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Conformations of Proline

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Abstract: The present study concerns the energies of the conformations of proline. We present results of an improved molecular mechanics calculation for ring conformations of Ac-Pro-OCH_3 and for the *s*-cis and *s*-trans conformations. Internal coordinates including all torsions have been calculated from crystal coordinates for more than 40 x-ray determinations to give a consistent set of data which define proline ring geometries. Results from the present work and from the many previous studies on proline derivatives by other workers permit the following definitive statements: (1) Although four parameters are theoretically necessary to define the conformational state of a five-membered ring having fixed bond lengths, in practice two parameters ordinarily suffice for the proline ring. (2) There are two broad energy minima (Figures 1 and 2) with a barrier high enough to rule out pseudorotation, but affording such flexibility of structure as to preclude the meaningful designation as *envelope* and *chair* or *exo* and *endo*. The most common conformational state approximates a range of C^{β}–C^{γ} half chairs.[1] (3) There is as yet no really good method to get experimental measures of the conformational state of the proline ring in solution, although useful limits can often be established by treating NMR coupling constants by the Karplus relationships. (4) ^{13}C NMR is especially useful for studying *s*-cis–*s*-trans equilibria of *N*-acylproline derivatives. Ratios range from about 15 to 40% *s*-cis for open chain derivatives. (5) The difference of the torsions $\chi_5 - \phi$ is not a constant but ranges from 54 to 80°. This lack of constancy must be taken into account if proper conclusions are to be drawn from energy maps of proline-containing peptides.

The importance of proline and of hydroxyproline in structural proteins, in enzymes, and in hormones is too well known to require comment. Structural features have been extensively investigated by x-ray crystallography, by ^1H and ^{13}C NMR, by various theoretical calculations, and by other methods such as IR and CD.

One purpose of the present study is to bring together this extensive and scattered body of information so as to provide a definitive picture of the conformational properties of proline, particularly the energies of ring conformations and of *s*-cis and *s*-trans acyl groups. We have also performed new and sophisticated molecular mechanics calculations which lead to the energy profiles shown in Figures 1 and 2. Since previous calculations by other groups based on simplified force fields have given generally similar results, we conclude that the energy profiles are not very sensitive to the details of the force field and are therefore reasonably well defined. Although x-ray data are available for some three dozen proline rings, it is almost impossible to make a rational comparison of the x-ray data because some of it is incomplete and because every author uses a different numbering system. We have therefore recalculated all the internal coordinates of the proline skeletal atoms from crystal coordinates and present a unified and accurate tabular summary of the x-ray results. We have made a complete survey of NMR studies on proline derivatives and show in what respect these are relatable to the energy profiles.

How to Describe Conformations of Five-Membered Rings. The biggest problem we faced in this study was to devise a convenient method for describing the conformational state of a five-membered ring. Even assuming that all bond lengths remain constant, there remain four angles and torsions to be defined. Is it necessary to treat these independently, or is there some sound reason for supposing that, say, two would suffice? We were eventually able to show by molecular mechanics calculations that two parameters give an adequate definition for conformations having energies up to a few kilocalories above the minimum, but that more parameters are necessary to define conformations of high energy. We present our recommendations below.

The starting point for defining conformations of five-membered rings is cyclopentane, and the recommended conformational equations may be represented by the equation[2-7]

$$\chi_i = a_0 \cos [t + (i - 1)4\pi/5] \qquad i = 1, 2, 3, 4, 5 \quad (1)$$

In the earliest paper χ_i represented the vertical displacement of a given atom from the average plane.[2,7] But χ_i can also represent a torsion; or it can represent certain other geometrical properties such as bond angles.[4] Whatever the meaning of χ, t is the same quantity throughout, a phase angle that defines the distribution of puckering. The constant a_0 is a puckering amplitude which defines the maximum value assumed by χ and will necessarily depend on what quantity is being represented by χ. For $t = 0°, 36°, 72°, \ldots$, the ring conformation is of C_2 symmetry ("half chair"). For $t = 18, 54°, \ldots$, the conformation is of C_s symmetry ("envelope"). For cyclopentane the conformational energy is independent of t, and in consequence the two normal ring vibrations are degenerate. The result is denoted as pseudorotation.[2,3,7,8] As rings are made less flexible by substitution, the energy becomes dependent on t and

