A Molecular Mechanics Study of Amide Conformations

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The MM2 force field has been extended to include amides using experimentally known geometries for formamide, acetamide, and their *N*-methyl derivatives in the parameterization. Relative stabilities of conformers, barriers to rotation, and dipole moments are reproduced within reported experimental error. Additionally, a conformational study of acylpiperidines was performed. Although primary and secondary amides are found to be planar or nearly so, use of the *N*-methyl derivatives in the parameterization results in a significant deviation from planarity for tertiary amides.

Introduction

The amide group, an important structural feature in organic[2] and biological[3] chemistry, has been the subject of many experimental and theoretical studies. Much of the early work has been summarized by Pauling,[4] who suggested the now widely accepted idea that the N–C (carbonyl) [N–C_{ox}] unit of this group should possess considerable double bond character. It is thus expected that (1) the N–C_{ox} amide bond should be shorter than an N–C (alkyl) amine or amide bond, (2) the amide group should be planar (or nearly so), and (3) there should be a high [relative to an N–C (alkyl) bond] rotational barrier around the N–C_{ox} amide bond.

With regard to each of these, the following observations are important. First, microwave[5] and electron diffraction[6–12] techniques provide evidence that the N–C (alkyl) bond length in amines is typically 1.451–1.477 Å; whereas in amides, the N–C_{ox} bond length is 1.352–1.386 Å. The other N–C (alkyl) bond lengths in amides (1.459–1.468 Å) are similar to those found in amines. These data are supported by ab initio calculations.[13] Second, with regard to planarity, microwave studies on formamide suggest a planar molecule[5,10] or one that is nearly planar with a slight out-of-plane wagging type vibration;[11] ab initio calculations support the former.[13] For acetamide, the out-of-plane bending force is very small and not only can nonplanarity, involving an extremely weak equilibrium motion, not be ruled out[14] but there is evidence for a small degree of pyramidalization.[15] A more complicated case, (*p*-nitrobenzoyl)piperidine, has been carefully studied by X-ray diffraction, and, for the crystalline material, the nitrogen atom deviates (by 0.045 Å) from the plane defined by the three carbon atoms to which it is attached.[16] Third, hindered rotation in amides, indicative of double-bond character, has been extensively studied in solution by nuclear magnetic resonance (NMR) spectroscopic methods.[17–20] Depending upon the species studied, the reported rotation barriers have covered a wide range (12–22 kcal/mol) of energies. Results from ab initio calculations[21] are in concert with the experimental values and support the assumptions that the barrier (a) is not simply the result of differential solvation of *E* and *Z* isomers and (b) is rotational and not one of inversion through nitrogen.

Since the ability to easily and accurately reproduce the structural and energetic characteristics of amides is critical to modeling studies of proteins and other biologically interesting molecules, other molecular mechanics studies of these systems are being pursued.[22,23] We report our results for simple amides here, emphasizing that, for these simple systems, intermolecular interactions (leading to dimers, etc.) have been ignored and that, in particular, specific hydrogen-bonding interactions[23b] are not considered.

Table I. Stretching and Dipole Moment Parameters for Amides 1–8 Inclusive

bond	K_s	r_o[a]	moment[b]
C_{sp^3}–N	5.10[c]	1.450	0.85
C_{ox}–N	6.30[c]	1.369	−0.80
N–H	6.10[c]	1.012	−0.50
C=O	10.80[d]	1.208	2.600
H–C_{ox}	4.60[d]	1.113	0.00
C_{sp^3}–C_{ox}	4.40[d]	1.509	0.300
H–C_{sp^3}	4.60[d]	1.113	0.00

[a] The values for r_o were taken, initially, from microwave or electron diffraction data[5–12] where available. Values not shown in this table were assigned by analogy to parameters already present in MM2. [b] The bond moments were assigned initially by analogy with similar bond types parameterized in MM2 and were adjusted to fit so as to reproduce experimental dipole moments as given in Tables IV and V. [c] The force constants are based on average IR[25–28] values or, where those were unavailable, developed by analogy with MM2 programmed parameters. [d] By analogy with internal MM2 parameters.

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Table II. Bending Parameters for Amides 1-8 Inclusive

angle	K_b[a]	σ_o[b]	angle	K_b[a]	σ_o[b]
C-C-N	0.57	109.47	C-N-C	0.63	107.70
H-C-N	0.50	109.30	C-N-H	0.50	118.00
C-C_{ox}-N	1.62	114.00	H-N-H	0.19	118.80
H-C_{ox}-N	0.50	109.40	C-N-C_{ox}	1.166	118.40
N-C_{ox}-O	1.035	122.60	C_{ox}-N-H	0.51	117.40

[a] The force constants are based on average IR[13b,25,30-32] values or, where those values were unavailable, developed by analogy with MM2 programmed parameters. [b] σ_o values were chosen on the basis of internal MM2 parameters for similar atom types or, if available, from electron diffraction or microwave spectroscopic data.[5-12] Parameters were adjusted to insure that the final calculated angle matched the experimental value where that information was available.

General Procedure and Amide Parameters

MM2[24a] parameterization and subsequent calculations were performed at Temple University on the CDC CYBER 750. As is standard[24b,c] in MM2 parameterizations, calculations were restricted to isolated molecules and intermolecular interactions were ignored. In general, electron diffraction, microwave, NMR, and gas-phase IR data were used for parameterization and comparison of calculated values.[25-28] Where parameters unrelated to the amide group were required, programmed values were used.

