The MM3 Force Field for Amides, Polypeptides and Proteins

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The potential functions for simple amides, several peptides and a small protein have been worked out for the MM3 force field. Structures and energies were fit as previously with MM2, but additionally, we fit the vibrational spectra of the simple amides (average rms error over four compounds, 34 cm^{-1}), and examined more carefully electrostatic interactions, including charge-charge and charge-dipole interactions. The parameters were obtained and tested by examining four simple amides, five electrostatic model complexes, two dipeptides, six crystalline cyclic peptides, and the protein Crambin. The average root-mean-square deviation from the X-ray structures for the six cyclic peptide crystals was only 0.10 Å for the nonhydrogen atomic positions, and 0.011 Å, 1.0°, and 4.9° for bond lengths, bond angles, and torsional angles, respectively. The parameter set was then further tested by minimizing the high resolution crystal structure of the hydrophobic protein Crambin. The resultant root-mean-square deviations for the non-hydrogen atomic data, in the presence of the crystal lattice, are 0.22 Å, 0.023 Å, 2.0°, and 6.4° for coordinates, bond lengths, bond angles, and torsional angles, respectively.

INTRODUCTION

The MM2 program[1] has been used for calculations on amides for some years now, and has given creditable results.[2] In updating to MM3,[3] we faced generally the same problems as with MM2, but additionally, we wanted to fit vibrational spectra as well. There are four simple amides for which electron diffraction geometries are known, and we first tried to fit these as well as possible. These are formamide, acetamide, Z-N-methylformamide, and Z-N-methylacetamide. The conformations of the peptide framework were studied beginning with the two standard dipeptides, which were N-acetylglycine N-methylamide (GA), and N-acetylalanine N-methylamide (AA), followed by six cyclic peptides, namely cyclo-(Ala-Ala-Gly-Gly-Ala-Gly-).1H$_2$O (CP1), cyclo-(Ala-Ala-Gly-Ala-Gly-Gly-).2H$_2$O (CP2), cyclo-(Gly-Gly-D-Ala-D-Ala-Gly-Gly-).3H$_2$O (CP3), cyclo-(Gly-L-Pro-Gly-Gly-L-Pro-Gly-).4H$_2$O (CP4), cyclo-(Gly-Pro-Gly-D-Ala-Pro-) (CP5) and cyclo(Cys-Gly-Pro-Phe-Cys-Gly-Pro-Phe-).4H$_2$O (CP6). The primary goal of this work was to develop a force field which would be able to represent the potential surfaces of proteins, and since the electrostatic interactions play an important role in the force field, we focused on the electrostatic interactions for the peptide residues. They were carefully examined by fitting the thermodynamic data and ab initio geometries of five simple models, namely the formamide dimmer, form-amide-water complex, formate ion-water complex, ammonium ion-water complex, and guanidinium ion-water complex. The parameter set arrived at was then further tested by the energy minimization of the protein Crambin. The resultant root-mean-square deviation for the nonhydrogen atomic positions of the six crystalline cyclic peptides and for Crambin (0.10 Å and 0.22 Å, respectively) show that the current MM3 force field is able to well describe the potential surfaces of the polypeptides, and also of the protein.

COMPUTATIONAL METHODS

Amides-Structures and Energies

The parameterization for the simple amides was carried out on four simple amides as mentioned previously. The bond lengths of the CO and CN bonds are known to be quite phase dependent.[2] As before with MM2, we tried to fit the gas phase numbers first, and to also fit these to the gas phase vibrational spectra. The spectra for these simple amides are not as unambiguously defined and assigned as one would like. Different experimental spectra often have the same frequencies reported at different values by 10 or 20 wave numbers. The assignments are not always agreed upon. Most of the frequencies are also moderately sensitive to phase, so that solution spectra and spectra determined at low temperatures in matrices are not well suited for present purposes.

The dipole moments of these molecules were also fit to by assigning bond moment parameters to C'—N (type 3-9), N—H (type 9-28), and C—N (type 1-9).

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Table I. The MM3 force field for amides, peptides, and protein.

Type	V_1	V_2	V_3
Torsional Parameter			
1-1-1-9	0.450	0.000	0.500
5-1-1-9	0.000	0.000	0.500
3-1-1-9	0.000	0.000	0.180
1-1-3-9	0.700	−1.100	0.300
1-1-3-47	−0.400	1.000	0.000
5-1-3-9	0.000	0.000	0.230
5-1-3-47	0.000	0.000	0.200
9-1-3-7	0.100	0.700	2.100
9-1-3-9	−0.700	0.700	0.200
9-1-3-47	0.000	0.800	1.500
39-1-3-7	0.000	0.000	0.100
39-1-3-9	0.000	0.000	0.100
1-1-9-3	−0.300	0.000	0.300
1-1-9-28	0.000	0.000	0.010
1-1-9-30	0.000	0.000	0.600
3-1-9-1	0.000	0.000	0.457
3-1-9-3	2.300	−1.200	0.800
3-1-9-28	0.000	0.000	0.300
5-1-9-1	0.000	0.000	0.460
5-1-9-3	0.000	0.000	0.010
5-1-9-28	0.000	0.000	0.080
5-1-9-30	0.000	0.000	0.100
1-1-39-48	0.000	0.120	0.100
3-1-39-48	0.000	0.000	0.200
5-1-39-48	0.000	0.000	0.250
1-3-9-1[a]	1.100	3.800	0.000
1-3-9-28[a]	0.000	3.800	0.000
5-3-9-1[a]	1.000	3.900	0.000
5-3-9-28[a]	0.000	4.600	0.000
7-3-9-1[a]	−0.600	4.200	0.000
7-3-9-28[a]	1.000	4.100	0.000
1-9-30-9	0.000	4.500	0.000
28-9-30-9	0.000	4.500	0.000
2-2-6-21	0.000	2.300	0.000
15-1-1-39	0.000	0.000	0.100
9-1-1-15	0.000	0.000	0.100
1-1-1-9 (5)	0.450	0.000	0.500
1-1-9-1 (5)	0.000	0.000	1.300

Stretching Parameter

Bond Type	K_s	L_o
1-9	5.210	1.4460
3-9[b]	6.700	1.3770
3-47	7.570	1.2500
9-28	6.770	1.0280
9-30	6.830	1.3250
39-48	6.100	1.0450
1-9 (5)	5.210	1.4700

Bending Parameter

Angle Type	K_b	Theta	Type
1-1-9	0.750	109.48	1
1-1-9	0.750	111.30	2
1-1-9	0.750	111.80	3
3-1-9	0.850	109.50	1
3-1-9	0.850	110.60	2
3-1-9	0.850	112.30	3
3-1-39	1.045	110.74	
5-1-9	0.760	111.00	1
5-1-9	0.760	111.00	2
5-1-9	0.760	111.00	3
2-2-6	0.600	120.00	
1-3-9	0.570	114.40	
1-3-47	0.850	125.10	

Table I. (Continued)