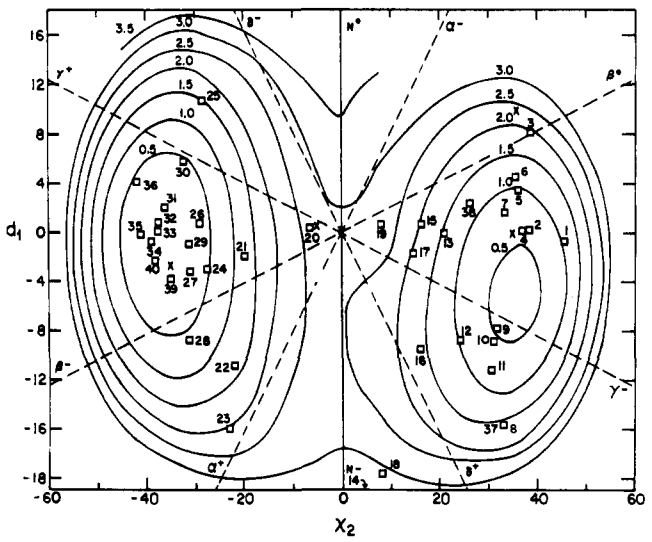


Figure 1. Energy contour plot for ring conformations of *s-trans*-Ac-Pro-OCH_3 defined by torsion χ_2 and d_1 (eq 2). ψ has whatever value that gives an overall minimum. Steric energies were computed by molecular mechanics. There are two regions of minimum energy. For both the innermost contour is 0.5 kcal/mol above the global minimum, which is located at $\chi_2 = -36$, $d_1 = -1$; the minimum at $\chi_2 = 36$, $d_1 = -5$ is 0.3 kcal/mol above the global minimum. Successive contours are at 1, 1.5, 2, 2.5, and 3 kcal. The region between the two 2.5-kcal contours includes the saddle point of the pass, whose minimum height is 2.7 kcal. The diagonal lines are loci of envelope forms with the indicated atom up (+) or down (−) with respect to the average plane. The carbethoxyl group is up. The numbered squares show conformations for proline rings studied by x-ray crystallography; the data are from Table I. The points x are the *s*-cis conformations reported in Table IV.

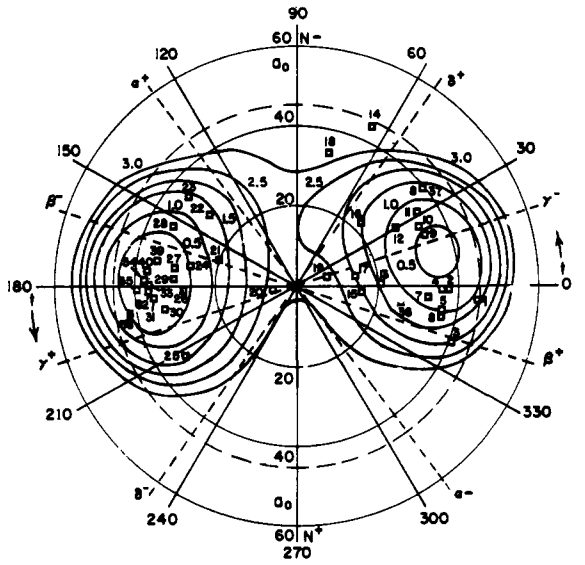


Figure 2. Polar plot of energy contours for *s-trans*-Ac-Pro-OCH_3. Conformations for proline are defined by $\chi_i = a_0 \cos [t + 4\pi(i-2)/5]$, eq 4. The puckering amplitude, a_0, is radial, the phase angle t, which defines the distribution of puckering, is angular. Energy definitions are the same as for Figure 1. The diagonals are the loci of envelope forms with the specified envelope atom up (+) or down (−) with respect to the average plane. These are at $t = 18°, 54°, 90°, \ldots$. The carbethoxyl group is up. The pseudorotation path for cyclopentane is the dotted circle at $a_0 = 45$; for cyclopentane all conformations represented by this circle have the minimum energy.

eventually one or two conformations have lowest energies; the term *pseudorotation* becomes less applicable and eventually unsuitable.[8] Incidentally, *parallel* treatments are applicable to rings of other sizes.[9,10]

There is no way both simple and rigorous to define the puckering geometry of a five-membered ring with lower symmetry than cyclopentane, but there are useful approximate definitions. Special aspects have been treated by Dunitz[11] and by Dunitz and Waser.[12,13] Altona and Sundaralingam[6] applied eq 1 empirically to some 60 furanoside rings of ribose and deoxyribose for which x-ray data are available. For treating proline polymers Venkatachalam et al.[14,15] define the puckering of the proline ring in terms of torsion angle χ_5 (= θ) and a bending parameter Γ. Symmetry is utilized better by using torsion χ_2 and bending angle τ, as is done in vibrational analysis of cyclopentanone and related compounds.[16] Vibrational analyses of ring puckering for five-membered rings have been reported by many workers.[17-23]

