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Molecular Mechanics (MM4) Calculations on Amides

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The amide compounds have been studied, and their parameters have been developed for the MM4 force field. The structures, moments of inertia, vibrational spectra, conformational energies, barriers to internal rotation and dipole moments have been examined for these compounds. The MM4 structures calculated for these compounds were fit to available electron diffraction (ED) and microwave data (MW). Structural parameters were fitted in favor to the MW moments of inertia, which are more accurately determined experimental quantities than ED measured bond lengths. For all of the 15 moments (5 molecules) experimentally known for the amide compounds, the MM4 rms error is 0.62%. For the calculated vibrational spectra of four amide compounds which were fully analyzed, the MM4 rms error from experiment was 27 cm^{-1} over a total of 108 weighted modes. Heat of formation parameters were optimized for 25 amide compounds whose gas-phase heats of formation were experimentally known. For 18 weighted compounds, the weighted standard deviation between MM4 and experiment was 0.53 kcal mol^{-1}.

Introduction

The study of amides and polypeptides and the development of their force field parameters had been done in earlier work[1] using MM3.[2] This paper is primarily concerned with amides in the gas phase, and subsequent papers will deal with nonbonded interactions in amide-amide and amide-water systems and with peptides. Here, the amide study was done using the newer and more refined MM4[3] force field. Also, the experimental data from which the older MM3 parameters were developed were reevaluated in this study, and more recent data were substituted and added. In particular, IR and microwave data published after the MM3 paper were used to determine the vibrational frequencies and moments of inertia.

For comparison, calculations with the presently used 1996 version of MM3 were also conducted in parallel with MM4 calculations. The older 1990 version of MM3 was used in the earlier amide study. Also, MM3 heat of formation calculations for the amides were never formally published, even though their heat of formation parameters were determined and published in the MM3 program.

In modeling proteins and the manner of their folding, the starting point is to develop parameters for the basic polypeptide backbone. The most important parameters are those describing torsions about the Φ and Ψ dihedrals because the three-dimensional structures of proteins are determined to a large extent by the torsion potentials about these dihedral angles.

However, before any attempt is made in modeling the folding of the basic polypeptide backbone in proteins, it is first necessary to have an adequate force field for amides, the precursors of peptides and proteins. In this work, parameters were developed for the MM4 force field for the following C′-alkyl amide compounds: acetamide, *N*-methylacetamide, propanamide, butanamide, and *N*-ethylacetamide. Likewise, parameters were obtained for the following *N*-substituted formamides: formamide, *N*-methylformamide, *N*,*N*-dimethylformamide, *N*-ethylformamide, and *N*-propylformamide. With the exception of *N*-propylformamide, the formamides will have no role in providing parameters for polypeptides and proteins because they have separate parameters for all practical purposes. Nevertheless, they are important in the modeling of organic molecules in general and, thus, were included in the present work. MM4 parameters were also obtained for three diamide compounds: propanediamide, 1,4-butanediamide and *N*-acetylacetamide.

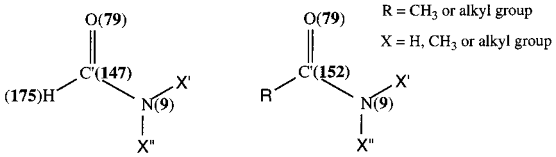

Figure 1. Different Carbonyl Carbon Atom Types for C′-alkylamides and Formamides.

Different atom types have been assigned for the carbonyl (C′) carbon in amides, depending on type of substitution at that carbon. In the case where there is a methyl or alkyl group attached to the C′ carbon (i.e., acetamide, propanamide, butanamide, and so on), the carbonyl carbon atom type is 152. In the case where a hydrogen is attached (formamide and *N*-substituted formamides), the C′ atom type is 147. (Figure 1). In addition, the atom type for the aldehydyl hydrogen in formamides has been changed from type 5 to type 175. Initially, it had the same atom type as that for the corresponding hydrogen in aldehydes. When studying nonbonded interactions involving this hydrogen in formamide, namely $H_2N(OC')\text{-}H\cdots O$ interactions, we found that it was a much stronger hydrogen bond donor than previously recognized. According to density functional calculations done by us at the B3LYP/6-311++G(d,p) level with basis set superposition error correction, the $C'{-}H\cdots O$

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TABLE 1: MM4 Parameters[a] for Amides

A. van der Waals' parameters

atom type	ε (kcal/mol)	r (Å)	atom type	ε (kcal/mol)	r (Å)
9	0.054	1.86	147	0.057	1.94
28	0.015	1.60	152	0.057	1.94
79	0.060	1.76			

B. stretching parameters

bond	k_s (mdyn/Å)	l_0 (Å)	bond	k_s (mdyn/Å)	l_0 (Å)
1−9	6.00	1.441	1−152	5.00	1.507
9−28	6.80	1.024	9−152	7.20	1.365
147−175	4.40	1.118	79−152	10.28	1.220
9−147	7.25	1.368	79−147	10.10	1.218

C. bending parameters

angle	k_b (mdyn Å/rad^2)	θ_0 (deg)	type[b]	angle (out-of-plane)	k_{oop} (kcal/mol)
1−9−1	0.74	115.40		0−9−1	0.80
1−9−28	0.19	122.40		0−9−28	−3.70
5−1−9	0.79	110.80	1	0−147−9	8.00
5−1−9	0.79	110.80	2	0−147−79	14.80
5−1−9	0.79	110.80	3	0−147−175	10.00
28−9−28	0.34	123.00		0−9−147	0.80
1−9−147	0.84	116.50		0−152−9	8.00
28−9−147	0.60	118.50		0−152−79	14.50
9−147−175	0.50	109.80		0−152−1	7.80
79−147−175	0.89	120.20		0−9−152	1.20
9−147−79	1.13	124.00			
1−1−152	0.93	109.60	1		
1−1−152	0.93	110.60	2		
1−1−152	0.93	110.85	3		
9−1−152	0.85	109.50	1		
9−1−152	0.85	110.60	2		
9−1−152	0.85	108.55	3		
1−152−9	0.71	113.90			
1−152−79	0.66	126.80			
1−9−152	0.84	117.65			
5−1−152	0.68	107.75	1		
5−1−152	0.65	108.65	2		
5−1−152	0.62	109.55	3		
152−1−152	0.97	109.47	1		
152−1−152	0.97	110.00	2		
152−1−152	0.97	110.20	3		
28−9−152	0.65	118.50			
152−9−152	0.90	127.40	1		
152−9−152	0.90	127.40	2		
9−152−79	1.05	124.53			

[a] Atom types: 147 − sp^2 carbonyl C in formamides, 152 − sp^2 carbonyl C in acetamides, 79 − carbonyl O in amides, 9 − amido N, 28 − amido H, 5 − alkyl H, 175 − aldehydyl H in formamides, 1 − sp^3-type alkane C. [b] Angle types: type 1 − $-CR_2$-, −NR−. type 2 − −CHR-, −NH−. type 3 − $-CH_2$-. Conversion factor: 143.88(kcal/mol)/(mdyne Å).

TABLE 2: MM4 Torsional Parameters for Amides

D. torsional parameters (units in kcal/mol)

dihedral	V_1	V_2	V_3	V_4	V_6
1−1−1−9	0.309	0.021	0.115	−0.058	−0.047
5−1−1−9	0.000	0.000	0.500	0.000	0.000
1−1−9−1	−0.278	−0.431	0.771	0.000	0.000
1−1−9−28	0.000	0.000	0.010	0.000	0.000
5−1−9−1	0.000	0.000	0.460	0.000	0.000
5−1−9−28	0.000	0.000	0.080	0.000	0.000
1−1−9−147	1.499	−1.311	0.476	−0.394	0.022
5−1−9−147	0.000	0.000	−0.138	0.000	0.000
1−9−147−175	1.000	7.450	0.000	0.000	0.000
28−9−147−175	0.000	7.000	0.000	−0.550	0.000
1−9−147−79	1.033	4.866	−1.191	−1.746	−0.281
28−9−147−79	0.000	7.000	0.000	−0.550	0.000
1−1−1−152	1.931	−1.568	0.669	−0.323	−0.049
5−1−1−152	0.000	0.000	−0.025	0.000	−0.012
152−1−1−152	7.870	−5.814	0.957	−0.292	−0.178
1−1−9−152	1.726	−1.449	0.453	−0.359	0.000
1−1−152−9	−0.164	0.000	−0.552	0.000	0.000
1−1−152−79	0.000	1.734	0.000	−0.185	0.011
1−9−152−1	1.638	0.000	0.376	0.000	0.000
1−9−152−79	0.000	13.571	0.656	−1.800	0.000
5−1−9−152	0.000	0.000	−0.180	0.000	0.000
5−1−152−9	0.000	0.000	−0.100	0.000	0.000
5−1−152−79	0.000	0.000	0.090	0.000	0.000
152−1−152−9	−0.490	0.000	0.500	0.000	0.000
152−1−152−79	2.272	0.211	2.323	1.221	−0.194
152−9−152−1	−2.528	0.000	0.014	0.000	0.000
152−9−152−79	0.017	5.859	−0.074	−0.043	0.142
28−9−152−1	0.000	5.570	0.000	−0.620	0.000
28−9−152−79	0.000	6.000	0.000	−0.200	0.000

interaction in formamide is nearly twice as strong as the same type interaction in aldehydes. Parameters for aldehydes[4] have already been optimized and fixed in MM4, including nonbonded parameters. Therefore, changing the atom type was the only way of making this interaction strong enough in formamides without affecting earlier MM4 work. This and other nonbonded interactions in amides will be discussed in greater detail in a separate paper, but the assignment of these new atom types had to be declared at this point in our study. The major justification for different atom types in formamides and acetamides is based on the same reasoning for assigning different atom types for aldehydes and ketones studied recently in MM4.[4,5] There are different electronic environments about the C′ carbons in the formamide- and acetamide-type configurations, and these are, from the molecular mechanics point of view, and from the general viewpoint of organic chemists, different classes of compounds.