Angle Type	K_b	Theta	Type
5-3-9	0.440	109.30	
7-3-9	1.070	124.80	
47-3-47	0.800	134.00	
1-9-1	0.760	122.50	
1-9-3	1.620	121.10	
1-9-28	0.190	122.40	
1-9-30	0.730	120.40	
3-9-28	0.580	118.50	
28-9-28	0.410	123.00	
28-9-30	0.580	120.50	
9-30-9	0.400	120.00	
1-39-48	0.500	109.47	
48-39-48	0.500	104.50	
1-1-9 (5)	0.750	109.48	1
1-1-9 (5)	0.750	111.90	2
1-1-9 (5)	0.750	108.50	3
1-9-1 (5)	0.760	117.10	
2-41	0.100		
3-9	1.500		
3-47	0.800		
9-1	0.010		
9-3	0.050		
9-28	0.020		
9-30	0.050		
30-9	0.150		

Van der Waals and Hydrogen Bonding Parameter

Atom Type	E_{ps}	R_v
28	0.015	1.60
30	0.056	1.94
48	0.034	1.60
6....28	3.150	2.25
6....48	4.200	1.88
7....28	5.100	2.03
7....48	6.000	2.00
47....21	3.150	2.15
47....28	4.125	2.03
47....48	5.100	2.00

Bond Moment Parameter

Bond Type	Bond Moment
1-9	1.65
3-9	−0.72
3-47	1.90
9-28	−1.58
9-30	−0.72
39-48	−1.58

Electronegativity Effect Parameter

Bond Type	Atom Type	Attached Atom Type	Correction
1-1	1	9	−0.015
1-9	9	28	0.001

Atomic Charge Parameter

Atom Type	Charge
30	1.00
39	1.00
47	−0.50

[a]Torsion potentials here are for the gas phase. The values for V_2 about bonds of the type X-3-9-Y have V_2 increased about 65% for solution and crystal phases ($D = 4.0$) relative to the gas phase ($D = 1.5$).

[b]This bond length is dielectric constant dependent, as is type 3-7 (reference 2).

Table II. Vibrational spectrum of formamide.

No.	Symmetry	Experiment[a]	Calculated	Assignment
1	A'	3545	3557	νNH_2 asym
2	A'	3450	3440	νNH_2 sym
3	A'	2852	2827	νCH
4	A'	1740	1784	$\nu CO + \nu CN$
5	A'	1572	1579	δNH_2
6	A'	1388	1357	$\delta CO + \nu NCO$
7	A'	1253	1197	$\nu CN + \delta NCO$
8	A'	1055	1062	$\nu CN + \nu CO$
9	A''	1030	1023	ωCH
10	A''	672	632	$\omega NH_2 + \tau NH_2$
11	A'	567	570	δNCO
12	A''	507	528	$\tau NH_2 - \omega NH_2$

[a]Reference 9.

The dipole energies are quite high in the gas phase.

There are a few other quantities that we wish to fit simultaneously. These included the E, Z equilibria in the case of the N-methyl compounds, and the rotational barriers about the C'—N bond (type 3-9). These are known from NMR data to be in the range of 16–20 kcal/mol for these compounds in solution,[36] but ab initio calculations suggest they are somewhat smaller in the gas phase.

Electrostatic Models

Five simple models given above were chosen for the parameterization for hydrogen bonding, dipole-dipole, and charge-dipole interactions. The hydrogen bonding and charge parameters were chosen to optimally reproduce the resultant geometries and interaction energies for all of these. The optimized geometries of the water molecule and isolated ions used in the calculation were the following: for the

water molecule, the O—H distance and HOH angle were 0.947 Å and 105°; for the ammonium ion, the optimized quantities were 1.045 Å and 109.5°; for the formate ion, the C—O and C—H bond lengths and OCO angle were 1.233 Å, 1.121 Å, and 130°, respectively; for guanidinium ion, the optimized value for C—N bond length was 1.350 Å. The interaction energy between two species is determined by the sum of the intermolecular interactions, specifically the van der Waals', dipole-dipole, charge-charge, charge-dipole, and hydrogen bonding interactions. Since we try to keep the force field as simple as possible, we placed a $+1$ charge on ammonium ion nitrogen, a -0.5 charge on each carboxylate ion oxygen, and a $+1$ charge on guanidinium ion carbon. These charge distributions can be refined later if necessary. (The reader should note that although a $+1$ charge is used on nitrogen in the ammonium ion, the large H—N dipoles (-1.58 D) actually redistribute the charge so that the nitrogen is effectively negative.)

Table III. Vibrational spectrum of acetamide.

No.	Symmetry	Experiment[a]	Calculated	Assignment
1	A'	3550	3557	νNH_2
2	A'	3450	3439	νNH_2
3	A''	2967	2971	νCH_3
4	A'	2900	2971	νCH_3
5	A'	2860	2875	νCH_3
6	A'	1733	1725	νCO
7	A'	1600	1602	δNH_2
8	A'	1472	1441	CH_3 def
9	A''	1456	1435	CH_3 def
10	A'	1381 (1385)	1417	CH_3 def
11	A'	1319	1298	νCN
12	A'	1124 (1134)	1095	rNH_2
13	A''	1040	957	rCH_3
14	A'	965	924	rCH_3
15	A'	858	813	$\nu CC + \nu CN$
16	A''	625	643	ωCH_3
17	A'	534 (548)	559	δOCN
18	A''	503 (507)	517	ωNH_2
19	A''	430 (452)	460	τNH_2
20	A'	409	421	δCCN
21	A''	144	147	τCH_3 (C—CH_3)

[a]References 9 and 10.

Table IV. Vibrational spectrum of Z-N-methylformamide.

No.	Symmetry	Experiment[a]	Calculated	Assignment
1	A'	3480	3481	νNH
2	A'	2934	2969	νCH$_3$
3	A''	2934	2967	νCH$_3$
4	A'	2860	2876	νCH$_3$
5	A'	2849	2825	νCH
6	A'	1743	1774	νCO
7	A'	1498	1540	δCNH
8	A''	1480	1467	CH$_3$ def
9	A'	1477	1455	CH$_3$ def
10	A'	1411	1427	CH$_3$ def
11	A'	1387	1339	νCO + δNCO
12	A'	1201	1157	νCN
13	A'	1149	1120	rCH$_3$
14	A''	1145	1101	rCH$_3$
15	A''	1014	1014	ωCH
16	A'	946	918	νNC + νCN
17	A'	769	744	δCNC + δNCO
18	A''	− (491)	535	ωNH
19	A'	267	338	δCNC
20	A''	330	301	τCN (C—NHMe)
21	A''	55	57	τCH$_3$ (N—CH$_3$)

[a]Reference 9.

Conformation of Peptide Backbone

Conformational energy surfaces were computed for two dipeptides and six cyclic peptide crystals as mentioned previously. The torsional angles for the peptide backbone, phi, psi, and omega, were carefully examined and fit to the reported structures and conformational energies. A dielectric constant of 1.5 was used in the calculations on the dipeptides (gas phase), while in order to simulate the crystalline environment, a dielectric constant of 4.0 was chosen for the crystal calculations.

Table V. Vibrational spectrum of Z-N-methylacetamide.