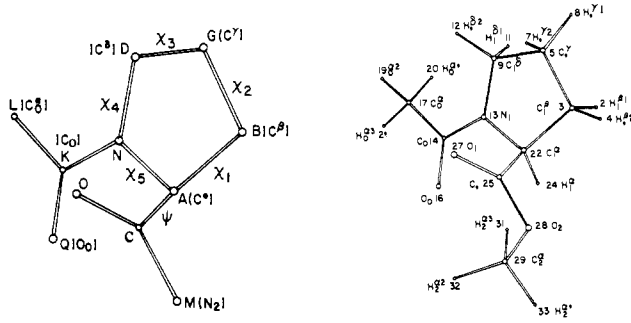
It is often convenient to relate all ring torsions to one "master" ring torsion as shown in eq 2. The relationships between eq 1 and 2 are summarized in eq 3, and for proline the appropriately indexed form of eq 1 is eq 4;

$$\begin{aligned} \chi_1 &= -0.809\chi_2 - d_1 \\ \chi_3 &= -0.809\chi_2 + d_1 \\ \chi_4 &= 0.309\chi_2 + d_2 \\ \chi_5 &= 0.309\chi_2 - d_2 \end{aligned} \qquad (2)$$

$$\begin{aligned} t &= \tan^{-1}[-d_1/\chi_2/\sin(4\pi/5)] \\ a_0 &= \chi_2/\cos t \\ d_1 &= -a_0 \sin(4\pi/5)\sin t \\ d_2 &= d_1 \sin(8\pi/5)/\sin(4\pi/5) \end{aligned} \qquad (3)$$

$$\chi_i = a_0 \cos[t + 4\pi(i-2)/5] \qquad (4)$$

the numerical constants in eq 2 are cosines of $4\pi/5$ and $8\pi/5$. Equations 2 provide an especially convenient way to get at a_0 and t. It takes only two torsions to calculate d_1 and χ_2 and hence all other torsions plus a_0 and t. If more than two torsions are available, it is simple to perform averaging to get "best" values. Maximum simplicity of the relationships of eq 2 depends on proper choice of the master torsion angle, namely χ_2. Equations 1, 2, and 4 are not exact; for most ranges of a_0 and t (or of χ_2 and d_1) the steric energy due to bond angle deformation, torsion strain, and van der Waals forces becomes a minimum in accordance with a geometry defined by these equations. At extremes of geometry (or of energy) there can be appreciable departures. In practice eq 2 or 4 correlates torsion values to within about ±2° and mostly within ±1° over ranges of conformations of usual interest. We note that eq 1 defined in terms of z_i, displacement of the ith atom from the average ring plane, requires that $\Sigma z_i = 0$ and that in terms of torsions, χ_i, eq 1 also predicts that $\Sigma\chi_i = 0$; that is, the sum of the torsions is zero. Such relationships do not hold for larger rings.[24]



Recalculation of X-Ray Data. The most definitive structural information for proline is based on the more than 20 x-ray studies of proline derivatives. However, we find that it is almost impossible to make effective use of the literature values because equivalent atoms are numbered differently in every paper and because many important internal coordinates are missing. We therefore have carried out a complete recalculation of all internal coordinates in a consistent way so as to present these valuable structural data in a readily usable form, Table I. In

Table I. Proline Bonds, Angles, Torsions, and Conformational Properties from Reported X-Ray Coordinates[a-d]