Parameters

The MM4 parameters which have been developed for both types of amides are listed in Tables 1 thru 4. Any cross term and electronegativity correction parameters not listed in Tables 3 and 4 have zero default values. The MM4 force field and its terms have been described in detail in an earlier paper.[3b] However, a general explanation of the parameterization procedure and the some of the MM4 cross-terms is worth mentioning. Bond length and bond angle parameters are determined from a best fit to available electron diffraction, microwave, and sometimes X-ray data. Where these are lacking, ab initio and/or density functional calculations are used. X-ray values (r_a) are the most straightforward way of measuring bond lengths experimentally. However, it is the distance between centers of electron densities which is actually measured in this case, and for bonds with lone pairs, such as the C═O bond, the reported value is usually longer than the actual internuclear distance, and corrections have to be made for these values. Bond lengths and bond angles reported in electron diffraction papers (r_g) are actually obtained by a best fit of the experimentalists' model to the radial distribution curve (what is actually determined experimentally). The errors reported are really the uncertainties in the model, not in the experiment itself. Potentially, different models can yield equally good fits, especially for molecules with four of more heavy atoms. For this reason, we use electron diffraction data only as a first approximation in modeling the molecular geometries. Moments of inertia from microwave spectroscopy are one of the most accurately available physical properties for molecules in the gas-phase. The bond lengths (r_0, r_z, r_s) and bond angles reported are, like those from electron diffraction, derived from models constructed by the spectros-

TABLE 3: MM4 Cross-Term Parameters for Amides

E. torsion-stretch parameters (k_{ts} units in kcal/Å mol)

dihedral	bond X−A			bond A−B			bond B−Y		
X−A−B−Y	k_{ts1}	k_{ts2}	k_{ts3}	k_{ts1}	k_{ts2}	k_{ts3}	k_{ts1}	k_{ts2}	k_{ts3}
1−9−147−79	0.00	18.00	0.00	0.00	36.00	0.00	0.00	0.00	0.00
28−9−147−79	0.00	7.30	0.00	0.00	34.50	0.00	0.00	0.00	0.00
1−1−152−79	0.00	7.80	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1−9−152−79	0.00	13.00	0.00	0.00	31.00	0.00	0.00	0.00	0.00
28−9−152−79	0.00	7.20	0.00	0.00	33.00	0.00	0.00	0.00	0.00
152−9−152−79	11.00	−20.30	0.00	0.00	5.60	0.00	0.00	0.00	0.00

F. bend-torsion-bend parameters

dihedral	k_{btb} (mdyn Å/rad^2)
1−9−147−79	−0.33
1−9−152−79	−0.39

G. torsion-bend parameters (k_{tb} units in mdyn Å/rad)

dihedral	angle XAB			angle ABY		
X−A−B−Y	k_{tb1}	k_{tb2}	k_{tb3}	k_{tb1}	k_{tb2}	k_{tb3}
1−9−147−79	0.000	0.044	0.000	0.00	0.00	0.00
28−9−147−79	0.000	0.035	0.000	0.00	0.00	0.00
1−1−152−79	0.000	0.008	0.000	0.00	0.00	0.00
1−9−152−79	0.000	0.052	0.000	0.00	0.00	0.00
28−9−152−79	0.000	0.022	0.000	0.00	0.00	0.00
152−9−152−79	0.000	0.100	0.000	0.00	0.00	0.00

H. stretch-stretch parameters

angle	k_{ss} (mdyn/Å)
1−9−1	0.50
1−9−147	0.10
28−9−28	0.00
9−147−79	0.59
1−152−9	0.19
1−152−79	0.12
1−9−152	0.10
9−152−79	0.45

I. stretch−bend parameters

angle	k_{sb} (mdyn/rad)
5−1−9	0.200
5−1−152	0.150
9−147−175	0.150
79−147−175	0.150
28−9−147	0.150
1−152−9	0.204
1−152−79	0.304
1−9−152	0.204
28−9−152	0.150
152−9−152	0.050
9−152−79	0.200

J. bend−bend parameters

angle	k_{bb} (mdyn Å/rad^2)
5−1−9	0.30
5−1−152	0.35

TABLE 4: Electrostatic and Electronegativity Effect Parameters for Amides

K. electronegativity correction

bond···attached atom	corr. (Å)
5−1···9	−0.0005
152−9···152	+0.0200
1−9···28	+0.0020

L. bond moments

bond	moment (Debye) w/o polarization	moment (Debye) w/ polarization
1−9	1.650	1.209
9−28	−1.580	−1.197
147−175	−0.750	−0.468
9−147	0.740	0.576
79−147	−1.860	−1.510
1−152	0.800	0.750
9−152	0.740	0.561
79−152	−1.860	−1.410

copist to fit the observed moments, and, for large molecules, these models are also prone to error if initial assumptions about the geometries are inaccurate. However, if there are microwave data available for several molecules of the same class, then the possibility that two or more molecular models with different sets of geometrical parameters having similar moments lessens. If this is the case, then this is the approach to parametrization we prefer to take. The bond length (l_0) and bond angle (θ_0) parameters in molecular mechanics are obtained indirectly by fitting the calculated moments of inertia to the observed moments, but our initial values for l_0 and θ_0 are based on electron diffraction data for small molecules (2−3 heavy atoms), which are usually more accurate.

Molecular mechanics torsion parameters (V_1, V_2, V_3, V_4, V_6) involving heavy atom torsion are obtained by best fits to torsion curves generated by ab initio or density functional (DFT) calculations. In this study, torsion curves were calculated by DFT using the GAUSSIAN94 software program.[6] DFT calculations were at the Becke3−Lee−Yang−Parr (B3LYP) level using a 6-31G** basis set. For similar basis sets, DFT calculations are computationally less expensive than MP2 calculations. We found that, in calculating the heavy-atom torsion potentials for 2-butanone,[5] the B3LYP calculated torsional barriers are very similar to the MP2 calculated barriers using the same 6-31G* basis set. Given the number of heavy-atom torsional curves (13) we had to generate and the total number of data points (149) calculated for these curves, choosing the B3LYP level of density functional theory was the most logical choice for us. For methyl rotation, we fitted the torsion parameters to the rotational barriers determined by microwave spectroscopy or, if such data were absent, to barriers calculated in this study at the B3LYP/6-311+G** level.

MM4 force constant parameters for the amides, stretching (k_s), bending (k_b), and out-of-plane bending (k_{oop}), were obtained by fitting the calculated vibrational spectra to observed gas-phase IR and/or Raman spectra. In this study, vibrational frequency calculations for the amides were carried out at the B3LYP/6-31G** level. The purpose of these calculations were 2-fold: (1) to confirm the experimental assignment of the observed modes and (2) to substitute DFT calculated modes for modes which were either unobserved or missassigned. Fortunately, this was done only for a few modes.

The cross terms in the MM4 force field are used to refine our primary parameter set and model physical phenomenon not sufficiently well modeled by the primary terms alone. Stretch−stretch, stretch−bend, and bend−bend interactions account for the couplings between modes in vibrational spectra as well as couplings between changes in geometry. As examples, the types 9−147−79 and 9−152−79 stretch−stretch parameters (k_{ss}) determine the degrees of coupling between the N−C′ and C′═O stretching modes in formamides and acetamides, respectively. In formamides, the C′−H stretching and O═C′−H bending modes are also highly coupled, and this coupling is accounted for by the type 79−147−175 stretch−bend parameter (k_{sb}).

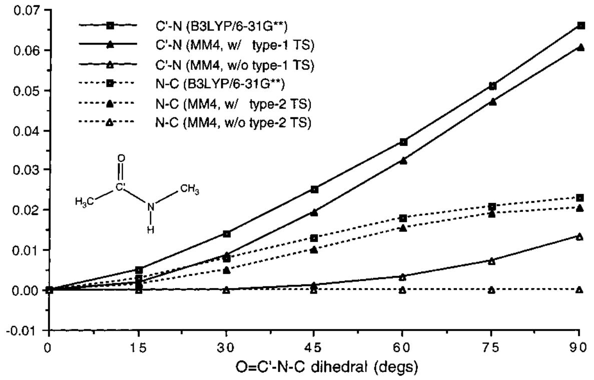


Figure 2. Types 1 and 2 torsion-stretch (TS) interactions in *N*-methylacetamide.

Bend−bend interactions account for coupled bendings between two or more adjacent angles with a common center atom, such as the H−C−N (type 5−1−9) and H−C−C′ (5−1−152) bond angles in the N- and C′-methyl groups in amides. These types of interactions account, to a large extent, the degrees of couplings among the bending and rocking modes of the methyl groups. The total bend−bend constant, k_{BB}, between two adjacent angles is taken as the geometric mean of the individual bend−bend parameters (k_{bb1} and k_{bb2}) for each angle: $k_{\mathrm{BB}} = (k_{\mathrm{bb1}}{*}k_{\mathrm{bb2}})^{1/2}$.

Torsion-stretch (k_{ts}) and torsion-bend (k_{tb}) terms were designed to more accurately describe structural changes, which cannot be fully accounted for by sterics alone, as the molecule undergoes internal rotation. Neither term has much effect on vibrational frequencies. These changes especially occur during rotation about the central C′−N bond in amides. For the X−A−B−Y dihedral, there are three torsion-stretch parameters (k_{ts1}, k_{ts2}, k_{ts3}) for each of the three bonds, X−A, A−B and B−Y, and three torsion-bend parameters (k_{tb1}, k_{tb2}, k_{tb3}) for each of the two bond angles, XAB and ABY, in the dihedral. These terms are usually quite important if X or Y is an atom with a lone pair of electrons. A positive k_{ts1} term indicates a maximum elongation of the bond in question when the dihedral is 0°, a positive k_{ts2} term indicates a maximum of bond elongation when the dihedral is 90°, and a positive k_{ts3} term indicates a maximum of elongation at 120°. Negative values of k_{ts1}, k_{ts2} and k_{ts3} correspond to maxima of bond shortening at these dihedral values. When the X−A−B−Y arrangement is in the trans configuration (180°), the bond lengths are unaffected. In the C−N−C′═O torsion (types 1−9−147−79 and 1−9−152−79) for example, there are conspicuously large values for the second torsion-stretch parameter (k_{ts2}) of the central N−C′ bond. This is referred to as a type-1 torsion-stretch interaction. As the C−N−C′═O dihedral is rotated, the N−C′ bond (types 9−147 and 9−152) lengthens as it becomes less amide-like and more amine-like. It is longest, by about 0.06 Å from its equilibrium value, when the dihedral is 90°, at which electron delocalization along the peptide bond is at a minimum. There is also a positive k_{ts2} term for the terminal C−N bond (type 1−9). At the 90° configuration, there is maximum donation of electron density from the σ orbital of the C−N bond to the π^* orbital of the C′═O bond. As a result, the C−N bond lengthens, by about 0.02 Å. This is a type-2 torsion-stretch interaction and is mainly due to hyperconjugation.[3e] This has been observed in ab initio and DFT calculations and is also seen in the C−C−C′═O group in aldehydes and ketones as well.[4,5] As an example, both type-1 and type-2 torsion-stretch interactions in *N*-methylacetamide are plotted as a function of O═C′−N−C dihedral angle in Figure 2.

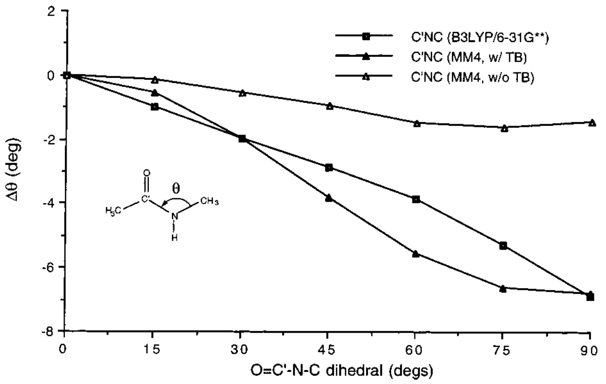


Figure 3. Torsion-bend (TB) interactions in *N*-methylacetamide.

In torsion-bend interactions, the k_{tb1}, k_{tb2}, and k_{tb3} parameters correspond to maxima for changes in bond angles XAB and ABY when the X−A−B−Y dihedral is 0°, 90°, and 120°, respectively. The angles are not affected when the dihedral is 180°. However, compared to the torsion-stretch parameters, the signs of the torsion-bend parameters have an opposite effect. Positive values of k_{tb1}, k_{tb2}, and k_{tb3} indicate bond angle closing, and negative values indicate bond angle opening. For torsion-stretch interactions involving the C−N−C′═O groups in formamides and acetamides, there are positive k_{tb2} terms for the C−N−C′ angles. When the dihedral is 90°, the bond angle closes in by about 7°. Like the torsion-stretch interaction for the C−N bond just described, this effect is also the result of hyperconjugation. The bond angle closes in to allow greater overlap between the σ and π^* orbitals for better transfer of electron density from the former to the latter. Torsion-bend interactions in *N*-methylacetamide are illustrated in Figure 3.

