproduced with the currect force field, a compromise value was used. We calculate these angles to be 113.07° and 112.06°, respectively. A more elaborate approach, which we have decided to forego at present, would be to use a torsion–bend interaction to reproduce these angles.

Stretching and Bending Constants. Fitting of the stretching and bending constants for the above angles was done by matching the assigned vibrational frequencies of the methylamines.[20] Fitting most stretching constants was straightforward. There is, however, one systematic error that remains. The CH bond anti to the lone pair on nitrogen is known to have a lower stretching frequency than the other CH bonds.[21] These so-called "Bohlmann" bands are consistently calculated at much too high of a frequency. The weakening of the anti CH bond should cause these bonds to be longer than the other CH bonds. However, the experimental data for the simple amines is not accurate enough to verify this. In order to improve the calculations for the Bohlmann bands, a torsionally dependent correction to k_s would be needed in the force field. In Tables VI–IX, which report calculated and experimental vibrational frequencies, the rms error is calculated with and without including the Bohlmann bands, as this error will be corrected at a later time.

The methylamines bending frequencies were used in fitting most of the bending constants. The NCC constant was fit to ethylamine (403 cm^{-1} observed[22] and 411 cm^{-1} calculated). As mentioned above, the two bulky amines, diisopropyl and di-*tert*-butyl, have large CNC angles, and to improve the fit to these, the CNC bending constant was set a little softer than the methylamines alone would require. Fitting the bending constants was complicated by the coupling of the vibrational motions. This was particularly a problem with the HCN and HNC angles. Except for the Bohlmann bands, the largest errors occur in modes involving these angles. The results of the fitting can be seen in Table VI–IX. As with the hydrocarbons,[6] improvements in these frequencies are possible through the use of cross-terms. Such terms are not

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expected to affect the structures of the molecules and have not yet been studied.

The inversion barrier of ammonia is calculated to be 5.5 kcal/mol, and the experimental value[23] is 5.8 kcal/mol.

Torsion Constants. Fitting of the torsion constants presented several problems. In a number of instances, the experimental data required to evaluate the torsion constants were not available. Therefore, ab initio data had to be used for a number of key rotational barriers (propylamine[24] and methylethylamine[25]). (For the nomenclature of the conformations of propylamine, see ref 24.) In addition, different molecules that contain the Lp–N–C–C unit sometimes show different quantitative and qualitative preferences for the arrangement of this group. For example, in ethylamine, having the lone pair anti to the carbon is preferred (over gauche) by 0.3 kcal/mol.[26] But in piperidine and isopropylamine, the double gauche arrangement is preferred by 0.4[27] and 0.45 kcal/mol[28] to the double anti and gauche–anti arrangements, respectively. Since MM3 does not use lone pairs, these torsion potentials must be reproduced by using the HNCC and HNCH constants. However, these constants also play an important role in other compounds containing the CN bond, which also must be fit. For example, the calculated frequency of the CH$_3$ rotation in methylamine depends primarily on the HNCH torsional constant. In addition, in a compound such as methylethylamine, the value of the CNCC torsion constant required depends on the values of the HNCC and HNCH constants.

In order to deal with this diverse set of data, that included both frequencies and barrier heights and multiple interrelated parameters, the following technique was developed. A program was written (TOR FITTER) which simultaneously minimizes the rms error for up to ten torsion parameters, contained in as many as ten compounds, with up to ten conformers per compound. For each conformation (which may be anywhere in the compounds torsional space—not just local minima) a relative energy is required. To insure that the required frequency data were also fit, a trial parameterization using as many simplifying assumptions as possible was first run by trial and error. The heights of the barriers required to fit the vibrational spectra were noted, and these were used as relative energies in the TOR FITTER program. For the final fitting, the torsion parameters were divided into groups based on the central bond defining the torsion angle. For each group, as many examples of compounds containing that rotor as could be found were included in the parameterization set.

An example may make the process clearer. In order to set the parameters that relate to rotations around the CN bond, the HNCH, HNCC, and CNCC parameters were determined as a group. The simplest compound containing one of these parameters is methylamine. The CH$_3$ torsion in methylamine is reported to occur at 264 cm^{-1}.[20a] A trial and error parameterization that assumed that the HNCH parameters consisted of only a V_3 term was carried out. Fitting the spectra required that the eclipsed conformation of methylamine be 1.44 kcal/mol higher in energy than the staggered. These two conformations and their relative energies were then included as one compound in the input to TOR FITTER. The Lp–N–C–C conformational preferences mentioned above must be imitated by appropriate choices for HNCH and HNCC parameters since MM3 does not contain lone pairs. Furthermore, simple V_3 terms will not be adequate to deal with the gauche–anti differences mentioned in ethylamine, piperidine, and isopropylamine. Therefore, the program was allowed to optimize the V_1 and V_2 as well as the V_3 term for each torsion set and included the gauche and anti ethylamine conformers, the equatorial and axial piperidines, and the gauche–gauche and gauche–anti isopropylamine rotamers.