		C-A	A-B	B-G	G-D	D-N	A-N	C-D	C-M
1	ACPRLAC 1	1.486	1.649	1.536	1.485	1.486	1.474	1.243E	1.339E
2	TOSPRHYHR	1.501	1.535	1.552	1.484	1.471	1.473	1.204A	1.326A
3	OIHYDRPRO	1.530	1.536	1.517	1.517	1.532	1.498	1.238A	1.242A
4	ACTIN BP2	1.524	1.555	1.502	1.572	1.450	1.500	1.267	1.322
5	CY-PR-LEU	1.507	1.515	1.485	1.513	1.481	1.464	1.228	1.356
6	CY-PR-GLY	1.507	1.514	1.528	1.506	1.458	1.457	1.233	1.331
7	ACTIN P2	1.522	1.562	1.463	1.545	1.499	1.511	1.257	1.311
8	CUBLPR2 1	1.516	1.538	1.557	1.501	1.547	1.534	1.268*	1.239*
9	H-HYP-OH	1.530	1.526	1.520	1.523	1.487	1.498	1.244A	1.242A
10	ANTAM P8	1.525	1.568	1.518	1.513	1.531	1.462	1.217	1.314
11	TOSPRHY H	1.527	1.534	1.544	1.530	1.428	1.443	1.192A	1.413A
12	ANTAM P3	1.508	1.555	1.530	1.554	1.470	1.512	1.247	1.356
13	Z4BR-GPLG	1.487	1.549	1.415	1.490	1.459	1.456	1.217	1.365
14	CUBLPR2 2	1.510	1.514	1.575	1.547	1.524	1.557	1.268*	1.310*
15	BOPPPPBL4	1.533	1.561	1.416	1.461	1.511	1.466	1.216E	1.293E
16	LEUPRGL 2	1.518	1.496	1.506	1.479	1.458	1.451	1.235	1.313
17	BOPPPPBL1	1.525	1.551	1.490	1.538	1.472	1.486	1.203	1.375
18	CY-PPH 2	1.533	1.561	1.515	1.509	1.476	1.485	1.212	1.335
19	ANTAM P7	1.540	1.575	1.488	1.472	1.536	1.483	1.232	1.352
20	ANTAM P2	1.508	1.562	1.407	1.540	1.507	1.469	1.243	1.352
21	AO-PPP P2	1.510	1.537	1.489	1.435	1.471	1.455	1.245	1.332
22	CY-PPH P3	1.538	1.545	1.519	1.515	1.483	1.473	1.213	1.346
23	OL-PROHCL	1.520	1.543	1.508	1.504	1.516	1.473	1.239A	1.323A
24	AO-PPP P1	1.534	1.553	1.518	1.532	1.465	1.446	1.222	1.328
25	TOSPRHY P	1.498	1.551	1.559	1.556	1.493	1.501	1.247	1.332
26	BOPPPPBL3	1.568	1.470	1.464	1.521	1.498	1.439	1.236	1.314
27	BCPPPPBL2	1.513	1.596	1.516	1.517	1.463	1.423	1.227	1.296
28	CY-PPH 1	1.541	1.537	1.528	1.527	1.492	1.470	1.224	1.338
29	LEUPRGLY1	1.518	1.496	1.517	1.527	1.458	1.451	1.235	1.313
30	TOSPRHYPR	1.521	1.535	1.495	1.544	1.468	1.476	1.225	1.329
31	AC-PRO-MA	1.530	1.530	1.503	1.530	1.476	1.471	1.231	1.317
32	AO-PPP P3	1.531	1.525	1.515	1.523	1.481	1.456	1.182A	1.335A
33	ACTIN BP1	1.511	1.488	1.595	1.476	1.465	1.472	1.208	1.325
34	ACTIN P1	1.492	1.567	1.590	1.517	1.516	1.441	1.250	1.338
35	L-PRO-OH	1.527	1.522	1.538	1.532	1.484	1.527	1.275A	1.239A
36	ACPRLAC 2	1.486	1.401	1.501	1.603	1.486	1.474	1.243E	1.339E
37	TRIENPRCO	1.508	1.554	1.496	1.510	1.486	1.493	1.218*	1.293*
38	Z2BGPLGP1	1.571	1.622	1.536	1.538	1.460	1.502	1.216	1.371
39	BOCPRO-OH	2.090*	1.529	1.505	1.508	1.478	1.452	2.636*	1.175*
40	Z2BGPLGP2	1.509	1.544	1.457	1.581	1.548	1.464	1.279A	1.484A
	AVERAGE	1.520	1.540	1.510	1.519	1.487	1.476	1.231	1.335
	STD. DEV.	.019	.040	.042	.032	.028	.028	.016	.020
	D.F.	39	40	40	40	40	40	25	25