The bend-torsion-bend interaction is a third order term. It was originally designed to improve the *gerade* and *ungerade* modes in ethane[3a], but it was also found to improve the in-plane O═C′−N and C′−N−C bending frequencies in N-substituted amides as well. This term accounts for the coupling between these two modes in the O═C′−N−C group. The coupling between the O═C′−N and C′−N−C bending modes is greatest when the O═C′−N−C dihedral is 0°, zero when the dihedral is 90°, and opposite at 180°. It should be noted that, when accompanying the torsion-bend interaction described above, the bend−torsion−bend interaction is not superfluous. It mainly affects the curvature at the bottom of the potential energy well for the angle bendings involved, not the actual equilibrium values for these angles. As a result, the vibrational frequencies are mainly affected, not the structure.

Results

Structures. The MM3 and MM4 thermally averaged structures (r_g) for the amides were calculated and compared to the available electron diffraction (ED) structures[7−11] in Table 5, and the equilbrium structures (r_e) are compared to the DFT [B3LYP/6-311++G(d,p)] calculated structures in Table 6. Due to delocalization along the O═C′−N group, the ED C′═O bond lengths in amides, which range from 1.212 to 1.224 Å, are slightly longer than C′═O bond lengths in aldehydes and ketones, which mostly range from 1.209 to 1.211 Å. Conversely, the C′−N bond lengths, which mostly range from 1.360 to 1.380 Å, are much shorter than the C−N bond lengths in amines, which range from 1.46 to 1.48 Å. Both the MM3 and MM4 values follow this same trend. However, there are some disagreements between the MM4 and the experimental values.

TABLE 5: Experimental and MM4 Calculated (r_g) Structures for Amides[a]

	FA	NMFA	AA	NMAA	DMFA
	ED, ref 7	ED, ref 8	ED, ref 9	ED, ref 10	ED, ref 11
parameter	*MM3 MM4*	*MM3 MM4*	*MM3 MM4*	*MM3 MM4*	*MM3 MM4*
C′═O	1.212(3)	1.219(5)	1.220(3)	1.225(3)	1.224(3)
	1.216 1.216	*1.217 1.217*	*1.218 1.221*	*1.219 1.222*	*1.217 1.217*
C′−N	1.368(3)	1.366(8)	1.380(4)	1.386(4)	1.391(6)
	1.372 1.362	*1.375 1.368*	*1.377 1.363*	*1.381 1.367*	*1.381 1.370*
C′−C			1.519(6)	1.520(5)	
			1.520 1.518	*1.520 1.520*	
H_3C−N (avg)		1.459(6)		1.469(6)	1.453(4)
		1.453 1.448		*1.453 1.448*	*1.457 1.448*
N−H (avg)	1.027(6)	nr	1.022(11)	nr	
	1.028 1.024	*1.030 1.025*	*1.028 1.024*	*1.029 1.024*	
carbonyl C′−H	1.125(12)	nr			nr
	1.119 1.117	*1.119 1.118*			*1.117 1.116*
methyl C−H (avg)		1.114(25)	1.124(10)	1.107(5)	1.112(3)
		1.111 1.110	*1.110 1.112*	*1.111 1.112*	*1.111 1.110*
∠N−C′═O	125.0(4)	124.6(5)	122.0(6)	121.8(4)	123.5(6)
	125.8 124.4	*126.4 126.4*	*122.8 121.7*	*123.5 123.4*	*126.6 125.2*
∠C−C′−N			115.1(16)	114.1(15)	
			115.3 115.4	*114.9 114.5*	
∠H_3C-N−C′ *trans*[b]		121.4(9)		119.7(8)	120.8(3)
		121.3 119.6		*121.3 119.6*	*120.2 120.5*
∠H_3C-N−C′ *cis*[b]					122.3(4)
					120.8 121.5
∠H_3C-N−CH_3					113.9(5)
					119.0 118.0

[a] Abbreviations: ED − electron diffraction, FA − formamide, NMFA − *N*-methylformamide, AA − acetamide,NMAA − *N*-methylacetamide, DMFA − *N*,*N*-dimethylformamide, and nr − not reported. [b] Cis and trans are defined with respect to the H(CH_3)-C′−N−CH_3 frame.

TABLE 6: Ab Initio, DFT, and MM4 Optimized Equilibrium (r_e) Structures for Amides[a]

	FA	NMFA	AA	NMAA	DMFA
	DFT	DFT	DFT	DFT	DFT
parameter	*MM3 MM4*	*MM3 MM4*	*MM3 MM4*	*MM3 MM4*	*MM3 MM4*
C′═O	1.212	1.215	1.218	1.221	1.217
	1.210 1.212	*1.210 1.212*	*1.212 1.217*	*1.213 1.218*	*1.211 1.212*
C′−N	1.361	1.360	1.368	1.368	1.363
	1.365 1.357	*1.369 1.362*	*1.370 1.358*	*1.374 1.362*	*1.374 1.365*
C′−C			1.519	1.519	
			1.510 1.511	*1.511 1.513*	
H_3C−N (avg)		1.456		1.454	1.453
		1.446 1.442		*1.445 1.442*	*1.449 1.442*
N−H (avg)	1.008	1.008	1.006	1.007	
	1.008 1.009	*1.010 1.010*	*1.008 1.009*	*1.010 1.009*	
carbonyl C′−H	1.106	1.105			1.106
	1.094 1.098	*1.094 1.099*			*1.093 1.097*
methyl C−H (avg)		1.092	1.092	1.092	1.093
		1.087 1.092	*1.087 1.094*	*1.087 1.094*	*1.087 1.092*
∠N−C′═O	124.9	125.6	122.1	122.9	125.8
	125.8 123.8	*126.8 125.6*	*122.8 121.5*	*123.4 123.0*	*126.6 124.6*
∠C−C′−N			115.8	115.5	
			115.3 115.4	*114.9 114.7*	
∠H_3C-N−C′ *trans*[b]		123.4		123.0	120.5
		121.9 119.5		*121.3 119.4*	*120.3 120.8*
∠H_3C-N−C′ *cis*[b]					121.7
					120.7 121.3
∠H_3C-N−CH_3					117.8
					119.0 117.9
imp. dihedral C′−N−X_{trans}−X_{cis} (X = CH_3 or H)	180.0	180.0	180.0	180.0	180.0
	180.0 180.0	*180.0 180.0*	*180.0 180.0*	*180.0 180.0*	*180.0 180.0*

[a] DFT: B3LYP/6-311++G(d,p). [b] Cis and trans are defined with respect to the H(CH_3)−C′−N−CH_3 frame.

For the H_3C−N bond lengths, the MM4 values are shorter than the corresponding ED values by 0.01−0.02 Å, and the MM4 C′−N bond lengths in the acetamides and *N*,*N*-dimethylformamide are also shorter than the ED bond lengths by about 0.02 Å. Agreement between MM4 and ED is somewhat better for the heavy atom bond angles, where differences range from a few tenths of a degree to about 2° for most of the angles listed.

There was difficulty in getting a satisfactory fit to the ED structures, partly because the accuracies of the ED structures are uncertain, and partly because an attempt was made at the same time to get a best fit to the moments of inertia. If we had adjusted the MM4 bond length parameters to fit the ED data more closely, the result was that the calculated moments of inertia were too large. Also, there are inconsistencies in the ED

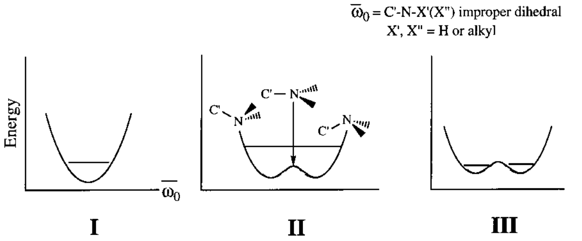


Figure 4. Different cases for planarity of amido group in amides.

data in general. The reported r_g values for the C′−N bonds of acetamide (1.380 Å), *N*-methylacetamide (1.386 Å) and *N*,*N*-dimethylformamide (1.391 Å) are noticably larger, by 0.012 to 0.025 Å, than the r_g values for the C′−N bonds of formamide (1.368 Å) and *N*-methylformamide (1.366 Å). However, for the corresponding r_e values calculated by DFT in Table 6, the range of differences among the bond lengths is smaller, 0.003 to 0.008 Å. The differences in ED values for the H_3C−N bonds among the N-substitiuted amides are also quite large, by 0.006 to 0.016 Å, whereas for the calculated DFT structures the H_3C−N bonds differ by no more than 0.003 Å. Also, the ED value for the H_3C−N−CH_3 bond angle (113.9°) is too short. It is 4° smaller than its equilibrium value according to DFT (117.8°) and MM4 (117.9°) calculations when it should, in theory, be greater. The MM4 equilibrium bond length and bond angles, in general, are in better agreement with the DFT values, even though the MM4 values for the H_3C−N bonds and the C′−N bond in acetamide are still shorter by about 0.010 Å.

Planarity of the Amido Group. The planarity of the amido group has been the subject of controversy for some time, so the first thing we considered in our MM4 parameter development was how to treat the degree of pyramidalization about the amido nitrogen.

Just what exactly is meant by "planarity" warrants some discussion. The issue of planarity of the amido group has been discussed in great and thoughtful detail by Fogarasi and Szalay,[12] and we will attempt to reiterate their conclusions here. In their theoretical study of formamide, they found that electron correlation tends to shift the ab initio structure toward nonplanarity, but that the barriers at planarity remain physically insignificant (well below the zero point energy). More importantly perhaps, they found that when quite large basis sets (in which higher angular momentum functions seem to be a factor) are used, the optimized structure is exactly planar. Samdal found a nonplanar NH_2 configuration for acetamide at the MP2/6-311++G** level.[13] However, the barrier at the totally planar configuration was determined to be only 0.007 kcal mol^{-1}, well below the zero point energy for the NH_2 inversion mode (refer to Table 13). Furthermore, using the same MP2 level but with a higher cc-pVTZ basis set, he found the planar configuration to be a minimum. In light of this, it would seem virtually impossible for spectroscopic studies to distinguish between a planar structure and a slightly nonplanar one with a very small barrier on a shallow potential surface. Consider the three possible inversion potentials for the amido group shown in Figure 4. The conformation of an amide molecule can only be truly considered nonplanar for Case III, where the zero point energy lies below the barrier. In this work, geometry optimizations and vibrational frequency calculations were carried out at the B3LYP/6-311++G** level for formamide, acetamide, *N*-methylformamide, *N*-methylacetamide, and *N*,*N*-dimethylformamide using the planar conformations as their starting geometries. The compounds remained in their planar configurations after optimization, and frequency analyses for the optimized geometries showed no negative eigenvalues. At this level of DFT theory, all of these compounds fall in Case I. Most likely, the amides discussed here fall either in Case I with no barrier or in Case II with a very small barrier. In our classical molecular mechanics model, the amido group in the ground states of amides can be considered virtually planar for our purposes. (Ab initio calculations will, of course, sometimes indicate that the amido group is nonplanar for Case II, but this refers to the equilibrium geometry, not to the ground state.)