Geometrical parameters, such as equilibrium bond lengths and bond angles, are taken from geometries of simple molecules (experimentally determined) and then adjusted to fit to those geometries with the results obtained from MM2 calculations. In the adjustment, parameters are manually set to obtain the best fit to known values and optimized by trial and error[24b,c] to give the total steric energy (E_{total}) of the molecule as shown in eq 1. The parameters required for each of the terms are discussed below.

$$E_{total} = E_{stretch} + E_{bend} + E_{str-bend} + E_{vdw} + E_{torsn} + E_{dipole} \quad (1)$$

Stretching Parameters. The parameters K_s, the stretching force constant (millidyne/angstrom), and r_o, the equilibrium bond length (angstroms), were developed to fit the MM2 standard force field expression of eq 2 (with $E_{stretch}$ in kilocalories/mole).

$$E_{stretch} = 71.94K_s(r - r_o)^2[1 - 2.00(r - r_o)] \quad (2)$$

The force constants shown in Table I are either average values for the corresponding IR force constants for compounds 1-6 (as appropriate) or were taken by analogy to internal MM2 parameters. The values for the equilibrium bond length, r_o, were taken initially from microwave or electron diffraction data where available as trial data and then adjusted until calculated bond lengths fit the experimental data.

Bending and Stretch-Bend Parameters. The parameters, K_b, the bending force constant in millidyne/angstrom rad^2, and σ_o (degrees), the equilibrium bond angle, were developed to fit the standard MM2 eq 3, where E_{bend} is in kilocalories/mole.

$$E_{bend} = (2.194 \times 10^{-2})K_b(\sigma - \sigma_o)^2[1 + (7.00 \times 10^{-8})(\sigma - \sigma_o)^4] \quad (3)$$

As indicated earlier, force constants were based on average IR values or developed by analogy with MM2 standard parameters (Table II). The values for equilibrium angles were obtained similarly. When a trigonal atom (e.g. carbonyl carbon) is the central atom of an angle, an out-of-plane bending component to the energy must be included. For this energy component, the force constant, K_b, was assigned a value of 0.050 for carbonyl carbon and oxygen in accord with programmed parameters.

A stretch-bend potential function (eq 4) is also included so that bonds tend to stretch when the angle is compressed and to shrink when the angle is widened.

$$E_{str-bend} = 2.51124K_{sb}(\sigma - \sigma_o)[r(1) - r_o(1) + r(2) - r_o(2)] \quad (4)$$

Here, K_{sb} is the stretch-bend constant (millidyne/rad), and the angle in question has the equilibrium value σ_o (degrees) between nuclei separated from the pivotal atom by equilibrium bond lengths $r_o(1)$ and $r_o(2)$. The programmed MM2 values for K_{sb} required no modification.

van der Waals Parameters. Nonbonded interaction energies (excluding 1,3-interactions) are calculated with the modified Buckingham equation as shown in eq 5 where

$$E_{vdw} = K_{vdw}[(2.90 \times 10^5)e^{-12.50/p} - 2.25p^6] \quad (5)$$

$p = r^*/r$, and r^* is the sum of van der Waals radii of two atoms, 1 and 2, while r is the distance between to two atoms. Here, the constant, K_{vdw}, is defined as $[\epsilon(1)\epsilon(2)]^{1/2}$, where $\epsilon(1)$ and $\epsilon(2)$ are the van der Waals constants (a measure of hardness) for the atoms 1 and 2, respectively, and whose values are in kilocalories/mole. The values of ϵ and r utilized in the calculations reported here were standard MM2 parameters except for those of the nitrogen and hydrogen attached to nitrogen (i.e., N-H) for compounds **1**, **2ab**, **4**, and **5a,b**, which were, however, developed by analogy to similar atom types in MM2. They are N_{amide} ($\epsilon = 0.055$, $r_o = 1.820$) and $H_{amide-N}$ ($\epsilon = 0.041$, $r_o = 1.420$).

Torsional Parameters. The parameters provided in Table III for the standard MM2 eq 6 were adjusted to fit experimentally determined rotational barriers.

$$E_{torsion} = (v_1/2)(1 + \cos\omega) + (v_2/2)(1 - \cos 2\omega) + (v_3/2)(1 + \cos 3\omega) \quad (6)$$

Here, ω is the dihedral angle (degrees) and v_1, v_2, and v_3 are 1-, 2-, and 3-fold torsional constants (kilocalories/mole). Since the amide C-N bond has nearly C_{2v} symmetry, the v_2 term is the predominant contributor to the torsional energy and v_2 is roughly equal to a quarter of the rotational barrier. The v_1 term was used to adjust the energy difference between E and Z isomers. Finally, the v_3 term was adjusted to "fine tune" the calculated torsional energy barrier to reproduce experimental results. Minor adjustments to all values were made as required for a best fit.

Dipole Interaction Energy and Dipole Moment. Bond moments for polar bonds are required to obtain dipole moments and dipole interaction energies. The bond moments are found by choosing an appropriate[24d] trial value which is then refined to reproduce experimental dipole moments. The dipole interaction energy is calculated by using eq 7 (which is standard to MM2). Where

$$E_{dipole} = k\mu_A\mu_B(\cos\chi - 3\cos\alpha_A\cos\alpha_B)/R^3D \quad (7)$$

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Table III. Torsional Parameters for Amides 1–8 Inclusive

general parameters for amides 1–8 inclusive[a]				additional parameters for amides 7 and 8[b]			
dihedral angle	v_1	v_2	v_3	dihedral angle	v_1	v_2	v_3
H–N–C=O	0.74	4.97	0.10	H–C–N–C	0.00	0.00	0.10
C–N–C=O	0.00	6.30	0.10	C–C–N–C	0.00	0.00	0.30
H–C–C_{ox}–N	0.00	0.00	0.10	H–C–C–N	0.00	0.00	0.30
H–C_{ox}–N–H	0.00	4.10	0.20	C–C–C–N	0.00	0.00	0.30
H–C_{ox}–N–C	0.46	4.80	0.40	C–C–N–C_{ox}	0.00	0.00	0.22
C–C_{ox}–N–H	0.00	3.37	0.40				
C–C_{ox}–N–C	0.65	4.30	0.80				
H–C_{sp^3}–N–C_{ox}	0.00	0.00	0.22				
H–C_{sp^3}–N–H	0.00	0.00	0.20				

[a] In general, the values for the parameters shown were adjusted to fit the observed rotation barrier as given in Tables IV and V. [b] By analogy to internal MM2 parameters.