		N-K	K-Q	K-L	C-A-B	B-A-N	A-B-G	B-G-D	G-D-N
1	ACPRLAC 1	1.331	1.262	1.508	105.5	98.1	101.2	101.1	105.9
2	TOSPRHYHR	1.329	1.225	1.521	109.8	102.7	103.9	101.4	106.6
3	OIHYDRPRO	7.397*	0.000*	0.000*	116.5	103.7	102.3	105.0	105.3
4	ACTIN BP2	1.302	1.289	1.545	112.0	103.2	104.2	103.0	104.7
5	CY-PR-LEU	1.342	1.244	1.522	115.3	103.2	103.0	107.2	101.5
6	CY-PR-GLY	1.321	1.231	1.512	116.1	102.7	102.8	105.4	103.1
7	ACTIN P2	1.311	1.247	1.542	107.6	101.8	107.0	105.3	104.3
8	CUBLPR2 1	2.047*	1.870*	1.848*	113.2	106.7	103.1	105.9	100.7
9	H-HYP-OH	11.319*	0.000*	0.000*	111.5	105.0	106.3	103.0	104.9
10	ANTAM P8	1.352	1.232	1.540	111.1	104.0	104.3	107.6	100.8
11	TOSPRHY H	1.332	1.247	1.498	114.1	103.8	102.5	106.4	98.4
12	ANTAM P3	1.352	1.243	1.508	110.9	102.7	107.1	106.1	102.3
13	Z4BR-GPLG	1.371	1.261	1.505	114.7	101.4	108.3	109.0	103.5
14	CUBLPR2 2	2.068*	1.848*	1.870*	112.0	104.2	107.6	102.4	101.8
15	BOPPPPBL4	1.314	1.236	1.568	110.6	102.4	106.4	114.0	101.4
16	LEUPRGL 2	1.338	1.272	1.499	113.3	103.7	107.8	107.1	103.2
17	BOPPPPBL1	1.336Z	1.233Z	1.381Z	109.3	103.0	107.1	110.3	101.7
18	CY-PPH 2	1.338	1.224	1.541	111.5	103.4	105.7	107.4	103.2
19	ANTAM P7	1.324	1.195	1.558	106.9	102.6	106.8	113.5	101.7
20	ANTAM P2	1.316	1.240	1.548	109.3	104.8	106.2	114.7	100.0
21	AO-PPP P2	1.328	1.222	1.534	111.8	103.5	104.6	111.0	104.1
22	CY-PPH P3	1.335	1.212	1.533	110.1	103.2	104.7	108.0	104.6
23	DL-PROHCL	6.301*	0.000*	0.000*	113.0	106.8	100.8	109.3	106.0
24	AO-PPP P1	1.337Z	1.219Z	1.361Z	110.7	105.4	102.0	108.9	102.4
25	TOSPRHY P	1.598*	1.345*	1.776*	101.3	98.8	115.4	94.8	108.5
26	BOPPPPBL3	1.296	1.227	1.513	111.1	105.6	106.0	107.7	100.6
27	BCPPPPBL2	1.375	1.203	1.525	110.7	104.1	101.7	106.5	104.6
28	CY-PPH 1	1.346	1.213	1.538	111.7	102.6	104.5	104.9	105.1
29	LEUPRGLY1	1.339	1.272	1.499	113.3	103.7	105.8	104.1	103.6
30	TOSPRHYPR	1.647*	1.442*	1.777*	108.6	102.2	108.2	102.3	103.8
31	AC-PRO-MA	1.338	1.244	1.490	111.5	103.4	104.7	104.2	102.8
32	AC-PPP P3	1.332	1.245	1.510	111.1	104.1	103.5	103.9	102.9
33	ACTIN BP1	1.302	1.268	1.524	112.0	102.4	102.5	101.5	104.3
34	ACTIN P1	1.354	1.263	1.528	110.9	104.6	100.3	104.4	102.5
35	L-PRO-OH	3.238*	0.000*	0.000*	111.5	106.2	100.8	103.7	105.3
36	ACPRLAC 2	1.331	1.262	1.508	120.2	103.8	108.4	99.6	98.6
37	TRIENPRCO	1.980*	9.842*	9.842*	114.4	106.8	103.4	103.7	103.4
38	Z2BGPLGP1	1.383	1.262	1.469	105.9	102.9	103.2	107.9	105.3
39	BOCPRO-OH	1.346Z	1.230Z	1.339Z	74.1*	102.0	104.1	105.8	102.5
40	Z2BGPLGP2	1.320	1.271	1.525	110.5	102.5	104.5	108.0	97.7
	AVERAGE	1.332	1.243	1.522	111.3	103.5	104.8	105.9	103.1
	STD. DEV.	.019	.023	.022	3.3	1.8	2.8	3.9	2.3
	D.F.	28	28	28	39	40	40	40	40

Table 1 (*continued*)