TABLE 7: Experimental and Calculated Moments of Inertia (units in 10^{-39} g cm^2)[a]

formamide	exp (ref 14)	MM3 (r_z)	MM4 (r_z)
I_x	1.1541	1.1394 (−1.27%)	1.1570 (+0.25%)
I_y	7.3786	7.5221 (+1.94%)	7.3620 (−0.22%)
I_z	8.5338	8.6562 (+1.43%)	8.5191 (−0.17%)
acetamide	exp (ref 15)[b]	MM3 (r_z)	MM4 (r_z)
I_x	7.7971	7.8040 (+0.12%)	7.6316 (−2.12%)
I_y	8.9874	9.0845 (+1.08%)	9.0530 (+0.73%)
I_z	16.2734	16.3523 (+0.48%)	16.2210 (−0.32%)
N-methyl-formamide	exp (ref 16)[c]	MM3 (r_z)	MM4 (r_z)
I'_x	4.3100	4.2317 (−1.82%)	4.3038 (−0.14%)
I'_y	13.3026	14.0083 (+5.30%)	13.3156 (+0.10%)
I'_z	17.1180	17.7000 (+3.40%)	17.1582 (+0.24%)
N-methyl-acetamide	exp	MM3 (r_z)	MM4 (r_z)
I_x	N/A	8.3803	8.2735
I_y	N/A	21.9235	21.3237
I_z	N/A	29.2881	28.7201
N,*N*-dimethyl-formamide	exp (ref 18)	MM3 (r_z)	MM4 (r_z)
I_x	9.4024	9.6313 (+2.43%)	9.4122 (+0.10%)
I_y	19.9630	20.2837 (+1.61%)	19.9876 (+0.12%)
I_z	28.3066	28.9111 (+2.14%)	28.4008 (+0.33%)
propanamide	exp (ref 17)	MM3 (r_z)	MM4 (r_z)
I_x	8.5044	8.4372 (−0.79%)	8.4689 (−0.42%)
I_y	22.1294	22.2808 (+0.68%)	22.1374 (+0.04%)
I_z	29.5024	29.6993 (+0.67%)	29.5594 (+0.19%)

[a] Conversion factors: 83 920.99 (MHz)(10^{-39}g·cm^2), 0.166 056 5 (10^{-39}g·cm^2)/(amu·Å^2) 2.799 302 8 (cm^{-1})(10^{-39}g·cm^2). [b] The effective moments for the rigid model of this molecule were reported by the authors to be $I'_x = 7.2878$, $I'_y = 9.0233$ and $I'_z = 16.2751 \times 10^{-39}$g⟨cm^2. %error(MM4 − MW) = +4.72, +0.33 and −0.33%, respectively. [c] Effective moments. Normal moments: $I_x = 4.1988$, $I_y = 13.1017$, $I_z = 17.1179 \times 10^{-39}$g·cm^2. %errors(MM4 − MW): +2.51, +1.64, +0.24%.

Moments of Inertia. The MM4 calculated moments of inertia are listed in Table 7 along with the microwave determined values.[14−18] With the exception of the I_x moment for acetamide, the MM4 calculated moments are, for the most part, to within about ±0.50% agreement with experiment. The total rms error between the MM4 and MW values is 0.62% (15 weighted moments). For MM3, the rms error is much greater, 2.10% (15 weighted moments). The MM4 moment whose percent deviation contributes most to the total rms error is the I_x moment for acetamide (%dev = −2.12%). If this moment were unweighted, the total rms error would be 0.30%. The experimental moments listed for acetamide[15] are the normal moments derived from the measured $A_{0,0}$, $B_{0,0}$, and $C_{0,0}$ spectroscopic constants of the molecule. The large percentage error between experiment and MM4 for the I_x moment is mainly due to the contribution of the internal moment of the methyl group, the axis of which is

TABLE 8: Gas-Phase Experimental and Calculated Dipole Moments (Debye)

compd	dip. mom.[a]		method[b]	ref	MM3/P[c]	dev (%)	MM4/P[c]	dev. (%)	MM4[c]	dev (%)
formamide	μx	3.61			3.66		3.65	0.0	3.66	
	μy	0.85	MW−S	19	0.58		0.70		0.31	
	μz	0.00			0.00		0.00		0.00	
	μ	3.71			3.71	0.0	3.71		3.68	−0.8
acetamide	μx	−1.22	MW−S	15	0.02		−0.09		−0.07	
	μy	3.47			3.74		3.68		3.67	
	μz	0.00			0.00		0.00		0.00	
	μ	3.68			3.74	+1.6	3.68	0.0	3.67	−0.3
acetamide	μ	3.75	VPDE	20	3.74	−0.3	3.68	−1.9	3.67	−2.1
N-methylformamide	μx	2.91	MW−S	16	2.97		2.90		3.25	
	μy	2.41			2.35		2.46		1.98	
	μz	0.00			0.00		0.00		0.00	
	μ	3.78			3.79	+0.3	3.80	+0.5	3.81	+0.8
N-methylformamide	μ	3.82	VPDE	20	3.79	−0.8	3.80	−0.5	3.81	−0.3
N-methylacetamide	μx		VPDE	20	1.06		1.19		1.36	
	μy				3.67		3.57		3.47	
	μz				0.00		0.00		0.00	
	μ	3.71			3.82	+3.0	3.76	+1.3	3.73	+0.5
N,*N*-dimethylformamide	μx				3.83		3.85		4.07	
	μy		VPDE	20	0.39		0.52		−0.08	
	μz				0.00		0.00		0.00	
	μ	3.80			3.85	+1.3	3.88	+2.1	4.08	+7.4
N,*N*-dimethylacetamide	μx				2.49		2.69		2.93	
	μy		VPDE	20	2.89		2.67		2.61	
	μz				0.00		0.00		0.00	
	μ	3.80			3.82	+0.5	3.79	−0.3	3.92	+3.2
propanamide	μx	0.64			1.20		1.34		1.28	
	μy	3.49	MW−S	17	3.54		3.44		3.31	
	μz	0.00			0.00		0.00		0.00	
	μ	3.55			3.74	+5.4	3.69	+3.9	3.55	0.0
N-methyl propanamide	μx				1.23		1.38		1.47	
	μy		VPDE	20	3.62		3.51		3.29	
	μz				0.00		0.00		0.00	
	μ	3.59			3.83	+6.7	3.77	+5.0	3.60	+0.3

[a] μx, μy, μz: projections of total dipole moment μ on moment of inertia axes I_x, I_y and I_z, respectively. Direction of μ defined as pointing in the more electronegative direction. Molecules listed are oriented so that the carbonyl oxygen lies above I_x and the amido nitrogen lies to the left of I_y, so that a positive μx points to the right and a positive μy points upward. [b] Method: MW−S: Microwave-Stark, VPDE: Vapor-Phase Dielectric Measurement. [c] MM3/P and MM4/P values for dipole moments calculated from permanent bond moments only (no induction). The MM4 values include induction.

almost parallel to the I_x moment. In acetamide and *N*-methylformamide, the methyl groups have very low rotational barriers (<0.1 kcal mol^{-1}) and are essentially free rotors (refer to Table 9). The MM4 program as of yet has no direct method for determining the contributions of internal rotations to the calculated moments of inertia. In the MW study of acetamide, the authors did report effective moments of inertia (I'_x, I'_y, I'_z) in which internal rotation of the methyl group is factored out. These are footnoted in the table. However, the percentage errors between the effective and the MM4 moments of this molecule are worse [%dev($I'_{x,\mathrm{MM4}} - I_{x,\mathrm{exp}}$) = +4.72%]. This disagreement may arise from calculations of the effective moments by the authors or from the limitations in the MM4 calculations just mentioned. However, better agreement is reached between MM4 and the effective moments of inertia for *N*-methylformamide,[16] which we used for direct comparison in Table 7. The normal moments of this molecule are footnoted in the table.

Dipole Moments. MM4 dipole moments for eight simple amides were calculated with and without inductive effects. The MM3 dipoles were only calculated without induction, since induction was never studied for amides in MM3. The calculated dipoles (μ) and their *x*-, *y*-, and *z*-projections (μ_x, μ_y, μ_z) on the moment of inertia axes are compared to the experimental values[15−17,19,20] in Table 8. Figures of the MM4 induced moments superimposed on the corresponding MM4 amide structures are shown in Figures 5−7 (in the Supporting Information). Experimental dipole moments listed were measured in the gas phase by microwave Stark effect (MW−S) and/or by vapor-phase dielectric measurement (VPDE). Both the induced and noninduced (where induction is and is not explicitly included, respectively) bond moment parameters were weighted more heavily on the MW data, since MW methods in general are more accurate than VPDE methods.

In MM4 and in earlier versions of our molecular mechanics programs, the chemistry convention is followed: individual bond moments point toward the more electronegative atom. Most spectroscopists use the opposite (physics) convention, so any signs for the experimental dipole moments which follow this convention, including those for the *x*-, *y*-, and *z*-components, were changed to our convention to avoid any confusion. In addition, there can also be ambiguity in orienting the directions of the moment of inertia axes I_x and I_y (left vs right, up vs down) which can lead to opposite signs for μ_x and μ_y. Therefore, for the molecules listed in Table 8, the directions for I_x and I_y are oriented so that the amido nitrogen lies to the left of I_y, and the carbonyl oxygen lies above I_x (refer to Figures 5−7, Supporting Information).

Using the amide group ($N{-}C'{=}O$) as a reference frame, the MM4 calculated dipole moments for the amides are, in general, oriented in the direction of the oxygen. The angle the dipole forms with respect to the $C'{=}O$ bond ($\angle O{=}C'{\rightarrow}$) ranges from approximately 20° to 30°, and with respect to the $C'{-}N$ bond ($\angle N{-}C'{\rightarrow}$) the angle ranges from 140° to 155°. For the noninduced MM4 dipole moments (MM4/P), there is good agreement between calculation and experiment, although the percentage deviation between the two for the dipole moments

TABLE 9: Barrier Heights[a] for Methyl Group Rotation (kcal mol^{-1})

CH_3—(C′O)N Type 5−1−152−79	MW	B3LYP/ 6-311+G**	MM3	MM4
acetamide	0.07[c]	0.20	1.24	0.12
N-methylacetamide	na	0.42	1.28	0.05
CH_3—CH_2(C′O)N Type 5−1−1−152				
propanamide	2.2[e]	2.06	3.00	2.00
CH_3—N(C′O) Types 5−1−9−147, 5−1−9−152				
N-methylformamide	0.17[d]	0.07	0.24	0.18
N,N-dimethylformamide				
trans methyl[b]	1.04[f]	1.06	0.90	1.44
cis methyl[b]	2.20[f]	2.11	0.96	1.39
N-methylacetamide	na	0.02	0.32	0.18
CH_3—CH_2N(C′O) Type 5−1−1−9				
N-ethylformamide	na	3.28	3.64	3.48
N-ethylacetamide	na	3.32	3.64	3.48

[a] All values are internal energy (ΔE) values unless otherwise indicated. na − not available. [b] *trans* and cis relative to aldehydic hydrogen. [c] Ref 15. [d] Ref 16. [e] Ref 17. [f] Ref 18.

of propanamide (%dev = +3.9%) and *N*-methylpropanamide (%dev = +5.0%) are somewhat high. For the MM4 dipole moments calculated with the induced moment method,[21] there is improved agreement with the experimental values for these molecules (%dev = 0.0% and +0.3% for propanamide and *N*-methylpropanamide, respectively). However, the MM4 induced moments are calculated somewhat too high for *N*,*N*-dimethylformamide (%dev = +7.4%) and for *N*,*N*-dimethylacetamide (%dev = +3.2%) compared to the experimental[20] moments for these molecules. But these experimental values are from dielectric constant measurements. The accuracy of the dipole moments determined by the microwave (Stark effect) method is usually 0.03 D or better, whereas those determined by other methods are usually of uncertain, but lower accuracy. Overall, the total rms errors, with and without the inclusion of induction, between the MM4 and the experimental values (for all 10 listed values) are 2.7% and 2.2%, respectively. The total rms error between the MM3 and experimental values is 3.0%. If we consider only the dipole moments determined by the microwave method, the rms errors for MM3, MM4 without induction, and MM4 with induction are 2.8, 2.0 and 0.6%, respectively.