Table X. Torsion Data for C–N Bond (kcal/mol)

		MM3	exp[4]	dif	
		Methylethylamine[a]			
C–N–C–C	180	0	0		
C–N–C–C	120	3.2453	3.44	–0.1947	
C–N–C–C (CH$_3$ gauche C and H)	60	1.1788	1.2	–0.0212	
C–N–C–C	0	5.9479	5.83	0.1179	ab initio –1.2
C–N–C–C (CH$_3$ gauche C only)	300	1.1989	0.93	0.2689	
C–N–C–C	240	3.0686	2.87	0.1986	
		2-Methylpiperidine			
	H–eq, Me–eq	0	0		
	H–eq, Me–ax	2.3865	2.52[29]	–0.1335	
		Ethylamine			
	trans	0	0		
	gauche	–0.1035	0.3	–0.4035	
		Piperidine			
	eq	0	0		
	ax	0.2894	0.4	–0.1106	
		Methylamine			
	staggered	0	0		
	Me eclipsed	1.4493	1.44[b]	0.0093	
		Isopropylamine			
2 × (Lp–N–C–C)	GG	0	0		
2 × (Lp–N–C–C)	GT	0.2181	0.446	–0.2279	

[a] The exp for this compound comes from geometry optimized 6-31G* calculations carried out in the present work. [b] This is an arbitrary number picked to fit the torsional frequency.

Since the CNCC parameters used in methylethylamine depend on the other two sets, this set was fit along with the HNCH and HNCC parameter sets. The inclusion of the HNCH and HNCC parameters for methylethylamine is important, since the rotation around the CN bond is not symmetrical. Starting from the anti arrangement of the CNCC group, for example, clockwise or counterclockwise rotation is the same with respect to the CNCC torsion energy. The other two sets of parameters do, however, differentiate between the conformations of methylethylamine. The other torsion set that might be considered with methylethylamine is the CNCH set. But, like the CNCC group, the CNCH group does not help in the fitting of the asymmetric rotation around the CN bond. This set was not included with the others although it could have been. It was set as a simple V_3 term to fit the torsion modes of trimethylamine. The relative energies of equatorial and axial 2-methylpiperidines are reported as 0.00 and 2.52 kcal/mol.[29] Here the difference between the two conformations is an anti–gauche CNCC group. Therefore, it was also included in this set.

In addition to the local minima, a number of transition states are also required. Reliable data for the transition states are harder to find. As mentioned above, 1.44 kcal/mol can be used for the torsion in methylamine. The data for methylethylamine come from ab initio calculations, and they include the transition states. However, ab initio (6-31G*) calculations overestimate the height of the barrier when two first row atoms eclipse one another.[30] To compensate, the ab initio barrier minus one kcal/mol was used for fitting. Finally, two transition states for ethylamine were also included. The experimental reliability of these data is questionable, but without it it is difficult to do the fitting. The results of the process described above are summarized in Table X.

Table XI summarizes the results of a similar fitting for rotation around the CC bond and includes the CCCN and HCCN groups.

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Table XI. Torsion Data for C–C (N) Bond (kcal/mol)

		MM3	exp[a]	dif
	Ethylamine Gauche			
		0	0	
	Me eclipsed	2.9967	2.91	0.0867
	Ethylamine Trans			
		0	0	
	Me eclipsed	2.9976	3.09	−0.0924
	Propylamine Trans			
	Tt	0	0	
ab initio + 0.1	Gt	0.8259	0.42	0.4059
ab initio − 1.2	Et-n	4.4847	4.29	0.1947
ab initio − 0.1	Et-h	3.7833	4.02	−0.2367
	Propylamine Gauche			
	Tg	0.0000	0	
ab initio + 0.1	G	0.8831	0.41	0.4731
ab initio + 0.1	G	0.4840	0.05	0.434
ab initio − 1.2	Er-r	4.1536	4.4	−0.2464
ab initio − 0.1	Eg-t	3.7695	3.72	0.0495
ab initio − 0.1	Eg-t	3.8292	3.55	0.2792
	N,3-Dimethylpiperidine			
	di-eq	0	0	
	3-ax, *N*-eq	1.4516	1.6	−0.1481

[a] The experimental data are cited in ref 4, except for propylamine, which are from ref 24.