		O-N-A	M-C-O	A-C-O	A-C-M	A-N-K	O-N-K	N-K-Q	N-K-L
1	ACPRLAC 1	112.2	121.4E	121.6E	117.0E	120.7	125.9	121.0	117.6
2	TOSPRHYHR	110.5	119.9A	122.2A	117.8A	119.9	129.6	121.1	115.7
3	OIHYORPRO	107.3	126.2A	115.3A	118.4A	17.3*	111.0*	90.0*	90.0*
4	ACTIN BP2	111.3	122.6	117.1	120.2	125.7	120.7	120.9	121.0
5	CY-PR-LEU	112.5	123.2	122.8	114.0	123.5	124.0	122.1	113.9
6	CY-PP-GLY	113.2	124.2	122.5	113.2	122.2	124.0	123.4	113.9
7	ACTIN P2	111.1	122.3	119.3	118.3	124.8	121.6	119.6	120.4
8	CUBLPR2 1	106.2	123.5*	115.3*	121.1*	106. *	115.6*	93.4*	95.8*
9	H-HYP-OH	109.1	125.6A	117.6A	116.6A	82.5*	39.3*	90.0*	90.0*
10	ANTAM P8	112.9	124.4	122.2	113.0	126.4	120.6	124.3	115.1
11	TOSPRHY H	116.3	124.7A	123.2A	112.1A	115.1	125.0	113.3	111.2
12	ANTAM P3	113.9	121.0	125.4	113.6	125.1	120.9	120.0	118.9
13	Z4BR-GPLG	113.6	122.0	122.0	116.0	121.6	123.9	119.7	118.5
14	CUBLPR2 2	103.3	121.7*	114.6*	122.7*	104.3*	114.5*	95.8*	85.6*
15	BOPPPPBL4	113.5	123.7E	122.5E	113.8E	118.6	127.9	122.2	116.2
16	LEUPRGL 2	113.3	123.2	121.4	115.3	120.6	126.1	122.5	118.5
17	BOPPPPBL1	115.3	121.9	120.7	117.1	123.6Z	120.3Z	124.3Z	109.9Z
18	CY-PPH 2	108.3	120.9	120.6	118.5	127.5	121.6	121.3	118.2
19	ANTAM P7	114.9	124.3	120.5	115.1	118.4	126.6	120.3	117.9
20	ANTAM P2	113.9	120.0	121.1	118.9	120.8	125.0	118.6	123.1
21	AC-PPP P2	113.1	121.5	120.5	118.0	118.4	128.3	120.3	118.2
22	CY-PPH P3	111.6	120.7	121.6	117.7	128.7	119.4	120.9	118.5
23	OL-PROHCL	104.6	124.4A	122.6A	112.9A	144.5*	45.0*	90.0*	90.0*
24	AO-PPP P1	113.8	120.3	121.5	118.2	123.5Z	120.9Z	124.9Z	109.7Z
25	TOSPRHY P	111.1	113.3	133.5	111.2	116.0*	120.9*	118.8*	109.8*
26	BOPPPPBL3	112.4	122.2	121.5	116.2	121.9	125.5	120.0	118.6
27	BOPPPPBL2	113.2	120.0	121.4	118.6	119.3	127.0	121.9	117.1
28	CY-PPH 1	111.1	121.3	120.4	118.2	129.3	118.3	120.7	117.7
29	LEUPRGLY1	113.3	123.2	121.4	115.3	120.6	126.1	122.5	118.5
30	TOSPRHYPR	112.5	121.1	123.2	115.7	117.2*	121.3*	104.3*	108.8*
31	AC-PRO-MA	112.2	124.4	117.7	117.9	121.4	125.5	120.1	117.0
32	AO-PPP P3	111.8	124.3A	124.9A	110.7A	121.1	127.1	121.5	118.0
33	ACTIN BP1	112.3	122.2	120.0	117.8	124.1	121.7	120.9	121.4
34	ACTIN P1	112.8	121.4	120.5	118.1	125.5	119.4	121.7	118.7
35	L-PRO-OH	107.1	119.4A	119.0A	121.5A	86.1*	119.1*	90.0*	90.0*
36	ACPRLAC 2	112.2	121.4E	121.6E	117.0E	120.7	125.9	121.0	117.6
37	TRIENPRCO	105.2	123.0*	121.6*	115.4*	107.6*	125.3*	79.9*	79.9*
38	Z2BGPLGP1	113.7	125.3	119.1	115.6	119.5	125.7	119.5	117.7
39	BOCPRO-OH	113.6	57.0*	59.7*	87.2*	124.9Z	121.2Z	124.1Z	110.5Z
40	Z2BGPLGP2	114.0	65.1A	110.9A	172.3A	124.8	121.0	119.4	118.6
	AVERAGE	111.6	121.9	121.5	116.5	122.4	124.1	120.7	117.8
	STD. DEV.	3.0	2.3	3.0	2.2	3.4	3.0	1.9	2.4
	D.F.	40	25	25	25	28	28	28	28