Methyl Rotation Barriers. The MM3 and MM4 calculated rotational barriers for the methyl groups in amides are compared to available microwave and DFT calculated values in Table 9. The MM4 values are in good agreement with both the MW and DFT values for most of the compounds listed. The MM3 calculated rotational barriers are also in good agreement, with the exception of the methyl groups substituted at the carbonyls in acetamide and *N*-methylacetamide, in which the barriers are calculated too high by 0.8−1.0 kcal mol^{-1}. In fitting the 3-fold torsional parameters for the methyl groups in MM4, both the barrier heights and the minimum energy conformations were considered. If the methyl group is attached to the amido nitrogen, DFT calculations on *N*-methylformamide at the B3LYP/6-311+G** level show that the eclipsed conformation with respect to the N−C′ bond is favored. However, the rotational barrier is very low, with the staggered conformation calculated to be only 0.07 kcal mol^{-1} higher in energy. From a fairly recent microwave study of this molecule,[16] the barrier was detemined to be only 0.17 kcal mol^{-1}. However, if the methyl group is attached to the carbonyl carbon of acetamide, the staggered conformation with respect to the C′=O bond is favored at the same level of theory. The rotational barrier for the methyl group in this molecule is also very low, with the eclipsed conformation being only 0.20 kcal mol^{-1} higher in energy. The low methyl rotational barrier for acetamide is also supported by the microwave study[15] on this molecule, where the methyl rotational barrier was found to be only 0.07 kcal mol^{-1}. Both DFT and microwave findings are in contrast with the MW rotational barriers of a-methyl groups in aldehydes and ketones such as acetaldehyde[22] and acetone,[23] in which the eclipsed conformation (with respect to the carbonyl) is favored and the barriers are significantly higher (1.16 and 0.78 kcal mol^{-1}, respectively). The microwave values for the methyl rotational barriers in both *N*-methylformamide and acetamide are among the lowest so far determined experimentally.

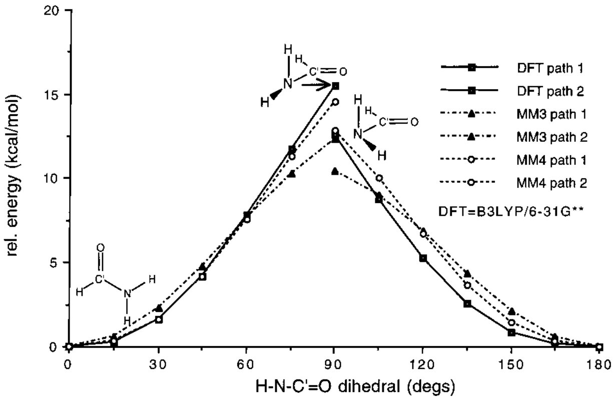
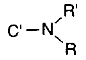


Figure 8. Type 28−9−147−79 Torsion Curve for Formamide.

C′−N and Heavy-Atom Torsion Potentials. Although the amido group can be considered to be virtually planar in the ground states of amides, as discussed earlier, pyramidalization of the group does occur during internal conformational changes in amides, and in polypeptides and proteins. During torsional rotation about the C′−N bond in amides, the amido group



increasingly pyramidalizes. This distortion lowers the torsional barrier by 8−10 kcal/mol from what it would have been if the amido group remained planar during complete torsion about the C′−N bond. Essentially, delocalization of π-electron density along the O=C′−N arrangement is broken during torsional motion, and the amido group becomes more amine-like. This phenomenon was taken into account in the MM4 parameterization for the C′−N torsion curves for formamide, acetamide, *N*-methylformamide and *N*-methylacetamide, plotted in Figures 8−11 (Figure 10 is in Supporting Information). In Figure 9, additional curves for the C′−N torsion in acetamide, with the amido group constrained in the planar form, are included. The MM4 curves were obtained from fits to DFT (B3LYP/6-31G**) calculated curves. For comparison, MM3 generated curves are also plotted in these figures.

The plots in Figures 8−11 are not of single curves with discontinuities but two separate ones generated separately for each of these compounds: one by driving the H(R)−N−C′=O dihedral from 0° to 90°, and another by starting at the opposite end at 180° and driving to 90°. When this dihedral is driven to greater than 90°, the other H−N−C′=O dihedral not being driven lags behind and prefers to follow an energetic pathway of greater out-of-plane bending rather than a torsional pathway.

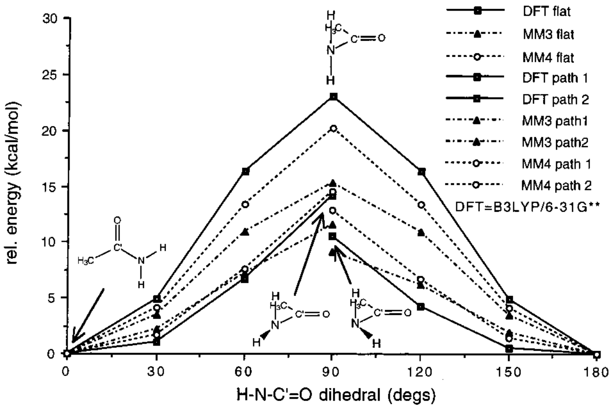


Figure 9. Type 28−9−152−79 Torsion Curve for Acetamide.

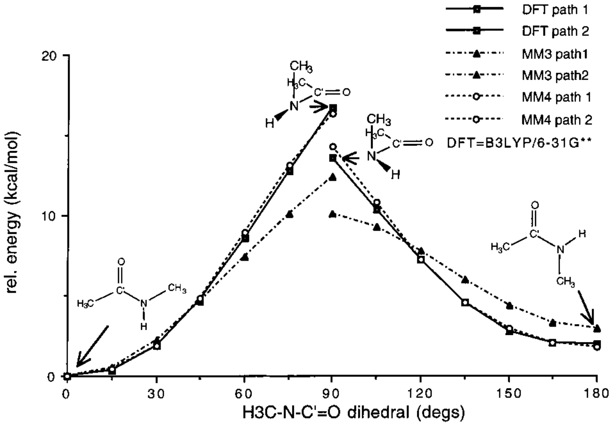


Figure 11. Type 1−9−152−79 Torsion Curve for *N*-methylacetamide.

The increasing pyramidalization of the amido group contributes to increasing strain energy in the conformation of the amide, and the transition state is not reached. If the amido group is flipped over into the opposite pyramidal form, there arises a discontinuity in the energy function, the strain energy is suddenly reduced by several kcal/mol, and relaxation to the other isomeric form is reached. Such discontinuities arise in part from the artificial constraints imposed by the dihedral drive and were often observed in earlier MM2 work, for example, when this method was used in probing the conformational spaces of cyclohexane and 1,3-cycloheptadiene.[24]

Additional MM4 heavy-atom torsion parameters for amides were obtained from fits to DFT calculated curves of *N*-ethylformamide (C−C−N−C′), *N*-ethylacetamide (C−C−N−C′), propanamide (C−C−C′=O), butanamide (C−C−C−C′), and *N*-propylformamide (C−C−C−N) (Figures 12 thru 16) (Figures 12, 15, and 16 are in the Supporting Information). For the last four compounds, these parameters are necessary for modeling the torsion potentials of alkyl R-group side chains in polypeptides and proteins, such as the $-CH_3$, $-CH(CH_3)_2$, and $-CH_2CH(CH_3)_2$ groups in the alanine, valine, and leucine residues, respectively. Because we were able to use the V_4 and V_6 terms present in the MM4 torsion potentials in our curve-fitting program, we were able to achieve an almost coincidental fit of the MM4 curves to the DFT curves for these molecules. There is a slight barrier on the C−C−C′=O torsion curve for propanamide at $w_{\mathrm{CCC'O}} = 0°$ in Figure 14. However, the calculated barriers are very low according to DFT calculations at the B3LYP/6-31G** (0.02 kcal mol^{-1}) and B3LYP/6-311+G** (0.09 kcal mol^{-1}) levels. The vibrationally averaged conformation of the ground state of propanamide can be safely regarded to have C_s symmetry.

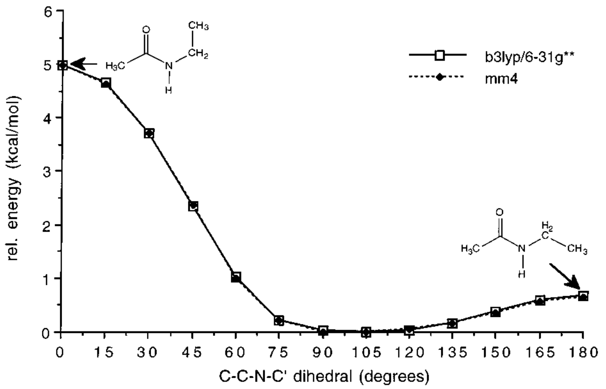


Figure 13. Type 1−1−9−152 Torson Curve for *N*-ethylacetamide.

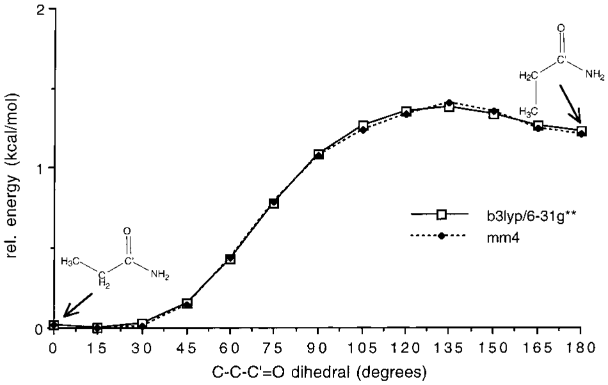


Figure 14. Type 1−1−152−79 Torsion Curve for Propanamide.

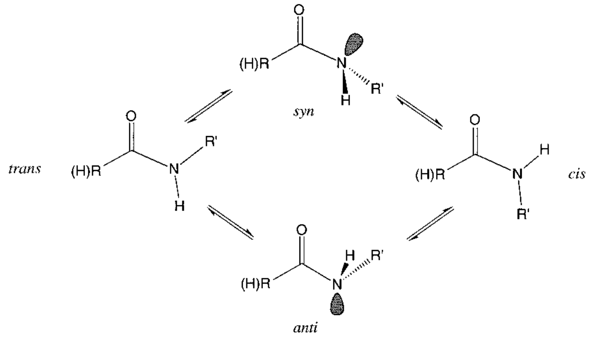


Figure 20. Cis−trans Isomerization and Transition States in Amides.