No.	Symmetry	Experiment[a]	Calculated	Assignment
1	A'	3495	3484	νNH
2	A'	2940	2971	νCH$_3$
3	A''	2940	2971	νCH$_3$
4	A'	2940	2969	νCH$_3$
5	A''	2940	2967	νCH$_3$
6	A'	2830	2876	νCH$_3$
7	A'	2830	2875	νCH$_3$
8	A'	1723	1710	νCO
9	A'	1494	1586	NH def + νCN
10	A'	1430	1486	CH$_3$ def
11	A''	1430	1468	CH$_3$ def
12	A'	1430	1446	CH$_3$ def
13	A''	1430	1435	CH$_3$ def
14	A'	1410	1417	CH$_3$ def
15	A'	1374	1337	CH$_3$ def
16	A'	1263	1214	
17	A'	1176	1154	
18	A''	− (1126)	1097	
19	A'	1092	1033	
20	A''	1042	958	
21	A'	973	919	
22	A'	830	846	
23	A'	− (632)	622	
24	A''	− (602)	582	
25	A''	− (391)[a]	507	
26	A'	431	434	δCCN
27	A'	279	308	δCNC
28	A''	− (150)	163	τCN (C—NHMe)
29	A''	—	144	τCH$_3$ (C—CH$_3$)
30	A''	—	66	τCH$_3$ (N—CH$_3$)

[a]References 10–12.

Table VI. Vibrational spectrum of *N,N*-dimethylformamide.

No.	Symmetry	Experiment[a]	Calculated	Assignment
1	A'	3000	2977	νCH_3
2	A'	2994	2974	νCH_3
3	A''	2978	2969	νCH_3
4	A''	2946	2969	νCH_3
5	A'	2937	2881	νCH_3
6	A'	2919	2880	νCH_3
7	A'	2847	2839	νCH
8	A'	1714	1791	$\nu CO + \nu CH$
9	A'	—	1564	$\nu CH + rCH_3$
10	A'	—	1532	$\nu CN + rCH_3$
11	A''	1496	1484	CH_3 def
12	A'	—	1471	CH_3 def
13	A''	—	1470	CH_3 def
14	A'	1457	1466	CH_3 def
15	A'	1407	1410	CH_3 def
16	A'	1382	1375	CH_3 def
17	A'	1270	1302	$\nu CO + \nu NC$ (trans)
18	A''	1150	1131	ωCH_3 (N)
19	A''	1091	1064	
20	A'	1082	1060	
21	A'	1074	1037	
22	A''	—	989	
23	A'	865	823	
24	A'	659	633	
25	A'	—	498	
26	A'	—	370	
27	A''	—	325	
28	A''	—	215	
29	A''	—	115	τCH_3 (N—CH_3)
30	A''	—	78	τCH_3 (N—CH_3)

[a]Reference 11.

In the calculations on the peptide crystals, the crystalline environment was generated according to the reported space group and cell constants as described in the previous article.[24] Since the experimental hydrogen positions are not accurately known, we optimized the hydrogens of the central molecule with the crystal lattice present, then regenerated the crystal lattice with the optimized hydrogen coordinates. The process was repeated until the average movement of the hydrogens was very small (0.0001 Å). We found that this procedure was necessary, since inaccurate hydrogen positions may distort the structure of the central molecule, especially the torsional angles, when there are low torsional barriers like those found in peptide bonds. For peptide I and II (CP1 and CP2), since the crystal structures were reported at low temperature (138 K), we expanded the unit cell 1% along each axis to simulate the room temperature crystal lattice. With the crystal environments fixed, the central molecules were then optimized and compared with the observed structures.

Conformational Analysis of Crambin

Two types of calculations were performed. In one, the isolated Crambin molecule was minimized from the reported X-ray structure. In the second, the pro-

tein Crambin was surrounded with a lattice cage of a 5.0 Å van der Waals and electrostatic shell, which was generated from a 1% expanded unit cell,[5] and the energy of the molecule within the rigid shell was minimized. For both calculations, a dielectric constant of 4.0 was chosen, and the energy minimization was continued until the energy difference between successive five-iteration cycles was within less than 0.06 kcal/mol. There are a total of six charged residues found in Crambin. They are three positively charged groups (+1.0) on **Thr**(1), **Arg**(10), and **Arg**(17), respectively, and three negatively charged groups (−1.0) on **Glu**(23), **Asp**(43), and **Asn**(46), respectively. In our calculations, the charge-charge, dipole-dipole, and charge-dipole interactions are all included. We found that when the charge-charge and charge-dipole interactions were added, some torsional angles became better, some got worse, but overall the results are about the same.

FORCE FIELD

The force field finally arrived at is presented in Table I in terms of atom type numbers.[2] These parameters are mostly included in MM3 (90),[3] except for 1-1-1-9 and 5-1-1-9, which have been updated.

RESULTS AND DISCUSSION

Amides

The vibrational spectra calculated for these compounds are given in Tables II–VI. The structure, properties, and spectra of each compound will be discussed in turn.

Formamide

This is the most simple, and best studied, of the amides. A comparison of the calculated structure with the electron diffraction structure[6] (in Table VII), shows agreement to approximately within experimental error. The moments of inertia calculated and found for this molecule also are given in Table VII. The experimental moments correspond to an r_a structure, whereas the MM3 moments correspond to r_g and hence should be little larger, and this is found, except for I_a which is calculated to be too small. The dipole moment of the molecule is also in good agreement with experiment 3.71 D (3.71); μ_a 3.66 (3.62); μ_b 0.58 (0.86). The rotational barrier observed for formamide is 18.8 kcal/mol in solution,[7] and 14.2 kcal/mol is the ab initio result.[8] The MM3 calculated value was made dielectric constant dependent, like the bond lengths, and for the same reason.[2] The calculated values are 14.3 kcal/mol for the gas phase (D = 1.5) and 18.6 kcal/mol for condensed phases (D = 4.0).

Table VII. Observed and calculated structures for amides.[a]

		Observed	MM3
Formamide	C'—N	1.368(4)[6]	1.372
	C'—O	1.212(3)	1.216
	C'—H	—	1.119
	N—H	—	1.028
	N—C'—O	125.0	125.8
	N—C'—H	112.7	113.7
	O—C'—H	122.3	120.5
	C'—N—H1	117.9	118.0
	C'—N—H2	119.8	120.0
	H1—N—H2	—	121.9
	I_a	1.168	1.150
	I_b	7.326	7.537
	I_c	8.495	8.687
	μ	3.71	3.71
Acetamide	C'—N	1.378(4)[6]	1.377
	C'—O	1.219	1.219
	C'—C	—	1.520
	N—H	—	1.028
	N—C'—O	122.0(6)	122.8
	N—C'—C	115.0	115.3
	O—C'—C	123.0	121.9
	C'—N—H1	—	117.9
	C'—N—H2	—	120.3
	H1—N—H2	—	121.8
(in atomic	I_a	—	47.325
units)	I_b	—	54.908
	I_c	98.000	98.921
	μ	3.74	3.74

Table VII. (Continued)