During this fitting it was found that the V_1 and V_2 terms for the HCCN set were generally small and that restricting them to be zero did not hurt the results. They were, therefore, restricted to be zero. After the initial fitting for these groups was completed, heat of formation calculations revealed some errors that could be improved by modifying the CCCN parameters. First quinuclidine, which contains three eclipsed CCCN fragments, was calculated to have too high of a heat of formation. To improve this, it was decided to use lower values for all of the transition states of propylamine during the fitting process. As a result, we used values obtained from ab initio calculations minus 1.2 kcal/mol for transition states in which the nitrogen and carbon were eclipsed and the ab initio value minus 0.1 kcal/mol if the nitrogen eclipsed a hydrogen. This resulted in a large improvement for the quinuclidine heat of formation. The heats of formation of most of the piperidines were calculated to be too low. Since a piperidine ring contains two gauche CCCN units, the energy used in fitting the propylamine conformers with a gauche CCCN unit was raised by 0.1 kcal/mol.

Ethylenediamine. (The nomenclature for the conformations is given in ref 31.) The NCCN torsion potential was not set in conjunction with the other parameters for rotation around the CC bond. It was fit to a series of conformers of ethylenediamine. Microwave studies of ethylenediamine[32] indicate that there are two low-energy forms of this compound, the gGg′ and tGg′ forms. An ab initio study[31] also reported that these two forms were the most stable of the ten conformers studied. No rotational transition states were reported. However, the NCCN torsion frequency was reported at 181 cm^{-1} (±20) in the tGg′ isomer. We calculated two transition states in which the NCCN angles were approximately 0° and 120°, and they were 7.7 and 6.5 kcal/mol above the tTt conformer, respectively. By using 6.7 and 6.5 kcal/mol for these barriers, a V_3 term of around 4 would have been needed to fit the barriers. This is about an order of magnitude larger than the expected value for the V_3 term. If these barriers were set to 4.5 and 3.8 kcal/mol (butane-like), a V_3 of about 1.5 was still needed, and this also seemed too large. Attempting to fit the torsion frequency (181 cm^{-1}) also required a very large V_3 term. The best fit was obtained with a V_3 term of about 3. Fitting to a frequency of ca. 161 cm^{-1} dropped the required V_3 term to about 1.5. The final result was a frequency of 161 cm^{-1} when V_1 = −0.069, V_2 = −1.267, and V_3 = 1.380.

The NCCN mode is coupled with the NCC bending. The NCC bending in ethylamine is, however, fit well (see above). The barriers aside, there are other problems also. The relative energies of the isomers with a gauche NCCN arrangement are not reproduced well. In general, gauche conformers other than the two expected low-energy forms are calculated to be too stable. The NCCN constant does not affect these differences. They depend on the HNCC and HNCH constants, the hydrogen bonding parameters, and the dipole–dipole interactions. Examination of Table XII suggests that the lack of a directional component in the hydrogen bonding function is the root cause of the problem. MM3 reports similar H bonding energies despite the orientation of the lone pairs with respect to the hydrogens. The torsion around the NC bond may also be a problem. (See above—ethylamine, piperidine, and isopropylamine).

Dipoles. Tables I–III include the dipole moments for the methylamines. Trial values for the bond moments were picked to fit ammonia in the case of the NH bond and trimethylamine in the case of the CN bond. Slight modifications were then made in order to evenly distribute the errors between the methylamines.

Moments of Inertia. An overall indication of the qualities of the structures obtained from the MM3 calculations can be noted by comparing the moments of inertia for the calculated structures to the moments measured by microwave spectroscopy. In general, a moment obtained from molecular mechanics will be slightly larger than that measured by microwave, since the former is parameterized to give r_g structures, while the latter gives r_0 structures (usually). The moments of inertia for a number of small amines are tabulated in Table XIII. The ground state of gauche ethylamine is split into four states because of two wide amplitude motions, and four sets of rotational constants have been reported. They differ from each other by no more than about 0.1%, so we have chosen one (se) for comparison.

Table XII. Ethylenediamine Rotamers

	energy (kcal/mol)				dipole (Debye)		
isomer	4-21G	MM3	∑H bonds	∑dipole	4-21G	MM3	MW
gGg′[a]	0.0 (ref)	0.0 (ref)	−0.5263	−0.1271	2.13	1.87	1.77
tGg′	0.0400	−0.2946	−0.6333	−0.4394	2.72	1.88	2.20
tTt	1.2500	1.6481	−0.1136	−0.1031	0.00	0.00	
gGg	1.2800	0.1235	−0.6004	−0.0641	0.39	1.08	
tGt	1.5500	0.5618	−0.6742	0.3085	0.42	1.45	
tTg	1.5600	1.6493	−0.1018	0.0116	2.48	2.12	
gTg′	1.6100	1.3480	−0.0906	−0.1851	0.00	0.00	
tGg	1.6200	0.5462	−0.6366	0.3343	2.41	2.50	
gTg	1.8000	1.5875	−0.0896	0.0625	1.81	2.09	
g′Gg′	4.0100	1.3590	−0.3122	0.8664	1.43	0.88	
		Ethylenediamine Transition States					
tGg′	0.0 (ref)	0 (ref)	−0.5872	−0.4394			
t(NNO)g′	5.6304[a]	5.6326	−1.0557	−0.0685			
t(NN120)g′	5.4727[a]	5.4699	−0.1709	0.0864			

[a] These numbers were arried at by starting with the 4-21G values and adjusting them to fit the torsional frequency at the lower error limit. [b] The tGg′ torsion mode around the CC bond is observed at 181 ± 20 cm^{-1} (gas phase from MW) (186 cm^{-1} in solution by Raman) and is calculated at 160.7 cm^{-1}.