		L-K-Q	C-A-N	N-A-B-G	A-B-G-O	B-G-D-N	G-O-N-A	O-N-A-B	B-A-C-O
1	ACPRLAC 1	121.4	115.2	-38.8	45.8	-35.3	9.8	18.2	-94.1E
2	TOSPRHYHR	123.2	109.7	-31.4	38.6	-30.9	12.0	12.6	68.0A
3	OIHYDRPRO	90.0*	112.8	-39.1	38.5	-23.1	-1.6	25.3	131.1A
4	ACTIN BP2	117.9	112.5	-30.5	37.0	-30.1	11.1	11.5	73.0
5	CY-PR-LEU	124.0	110.9	-31.6	36.0	-25.1	4.4	17.0	-28.1
6	CY-PR-GLY	122.8	111.1	-32.4	35.6	-24.0	3.2	16.9	-25.4
7	ACTIN P2	119.9	112.6	-28.2	33.3	-24.8	6.9	12.2	77.9
8	CUBLPR2 1	175.6*	107.3	-10.3	33.2	-41.9	34.9	-15.1	71.2*
9	H-HYP-OH	90.0*	110.7	-18.3	32.0	-33.5	23.1	-3.0	113.4A
10	ANTAM P8	120.5	108.4	-15.4	31.3	-33.0	23.7	-5.4	73.8
11	TOSPRHY H	133.5	117.8	-13.5	30.8	-34.9	28.0	-9.7	78.7A
12	ANTAM P3	121.1	106.9	-11.0	24.6	-27.9	22.2	-7.5	68.7
13	Z4BR-GPLG	121.7	116.7	-16.2	20.9	-16.6	5.9	5.8	-93.0
14	CUBLPR2 2	175.6*	104.3	8.4	19.0	-39.4	45.6	-33.5	82.2*
15	BOPPPPBL4	121.5	113.9	-13.0	16.3	-12.0	2.6	6.2	-100.9E
16	LEUPRGL 2	118.9	111.2	-3.4	16.1	-21.8	21.0	-11.1	94.4
17	BOPPPPBL1	125.8Z	111.4	-9.8	14.7	-13.2	6.9	1.5	80.2
18	CY-PPH 2	120.4	108.6	13.0	8.0	-26.1	35.6	-30.4	25.3
19	ANTAM P7	121.7	110.1	-5.3	8.0	-6.8	3.1	1.3	82.1
20	ANTAM P2	117.9	112.0	4.7	-6.5	5.5	-2.1	-1.4	85.0
21	AC-PPP P2	121.5	110.3	17.0	-19.7	13.6	-1.9	-9.7	72.8
22	CY-PPH P3	120.6	109.5	27.8	-21.8	7.0	11.6	-24.9	29.2
23	OL-PROHCL	90.0*	111.3	35.0	-23.1	3.8	18.4	-33.7	-131.1A
24	AO-PPP P1	125.3Z	111.3	24.8	-27.5	19.4	-2.7	-14.3	89.1
25	TOSPRHY P	105.7*	109.5	13.7	-28.6	32.4	-28.9	9.2	98.6
26	BOPPPPBL3	121.4	109.6	21.9	-28.9	23.3	-9.7	-7.2	85.7
27	BOPPPPBL2	120.7	110.1	28.2	-31.0	22.8	-3.9	-15.4	99.6
28	CY-PPH 1	121.6	108.4	33.7	-31.4	16.6	5.0	-24.2	18.5
29	LEUPRGLY1	118.9	111.2	26.1	-31.4	23.8	-8.2	-11.1	94.4
30	TOSPRHYPR	106.3*	111.4	20.6	-32.4	31.2	-20.0	.3	87.2
31	AC-PRO-MA	122.9	114.3	27.0	-36.2	30.7	-14.2	-7.7	-78.0
32	AO-PPP P3	120.5	109.9	29.3	-37.5	30.8	-12.8	-10.3	97.3A
33	ACTIN BP1	117.7	113.2	33.8	-41.6	31.6	-11.7	-15.3	84.2
34	ACTIN P1	119.6	113.3	31.9	-39.1	30.9	-10.8	-14.3	85.4
35	L-PRO-OH	90.0*	106.4	33.6	-41.0	33.6	-12.4	-13.7	108.6A
36	ACPRLAC 2	121.4	115.2	29.7	-42.2	35.6	-20.8	-3.9	-75.7E
37	TRIENPRCO	0.0*	110.2	-11.3	32.6	-42.7	35.2	-14.8	-40.1*
38	Z2BGPLGP1	122.8	113.2	-23.4	26.6	-19.5	3.5	12.7	-92.2
39	BOCPRO-OH	125.3Z	153.7*	31.1	-35.0	24.0	-4.0	-17.0	122.8*
40	Z2BGPLGP2	122.0	110.2	31.6	-37.9	27.2	-6.6	-14.6	-88.2A
	AVERAGE	121.4	111.1	3.5	-.3	-3.0	5.0	-5.4	47.5
	STD. DEV.	2.9	2.7	24.9	31.3	27.2	17.1	14.7	61.9
	D.F.	28	39	40	40	40	40	40	25

Table I (*continued*)