		Observed	MM3
Z-N-Methyl-formamide	C'—N	1.366(8)[6]	1.375
	C'—O	1.217	1.217
	N—C	1.459(6)	1.453
	C'—H	—	1.119
	N—H	—	1.030
	N—C'—O	124.6(5)	126.4
	C'—N—C	—	121.3
	N—C'—H	114.1(15)	113.3
	O—C'—H	—	120.3
	C'—N—H	—	118.9
	C—N—H	—	119.9
	I_a	—	4.291
	I_b	—	13.858
	I_c	—	17.608
	μ	—	3.79
Z-N-Methyl-acetamide	C'—N	1.386(4)[6]	1.381
	C'—O	1.225(3)	1.219
	C'—C	—	1.520
	N—C	1.469(6)	1.453
	N—H	—	1.029
	N—C'—O	121.8(4)	123.5
	N—C'—C	114.1(5)	114.9
	O—C'—C	124.1(4)	121.6
	C'—N—C	119.7(8)	121.3
	C'—N—H	—	119.1
	C—N—H	—	119.6
	I_a	—	8.489
	I_b	—	22.021
	I_c	—	29.418
	μ	—	3.83
N,N-Dimethyl-formamide	C'—N	1.343[13]	1.381
	C'—O	1.221	1.217
	N—C1	1.460	1.458
	N—C2	1.455	1.457
	C'—H	—	1.117
	N—C'—O	124.8	126.6
	C'—N—C1	118.5	120.8
	C'—N—C2	122.2	120.3
	C1—N—C2	119.7	119.0
	N—C'—H	114.1	113.7
	O—C'—H	—	119.7
	I_a	—	9.704
	I_b	—	20.386
	I_c	—	29.014
	μ	—	3.85

[a]Bond lengths in Å, angles in °, moments of inertia (I) in 10^{-39}g · cm^2, and dipole moments (μ) in Debyes.

The vibrational spectra of formamide have been determined, and the bands assigned, apparently without dispute. The discrepancies between the calculated and experimental frequencies for this molecule may be presumed to be mainly due to computational error. Note that the largest errors (Table II) are in bands (7), (10), and (4), and are −56, −40, and +44 wave numbers, respectively. The root-mean-square error is 28 cm^{-1}. Some of the frequencies are coupled in such a way that it is difficult to obtain agreement with experiment without adding

additional cross terms. Frequency (4), which mainly the CO stretch, is coupled with the CH and CN stretches (bands (6) and (8)) in such a way that adjusting a force parameter to improve one of these leads to large effects on the other two as well. When the whole set of molecules is considered, the numbers that we settled on are regarded as approximately optimum. Further improvement would require either a change in the CO force parameter, which was previously fixed from studies on ketones,[14] or a change in one or more of the off-diagonal parameters. The coupling between CN and CO, a stretch-stretch interaction, is not included in MM3. The stretch-bend interaction is included, but the parameters are fixed from previous geometric studies. Without addition of some additional parameters here, it is hard to see how the overall results could be improved.

Acetamide

The structure calculated here is in good agreement with experiment, as shown in Table VII. The moments of inertia are known experimentally, but only with respect to axes defined in an unusual way, not with respect to the principle axes. We have not been able to relate I_a and I_b to these experimental measurements. However, I_c should be the same, and the agreement here is satisfactory; I_c 98.921 (98.000). The dipole moment is available only from solution measurements, but again, the calculated value 3.74 is satisfactory. The theoretical and calculated vibrational spectra are presented in Table III. There are only a few major discrepancies here, band (13), which is a methyl rocking frequency, is calculated too low by 83 cm^{-1}, and one of the CH stretching frequencies (4) is calculated too high by 71 cm^{-1}. These are problems which stem from the hydrocarbon or ketone part of the force field. The next most serious errors, (14) and (15) are methyl rocking (-41 wave numbers) and the CN stretching frequency, (-45 wave numbers). The first of these is again a hydrocarbon and ketone[3,14] number, and is uncontrollable. The second of these involves the CN stretching frequency, and cannot really be improved significantly, because of the coupling with other frequencies, as mentioned earlier under the discussion of formamide. The overall fit is nonetheless good, the rms error is about 32 cm^{-1}. The rotational barrier about the CN bond in acetamide was calculated to be 13.3 kcal/ mol, and the corresponding ab initio number is 12.5 kcal/mol.[8]

Z-N-Methylformamide

Again, for this compound the dipole moment is in good agreement with the solution value, but the moments of intertia are not experimentally known. The structure (Table VII) is also in good agreement with

experiment. The Z form is the stable form by 1.84 kcal/mol. The vibrational spectrum (Table IV) is in reasonable agreement with experiment, with an rms error of 33 cm^{-1}. Some of the larger errors include the CO stretching frequency, which is too high by 31 cm^{-1} as in formamide itself, coupled with the CN
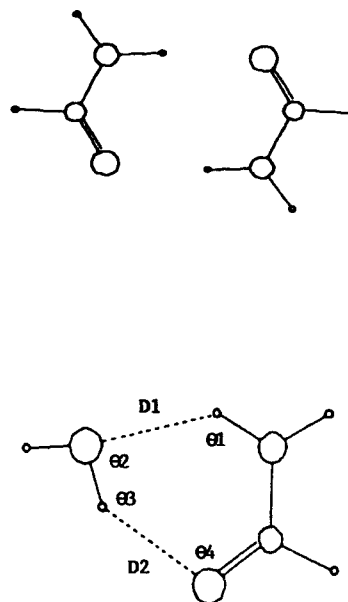

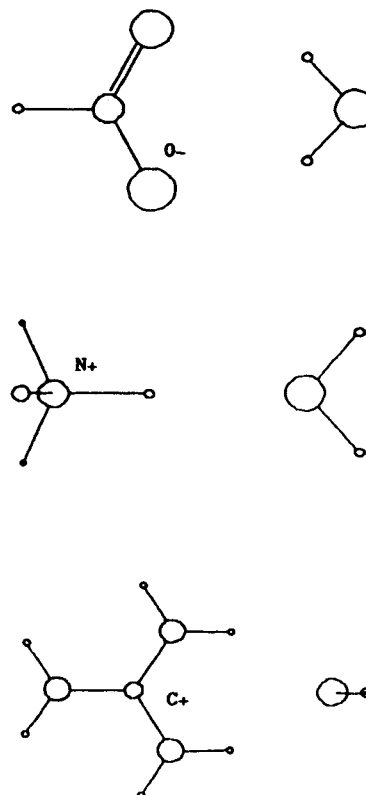**Figure 1(a).** MM3 calculated geometries for formamide dimer and formamide-water complex.

Figure 1(b). MM3 calculated geometries for formate ion-water complex, ammonium ion-water complex, and guanidinium ion-water complex.

Table VIII. Formamide complexes.