Table XIII. Moments of Inertia (amux Å^2)

		I_a	I_b	I_c
methylamine[33]	exp	4.9020	22.3450	23.2980
	MM3	4.9609	22.2853	23.2362
	% dif	1.20	−0.27	−0.27
ethylamine (trans)[26a]	exp	15.9133	57.7631	64.8013
	MM3	16.5321	56.7842	64.2156
	% dif	3.89	−1.69	−0.90
ethylamine (gauche)[26b]	exp (se)	15.5868	56.5169	64.5809
	MM3	15.3518	58.1360	65.8644
	% dif	−1.51	2.86	1.99
dimethylamine[12]	exp	14.7589	54.1435	61.5115
	MM3	14.8499	54.5580	61.8268
	% dif	0.62	0.77	0.51
trimethylamine[15]	exp	NA	57.9504	NA
	MM3	58.5473	58.5473	103.2886
	% dif	NA	1.03	NA
isopropylamine[34]	exp	60.6562	63.3525	108.9900
	MM3	61.6128	63.8159	109.6782
	% dif	1.58	0.73	0.63
azetane[44]	exp	44.1429	44.5792	76.4683
	MM3	44.3840	44.5569	75.8386
	% dif	0.55	−0.05	−0.82
pyrrolidine[37]	exp	73.9449	75.6710	129.9822
	MM3	74.1838	75.3309	129.0938
	% dif	0.32	−0.45	−0.68

Table XIV. Structural Data on Pyrrolidines (Å/deg)

pyrrolidine (ax)	r_a[35]	MM3
C–N	1.469	1.470
C–N–C	105.2	105.1
flap angle	39.0	39.0
N-methylpyrrolidine (eq)	r_a[36]	MM3
C–N	1.455	1.462
C–N–C	107.4	107.2
flap angle	41.7	40.8

Table XV. Azetane Structure (Å/deg)

	MW/ED (rz)[44]	MM3
CN	1.473	1.475
CC	1.563	1.563
CNC	91.2	91.26
NCC	88.2	88.24
CCC	84.6	84.85
puckering angle	29.7	29.0

Five-Membered Rings. Combined ab initio and gas electron diffraction studies of both pyrrolidine[35] and *N*-methylpyrrolidine[36] have been reported. The experimental and MM3 results are summarized in Table XIV. In addition, moments of inertia are available for pyrrolidine.[37] For pyrrolidine, an envelope conformation with the N out of plane and the imino hydrogen in the axial orientation was found to be the most stable. MM3 calculates the conformer with an equatorial hydrogen to be slightly more stable (0.34 kcal/mol). For *N*-methylpyrrolidine, an envelope conformation with the N out of plane and the methyl group in the equatorial orientation was preferred by experiment and by MM3 calculation (2.02 kcal/mol). The experimental and MM3 structures are compared below. Each of these compounds has C_s symmetry, with the I_a axis in the symmetry plane.

Four-Membered Rings. Parameterization for these compounds was based on the known structure of azetane. There is, however, one major area of controversy with regard to azetane. The early IR and Raman work on azetane seemed to indicate there was a double well potential in which separate axial and equatorial isomers existed.[38] The isomer with the equatorial amino hydrogen was the lower energy species. These data were later found to also be consistent with a single minimum potential.[39] Further Raman studies revealed the spectral intensities were only consistent with the single minimum potential.[40] The latest gas-phase NMR work, however, clearly demonstrates the presence of two conformers.[41] Within the molecular mechanics framework, we were only able to reproduce the double well potential. The equatorial conformer is found to be more stable by MM3, by 0.06 kcal/mol.

The complete structure of azetane has been determined by electron diffraction,[42] by combined MO and ED studies,[43] and by a joint MW/ED study.[44] The results of the joint MW/ED study and of the MM3 parameterization are shown in Table XV.