In addition, DFT and MM4 curves are also plotted for the C′−C−C′=O torsion (type 152−1−152−79) in propanediamide (Figure 17, Supporting Information), the C′−C−C−C′ torsion (type 151−1−1−152) in 1,4-butanediamide (Figure 18, Supporting Information) and the C′−N−C′=O torsion (type 152−9−152−79) in *N*-acetylacetamide (Figure 19, Supporting Information). In both the DFT and the MM4 torsion drives for these compounds, the amide groups were constrained in planar configurations to prevent relaxation effects which might introduce errors in fitting these torsion parameters.

Transition States. It must be stressed that the 90° conformations for the amides in Figures 8−11 are not transition states. For formamide, acetamide, and their *N*-substituents, cis↔trans isomerization occurs via two transition states, the syn and anti forms shown in Figure 20. (To be consistent as possible with the majority of the experimental literature cited herein, the terms trans, cis, syn, and anti are defined in this manuscript with respect to the H(R)-C′−N−R′ frame. Some authors have defined these terms with respect to the O−C′−N−R′ frame.) The MM4 equilibrium energy (ΔE) barriers through these transition states

TABLE 10: Equilibrium Energy Barriers (ΔE) for cis−trans Isomerization (in kcal/mol)

	conformation					
compd	trans	TSanti	TSsyn	cis	level	ref
formamide	0.00	16.57	18.92	0.00	MP2/6-31G**	25
	0.00	15.00	17.30	0.00	CCSD/6-31G**	25
	0.00	15.15	17.43	0.00	CCSD(T)/6-31G**	25
	0.0	14.9	nr	0.0	CCSD/TZ2P	12
	0.0	15.7	nr	0.0	CCSD/PVTZ	12
	0.0	15.0	nr	0.0	CCSD(T)/TZ2P	12
	0.0	15.8	nr	0.0	CCSD(T)/PVTZ	12
	0.00	*11.11*	*14.26*	*0.00*	*MM3*	
	0.00	**14.74**	**17.27**	**0.00**	**MM4**	
acetamide	0.00	16.50	19.89	0.00	MP2(fc)/6-31+G*	this work
	0.00	15.95	18.62	0.00	MP2(fc)/6-311++G**	this work
	0.00	13.21	nr	0.00	MP3/6-31G*	26
	0.00	12.45	nr	0.00	MP3/6-311G**	26
	0.00	13.26	nr	0.00	MP4(SDTQ)/6-31G*	26
	0.00	13.98	nr	0.00	CISD/6-31G*	26
	0.00	*9.73*	*13.32*	*0.00*	*MM3*	
	0.00	**12.17**	**14.69**	**0.00**	**MM4**	
N,*N*-dimethylformamide	0.00	20.14	20.45	0.00	MP2(fc)/6-31+G*	27
	0.00	19.30	19.28	0.00	MP2(fc)/6-311++G**	27
	0.00	*11.44*	*14.49*	*0.00*	*MM3*	
	0.00	**16.48**	**15.60**	**0.00**	**MM4**	
N,*N*-dimethylacetamide	0.00	14.08	18.28	0.00	MP2(fc)/6-31+G*	28
	0.00	14.32	18.55	0.00	MP4(fc)SDTQ/6-31G(d)	29
	0.00	*8.43*	→*anti*	*0.00*	*MM3*	
	0.00	**13.53**	**18.98**	**0.00**	**MM4**	
N-methylformamide	0.00			1.42	MP2(fc)/6-31+G*	this work
	0.00			1.46	MP2(fc)/6-311++G**	this work
	0.00	*11.90*	*15.55*	*1.84*	*MM3*	
	0.00	**16.20**	**17.17**	**0.90**	**MM4**	
N-methylacetamide	0.00	16.83	21.21	2.22	MP2/6-31G*	30
	0.00	16.65	20.90	2.23	MP4#/6-31G*[a]	30
	0.00	*10.78*	*15.60*	*2.94*	*MM3*	
	0.00	**15.00**	**17.68**	**1.93**	**MM4**	

[a] According to the authors, a small correction up to the MP4 level was computed at the 6-31G level and added to the MP2/6-31G* value. This final value they denoted as MP4#/6-31G*. nr − not reported.

are compared to reported ab initio energies[12,25−30] in Table 10. From both ab initio and MM4 calculations, the anti conformation appears to be the more stable transition state for most of the amides listed, being lower than the syn form by about 2−3 kcal mol^{-1}. The close exception is the case of *N*,*N*-dimethylformamide, for which the anti and syn forms are almost equal in energy according to MP2 calculations.[27] According to MM4 calculations, the syn form is more stable, but by only 0.9 kcal mol^{-1}. MM3 calculates the syn form to be is less stable than the anti form, by 3.0 kcal mol^{-1}. This offset in stability in the anti form for this molecule in MP2 and MM4 can be partly explained by a less favorable steric interaction among the methyl groups and the oxygen. In *N*,*N*-dimethylacetamide, however, the relative energies of the transition states follow the same trend as that for the other amides. Even though this same steric hindrance is present in the anti form of this molecule as it is for *N*,*N*-dimethylformamide, the presence of an opposing methyl group at the carbonyl makes the syn form for this molecule much more unstable. We could not optimize the syn transition state for this molecule in MM3, which optimized to the anti form instead, even when the MM4 optimized structure was used as the starting geometry.

For MP2 values using modest size basis sets (6-31G** and 6-31+G*), the respective MM4 values for the rotational barriers are, in general, lower by 0.5−5.0 kcal mol^{-1}. The MM3 values are, in turn, lower than the MM4 values by 1−5 kcal mol^{-1}. As the basis set size is increased and the level of theory becomes higher, the differences between the MM4 and theoretical values appear to decrease. Promisingly, the MM4 ΔE values for the transition states of formamide are in close agreement with the ΔE values calculated at the CCSD and CCSD(T) levels.[12,25] The same can almost be said for the ΔE values for acetamide calculated at the MP3, MP4 and CISD levels.[26] It would therefore be premature to conclude that the results of MM4 and ab initio calculations are in disagreement for the larger sized amide compounds listed until calculations at similar high levels of quantum mechanics theory become available for these compounds.

TABLE 11: Free Energy Barriers (ΔG) for *Cis*−*trans* Isomerization (kcal/mol)

	(ΔG) *MM3* **MM4**				$(\Delta G_{\mathrm{eff}}^{\ddagger})$	
compd	trans	anti	syn	cis	NMR (gas)	ref
formamide	*0.0*	*11.2*	*13.9*	*0.0*	16.0	31
	0.0	**14.7**	**16.6**	**0.0**		
acetamide	*0.0*	*9.7*	*13.0*	*0.0*		
	0.0	**12.2**	**14.5**	**0.0**		
N-methylformamide	*0.0*	*12.0*	*15.2*	*1.7*		
	0.0	**15.0**	**16.0**	**0.6**		
N-methylacetamide	*0.0*	*11.2*	*15.1*	*3.5*		
	0.0	**13.7**	**16.8**	**1.8**		
N,*N*-dimethylformamide	*0.0*	*11.9*	*14.4*	*0.0*	19.4	32
	0.0	**15.5**	**14.7**	**0.0**		
N,*N*-dimethylacetamide	*0.0*	*8.5*	→*anti*	*0.0*	15.6	33
	0.0	**13.1**	**18.4**	**0.0**	15.3	34

The free energy (ΔG) values for these transition states have also been calculated by MM4 and are listed in Table 11 alongside effective barriers ($\Delta G_{\mathrm{eff}}^{\ddagger}$) determined by NMR spectroscopy[31−34] in the gas phase. Unfortunately, we could not find gas-phase data for acetamide, *N*-methylformamide, and *N*-methylacetamide despite an extensive search through the

TABLE 12: Formamide Exp. and Calculated Vibrational Frequencies (in cm^{-1})[a]

mode	assignment	sym	exp ref 35	wgt	MM3	dev	wgt	MM4	dev
1	νaNH$_2$	A′	3564	1	3557	−7	1	3556	−8
2	νsNH$_2$	A′	3440	1	3440	0	1	3453	13
3	νC′H	A′	2854	1	2827	−27	1	2847	−7
4	νC′O − νC′N	A′	1754	1	1784	30	1	1750	−4
5	δNH$_2$ + νC′N	A′	1579	1	1579	0	1	1533	−46
6	δHC′O + νC′N	A′	1391	1	1357	−34	1	1397	6
7	νC′N + δNC′O	A′	1258	1	1197	−61	1	1234	−24
8	νC′N + ρNH$_2$	A′	1046	1	1062	16	1	1085	39
9	ωCH	A″	1033	1	1028	−5	1	1040	7
10	ωNH$_2$ + τNH$_2$	A″	602	1	632	30	1	588	−14
11	δNC′O	A′	566	1	570	4	1	564	−2
12	τNH$_2$ − ωNH$_2$	A″	289	0	528	239	1	312	23
					rms	**26**		**rms**	**21**

[a] νa/νs − asymmetric/symmetric stretch, δ − in-plane bending ρ − in-plane rocking, ω − out-of-plane rocking/bending, τ − torsion.

TABLE 13: Acetamide Exp. and Calculated Vibrational Frequencies (in cm^{-1})

mode	assignment	sym	exp ref 36	wgt	MM3	dev	wgt	MM4	dev
1	νaNH$_2$	A′	3550	1	3557	7	1	3560	10
2	νsNH$_2$	A′	3450	1	3439	−11	1	3456	6
3	νaCH$_3$	A′	2967	1	3015	48	1	2981	14
4	νaCH$_3$	A″	2967	1	2986	19	1	2974	7
5	νsCH$_3$	A′	2860	1	2899	39	1	2889	29
6	νC′O − νC′N	A′	1733	1	1725	−8	1	1739	6
7	δNH$_2$	A′	1600	1	1602	2	1	1583	−17
8	δaCH$_3$	A′	1433[a]	1	1443	10	1	1444	11
9	δaCH$_3$	A″	1433[a]	1	1442	9	1	1420	−13
10	δsCH$_3$	A′	1385	1	1425	40	1	1411	26
11	νC′N	A′	1319	1	1304	−15	1	1319	0
12	ρNH$_2$	A′	1134	1	1095	−39	1	1133	−1
13	ω CH$_3$ + ω C′O	A″	1040	1	962	−78	1	1021	−19
14	ρCH$_3$	A′	965	1	928	−37	1	983	18
15	νCC′ + nC′N	A′	858	1	813	−45	1	853	−5
16	ω skel.	A″	628[a]	1	644	16	1	640	12
17	δOC′N	A′	548	1	559	11	1	558	10
18	τC′N	A″	507	1	460	−47	1	464	−43
19	δCC′N	A′	427[a]	1	422	−5	1	442	15
20	ωNH$_2$	A″	269[a]	0	518	249	1	255	−14
21	τCH$_3$	A″	*47*[b]	0	147	100	0	39	−8
					rms	**32**		**rms**	**17**

[a] Ref 37. [b] DFT=B3LYP/6-31G** (unscaled)

literature. It must be emphasized that this is not a direct comparison between MM4 and experiment. The NMR barrier heights listed are thermal averages of barriers not only through both the syn and anti transition states but also in both the trans-to-cis and cis-to-trans directions.