Formamide Dimer (Å, kcal/mol)

	$D(N\cdots O)$	$D(H\cdots O)$	E(dimer)	$E(\infty)$	ΔE
Exptl.	2.948	1.946	—	—	14.0
MM3	2.956	1.932	-20.02	-6.24	13.8

Formamide-Water Complex (Å, kcal/mol)

	$D1$	$D2$	$\theta 1$	$\theta 2$	$\theta 3$	$\theta 4$	ΔE
Exptl.	2.161	2.061	138.6	83.7	143.3	110.1	9.5
MM3	2.165	2.078	137.6	86.6	140.8	110.8	9.5

stretching frequency (12) which is 44 cm^{-1} too low. The CH (11) bending frequency is 48 wave numbers too low, while the NH(7) frequency is 42 wave numbers too high. Improvement in the latter would require a vicinal bend-bend interaction, previously noted as desirable in the hydrocarbon work.[3] The out-of-plane waging of the NH (18) is 43 cm^{-1} too high. Most of the larger remaining errors are due to the methyl group, and are essentially uncontrollable,[3,14] as was previously discussed. The overall spectrum is calculated in fair agreement with experiment.

Z-N-Methylacetamide

The calculated dipole moment and structure are in agreement with experiment, and the moments of inertia for this molecule are experimentally unknown. The Z form is calculated to be more stable than the E form by 2.94 kcal/mol. The calculated spectrum is in slightly poorer agreement with experiment (rms error 39 cm^{-1}) than those for the three molecules described earlier (Table V). The CH stretching frequencies are systematically too high by about 30 cm^{-1}. This is also noted with acetamide and N-methylformamide, and suggests that if an alkyl group is attached either to the nitrogen or to the carbonyl carbon of an amide, there is systematic decrease in the C—H stretching frequencies.

Note that the CO frequency is about right here, and also in acetamide. This means that the large systematic error in the carbonyl frequencies is limited to the formamides, which are a special case anyway. Hence we are fitting best to the things that we really need to fit.

N,N-Dimethylformamide

There is no electron diffraction or X-ray structure for this compound, but there is an ab initio calculation with the geometry optimized at the 4-31G level.[13] The calculated and MM3 structures are shown in Table VII. The infrared spectrum of the compound was reported by Jones, and the spectra and assignment are given in Table VI. Unfortunately, Jones did not find all of the transitions at longer wave lengths, and found nothing below 600 wave numbers. Considering the available information, the agreement with experiment seems adequate. Also reported by Dimitrov and Ladd were rotational barriers for the two methyl groups. The experimental values for the rotational barriers for the two methyls are quite different. The higher rotational barrier is observed for the methyl trans to the carbonyl (2.70(0.60) and 3.90(0.31) kcal/mol, respectively). The corresponding ab initio numbers are 0.91 and 1.82 kcal/mol, and MM3 barriers are 0.90 and 0.96 kcal/mol. The trans methyl group is found to have a shorter C—N bond by 0.005 (ab initio), and by 0.001 Å (MM3).

Electrostatic Models

A comparison of the calculated structures and energies and the reported values are given in Tables VIII and IX. Further details will be discussed below.

Formamide Dimer and Formamide-Water Complex

The MM3 geometries for both formamide dimer and formamide-water complex are in fair agreement with the reported ab initio values[15,16] (Fig. 1(a)). The MM3

Table IX. Ion-water complexes (Å, kcal/mol).

Complex	Method	R	E	Ref.
Formate-Water	MM3	3.13 (C..O)	19.5	this work
	6-31G*	3.23 (C..O)	22.0	18
	OPLS	3.08 (C..O)	19.0	19
Ammonium-Water	MM3	2.76 (N..O)	15.6[a]	this work
	6-31G*	2.77 (N..O)	21.2	19
	OPLS	2.70 (N..O)	18.6	19
Guanidinium-Water	MM3	3.46 (C..O)	14.5	this work
	6-31G*	3.41 (C..O)	18.2	20
	OPLS	3.33 (C..O)	16.1	20

[a]This value may be compared with the literature values, which may not have been optimized. (It was not stated.) Our minimum is a bifurcated (C_{2v}) structure with an energy of 19.16 kcal/mol.

Table X. *N*-Acetylglycine *N*-Methylamide (GA) conformations/energies.[a]

Force field	Gauche		Anti		Ref.
	(ϕ,ψ)	E	(ϕ,ψ)	E	
MM3	(82,−62)	0.0	(180,178)	1.7	this work
AMBER/OPLS	(82,−67)	0.0	(180,180)	1.7	20
AMBER	(77,−64)	0.0	(180,180)	3.2	21
UNICEPP	(83,−76)	0.0	(180,180)	0.9	22
ECEPP/2	(79,−73)	0.0	(180,180)	1.2	23
4-21G	(83,−71)	0.0	(180,180)	0.8	24
PCILO	(80,−40)	0.0	(180,180)	2.0	25
IR,NMR(CCl$_4$)	(75,−50)				26
X-ray (crystal)	(109,−21)				27

[a]MM3 uses 1.5 for the dielectric constant of a molecule in the gas phase.

Table XI. *N*-acetylalanine *N*-Methylamide (AA) conformations/energies.[a]

Force field	Gauche		Anti		Ref.
	(ϕ,ψ)	E	(ϕ,ψ)	E	
MM3	(−83,66)	0.0	(−164,154)	1.0	this work
AMBER/OPLS	(−84,70)	0.0	(−150,162)	1.5	20
AMBER	(−79,69)	0.0	(−150,154)	2.3	21
UNICEPP	(−83,81)	0.0	(−152,147)	0.7	22
ECEPP/2	(−80,76)	0.0	(−155,157)	0.7	23
4-21G	(−85,73)	0.0	(−166,167)	1.4	24
PCILO	(−78,40)	0.0	(−171,164)	1.7	25
IR,NMR(CCl$_4$)	(−75,50)				26

[a]MM3 uses 1.5 for the dielectric constant of a molecule in the gas phase.
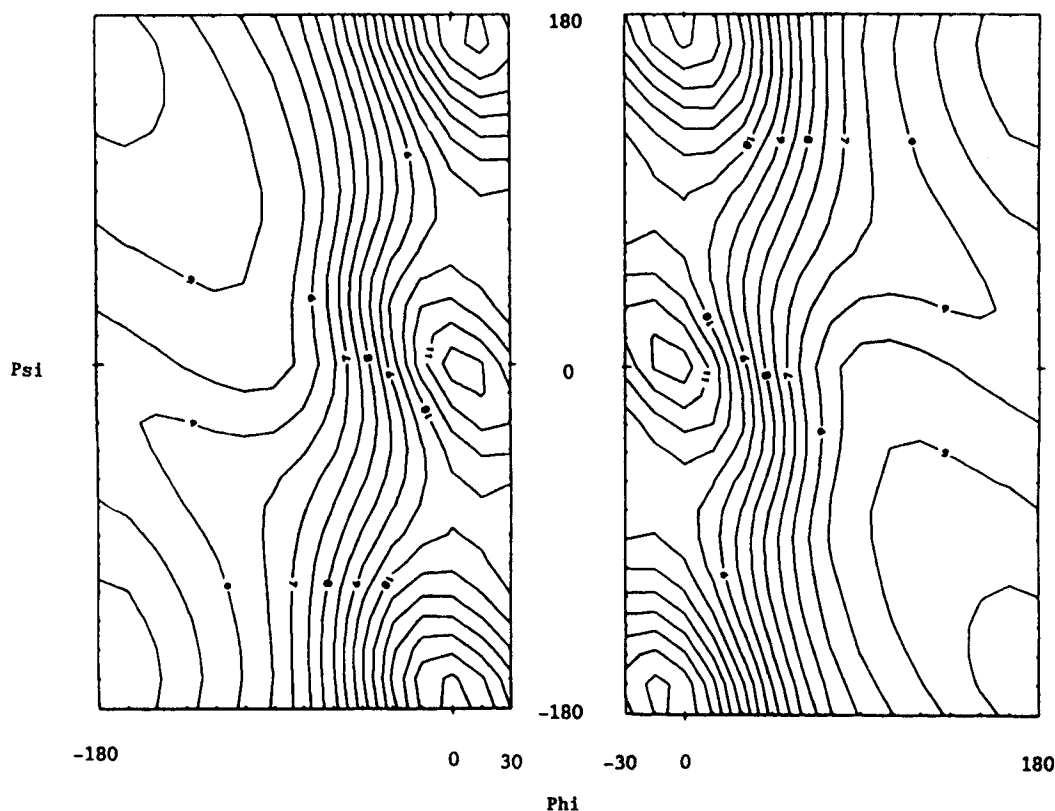
Figure 2. Energy contour map for N-acetylglycine N-methylamide for a dielectric constant of 4.0. Contours are in kcal/mole. The usual IUPAC convention for Phi and Psi is used.