The relative sizes of the CCC, NCC, and CNC angles required that the four-membered ring bending parameters increase in that order through the series. This resulted in the CNC bending parameter being unexpectedly large (0.580). However, since the CCC bending parameter was already fixed to fit cyclobutane, the large value seems required if MM3 is to reproduce the structure. The stiff bending parameters and the high degree of puckering (azetane is more puckered than cyclobutane) result in the need to set high torsion parameters for the four-membered ring NCCC and CNCC torsions ($V_1 = 0$, $V_2 = 0$, and $V_3 = 3.10$). The type 56–56 bond length was calculated to be too short with the normal (type 1–1) correction to the bond length due to the electronegativity of the nitrogen. Therefore, this bond length correction was set to zero in four-membered rings, based on this one example.

Hydrogen Bonding. In the original MM2 force field hydrogen bonding was not treated any different than other intermolecular forces. That is, it was just the sum of the van der Waals interactions and the dipole–dipole interactions between the appropriate atoms. In MM3 (and in more recent versions of MM2) a special

Table XVI. Heat of Formation Data for Aliphatic Amines[a]

eq	wt	$H_f°$	sumh	steric	pop	tors	T/R	compound
1	10	−5.50	−13.77	−0.45	0.00	0.00	2.40	methylamine
2	10	−4.43	−27.54	1.37	0.00	0.00	2.40	dimethylamine
3	10	−5.67	−41.31	5.41	0.00	0.00	2.40	trimethylamine
4	10	−11.35	−19.46	0.87	0.03	0.42	2.40	ethylamine
5	10	−17.33	−38.92	4.00	0.47	0.84	2.40	diethylamine
6	10	−22.17	−58.38	14.65	0.06	1.26	2.40	triethylamine
7	10	−16.77	−26.20	1.95	0.24	0.84	2.40	*n*-propylamine
8	10	−20.02	−25.15	2.54	0.11	0.42	2.40	isopropylamine
9	10	−21.98	−32.93	3.01	0.59	1.26	2.40	*n*-butylamine
10	10	−25.06	−31.88	4.64	0.32	0.84	2.40	*sec*-butylamine
11	10	−23.57	−34.51	3.67	0.27	0.84	2.40	isobutylamine
12	10	−28.90	−30.84	4.17	0.00	0.42	2.40	*tert*-butylamine
13	10	−11.76	−36.11	7.98	0.10	0.00	2.40	piperidine
14	10	−20.19	−41.80	9.58	0.16	0.00	2.40	2-methylpiperidine
15	10	9.90	−24.11	33.54	0.24	0.84	2.40	cyclobutylamine
16	10	−13.13	−34.58	18.12	0.15	0.84	2.40	cyclopentylamine
17	10	−1.03	−47.62	25.41	0.00	0.00	2.40	quinuclidine
18	0	−34.41	−50.29	10.39	0.07	0.84	2.40	diisopropylamine
19	10	−25.06	−35.81	8.52	0.24	0.42	2.40	cyclohexylamine
20	10	−0.80	−34.89	17.19	0.14	0.42	2.40	pyrrolidine
21	10	24.62	−24.42	39.30	0.03	0.42	2.40	azetane

[a] For definitions, see preceding paper in this issue.

Table XVII. Heat of Formation Data for Aliphatic Amines (Number of Parameters)

compound	C–N	N–H	N–Me	NISO	NSEC	NTER	TBUN	NCBU	8–56
1 methylamine	1	2	1	0	0	0	0	0	0
2 dimethylamine	2	1	2	0	1	0	0	0	0
3 trimethylamine	3	0	3	0	0	1	0	0	0
4 ethylamine	1	2	0	0	0	0	0	0	0
5 diethylamine	2	1	0	0	1	0	0	0	0
6 triethylamine	3	0	0	0	0	1	0	0	0
7 *n*-propylamine	1	2	0	0	0	0	0	0	0
8 isopropylamine	1	2	0	1	0	0	0	0	0
9 *n*-butylamine	1	2	0	0	0	0	0	0	0
10 *sec*-butylamine	1	2	0	1	0	0	0	0	0
11 isobutylamine	1	2	0	0	0	0	0	0	0
12 *tert*-butylamine	1	2	0	0	0	0	1	0	0
13 piperidine	2	1	0	0	1	0	0	0	0
14 2-methylpiperidine	2	1	0	1	1	0	0	0	0
15 cyclobutylamine	0	2	0	1	0	0	0	1	1
16 cyclopentylamine	1	2	0	1	0	0	0	0	0
17 quinuclidine	3	0	0	0	0	1	0	0	0
18 diisopropylamine	2	1	0	2	1	0	0	0	0
19 cyclohexylamine	1	2	0	1	0	0	0	0	0
20 pyrrolidine	2	1	0	0	1	0	0	0	0
21 azetane	0	1	0	0	1	0	0	0	2