Vibrational Spectra. The MM4 spectra are compared to the experimentally determined spectra[35−43] in Tables 12 thru 16. The total MM4 rms deviation from experiment was 27 cm^{-1} over a total of 108 weighted modes. The MM4 calculated vibrational frequencies are significantly improved over the MM3 frequencies, for which the total rms deviation was 36 cm^{-1} (106 weighted modes). The frequencies for modes which were not observed experimentally or which were suspected of being misassigned were substituted with unscaled DFT (B3LYP/6-31G**) calculated frequencies. Rotational modes of the methyl groups were not weighted in the MM3 and MM4 rms calculations because they are not normally observed in IR spectra, and because DFT calculated frequencies for these type modes are usually not accurate enough, although these DFT frequencies are listed for qualitative purposes. In the MM3 rms calculation, the calculated frequencies for the NH$_2$ inversion mode in formamide (mode 12) and in acetamide (mode 20) were also not weighted. The MM3 frequencies for these modes are abnormally high, 528 and 518 cm^{-1} for formamide and acetamide, respectively, whereas the reported experimental values are 289 and 269 cm^{-1}. In the MM3 paper,[1] the calculated frequencies were fitted to frequencies (507 and 503 cm^{-1}) reported in an earlier HF/4-21G study.[44] Apparently, the scaling factors used in that study were inaccurate for these modes.

Heats of Formation. Ten MM4 bond and structural enthalpy parameters, listed in Table 17, were obtained by a best fit to the experimental heats of formation for 25 amide compounds, 18 of which were weighted. The different types and numbers of bond and structural enthalpy parameters are enumerated for each of the amides studied in Table 18. The structural enthalpy parameters N-ME and C′-ME are methyl additions at the amido nitrogen and carbonyl carbon respectively, which have a stabilizing effects in these compounds. C′-SEC and C′-TERT account for isopropyl and *tert*-butyl additions at the carbonyl carbon. There are two additional terms, TOR and POP, which are taken into acount in the heat of formation calculation. The TOR term accounts for the contribution to the calculated heat of formation by populated torsional energy levels.[45,46] This term was counted for heavy atom torsions having less than 5.0 kcal mol^{-1} barrier heights. (In reality, the value of TOR is a complicated function, but it is approximated by a constant.) Therefore, torsions about the central C′−N bond in amides, which have higher barrier heights, were not counted. The TOR term has already been fixed (TOR = 0.5715 kcal mol^{-1}) in the MM4 program and was not changed in the present MM4 heat of formation calculations. In MM3, TOR is fixed to 0.42 kcal mol^{-1}. The POP term is the contribution from the Boltzmann

TABLE 14: *Z-N*-Methylformamide Exp and Calcd Vibrational Frequencies (in cm^{-1})

mode	assignment	sym	exp ref 38	wgt	MM3	dev	wgt	MM4	dev
1	νNH	A′	3490	1	3480	−10	1	3497	7
2	νa CH$_3$	A′	2960	1	2992	32	1	2992	32
3	νa CH$_3$	A″	2944	1	2991	47	1	2985	41
4	νs CH$_3$	A′	2942	1	2899	−43	1	2913	−29
5	νCH	A′	2854	1	2825	−29	1	2836	−18
6	ν C′O − ν C′N	A′	1750	1	1774	24	1	1754	4
7	δNH	A′	1528	1	1542	14	1	1527	−1
8	δa CH$_3$	A′	1467	1	1457	−10	1	1461	−6
9	δa CH$_3$	A″	1458	1	1470	12	1	1455	−3
10	δs CH$_3$	A′	1410	1	1428	18	1	1448	38
11	δ HC′O	A′	1392	1	1339	−53	1	1360	−32
12	ν C′N − ν NC	A′	1207	1	1120	−87	1	1170	−37
13	ρ CH$_3$	A′	1148	1	1158	10	1	1126	−22
14	ω CH$_3$	A″	1148	1	1103	−45	1	1109	−39
15	ω C′O	A″	*1037*[a]	1	1020	−17	1	1057	20
16	ν NC − ν C′N	A′	951	1	919	−32	1	972	21
17	δ C′NC − δ NC′O	A′	761	1	744	−17	1	739	−22
18	τ C′N	A″	570	1	535	−35	1	560	−10
19	δ C′NC + δ NC′O	A″	*266*[a]	1	338	72	1	311	45
20	ω NH	A″	237	1	301	64	1	270	33
21	τ CH$_3$	A″	*77*[a]	0	57	−20	0	52	−25
					rms	**40**		**rms**	**27**

[a] DFT=B3LYP/6-31G** (unscaled)

TABLE 15: *Z-N*-Methylacetamide Exp and Calcd Vibrational Frequencies (in cm^{-1})

mode	assignment	sym	exp ref 39	wgt	MM3	dev	wgt	MM4	dev
1	νNH	A′	3498[a]	1	3484	14	1	3507	9
2	νa CH$_3$ acetyl	A′	2994	1	3015	21	1	2982	−12
3	νa CH$_3$ amino	A′	2994	1	2992	−2	1	2978	−16
4	νa CH$_3$ acetyl	A″	2981	1	2986	5	1	2974	−7
5	νa CH$_3$ amino	A″	2981	1	2991	10	1	2969	−12
6	νs CH$_3$ acetyl	A′	2935	1	2898	−37	1	2889	−46
7	νs CH$_3$ amino	A′	2915[a]	1	2899	−16	1	2898	−17
8	νC′O − νC′N − νC′C	A′	1730[b]	1	1710	−20	1	1734	4
9	δNH − νC′N	A′	1569	1	1586	17	1	1560	−9
10	δs CH$_3$ amino	A′	1471	1	1488	17	1	1470	−1
11	δa CH$_3$ amino	A′	1458	1	1449	−9	1	1455	−3
12	δa CH$_3$ amino	A″	1451	1	1471	20	1	1462	11
13	δa CH$_3$ acetyl	A″	1441	1	1443	2	1	1421	−20
14	δa CH$_3$ acetyl	A′	1414	1	1425	11	1	1422	8
15	δs CH$_3$ acetyl	A′	1374	1	1342	−32	1	1332	−42
16	ν C′N + δNH	A′	1266[a]	1	1216	−50	1	1228	−38
17	ρCH$_3$ amino	A′	1161	1	1155	−6	1	1157	−4
18	ω CH$_3$ amino	A″	1125[c]	1	1099	−26	1	1105	−20
19	ρCH$_3$ acetyl	A′	1114	1	1034	−80	1	1078	−36
20	ω CH$_3$ acetyl + ω C′O	A″	1044	1	962	−82	1	1020	−24
21	νC′C + ρCH$_3$ acetyl	A′	991	1	923	−68	1	983	−8
22	νNC + ρCH$_3$ amino	A′	883	1	847	−36	1	871	−12
23	δskel	A′	628	1	622	−6	1	639	11
24	ω C′O + τC′−N	A″	600	1	584	−16	1	624	24
25	ωNH + τN−CH$_3$	A″	454[c]	1	508	54	1	518	64
26	δCC′N	A′	439	1	435	−4	1	430	−9
27	δC′NC	A′	289	1	308	19	1	274	−15
28	τC′−N − ωNH	A″	192	1	163	−29	1	128	−64
29	τCH$_3$ amino	A″	*83*[d]	0	66	−17	0	50	−33
30	τCH$_3$ acetyl	A″	*51*[d]	0	145	94	0	27	−24
					rms	**34**		**rms**	**26**

[a] Ref 38. [b] Ref 40. [c] Ref 41. [d] DFT=B3LYP/6-31G** (unscaled)

distribution of higher energy conformers of a compound to the calculated heat of formation of its lowest energy conformer. (Thus, TOR and POP are not adjustable parameters.)

In the MM3 and MM4 root-mean-square (rms) error calculations, deviations from experiment were weighted according to the scheme prescribed in previous papers,[47,48] as follows: if the reported error in the experimental heats of formation was 0.2 kcal mol^{-1} or less, then the weight was 10; if it was in the range of 0.21−0.40 kcal mol^{-1}, the weight was 8; and for each 0.20 kcal mol^{-1} increment in error beyond this range, 2 more is subtracted from this weight. So when the reported error is greater than 1.0 kcal mol^{-1}, then the weight is 0. The values of the POP and TOR terms, which are not accurately known quantities, also affect the weighting scheme. If POP + TOR $\geq$ 1.0, then 1 is also subtracted from this weight, and when this sum $\geq$2.0, then 2 is subtracted from the weight, and so on. Because POP and TOR are different in MM3, the weights used in the MM3 rms calculation are slightly different. The calculated heats of formation are compared to the experimental values in Table 19. Considering the fact that there are marginally enough accurate data[49−61] for the amide compounds, the rms error between MM4 and experiment is satisfactory. For 18 weighted

TABLE 16: *N,N*-Dimethylformamide Exp and Calcd Vibrational Frequencies (in cm^{-1})

mode	assignment	sym	exp ref 42	wgt	MM3	dev	wgt	MM4	dev
1	$\nu\mathrm{aCH}_3 + \nu\mathrm{aCH}_3$	A′	2998	1	3001	3	1	2994	−4
2	$\nu\mathrm{aCH}_3 + \nu\mathrm{aCH}_3$	A″	2998	1	2993	−5	1	2987	−11
3	$\nu\mathrm{aCH}_3 - \nu\mathrm{aCH}_3$	A′	2956	1	2997	41	1	2992	36
4	$\nu\mathrm{aCH}_3 - \nu\mathrm{aCH}_3$	A″	2956	1	2992	36	1	2986	30
5	$\nu\mathrm{sCH}_3 - \nu\mathrm{sCH}_3$	A′	2930	1	2904	−26	1	2913	−17
6	$\nu\mathrm{s\ CH}_3 + \nu\mathrm{sCH}_3$	A′	2884R	1	2902	18	1	2914	30
7	$\nu\mathrm{C'H}$	A′	2857	1	2839	−18	1	2858	1
8	$\nu\mathrm{C'O} - \nu\ \mathrm{C'N}$	A′	1715[a]	1	1791	76	1	1759	44
9	$\delta\mathrm{CH}_3$	A′	1507	1	1565	58	1	1548	41
10	$\delta\mathrm{CH}_3$	A′	1460	1	1534	74	1	1504	44
11	$\delta\mathrm{CH}_3$	A″	1460	1	1487	27	1	1481	21
12	$\delta\mathrm{CH}_3$	A′	1439	1	1474	35	1	1471	32
13	$\delta\mathrm{CH}_3$	A″	1439	1	1472	33	1	1465	26
14	$\delta\mathrm{CH}_3 - \delta\mathrm{HC'O}$	A′	1406	1	1468	62	1	1460	54
15	$\delta\mathrm{CH}_3$	A′	1388	1	1411	23	1	1449	61
16	$\delta\mathrm{HC'O} - \nu\mathrm{C'N}$	A′	1388	1	1375	−13	1	1372	−16
17	$\nu\mathrm{aCNC}$	A′	1257	1	1303	46	1	1327	70
18	$\omega\ \mathrm{CH}_3 + \omega\ \mathrm{CH}_3$	A″	1152	1	1132	−20	1	1154	2
19	$\omega\ \mathrm{CH}_3 - \omega\ \mathrm{CH}_3$	A″	1093	1	1066	−27	1	1088	−5
20	$\rho\mathrm{CH}_3$	A′	1093	1	1062	−31	1	1079	−14
21	$\rho\mathrm{CH}_3$	A′	1064	1	1038	−26	1	1067	3
22	$\omega\ \mathrm{C'H}$	A″	1014	1	994	−20	1	1065	51
23	$\nu\ \mathrm{C'N} + 2\nu\mathrm{NC}$	A′	866	1	823	−43	1	911	45
24	$\delta\mathrm{NC'O}$	A′	659	1	633	−26	1	638	−21
25	$\delta\mathrm{CNC}$	A′	405	1	498	93	1	397	−8
26	$\omega\ \mathrm{N(CH_3)_2}$	A″	345	1	325	−20	1	335	−10
27	dC′NC	A′	318	1	370	52	1	262	−56
28	$\tau\ \mathrm{C'{-}N}$	A″	224R	1	215	−9	1	200	−24
29	$\tau\ \mathrm{CH}_3 - \tau\ \mathrm{CH}_3$	A″	*179*[b]	0	115	−64	0	147	−32
30	$\tau\ \mathrm{CH}_3 + \tau\ \mathrm{CH}_3$	A″	*123*[b]	0	79	−44	0	104	−19
					rms	**41**		**rms**	**34**

R− Raman. [b] ref 43. [c] B3LYP/6-31G** (unscaled).