R is the distance between the midpoints of the two bonds (angstroms), μ_A and μ_B are their respective bond moments (Debye), χ is the angle between the bond vectors, α_A and α_B are the angles between the bond axes and the line along which R is measured, and D is the effective dielectric constant[24b,c] (here taken as 1.5); the energy is converted to kilocalories/mole by use of the conversion factor k (erg/molecule to kilocalories/mole) whose value is taken as 14.39418.

For the amides **1–6**, the parameters not already defined in MM2 (Table I) were determined by analogy with similar bond types provided in MM2, and then they were adjusted so as to generate the experimentally determined dipole moments (where available, Tables IV and V).

Results and Discussion

As shown in Tables IV and V, the MM2 calculated carbonyl oxygen bond lengths are, uniformly, shorter than those found experimentally. Indeed, the calculated values are closer to the C=O distance in formaldehyde [1.209 (3) Å] than in acetone [1.214 (4) Å][29] and thus, although MM2 underestimates the C=O bond length for the amides, it is nonetheless noteworthy that (compared to acetone) there does not appear (experimentally) to be much C=O bond lengthening when a methyl is replaced by nitrogen (either hydrogen or alkyl substituted).[49]

The experimental N—C=O angle in formamide (**1**) and its N-methylated derivatives **2a**, **2b**, and **3** (123.0–125.0°) is larger than the corresponding angle in acetamide (**4**) and *N*-methylacetamide (**5a,b**) (121.8–122.0°). This is mirrored in the MM2 calculations and parallels an analogous trend in acetaldehyde and acetone. Indeed, this angle in formamide (**1**) and its derivatives (**2a,b** and **3**) is similar to the C—C=O angle in acetaldehyde (124.0°) and the C—C=C angle in propene (124.3°) while the same angle in acetamide (**4**) and its derivatives (**5a,b** and **6**) is closer to the C—C=O angle in acetone (121.4°) and the C—C=C angle in 2-methylpropene (122.4°).[29]

The calculated values for the H–N–C_{ox} angle subtended between the *E*-hydrogen and carbon of the carbonyl for formamide (**1**) (121.1°), (*Z*)-*N*-methylformamide (**2a**) (119.8°), acetamide (**4**) (120.4°), and (*Z*)-*N*-methylacetamide (**5a**)(120.0°) are all very close. However, the value for the corresponding H–N–C_{ox} angle for the *Z*-hydrogen is significantly smaller for formamide (**1**) (119.0°) and continues to shrink [acetamide (**4**) (118.9°), (*E*)-*N*-methylformamide (**3b**) (118.1°), (*E*)-*N*-methylacetamide (**5b**) (117.0°)] with increasing substitution. This correlates with the well known preference for the (trans or) *Z* configuration for these compounds, which, while clearly related to steric[50] and torsional[15] effects, must also have an electronic component to account for the *N*-methylformamide (**2a,b**) isomers.[51]

With regard to rotational barriers, formamide (**1**) may be compared to acetamide (**4**) and their respective *N*-methyl derivatives to each other. The barrier to rotation around the N–C_{ox} bond in **1** is found to be 18.0[33] or 17.8 kcal/mol[34] by line shape analysis on ^{15}N-enriched samples. In **4**, values of 16.75–17.38 kcal/mol (by line shape analysis)[47] and 16.3–17.3 kcal/mol (by ^{14}N double resonance techniques)[48] have been found. Ab initio calculations for the barrier in **1** range from 14.84[21] to 18.68[13] and 18.14 kcal/mol[52] while those for **4** range from 14.49[21] to 16.43[13] and 16.88 kcal/mol.[52] Thus, despite neglect of possible solute–solute and solvent–solute interactions, there is excellent agreement between experiment and theory. Similarly, MM2 calculates barriers of 17.82 kcal/mol and 16.86 kcal/mol for **1** and **4**, respectively. Presumably, the lower barrier to rotation in acetamide (**4**) [relative to formamide (**1**)] is due to a diminution of the effective positive charge on the carbon of the carbonyl in the replacement of hydrogen by methyl. In concert with this suggestion is the corresponding lengthening of the N–C_{ox} bond [1.368 (3) Å in **1** and 1.380 (4) Å in **4**].

The same ideas can be applied to *N*-methylformamide (**2a,b**) and *N*-methylacetamide (**5a,b**) although the problem is complicated by the possibility of *E* and *Z* isomers in these compounds.[53] In that vein, experimental values

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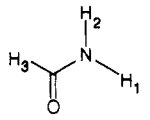
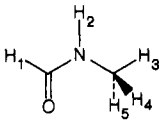
Table IV. Experimental and Calculated Structural Data for Amides 1–3



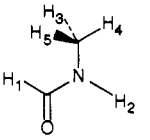
formamide (1)

bond	expt[a,b]	calcd[c]
C=O	1.212 (3)	1.207
N–C_{ox}	1.368 (3)	1.364
C–H_3	1.125 (12)	1.114
N–H_1	1.207 (6)	1.011
N–C=O	125.0 (4)	123.9
C–N–H_1	118.5 (10)	119.0
C–N–H_2	119.4 (10)	120.1
N–C–H_3	112.7	113.0
H_3–C=O	122.4	123.1
H_1–N–H_2	121.6	120.9
dipole	3.29D[e] 3.85D[f]	3.49D
I_x	1.154	1.169
I_y	7.377	7.328
I_z	8.533	8.497
rotat barrier	17.8–18.0[g]	17.82