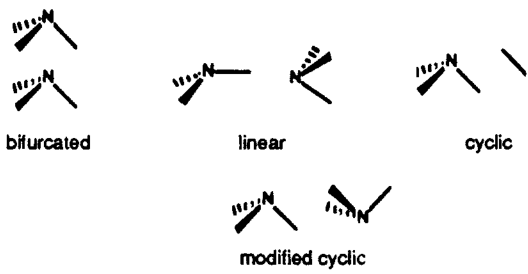
Table XVIII. Heat of Formation Data for Aliphatic Amines (kcal/mol)[a]

eq	wt	$H_f°$ calc	$H_f°$ exp[50]	difference (calc – exp)	compound
1	10	–5.04	–5.50	0.46	methylamine
2	10	–4.04	–4.43	0.39	dimethylamine
3	10	–6.09	–5.67	–0.42	trimethylamine
4	10	–11.92	–11.35	–0.57	ethylamine
5	10	–17.41	–17.33	–0.08	diethylamine
6	10	–21.49	–22.17	0.68	triethylamine
7	10	–16.95	–16.77	–0.18	*n*-propylamine
8	10	–20.31	–20.02	–0.29	isopropylamine
9	10	–21.85	–21.98	0.13	*n*-butylamine
10	10	–24.31	–25.06	0.75	*sec*-butylamine
11	10	–23.51	–23.57	0.06	isobutylamine
12	10	–28.90	–28.90	0.00	*tert*-butylamine
13	10	–11.83	–11.76	–0.07	piperidine
14	10	–20.30	–20.19	–0.11	2-methylpiperidine
15	10	9.90	9.90	0.00	cyclobutylamine
16	10	–13.70	–13.13	–0.57	cyclopentylamine
17	10	–1.29	–1.03	–0.26	quinuclidine
18	0	–31.67	–34.41	2.74	diisopropylamine
19	10	–24.86	–2.06	0.20	cyclohexylamine
20	10	–0.94	–0.80	–0.14	pyrrolidine
21	10	24.62	24.62	0.00	azetane

[a] Best values: C–N = 6.173, N–H = –1.178, N–Me = 2.965, NISO = –4.442, NSEC = 2.635, TBUN = –8.867, NCBU = 1.171, 8–56 = 2.617. Fixed values: NTER = 0.000. Standard Deviation = 0.354. Based on 20 equations with nonzero weights.

hydrogen bonding term has been studied. This term amounts to replacing the normal van der Waals parameters for the interacting atoms with a special van der Waals parameter. This allows a better estimation of the interaction energy, which was generally underestimated by about 20% in the original MM2 force field.

The key model for deducing the appropriate parameters for hydrogen bonding in amines is the ammonia dimer. Since the N–H hydrogen bond is very weak (ca. = 2 kcal/mol), both quantum mechanics and experimental methods have predicted a variety of structures and relative energies for the ammonia dimer. Some of the proposed structures are shown below. At the time that this work was originally carried out, it appeared that either the cyclic or the linear structure was the most stable but that the energies of the two structures were similar. There was little support for the bifurcated structure. One group supported a modified cyclic structure.[45] Subsequently, more evidence supporting the modified cyclic structure has appeared.[47,48]



Our first parameterization attempted to create local minima for the cyclic and linear structures on the MM3 surface. At first there was a decided tendency for the "linear" structure to collapse to a structure similar to the bifurcated structure. However, in this structure, the hydrogens were staggered around the NN axis rather than eclipsed. In order to prevent this collapse, it was necessary to increase the size of the type 23 hydrogen to 1.40 Å (from 1.28 Å). Making this hydrogen even larger starts to destabilize the cyclic structure too much, since there is a substantial van der Waals repulsion between the two hydrogens involved in the hydrogen bonds. In order to best fit the interaction energies, the sum of the van der Waals radii of an interacting type 23 hydrogen and nitrogen was set to 2.25 Å and ϵ to 0.450. This results in interaction energies of –2.28 and –2.27 kcal/mol for the cyclic and linear structures, respectively. This is in relatively good agreement with the work of Scheiner.[46] Unfortunately, when the energies are correct, the structures of the dimers were compromised. Thus, the expected NN distances of 3.15 and 3.34 Å for the cyclic and linear dimers, respectively, are calculated to

Table XIX. Strainless Heat of Formation Data for Aliphatic Amines (kcal/mol)

eq	wt	MM3 $H_f°$	sumh	steric	pop	tors	T/R	compound
1	10	–5.04	–13.77	0.00	0.00	0.00	2.40	methylamine
2	10	–4.04	–27.54	0.00	0.00	0.00	2.40	dimethylamine
3	10	–6.09	–41.31	0.00	0.00	0.00	2.40	trimethylamine
4	10	–11.92	–18.45	0.00	0.03	0.42	2.40	ethylamine
5	10	–16.94	–24.12	0.00	0.24	0.84	2.40	*n*-propylamine
6	10	–20.30	–23.12	0.00	0.11	0.42	2.40	isopropylamine
7	10	–28.89	–27.80	0.00	0.00	0.42	2.40	*tert*-butylamine