TABLE 17: MM4 Bond and Structural Enthalpy Parametersfor Amide Compounds

bond	bond type	kcal mol^{-1}	structure	kcal mol^{-1}
C′═O	147−79, 152−79	−195.4650	N-ME	0.3025
C′−C	152−1	−73.4959	C′-ME	−0.2125
C′−N	147−9, 152−9	−88.1534	C′-SEC	−0.6773
N−C	9−1	−81.5782	C′-TERT	−3.5928
C′−H	147−175	−84.3620	torsion	kcal mol^{-1}
N−H	9−28	−102.5890	TOR[a]	0.5715

[a] The TOR parameter has already been set to a fixed value in the MM4 program.

compounds, the weighted standard deviation for the MM4 heats of formation was 0.53 kcal mol^{-1} and the standard deviation was 0.56 kcal mol^{-1}. This is more than a factor of 2 improvement over the MM3 heats of formation, for which the weighted and standard deviations (19 weighted compounds) were 1.30 and 1.27 kcal mol^{-1}, respectively.

In both the MM3 and MM4 rms calculations, there were some molecules which were weighted zero regardless of the above scheme. Those compounds for which no experimental error was reported were not weighted. Also, pentanamide and *N*-acetyl-*N*-butylacetamide were not weighted because we believe the experimental values are inaccurate. The experimental value for pentanamide seems to be wrong just from comparison to the other unbranched C′-alkyl amides. The heat of formation should increase by about 5 kcal mol^{-1} for every $-\mathrm{CH}_2-$ addition to the alkyl chain, and the reported value for pentanamide does not fit into this pattern. The adamantane derivatives, though weighted, may exhibit polymorphism, which has been observed in adamantane itself.[62] Different crystal structures of the same compound will have different heats of sublimation, and if this is not known by the experimentalist, then studies using different crystalline forms may manifest themselves as errors in the heat of formation.[63] It must also be mentioned that amides in general tend to form dimers, and this property may further contribute to the experimental errors in the heats of formation for all of the amides listed.

Conclusion

Overall, there is significant improvement of the MM4 calculations of small to medium size amides (3 to 6 heavy atoms) over the MM3 calculations done in parallel in this study. In particular, there were significant improvements for the calculated moments of inertia, the vibrational frequencies and heats of formation. Two major factors for these improvements are (1) the MM4 force field itself with its additional cross-terms, and (2) more recent experimental and theoretical data, not available in the earlier MM3 study, used in the MM4 parametrization process. Nevertheless, the presently available gas-phase data for the amides are still not as abundant as data found for other common classes of organic compounds, like aldehydes and ketones, studied previously in MM4. Gas-phase data for larger amide compounds (7 or more heavy atoms), which could be used to test the predicability of our MM4 parameter set, are almost nonexistent. However, the MM4 force field for amides was developed with the future intent of modeling peptides and proteins in both their aqueous and crystal environments. Before these can be studied, both the nonbonded interactions in amide−amide and amide−water sytems and the conformations of small peptides have to be investigated and modeled, and these will be dealt with in detail in forthcoming MM4 papers.

Supporting Information Available: Figures of MM4 optimized structures for amide compounds superimposed with dipole moments ($\boldsymbol{\mu}\mathbf{T}$) and corresponding *x*,*y*-projections (μ_x and μ_y): formamide, *N*-methylformamide and *N*,*N*-dimethylformamide (Figure 5); acetamide, *N*-methylacetamide and *N*,*N*-dimethylacetamide (Figure 6); propanamide and *N*-methylpro-

TABLE 18: Number of Bond and Structural Enthalpy Parameters[a] for Amide Compounds

compd	*C′═O*	C′−H	N−H	C′−N	N−C	C′−C	N-ME	C′-ME	C′-SEC	C′-TERT′	TOR	POP
formamide	1	1	2	1	0	0	0	0	0	0	0	0.00
N, *N*-dimethylformamide	1	1	0	1	2	0	2	0	0	0	0	0.00
acetamide	1	0	2	1	0	1	0	1	0	0	0	0.00
propanamide	1	0	2	1	0	1	0	0	0	0	1	0.00
butanamide	1	0	2	1	0	1	0	0	0	0	2	0.01
pentanamide	1	0	2	1	0	1	0	0	0	0	3	0.20
hexanamide	1	0	2	1	0	1	0	0	0	0	4	0.48
octanamide	1	0	2	1	0	1	0	0	0	0	6	1.06
2-methylpropanamide	1	0	2	1	0	1	0	0	1	0	1	0.10
2,2-dimethylpropanamide	1	0	2	1	0	1	0	0	0	1	1	0.00
N-methylacetamide	1	0	1	1	1	1	1	1	0	0	0	0.07
N,*N*-dimethylacetamide	1	0	0	1	2	1	2	1	0	0	0	0.00
N,*N*-diethylacetamide	1	0	0	1	2	1	0	1	0	0	2	0.20
N-butylacetamide	1	0	1	1	1	1	0	1	0	0	3	0.22
N,*N*-dimethylpropanamide	1	0	0	1	2	1	2	0	0	0	1	0.00
N,*N*-dimethyl-*tert*-butylcarboxamide	1	0	0	1	2	1	2	0	0	1	1	0.00
N,*N*-dimethylbutanamide	1	0	0	1	2	1	2	0	0	0	2	0.37
N,*N*-dimethylnonamide	1	0	0	1	2	1	2	0	0	0	7	1.23
ϵ-caprolactam	1	0	1	1	1	1	0	0	0	0	0	0.00
1-adamantanecarboxamide	1	0	2	1	0	1	0	0	0	1	1	0.00
N,*N*-dimethyl-1-adamantanecarboxamide	1	0	0	1	2	1	2	0	0	1	1	0.00
propanediamide	2	0	4	2	0	2	0	0	0	0	2	0.00
N-acetyl-*N*-butylacetamide	2	0	0	2	1	2	0	2	0	0	3	0.26
N,*N*-diacetylacetamide	3	0	0	3	0	3	0	3	0	0	0	0.00
glutarimide	2	0	1	2	0	2	0	0	0	0	0	0.00
Total no. of instances each parameter is found:	30	2	28	30	20	28	15	10	1	4	41	

[a] The enumerated bond and structural enthalpy parameters (*C′═O−TOR*) are in units of kcal/mol. The *POP* term (same units) is already calculated. The TOR term is counted for heavy-atom torsions with rotational barriers ≤ 5.0 kcal/mol.

TABLE 19: Heats of Formation for Amides (in kcal mol^{-1})

compd	experiment		MM3[a]			MM4		
	ΔH_f°	ref	wgt	ΔH_f°	dev	wgt	ΔH_f°	dev
formamide	−46.34 (0.48)	54	6	−46.91	−0.57	6	−45.70	0.64
N, *N*-dimethylformamide	−45.82 (0.48)	50	6	−45.80	0.02	6	−46.46	−0.64
acetamide	−56.96 (0.19)	51	10	−57.12	−0.16	10	−57.28	−0.32
propanamide	−61.89 (0.16)	51	10	−61.95	−0.06	10	−61.93	−0.04
butanamide	−66.49 (0.24)	50	8	−66.21	0.28	7	−67.24	−0.75
pentanamide	−69.36 (0.29)	50	0	−72.20	−2.84	0	−72.36	−3.00
hexanamide	−77.48 (0.43)	50	4	−77.19	0.29	4	−77.58	−0.10
octanamide	−86.69 (0.74)	50	1	−87.14	−0.45	0	−87.57	−0.88
2-methylpropanamide	−67.54 (0.22)	52	8	−69.51	−1.97	8	−67.54	0.00
2,2-dimethylpropanamide	−74.83 (0.33)	52	8	−76.53	−1.70	8	−75.34	−0.51
N-methylacetamide	−59.27 (1.31)	53	0	−57.85	1.42	0	−57.23	2.04
N,*N*-dimethylacetamide	−54.49 (0.43)	54	6	−53.71	0.78	6	−54.43	0.06
N,*N*-diethylacetamide	−68.64 (−)	55	0	−67.18	1.46	0	−64.79	3.85
N-butylacetamide	−72.85 (0.50)	50	5	−75.27	−2.42	5	−73.70	−0.85
N,*N*-dimethylpropanamide	−59.79 (−)	56	6	−58.35	1.44	6	−59.00	0.79
N,*N*-dimethyl-*tert*-butylcarboxamide	−68.38 (0.50)	57	6	−67.78	0.60	6	−68.64	−0.26
N,*N*-dimethylbutanamide	−64.74 (−)	56	0	−63.19	1.55	0	−63.98	0.76
N,*N*-dimethylnonamide	−89.38 (−)	56	0	−88.69	0.69	0	−90.16	−0.78
ϵ-caprolactam	−58.84 (0.31)	50	8	−59.76	−0.92	8	−58.51	0.33
1-adamantanecarboxamide	−76.24 (0.60)	52	6	−76.35	−0.11	6	−75.13	1.11
N,*N*-dimethyl-1-adamantanecarboxamide	−68.38 (0.65)	57	4	−67.26	1.12	4	−68.27	0.11
propanediamide	−99.52 (0.10)	60	10	−101.92	−2.40	10	−99.21	0.31
N-acetyl-*N*-butylacetamide	−113.41 (0.41)	54	0	−113.87	−0.46	0	−108.35	4.56
N,*N*-diacetylacetamide	−131.48 (0.31)	54	8	−131.35	0.13	8	−131.21	0.27
glutarimide	−94.07 (0.43)	61	6	−96.64	−2.57	6	−95.04	−0.97
	Total Rms		standard:	1.27	standard:	0.56		
	Deviation[b]		weighted:	1.30	weighted:	0.53		

[a] Previously unpublished data, MM3 heats of formation calculations done in this work. [b] Calculations for the standard and weighted rms deviations were based on 19 weighted equations.for MM3 and 18 weighted equations for MM4. Optimization and analysis ignores all equations whose weight is zero.

panamide (Figure 7). Figure of density functional theory (B3LYP/6-31G**), MM3 and MM4 heavy-atom torsion curves for *N*-methylformamide (Figure 10). Figures of B3LYP/6-31G** and MM4 heavy-atom torsion curves for *N*-ethylformamide (Figure 12), butanamide (Figure 15), *N*-propylformamide (Figure 16), propanediamide (Figure 17), 1,4-butanediamide (Figure 18), and *N*-acetylacetamide (Figure 19). This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) The MM3 program is available to all users from Tripos Inc., 1699 South Hanley Road, St. Louis, MO 63144. Academic users, and others from nonprofit organizations, may alternatively obtain the program from the Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN 47405. The program is described in the following references: (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551; (b) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566, 8576.

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