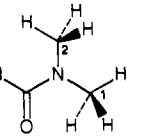
(*Z*)-*N*-methylformamide (2a)

bond	expt[a,b,d]	calcd[c]
C=O	1.219 (5)	1.207
N–C_{ox}	1.366 (8)	1.367
N–C_{sp^3}	1.459 (6)	1.455
H_1–C_{ox}	–	1.114
H_2–N	–	1.014
H_3–C	1.114	1.114
H_4–C	1.114	1.114
H_5–C	1.114	1.114
N–C=O	124.6 (5)	124.55
C_{ox}–N–C_{sp^3}	121.4 (9)	120.44
N–C_{ox}–H_1	–	112.75
H_2–N–C_{sp^3}	–	119.78
O=C–H_1	–	120.70
N–C–H_3	–	109.85
N–C–H_4	–	110.22
N–C–H_5	–	110.30
H_4–C–H_5	–	109.72
H_3–C–H_5	–	108.34
H_3–C–H_4	–	108.37
H_1–C_{ox}–N–H_2	–	0.18
O–C_{ox}–N–H_2	–	–179.82
H_2–N–C–H_3	–	–1.34
H_2–N–C–H_4	–	118.0
H_2–N–C–H_5	–	–120.70
H_5–C_{sp^3}–N–C_{ox}	–	59.60
H_4–C_{sp^3}–N–C_{ox}	–	–61.70
H_3–C_{sp^3}–N–C_{ox}	–	178.96
O–C_{ox}–N–C_{sp^3}	–	–0.12
H_1–C_{ox}–N–C_{sp^3}	–	179.88
dipole	3.8D[h] 3.84D[f]	3.48D
I_x	–	4.349
I_y	–	13.354
I_z	–	17.149
$\Delta G°$ ($Z \rightarrow E$)	1.3–1.6[h]	0.99
rotat barrier	20.6[i]	20.24



(*E*)-*N*-methylformamide (2b)

bond	expt[a,b,d]	calcd[c]
C=O	1.219 (5)	1.206
N–C_{ox}	1.366 (8)	1.365
N–C_{sp^3}	1.459 (6)	1.455
H_1–C_{ox}	–	1.114
H_2–N	–	1.012
H_3–C	1.114	1.114
H_4–C	1.114	1.114
H_5–C	1.114	1.114
N–C=O	124.6 (5)	123.07
C_{ox}–N–C_{sp^3}	121.4 (9)	121.26
N–C_{ox}–H_1	–	113.97
H_2–N–C_{sp^3}	–	120.62
O=C–H_1	–	122.96
N–C–H_3	–	110.17
N–C–H_4	–	109.82
N–C–H_5	–	110.24
H_4–C–H_5	–	110.24
H_3–C–H_5	–	109.67
H_3–C–H_4	–	108.47
H_1–C_{ox}–N–H_2	–	179.83
O–C_{ox}–N–H_2	–	–0.16
H_2–N–C–H_3	–	–118.10
H_2–N–C–H_4		1.32
H_2–N–C–H_5	–	120.73
H_5–C_{sp^3}–N–C_{ox}	–	–59.61
H_4–C_{sp^3}–N–C_{ox}	–	–179.02
H_3–C_{sp^3}–N–C_{ox}	–	61.56
O–C_{ox}–N–C_{sp^3}	–	–179.83
H_1–C_{ox}–N–C_{sp^3}	–	0.16
dipole	–	3.82D
I_x	–	1.999
I_y	–	18.869
I_z	–	20.314



N,*N*-dimethylformamide (3)

bond	expt[a,b]	calcd[c]
C=O	1.20	1.207
N–C_{ox}	1.34 (2)	1.355
N–C_1	1.45 (2)	1.458
N–C_2	–	1.458
H–C_{ox}	–	1.114
N–C=O	123	124.40
C_1–N–C_{ox}	117.5 ± 2	121.55
C_2–N–C_{ox}	117.5 ± 2	122.28
C_1–N–C_2	–	116.17
N–C–H_5	–	113.61
O=C–N–C_1	–	1.13
O=C–N–C_2	–	179.82
dipole	3.77D[h] 3.92D[i]	3.81D
I_x	9.45	9.575
I_y	–	20.077
I_z	–	28.553
rotat barrier	20.94[j]	20.92

[a] Electron diffraction data[6–14] unless otherwise noted. Microwave data[5] is also available for selected values but it is less complete and does not differ significantly where comparison is possible. [b] Angles are given in degrees, bond lengths in angstroms, energies in kilocalories/mole, and moments of inertia × 10^{-39} g cm^2. [c] Calculations are for this work only. The text contains references to results from other computational methods. [d] Experimental results are not available for the separate *Z* and *E* isomers. [e] Linderberg, A. B. *Compt. Rend., Ser. C* **1966**, *262*, 1504. [f] Aroney, M. J.; Le Fevre, R. J. W.; Singh, A. N. *J. Chem. Soc.* **1965**, 3179. [g] After ref 33 and 34. [h] Meighan, R. M. *Diss. Abstr.* **1965**, *25*, 4427. [i] Lee, C. M.; Kumler, W. D. *J. Am. Chem. Soc.* **1962**, *84*, 571. [j] After ref 19, 35–42. [k] After ref 43–45. [l] After ref 43 and 45. See, however, ref 30 and 46.

of 1.6,[43] 1.44,[45] and 1.3 kcal/mol[44] have been reported for the energy differences between **2a** and **2b**. Ab initio calculated values range from 2.0 to 2.7 kcal/mol in the same direction.[13,59] For **5a** and **5b**, an experimental value of 2.8 kcal/mol[43] and a calculated (ab initio) value of 3.66 kcal/mol[60] have been reported. Thus, for both sets of isomers, the ab initio values are about 1 kcal/mol higher than those determined experimentally. Our MM2 calculated values (0.99 and 2.36 kcal/mol, respectively) are lower than the experimental values by about 0.5 kcal/mol, and both sets of calculations suffer from the usual inability to estimate solute–solute and solute–solvent interactions affecting the experimental results.