Table XX. Stainless Heat of Formation Data for Aliphatic Amines[a,b]

eq	wt	$H_f°$ calc	$H_f°$ exp	difference (calc–exp)	compound
1	10	−5.04	−5.04	0.00	methylamine
2	10	−4.04	−4.04	0.00	dimethylamine
3	10	−6.09	−6.09	0.00	trimethylamine
4	10	−11.91	−11.92	0.01	ethylamine
5	10	−16.95	−16.94	−0.01	*n*-propylamine
6	10	−20.30	−20.30	0.00	isopropylamine
7	10	−28.89	−28.89	0.00	*tert*-butylamine

[a] Best values: C–N = 8.300, N–H = −2.305, N–Me = 2.640, NISO = −3.800, NSEC = 1.525, TBUN = −7.600. Fixed values: NCBU = 0.000, 8–56 = 8.300. Standard deviation = 0.005. [b] For strainless heats of formation the simple compounds in Table XX are defined as strainless in their most stable conformations. The exp column are the heats of formation for these compounds (stable conformation) calculated by MM3. The calc column gives these heats as calculated from the "strainless increments" being fit. These increments can then be used to calculate "inherent strain energies" with MM3 and are the strains of these compounds minus any extraneous contributions from the pop and tors terms. They are all zero for the compounds in Table XX (to within roundoff error).

be 2.878 and 3.017 Å. Furthermore, if the NN distance is increased, the problem of collapse to a bifurcated-like structure returns.

Since the original fitting for the ammonia dimer, two more papers have appeared that support the modified cyclic structure for the ammonia dimer in a matrix[47] and in the gas phase.[48] On the basis of these results, we no longer feel that a simple cyclic structure is a low-energy species. Therefore, the radius of the type 23 hydrogen was increased to 1.6 Å, similar to the values used for type 5 and type 21 hydrogens. This resulted in interaction energies of −2.17 and −0.56 kcal/mol and NN distances of 3.073 and 2.50 Å for the linear and modified cyclic structures, respectively.

Heats of Formation. The same seven parameters used in MM2 to fit heats of formation were also used in MM3. These are as follows: CN bond energy (CN), NH bond energy (NH), and then several structural parameters, *N*-methyl (N-Me), nitrogen attached to a secondary carbon (NISO), a secondary amine (NSEC), a tertiary amine (NTER), and nitrogen attached to a tertiary carbon group (TBUN). In addition, two new parameters were added. These are special parameters for the four-membered ring: for the type 8–type 56 bond (8–56) and for a type 8 nitrogen attached exo to a four-membered ring (NCBU). As mentioned previously, in order to improve the heats of formation, some of the torsion constants were compromised slightly. The input data

Table XXI. MM3 Structural Parameters for Amines

Torsional Parameters[a]

atom type nos.				V_1	V_2	V_3	
8	1	1	8	−0.069	−1.267	1.380	
5	1	8	1	0.072	−0.012	0.563	
5	1	8	23	0.121	−0.648	0.199	
1	1	8	23	0.073	−0.422	0.327	
*5	56	56	8	0.000	0.000	0.374	
*8	56	56	56	−0.302	0.696	0.499	
*56	8	56	56	0.958	−0.155	0.766	
*56	8	56	5	0	0	0.563	
8	56	56	56	0.000	0.000	3.100	*4
56	8	56	56	0.000	0.000	3.100	*4
1	1	1	8	−0.302	0.696	1.360	*5
1	1	8	1	0.958	−0.155	1.360	*5

Torsion-Stretch Parameter

atom type nos.		KTS
1	8	0.0610

Stretching Parameters

bond type	K(S)	L(O)	
1–8	5.3000	1.4480	
*8–56	5.3000	1.4480	
8–56	5.3000	1.4540	*4
1–8	5.3000	1.4530	*5
8–23	6.4200	1.0150	

Electronegativity Corrections to LO

bond type	end of bond	atom type	correction to LO
1–8	8	23	0.00600
56–56	56	8	0.00001
1–1	1	8	−0.00500
1–5	1	8	−0.00300

Dipole Parameters

bond type	moment
1–8	0.6800
8–23	−1.3400

VDW Parameters

atom type		ϵ	radius
8	23	0.675	2.250 H bonding
8	21	3.720	1.740 H bonding
	23	0.018	1.600
	8	0.043	1.930