Table XII. Experimental data on cyclic peptide crystals.

Ident.	Peptide	Space Group	Z	Ref.
CP1	cyclo-(Ala-Ala-Gly-Gly-Ala-Gly)	$P2_1$	2	28
CP2	cyclo-(Ala-Ala-Gly-Ala-Gly-Gly)	$P2_12_12_1$	4	28
CP3	cyclo-(Gly-Gly-D-Ala-D-Ala-Gly-Gly)	$P2_12_12_1$	4	29
CP4	cyclo-(Gly-Pro-Gly-Gly-Pro-Gly)	$P2_1$	2	30
CP5	cyclo-(Gly-Pro-Gly-D-Ala-Pro)	$P2_12_12_1$	4	31
CP6	cyclo-(Cys-Gly-Pro-Phe)$_2$	$P2_1$	2	32

optimal interaction energies in both cases are also in good agreement with the reported values, (Table VIII).

Formate Ion-Water Complex

Ab initio calculations have been reported previously for the formate ion-water complex by several groups.[17,18] The conclusion in each case was that the bifurcated form is the most stable. The fully optimized 6-31G* calculation yielded an interaction energy of 21.8 kcal/mol, and a C··O distance of 3.23 Å.[19] The corresponding MM3 values for the complex are 19.6 kcal/mol and 3.13 Å (Table IX).

Ammonium Ion-Water Complex

The interaction energy and optimal N··O distance for the ammonium ion-water complex are 15.6 kcal/mol and 2.76 Å (Table IX) from MM3. The energy is about 20% lower than the ab initio value.[19] We found that there are two negative eigenvalues in our normal mode calculation, which means that the complex (Fig. 1(b)) on the MM3 potential surface is on a hilltop, not a stable conformation.

Table XIII. The root-mean-square errors for cyclic peptides.[a]

	CP1[b]	CP2[b]	CP3	CP4	CP5	CP6
x	0.096	0.089	0.113	0.151	0.084	0.088
l	0.006	0.006	0.012	0.011	0.013	0.017
θ	0.79	0.91	0.75	1.33	1.15	1.01
opb	0.38	0.52	0.53	0.78	0.85	0.69
τ	4.4	4.4	6.0	6.5	4.8	3.2

[a]The symbols represent total rms motion of the parameter from the X-ray structures (Å,°) where x is a nonhydrogen Cartesian coordinate, l is a backbone bond length, θ is a backbone bond angle, opb is an out-of-plane angle, and τ is the backbone torsion angle (phi, psi).

[b]These crystal structures were determined at liquid nitrogen temperature, the others were determined at room temperature and the experimental bond lengths were not corrected for rigid-body motion. Thus the .006 Å deviation for CP1 and CP2 is a good comparison of the calculated and experimental bond lengths. The other bond length discrepancies are largely due to the shortening of the apparent experimental bond lengths by the rigid body motion.

Guanidinium Ion-Water Complex

The optimal interaction energy and C··O distance from the MM3 results for the guanidinium ion-water complex are 14.4 kcal/mol and 3.46 Å (Table IX), whereas the 6-31G(d) values with the fixed water and guanidinium ion geometries are 18.2 kcal/mol and 3.41 Å.[20] If we spread out the charge distribution on guanidinium ion, the results can be improved, but this would make the force field more complicated and has not been done.

PEPTIDES

Dipeptides

The local energy minima of two dipeptides (GA and AA) were located by minimizing the energy starting from conformations in the low energy regions with a dielectric constant of 1.5. The results are summarized in Tables X and XI, in which the relative energies of the anti and gauche conformations are reported, along with the phi and psi values for the minima.

For both GA and AA, the MM3 calculated geometries are very close to the reported values. The relative energies of the two local minima show a scatter among the reported values, and the MM3 results are in these ranges. Figure 2 shows a plot of the conformational energy surface (with dielectric constant 4.0) of the dipeptides GA in the conventional ϕ, ψ map.

Cyclic Peptides

The structures for the six cyclic polypeptide crystals listed in Table XII (CP1-6) were calculated with the

Table XIV. RMS Nonhydrogen atomic shift for cyclic peptides (x in Å).

Peptide	Cell	AMBER/normal	AMBER/OPLS	MM3
CP1	exptl.	0.11	0.09	0.10
CP2	exptl.	0.22	0.14	0.09
CP3	exptl.	0.07	0.09	0.11
CP4	exptl.	0.31	0.23	0.15
CP5	exptl.	0.08	0.16	0.08
CP6	exptl.	—	—	0.09
av.[a]	exptl.	0.16	0.14	0.11

[a]The average is over all values except CP6.

Table XV. Intramolecular hydrogen bond lengths for cyclic peptides (Å).

Peptide	Residue C=O	H—N	Exptl.	MM3	AMBER	AMBER/OPLS
CP1	Gly-6	Gly-3	2.92	2.91	3.02	2.98
CP1	Gly-3	Gly-6	3.35	3.13	3.71	3.49
CP2	Gly-6	Gly-3	3.10	3.05	2.89	3.10
CP2	Gly-3	Gly-6	2.99	3.03	2.85	2.88
CP3	Gly-5	Gly-2	3.04	3.05	3.14	3.22
CP3	Gly-2	Gly-5	3.16	3.03	3.13	3.13
CP4	Gly-4	Gly-1	2.91	2.98	2.91	2.95
CP5	Gly-1	D-Ala-4	2.87	2.97	2.87	2.94
CP5	D-Ala-4	Gly-1	2.92	2.86	2.86	2.81

MM3 force field. In these calculations, the thickness of shell for the van der Waals and dipole-dipole (and/or charge-dipole) interactions are 6.0 Å and 4.5 Å, respectively. The averaged root-mean-square deviations from the X-ray structures of the six cyclic peptide crystals for the non-hydrogen atoms are calculated to be 0.10 Å for the atomic positions, and 0.011 Å, 1.0°, and 4.9° for bond lengths, bond angles, and torsional angles, respectively. The root-mean-square errors in atomic positions and the other parameters for each peptide are summarized in Table XIII.