The MM2 calculated rotational barriers about the N–C_{ox} bond in *N*-methylformamide (**2a**,**b**) [20.24 kcal/mol] and *N*-methylacetamide (**5a**,**b**) [19.23 kcal/mol] are 3–4 kcal/mol higher than the same barrier in their respective unmethylated putative progenitors **1** and **4**, and while it can be argued that they do not differ significantly from each other, the difference (ca. 1 kcal/mol) is about the same magnitude and in the same direction as it was in **1** and **4**.

(53) The interconversion between the *E* and *Z* isomers of *N*-methylformamide (**2a**,**b**) and *N*-methylacetamide (**5a**,**b**), respectively, has been studied by dipole moment,[54] dielectric constant measurements,[55] and by infrared and Raman,[30–32] X-ray,[56] electron diffraction,[7,9] and NMR[43–45,50,57,58] spectroscopy. It is concluded that the *Z* isomer generally predominates, although some controversy regarding the exact ratio remains. Thus, it has been estimated that, at room temperature, there is 5% *E* isomer in each (IR),[32] 17 ± 10% **2b** at 130 °C, and "no trace" of **5b** at 160 °C (ED),[7] and 8% **2b** by ^{15}N NMR.[58]

(54) Mizushima, S.; Simanouti, T.; Nagakura, S.; Kuratani, K.; Tsuboi, M.; Baba, H.; Fujioka, O. *J. Am. Chem. Soc.* **1950**, *72*, 3490.

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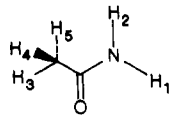
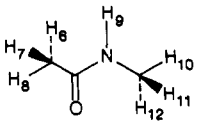
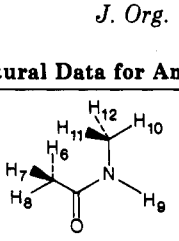
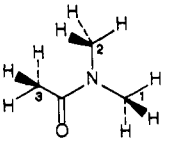
Table V. Experimental and Calculated Structural Data for Amides 4-6









acetamide (4)			(*Z*)-*N*-methylacetamide (**5a**)			(*E*)-*N*-methylacetamide (**5b**)			*N*,*N*-dimethylacetamide (**6**)		
bond	expt[a,b]	calcd[c]	bond	expt[a,b,d]	calcd[c]	bond	expt[a,b,d]	calcd[c]	bond	expt[a,b]	calcd[c]
C=O	1.220 (3)	1.209	C=O	1.225 (3)	1.209	C=O	1.225 (3)	1.208	C=O	–	1.209
N-C_{ox}	1.380 (4)	1.368	N-C_{ox}	1.386 (4)	1.371	N-C_{ox}	1.386 (4)	1.371	N-C_{ox}	–	1.377
H_3-C_{sp^3}	1.124 (10)	1.114	H_6-C_{sp^3}	1.107	1.114	H_6-C_{sp^3}	1.107	1.113	N-C_1	–	1.460
H_4-C_{sp^3}	1.124 (10)	1.114	H_7-C_{sp^3}	1.107	1.114	H_7-C_{sp^3}	1.107	1.113	N-C_2	–	1.461
H_5-C_{sp^3}	1.124 (10)	1.114	H_8-C_{sp^3}	1.107	1.114	H_8-C_{sp^3}	1.107	1.114	C_3-C_{ox}	–	1.521
N-H_1	1.022 (11)	1.011	N-C_{sp^3}	1.469 (6)	1.455	N-C_{sp^3}	1.469 (6)	1.456	N-C=O	–	122.60
N-H_2	1.022 (11)	1.011	C_{sp^3}-C_{ox}	1.520 (5)	1.518	C_{sp^3}-C_{ox}	1.520 (5)	1.520	C_1-N-C_{ox}	–	121.26
C_{sp^3}-C_{ox}	1.519 (6)	1.518	N-H_9	1.002	1.013	N-H_9	1.002	1.012	C_2-N-C_{ox}	–	123.37
N-C=O	122.0 (6)	122.25	H_{10}-C_{sp^3}	–	1.114	H_{10}-C_{sp^3}	–	1.114	C_1-N-C_2	–	115.28
H_1-N-C_{ox}	118.5	118.94	H_{11}-C_{sp^3}	–	1.114	H_{11}-C_{sp^3}	–	1.113	N-C_{ox}-C_3	–	116.37
H_2-N-C_{ox}	120.0	120.40	H_{12}-C_{sp^3}	–	1.114	H_{12}-C_{sp^3}	–	1.113	O=C-N-C_1	–	0.34
N-C_{ox}-C	115.1	114.94	N-C=O	121.8 (4)	122.88	N-C=O	121.8 (4)	121.00	dipole	3.75D[e] 3.81D[f]	3.85D
C-C=O	119.7[g]	122.81	N-C_{ox}-C	114.1 (15)	114.79	N-C_{ox}-C	114.1 (15)	116.73	I_x	–	17.329
H_3-C-C	109.8 (20)	110.78	C-N-C	119.7 (8)	120.44	C-N-C	119.7 (8)	123.21	I_y	–	24.622
H_4-C-C	109.8 (20)	110.40	H_9-N-C_{ox}	110.5 (5)	120.00	H_9-N-C_{ox}	110.5 (5)	117.00	I_z	–	40.346
H_5-C-C	109.8 (20)	110.40	C-C=O	124.1	122.88	C-C=O	124.1	121.00	rotat barrier	18.43[h]	18.70
dipole	3.72D[e] 3.75D[i] 3.38D[j] 3.87D[k]	3.55D	H_9-N-C_{sp^3}	–	119.56	H_9-N-C_{sp^3}	–	119.79			
			N-C-H_{10}	–	109.83	N-C-H_{10}	–	109.43			
			N-C-H_{11}	–	110.25	N-C-H_{11}	–	110.75			
I_x	–	7.744	N-C-H_{12}	–	110.32	N-C-H_{12}	–	110.77			
I_y	–	9.058	H_{10}-C-H_{11}	–	108.34	H_{10}-C-H_{11}	–	107.66			
I_z	–	16.251	H_{10}-C-H_{12}	–	108.29	H_{10}-C-H_{12}	–	107.66			
rotat barrier	16.7–17.4[l]	16.86	H_{11}-C-H_{12}	–	109.78	H_{11}-C-H_{12}	–	110.47			
			C-C-N-C	–	-179.92	C-C-N-C	–	0.10			
			C-C-N-H_9	–	-0.13	C-C-N-H_9	–	-180.00			
			C-N-C-H_{10}	–	-179.32	C-N-C-H_{10}	–	-179.90			
			C-N-C-H_{11}	–	61.36	C-N-C-H_{11}	–	61.57			
			C-N-C-H_{12}	–	-60.04	C-N-C-H_{12}	–	-61.36			
			N-C-C-H_6	–	-60.29	N-C-C-H_6	–	-61.52			
			N-C-C-H_7	–	60.47	N-C-C-H_7	–	61.59			
			N-C-C-H_8	–	-179.91	N-C-C-H_8	–	-179.87			
			O-C-C-H_6	–	119.72	O-C-C-H_6	–	118.73			
			O-C-C-H_7	–	-119.52	O-C-C-H_7	–	-118.36			
			O-C-C-H_8	–	0.09	O-C-C-H_8	–	0.18			
			C-N-C-O	–	0.08	C-N-C-O	–	-179.95			
			H_9-N-C-H_{10}	–	0.88	H_9-N-C-H_{10}	–	0.20			
			H_9-N-C-H_{11}	–	-118.43	H_9-N-C-H_{11}	–	-118.33			
			H_9-N-C-H_{12}	–	120.17	H_9-N-C-H_{12}	–	118.74			
			dipole	3.68 D[e] 3.85D[m]	3.51D	dipole	–	3.88D			
			I_x	–	8.385	I_x	–	9.599			
			I_y	–	21.733	I_y	–	20.092			
			I_z	–	29.012	I_z	–	28.575			
			$\Delta G°$ ($Z \rightarrow E$)	2.8[n]	2.36						
			rotat barrier	20.8[p]	19.23						