Bending Parameters

atom types			K(B)	θ (O)	ED type	
23	8	23	0.605	106.400	1	
23	8	23	0.605	107.100	2	
1	8	23	0.600	108.100	1	
1	8	23	0.600	110.900	2	
1	8	1	0.720	107.200	1	
1	8	1	0.720	108.200	2	
56	8	56	0.580	107.200	1	*4
56	8	56	0.580	108.200	2	*4
1	8	1	0.720	114.000	1	*5
1	8	1	0.720	112.000	2	*5
5	1	8	0.820	109.300		
1	1	8	0.780	109.470	1	
1	1	8	0.780	108.000	2	
1	1	8	0.780	111.000	3	
56	56	8	0.300	109.470	1	*4
56	56	8	0.300	108.000	2	*4
56	56	8	0.300	111.000	3	*4
1	1	8	0.780	109.470	1	*5
1	1	8	0.780	108.000	2	*5
1	1	8	0.780	109.600	3	*5

Stretch–Bend Parameters

3	0.050	X–N–Y
4	0.030	X–N–H

[a] *N for four- and five-membered ring; * at left means preliminary value.

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are given in Tables XVI and XVII. As can be seen in Table XVIII, the calculated heats of formation are in excellent agreement with the experimental values, with one exception, diisopropylamine. This number is so far off we concluded the experimental value must be in error, and we did not weight this compound in the parameterization. (Ab initio calculations recently confirmed that the experimental value is indeed in error.[49])

Strain energies may be calculated in the usual way.[1] (Further discussion is given in the MM2(87) (and earlier) and MM3 manuals.) The strainless group increments were fit for the group of compounds as shown by the input in Table XIX. The strainless increment for the 8–56 bond was arbitrarily set equal to that of a C–N (1–8) bond, and the strainless increment for NCBU was set to zero. The results are given in Table XX.

The complete set of structural parameters (which must be added to those already developed for alkanes[6]) for amines is given in Table XXI.

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NMR Study of Heme Pocket Polarity/Hydrophobicity of Myoglobin Using Polypropionate-Substituted Hemins

Jón B. Hauksson, Gerd N. La Mar,* Ravindra K. Pandey, Irene N. Rezzano, and Kevin M. Smith

Contribution from the Department of Chemistry, University of California, Davis, California 95616.

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Abstract: The products of the reconstitution of sperm whale apomyoglobins with a series of synthetic hemins possessing a wide variety of substitution patterns for two and three propionates on the methyl-containing heme periphery were studied by NMR in the metaquo and metcyano derivatives to investigate the prospects for, and structural and thermodynamic consequences of, the location of propionates in the hydrophobic interior of the pocket. The orientations for the propionates for the various hemins were determined by the nuclear Overhauser effect in the metcyano complexes. In all but one case, a single, unique orientation was found for each hemin which resulted in the occupation by a propionate, in at least one case, in each of the possible eight heme pocket sites without disruption of the heme pocket structure. While propionate orientations into the protein interior were readily attainable, indicating a surprising polar pocket environment, these propionates exhibited extraordinarily elevated p*K*s > 8 indicative of the highly hydrophobic contacts in the interior of the heme pocket. For propionates situated in the sites of the usual protohemin vinyl groups, we observe pH-modulated structural transitions involving deprotonation of the propionate that results in changes in the orientations of the hemins. The detection of saturation transfer between these alternate orientations identifies the interconversion mechanism as rotational "hopping" of the hemin about the intact iron–histidine bond. The thermodynamics of the carboxylate side chains and dynamics of isomer interconversion can serve as sensitive probes of heme pocket structure among both natural and synthetic myoglobin variants.

Introduction

The heme pockets of the molecular oxygen binding hemoproteins, myoglobin, Mb, and hemoglobin, Hb, are generally described as hydrophobic and nonpolar except for a region near the protein surface where the ubiquitous hydrophilic heme propionate side chains make salt bridges to the protein matrix.[1-4] The apparently apolar environment of most of the heme pocket is supported by the large number of hemeprotein contacts with nonfunctionalized aliphatic and aromatic side chains, particularly in the region of the vinyl bearing pyrroles of the native protohemin prosthetic group. Recent spectroscopic investigations of complexes of sperm whale apomyoglobin, apoMb, with a dye intercalated into the heme pocket,[5] however, have suggested that the heme pocket of Mb may be more polar than previously thought.[4] The overwhelming preference for the ubiquitous 6,7-propionate groups for the unique orientations as described in numerous X-ray crystallographic[2,3] studies provides another measure of the relatively localized hypophobic and hydrophobic regions of the heme pocket. While it is now recognized that the heme can sit in the pocket in more than one orientation, at least initially during assembly of holoprotein from hemin and apoMb,[6,7] and at equilibrium for some Mbs and Hbs,[8-11] this transient or equilibrium orientational disorder leaves the two salt bridges unaltered and simply permutes the hydrophobic contacts. This hydrophobic region of the heme pocket of Mb is found to be remarkably adaptable in that hemins with bulky substituents readily incorporate into an otherwise essentially unperturbed holoprotein.[12] Recent studies with hemins possessing a single propionate group[13]

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