The comparison of the calculated root-mean-square deviations of the nonhydrogen atomic coordinate shifts for the six cyclic peptides for MM3 and other calculations,[20] compared to experiment, are summarized in Tables XIV and XV. The results indicate that our calculation is competitive with the other calculations.

The studies of three cyclic hexapeptides (CP1, CP2,

and CP3) in the crystal lattice with a wide variety of force fields are summarized in Table XVI. From this table, it is seen that the accuracy of the MM3 force field is comparable to or better than other more specialized force fields by this test. The MM3 rms deviation of the backbone torsional angles and in coordinates is greater than those calculated by the AMBER united atom force field, according to the study of Hall and Pavitt,[33] but better than the others.

CRAMBIN

There are two sites of microheterogeneities found in Crambin. Residue 22 can be **Pro** or **Ser**, and residue 25 can be **Leu** or **Ile**. All four forms exist in the seed of *Crambe abyssinica* from which Crambin is isolated. The **Pro(22)-Ile(25)** is the most abundant form found in the crystal structure of Crambin, and it was

Table XVI. RMS differences between the observed and calculated models for the torsion angles, the atom positions, and the lengths of intra and intermolecular hydrogen bonding for CP1-3.[a]

Field[b]	x	ω	τ	opb	l (N..O) intra Mean	l (N..O) intra RMS	l (N..O) inter Mean	l (N..O) inter RMS
KOL2	9	2.3	3.7	2.4	−08	12	−01	03
MM3[d]	10	2.4	6.0	1.6	−06	11	+06	09
ECEP2	10	4.8	6.5	2.4	+03	08	+02	07
ECEP1	11	6.1	8.1	6.2	+01	08	+01	09
LEVB	16	4.3	7.7	6.6	+08	14	+08	13
TRIPOS (5.2)[c]	16	3.8	9.9	—	−05	09	—	—
LEVB-5	19	4.1	8.5	6.6	+10	16	+12	20
KOL1	23	4.6	10.8	2.2	+24	36	00	07
MM2[e]	23	3.1	12.1	—	−12	19	+09	11
LEVC	23	5.1	15.9	4.5	00	10	+03	19
RKR-S	24	4.7	13.3	2.7	−28	30	−16	25
LEVD	24	5.5	14.0	5.0	+09	33	+18	29
RKR-T	25	4.3	14.2	2.8	−28	30	−16	24
LEVO	26	5.1	18.2	16.7	−13	17	+19	31
GK	27	5.6	13.8	5.7	−13	17	−01	12
LEVA	28	5.0	16.4	4.6	−14	18	+24	42
CFF-S	30	8.9	17.9	3.4	+29	34	+06	15
CFF-T	30	9.0	19.6	3.7	+32	38	+08	18

[a] See Footnote [a] to Table XIII for definitions. Here, the values of x are in hundredths of an Å.
[b] The data (and symbols) here unless otherwise identified, are taken from reference 33.
[c] Reference 35.
[d] Present work.
[e] Reference 2.

Table XVII. The calculated root-mean-squares errors for crambin.[a]

RMS	Without crystal lattice				With crystal lattice		
	MM3	MM2	AMBER	TRIPOS	MM3	AMBER	AMBER/O
x	0.25	0.31	0.35	0.42	0.22	0.22	0.17
l	0.023	0.022	—	0.025	0.023	—	—
θ	2.01	2.22	—	2.97	1.98	—	—
opb	1.13	1.33	—	—	1.06	—	—
τ	8.7	12.8	—	13.4	6.4	—	—
Phi	10.3	15.1	17.0	17.3	8.2	7.2	6.1
Psi	12.1	18.1	16.0	15.5	8.1	7.9	5.6
Omega	4.5	5.5	—	4.2	3.4	4.1	4.6

[a]For definitions see Footnote [a], Table XIII.

used in this calculation. The crystal coordinates used in our calculations are from a refined low temperature structure ($R = 0.113$ at 130 K).[34] There are a total of six charged residues found in the Crambin; Thr(1), Arg(10), Arg(17), Glu(23), Asp(43), and Asn(46).