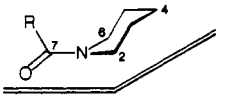
[a] Electron diffraction data[6-14] unless otherwise noted. Microwave data[5] is also available for selected values but it is less complete and does not differ significantly where comparison is possible. [b] Angles are given in degrees, bond lengths in angstroms, energies in kilocalories/mole, and moments of inertia × 10^{-39} g cm^2. [c] Calculations are for this work only. The text contains references to results from other computational methods. [d] Experimental results are not available for the separate *Z* and *E* isomers. [e] Meighan, R. M. *Diss. Abstr.* **1965**, *25*, 4427. [f] Price, A. H.; Brownsell, V. L. *J. Phys. Chem.* **1970**, *74*, 4004. [g] After ref 33 and 34. [h] After ref 35–42. [i] Meighan, R. M.; Cole, R. H. *J. Phys. Chem.* **1964**, *68*, 503. [j] Purcell, W. P.; Singer, H. A. *J. Phys. Chem.* **1967**, *71*, 4316. [k] Aroney, M. Y.; Le Fevre, R. J. W.; Singh, A. N. *J. Chem. Soc.* **1965**, 3179. [l] After ref 47 and 48. [m] Lumbroso, H.; Pigenet, C. *Compt. Rend., Ser. C* **1968**, *266*, 735. [n] After ref 43. [p] After ref 43–45.

Experimentally, barriers of 20.6 kcal/mol for **2a,b** and 20.8 kcal/mol for **5a,b** (both in 1,2-dichloroethane)[43] and 21.3 kcal/mol for the latter in water[43] and 22.0 kcal/mol for the former (by ^{1}H NMR equilibrium trapping)[45] have been reported. Ab initio calculations provide values that are 2–4 kcal/mol lower than the experimental ones noted above.[21] While the usual caveats concerning intermolecular interactions can be made, the problem is doubtless exacerbated by the difficulty that *E* and *Z* isomers may be differently solvated, and thus there may be greater or lesser association as dimers or polymers between the different forms of the amides themselves.[50]

Finally, regarding the data in Tables IV and V, *N*,*N*-dimethylformamide (**3**) and *N*,*N*-dimethylacetamide (**6**) can be compared. Despite the paucity of experimental data[61,62] and the additional complications concerning different geometries resulting from methyl group rotational isomers, the parameters obtained from **1**, **2a,b**, **4**, and **5a,b**

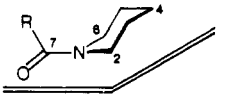
(61) Vilkov, L. V.; Akishin, P. A.; Presnyakova, V. M. *Zh. Strukt. Khim.* **1962**, *3*, 3.
(62) Schmid, E. D.; Brodbeck, D. *J. Mol. Struct.* **1984**, *108*, 17.

Table VI. Calculated Structural Data for Amides 7 and 8[a]



N-formylpiperidine (R = H, 7)

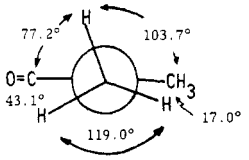
bond	value	bond	value
$N-C_2$	1.459	$N-C_6$	1.460
$N-C_7$	1.369	C_2-C_3	1.536
C_3-C_4	1.536	C_4-C_5	1.536
C_5-C_6	1.536	$N-C_2-C_3$	110.0
$N-C_6-C_5$	109.9	$N-C_7-O$	124.7
C_2-N-C_6	114.0	C_2-N-C_7	122.8
C_6-N-C_7	123.2	$C_2-C_3-C_4$	110.3
$C_3-C_4-C_5$	110.0	$C_4-C_5-C_6$	110.3
$N-C_2-C_3-C_4$	56.0	$C_2-C_3-C_4-C_5$	-55.3
$C_3-C_4-C_5-C_6$	53.3	$C_4-C_5-C_6-N$	-56.0
$C_2-N-C_6-C_5$	58.9	$C_6-N-C_2-C_3$	-58.9



N-acetylpiperidine (R = CH_3, 8)

bond	value	bond	value
$N-C_2$	1.461	$N-C_6$	1.463
$N-C_6$	1.378	C_2-C_3	1.536
C_3-C_4	1.537	C_4-C_5	1.537
C_5-C_6	1.536	$N-C_2-C_3$	109.0
$N-C_6-C_5$	109.0	$N-C_7-O$	122.6
C_2-N-C_6	112.4	C_2-N-C_7	121.9
C_6-N-C_7	125.2	$C_2-C_3-C_4$	110.2
$C_3-C_4-C_5$	110.5	$C_4-C_5-C_6$	110.2
$N-C_2-C_3-C_4$	57.1	$C_2-C_3-C_4-C_5$	-53.9
$C_3-C_4-C_5-C_6$	54.0	$C_4-C_5-C_6-C_7$	-57.3
$C_2-N-C_6-C_5$	63.0	$C_6-N-C_2-C_3$	-62.9

[a] Calculations are for this work only. Angles are given in degrees and bond lengths in angstroms.



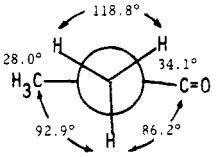
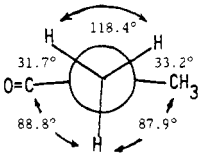


Figure 1. A pictorial Newman type representation of the MM2 calculated minimum energy conformation of *N,N*-dimethylformamide (**3**). Angles are given in degrees. On the left, the view is directed down the C_1-N (the *Z*-methyl) bond while on the right, the view is directed down the C_2-N (the *E*-methyl) bond.



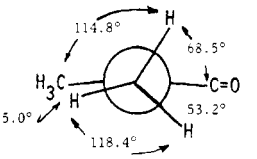


Figure 2. A pictorial Newman type representation of the MM2 calculated minimum energy conformation of *N,N*-dimethylacetamide (**6**). Angles are given in degrees. On the left, the view is directed down the C_1-N (the *Z*-methyl) bond while on the right, the view is directed down the C_2-N (the *E*-methyl) bond.

and those standard in MM2 can be applied. We notice, first, that the low barrier to rotation of the methyl groups on nitrogen leads to similar steric energies for those rotational isomers. Second, the $N-C_{ox}$ and $N-C_{sp^3}$ bonds in **6** (1.377 and 1.460 Å, respectively)[63] are lengthened further than those in **3** (1.355 and 1.458 Å, respectively),[63] and the angle subtended between the (*E*)-methyl group and the amide carbonyl is wider in **6** (123.37°) than in **3** (122.28°) while the same angle for the (*Z*)-methyl group is similar in both. The early experimental work on the barrier to rotation around the $N-C_{ox}$ bond in both **3** and **6** has been summarized,[19] and average values from this early work are 21.0 and 18.2 kcal/mol, respectively. Later work[35,36-42] has provided values of 20.94 and 18.43 kcal/mol, respectively. Our calculations give values of 20.92 for **3** and 18.70 kcal/mol for **6**. The small increase in the barrier on going from **2a,b** to **3** (20.24 to 20.92 kcal/mol) is not unexpected while the small decrease on going from **5a,b** to **6** (19.23 to 18.70 kcal/mol) may be the result of sterically induced ground state destabilization.

For the most stable isomers of **3** and **6** the nitrogen atom is calculated to be, respectively, 6×10^{-3} and 2.3×10^{-2} Å out of the plane defined by the three carbon atoms bonded to it, and both methyl groups on nitrogen are twisted so that their hydrogen atoms have minimum interaction with each other (Figures 1 and 2).

Finally, the parameters developed here and others extant in MM2[24] have been applied to *N*-formylpiperidine (**7**) and *N*-acetylpiperidine (**8**), and the calculated structural data is provided in Table VI for the chair forms of these compounds. Although neither experimental nor other theoretical conformational studies for **7** and **8** have been reported, we have assumed that the ring conformations are similar to those of cyclohexanone and methylenecyclohexane because, to the extent that there is overlap between the occupied orbital on nitrogen and the carbon of the carbonyl group, all four compounds may be considered to possess an sp^2 or sp^2-like hybridized atom in the six-membered ring.

The barriers to ring inversion in cyclohexanone (4.0–4.9 kcal/mol)[64,65] and methylenecyclohexane (7.7–8.4 kcal/mol)[64,66] are substantially lower than that for cyclohexane (10.1–10.8 kcal/mol),[20,67] and all three have successfully been treated by MM2.[68-70] The differences in energy are attributed primarily to the torsional barriers about the bond between the sp^2 hybridized carbon in the first two (missing in the last) and the carbon α to it.