The MM3 minimized structure of Crambin was examined for the following information, and compared with the crystal structure. (1) rms atomic position shift; (2) rms deviation of bond length; (3) rms deviation of bond angle; (4) rms deviation of out-of-plane angle; (5) rms deviation of torsional angle; and
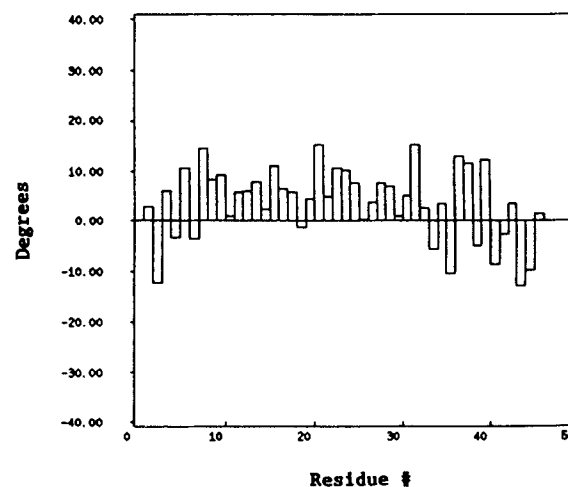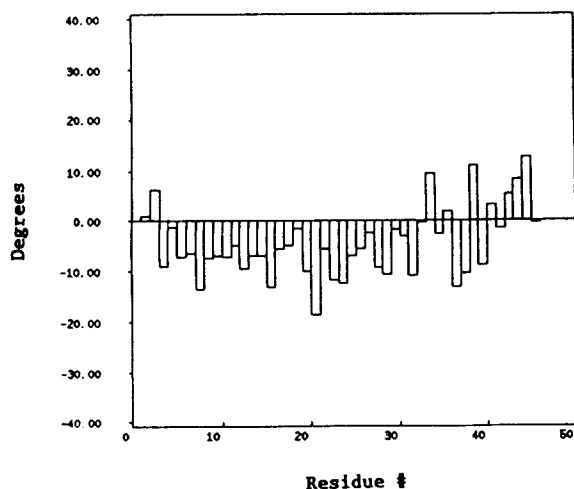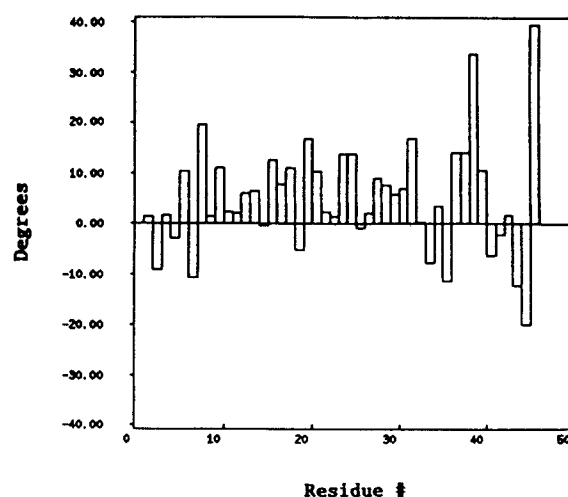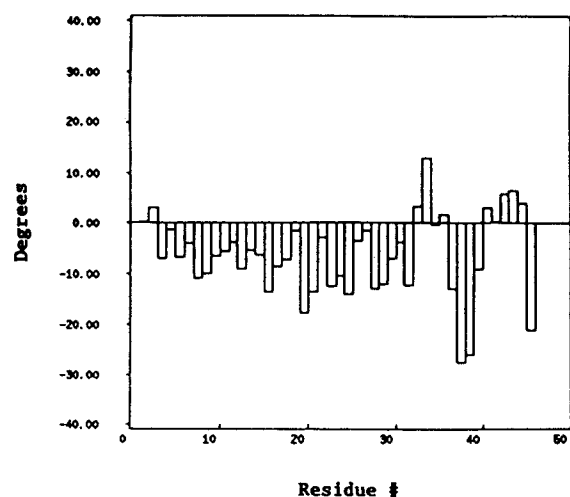
Figure 3(a). Deviation in Phi between the crystal structure and the minimized structure of Crambin for a constant dielectric of 4.0 by using MM3(90) force field: above— without crystal lattice, and below—with crystal lattice.
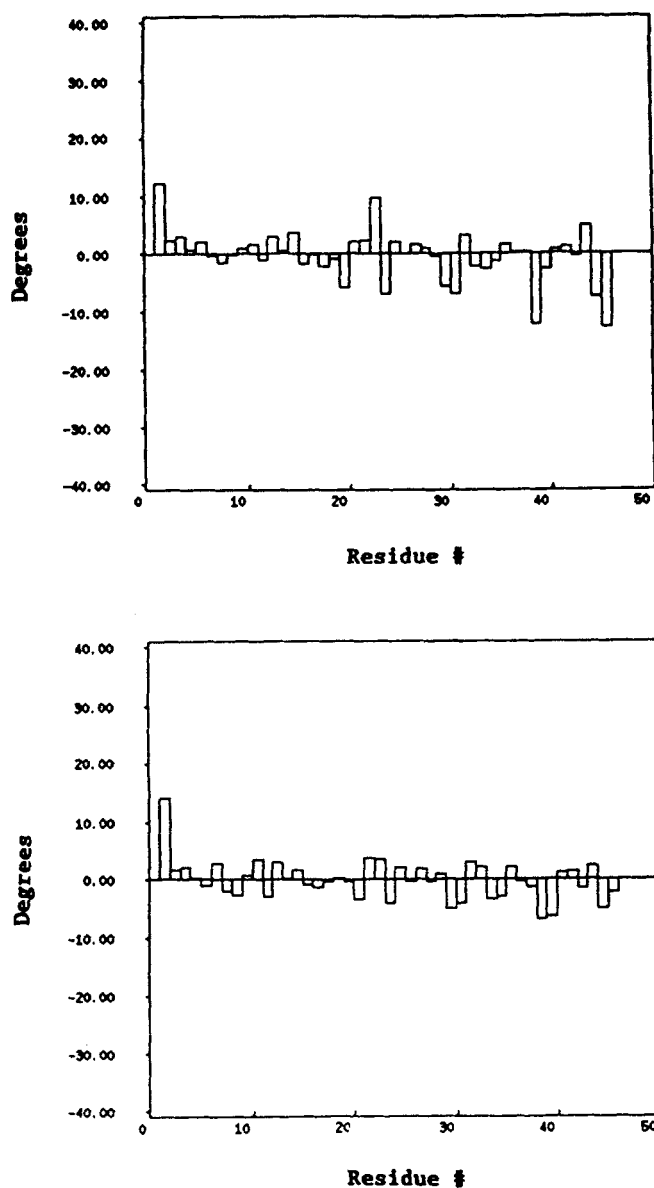
Figure 3(b). Deviation in Psi between the crystal structure and the minimized structure of Crambin for a constant dielectric of 4.0 by using MM3(90) force field: above— without crystal lattice, and below—with crystal lattice.

Figure 3(c). Deviation of Omega between the crystal structure and the minimized structure of Crambin for a constant dielectric of 4.0 by using MM3(90) force field: above—without crystal lattice, and below—with crystal lattice.

(6) rms deviations of backbone torsional angles phi, psi, and omega. The comparison of the calculated results for all nonhydrogen atoms with other calculations[20,35] is summarized in Table XVII. From Table XVII, one can see that the MM3 calculation (without the crystal lattice) gives better results than other comparable calculations. The distribution of the phi, psi, and omega deviations from the crystal structure are somewhat systematic as seen in Figures 3(a)–(c). The MM3 calculated values of phi are shifted to more negative values (without crystal lattice: rms 10.3, mean −6.4, extreme −27.4; with crystal lattice: rms 8.2, mean −4.4, extreme −18.7), whereas the psi values are shifted to more positive values (without crystal lattice: rms 12.1, mean 5.2, extreme 39.6; with crystal lattice: rms 8.1, mean 3.7,

extreme 15.5), and the omega values are about right on average (without crystal lattice: rms 4.5, mean −0.3, extreme 12.6; with crystal lattice: rms 3.4, mean 0.0, extreme 14.1).

CONCLUDING REMARKS

The MM3 force field for simple amides gives good results for either gas phase or crystal structures, and fair results for vibrational spectra. For peptides, and the protein Crambin, the structural results are better than those with MM2, and comparable with the better specialized protein force fields available today.

It is worth noting that the bond lengths of simple peptides are calculated with an rms value of 0.006

Å, compared with low temperature crystal data. For room temperature data on peptides, the discrepancies are larger, not because of calculational error, but because of the systematic apparent bond shortening due to thermal motion. For the protein calculations, the rms discrepancy is much larger, again, not because of calculational error, but because of experimental error. The MM3 bond lengths are believed to be good with a probable error of about 0.005 Å, in peptides, and for bond lengths in general. Because this accuracy is so much greater than can be obtained from crystallographic work on proteins, we suggest that it would be routinely advantageous to use these bond lengths as constraints in solving the crystallographic structures of proteins.

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3. The MM3 force field [MM3(89)] is similar in spirit to the MM2 force field (reference 1), but it differs from it in many details. The program is available from the Technical Utilization Corporation, Inc., 235 Glen Village Court, Powell, OH 43065, and from Molecular Design Limited. The details of the force field, and how they were arrived at, are given in the paper by N.L. Allinger, Y.H. Yuh, and J.-H. Lii, *J. Am. Chem. Soc.*, **111**, 8551 (1989), and the following articles.

4. The crystalline environment was provided by using translated images of the unit cell in all directions. The unit cell was surrounded by 124 images of itself. The effective surrounded atoms and bonds were then selected according to the desired van der Waals' and electrostatic interaction shells.

5. The reported X-ray Crambin crystal in the monoclinic space group P21 with $a = 40.76$, $b = 18.49$, $c = 22.34$, and beta $= 90.6°$. The values used in constructing the shell were: $a = 41.17$, $b = 18.67$, and $c = 22.56$, respectively. (Personal communication from M. Teeter.)

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