There are two chair forms of piperidine; one with the hydrogen on nitrogen equatorial and the other with the hydrogen on nitrogen axial. The energy difference between the two isomers has been found to be 0.4 kcal/mol (dipole moment)[71] and 0.36 kcal/mol (^1H NMR).[72] Both methods favor the lowest energy form being that with the hydrogen equatorial. However, these are interconvertable either through ring inversion (10.4 kcal/mol by NMR)[73] as with cyclohexane, cyclohexene, and cyclohexanone or by inversion through nitrogen (6.1 kcal/mol)[72] as with ammonia.

Using MM2, the ring-inversion process for **7** and **8** may be examined. Unlike the carbocyclic systems, the sub-

(63) Since experimental values for **6** are unavailable, calculated values for **3** and **6** are used for comparison. Table IV presents a comparison of calculated and experimental values for **3**.

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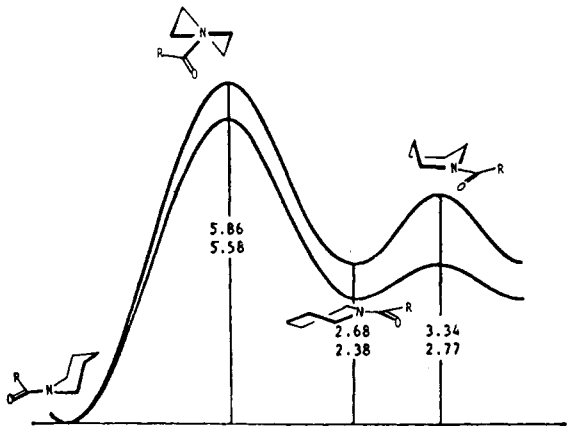

Figure 3. A representation of a portion of the calculated energy profile for ring inversion for *N*-formylpiperidine (**7**) and *N*-acetylpiperidine (**8**). The top curve and upper set of numbers are for **7** and the bottom curve and lower set of number are for **8**. The numbers are the calculated energies for the forms shown and their units are kilocalories/mole.

stituent on nitrogen in **7** and **8** renders them unsymmetrical, and thus there are more variations to consider; therefore, in order to find the lowest energy inversion pathway, steric energy calculations were performed for 19 possible energy maximum and minimum conformations—chair, boat, twist-boat, half-chair, and sofa—for each of the piperidine derivatives [reached by rotating (at 5-deg intervals via the dihedral driver) the C–N–C–C torsional angle in the ring of the chair conformation and minimizing the steric energies with each rotation]. The energy profile obtained is shown in Figure 3 for both **7** and **8**. The highest barriers to ring inversion for these compounds are located between the chair and twist-boat, and the energies of the barriers are 5.86 and 5.58 kcal/mol, respectively. These energies are near the average values for methylenecyclohexane and cyclohexanone. Additionally, there is a small energy barrier between the twist-boat and its mirror image. The boat conformation appears as a maximum. Rotation of the ring torsional angle N–C–C–C, in an attempt to examine another potential ring inversion path, generates a barrier exactly the same as that found above, although the path itself is clearly different. Clearly, there are various routes to reach one transition-state conformation from another (which may be the mirror image of the first) since the steric energies of the several boat and twist-boat conformations are similar (within 1.2 kcal/mol of each other).

Further, the steric energies of the various ring conformations of **7** and **8** are little influenced by the geometries of the respective acyl groups, and (as shown in Figure 3) (a) relative energies of **7** are generally higher than those of **8** for each similar conformation (which is directly comparable to the observation that the barrier in **3** is higher than that in **6** as shown earlier); (b) the conformations having energy maxima and minima are similar in both piperidine derivatives (despite the absolute differences in the amounts of energies); and, (c) as with the carbocycles to which comparison is made, the most stable conformers for both **7** and **8** are the chair forms with the relative energies of the twist-boat forms of both amides somewhat similar to cyclohexanone but substantially lower than cyclohexane and methylenecyclohexane.

Conclusion

We have extended MM2 to molecules containing the amide group and, in doing so, have successfully developed a set of parameters which reproduce, with reasonable accuracy, experimentally available data. The parameters developed for simple amides have been extended to more complicated systems, and predictions have been made. Among these the most striking may be that in dialkyl-substituted amides, the nitrogen atom deviates from the plane of the three carbon atoms to which it is attached.

Formation and Characterization of 3-*O*-Arenediazoascorbic Acids. New Stable Diazo Ethers

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Ascorbic acid reacts with arenediazonium salts to form stable compounds whose structures have been spectroscopically identified as 3-*O*-arenediazoascorbic acids. The pK_a values of the *p*-nitro- and *p*-chlorobenzenediazo derivatives are 10.2 and 10.1, respectively, which also correspond to arenediazonium ion attachment at the 3-hydroxyl position of ascorbic acid. These diazo ethers are stable in the pH range of 3 to 11, and they are resistant to nucleophilic displacement and electron-transfer reactions that commonly occur with the unassociated diazonium ions. Reaction rates for diazo ether formation are first order in ascorbic acid and arenediazonium ion concentrations, and they exhibit inverse first-order dependence on the hydrogen ion concentration over the pH range of 6.0–8.0.

Oxidation–reduction reactions of hydroquinone (H_2Q) and ascorbic acid (H_2A) are formally equivalent. Both substrates undergo one-electron-transfer processes through semidione intermediates. Their redox potentials, whose values are pH dependent,[1-4] converge with differences of as little as 15 mV at pH 13.5 and 50 mV at pH 0.[5] Rate constants for outer-sphere electron transfer with metal ions are only 2 to 3 orders of magnitude lower for H_2A than for H_2Q when compared under identical conditions,[6-8] al-

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