		B-A-C-M	N-A-C-O	N-A-C-M	K-N-A-C	K-N-A-B	K-N-O-G	C-A-B-G	C-A-N-O
1	ACPRLAC 1	84.1E	158.9E	-22.9E	-62.0	-173.4	-157.9	-157.9	129.6
2	TOSPRHYHR	-109.2A	-44.1A	138.7A	-50.5	-167.2	-168.1	-148.0	129.4
3	DIHYORPRO	-51.4A	11.3A	-171.2A	-102.7*	130.4*	-19.5*	-163.7	152.2
4	ACTIN BP2	-103.2	-42.7	141.1	-64.9	174.3	-152.6	-151.7	132.4
5	CY-PR-LEU	150.4	-144.8	33.7	-41.6	-165.6	-172.9	-152.6	141.0
6	CY-PR-GLY	155.5	-142.2	38.7	-44.3	-169.0	-168.8	-153.8	143.6
7	ACTIN P2	-100.3	-33.5	148.4	-71.0	174.1	-155.7	-146.8	127.2
8	CUBLPR2 1	-106.1*	-171.2*	11.4*	-12.9*	108.6*	-83.3*	107.6	-136.8
9	H-HYP-OH	-64.7A	-3.2A	178.7A	146.8*	26.3*	-27.0*	-138.3	117.5
10	ANTAM P8	-99.1	-39.9	147.2	-70.9	170.8	-152.7	-131.8	112.9
11	TOSPRHY H	-101.4A	-43.5A	136.4A	-42.2	-169.5	-174.4	-143.1	117.6
12	ANTAM P3	-110.0	-42.6	138.8	-67.5	175.7	-160.9	-124.9	109.3
13	Z4BR-GPLG	85.0	148.6	-33.4	-57.6	177.1	-165.1	-142.9	131.1
14	CUBLPR2 2	-86.6*	-165.7*	25.5*	-31.0*	86.5*	-67.2*	120.6	-151.0
15	BOPPPPBL4	76.0E	144.5E	-38.7E	-57.0	-176.4	-174.4	-134.7	125.6
16	LEUPRGL 2	-81.7	-22.0	161.9	-68.2	169.7	-159.9	-124.1	111.0
17	BOPPPPBL1	-94.8	-33.0	152.0	-67.4Z	175.5Z	-167.2Z	-128.4	118.6
18	CY-PPH 2	-155.0	-88.0	91.7	-110.2	131.2	-127.4	-103.5	88.1
19	ANTAM P7	-100.3	-28.5	149.0	-69.6	176.9	-172.0	-121.1	114.8
20	ANTAM P2	-93.9	-30.7	150.4	-69.4	172.1	-175.3	-115.6	117.0
21	AO-PPP P2	-106.6	-41.8	138.9	-66.0	174.3	173.6	-101.7	110.0
22	CY-PPH P3	-150.4	-83.7	96.8	-94.8	148.0	-162.0	-89.1	92.4
23	OL-PROHCL	47.4A	-10.9A	167.8A	175.8*	-60.4*	176.7*	157.8	-157.5
24	AO-PPP P1	-88.1	-27.6	155.1	-59.0Z	-179.0Z	162.4Z	-95.6	105.7
25	TOSPRHY P	-99.3	-5.1	157.0	-102.1*	152.5*	-170.1*	-98.4	114.6
26	BOPPPPBL3	-91.4	-30.6	152.2	-62.2	178.1	164.8	-96.8	112.6
27	BOPPPPBL2	-80.8	-15.0	164.6	-69.9	171.4	168.6	-90.1	103.3
28	CY-PPH 1	-164.2	-93.9	83.5	-99.5	142.3	-163.1	-82.2	94.1
29	LEUPRGLY1	-81.7	-22.0	161.9	-68.2	169.7	170.9	-94.7	111.0
30	TOSPRHYPR	-91.0	-24.6	157.2	-96.2*	148.0*	-166.1*	-97.2	116.1
31	AC-PRO-MA	101.0	165.2	-15.9	-76.3	162.3	176.3	-96.3	113.7
32	AO-PPP P3	-79.2A	-17.4A	166.1A	-73.2	167.7	169.3	-89.0	108.8
33	ACTIN BP1	-94.8	-31.0	150.0	-89.6	149.6	-177.0	-87.9	105.5
34	ACTIN P1	-91.7	-31.9	151.0	-91.1	148.1	-174.3	-90.5	106.6
35	L-PRO-OH	-74.6A	-6.9A	170.0A	-14.0*	-133.0*	82.7*	-82.0	105.3
36	ACPRLAC 2	102.5E	158.9E	-22.9E	-62.0	164.5	171.6	-100.8	129.6
37	TRIENPRCO	141.6*	-160.5*	21.2*	-25.6*	-150.4*	160.3*	-133.5	110.0
38	Z2BGPLGP1	85.4	155.8	-26.7	-65.0	-178.8	-164.2	-142.5	126.6
39	BOCPRO-OH	175.7*	38.0*	90.8*	-113.3*	168.4Z	170.8Z	-122.1*	61.2*
40	Z2BGPLGP2	-31.0A	159.2A	-143.6A	-72.2	170.2	168.8	-85.8	103.0
	AVERAGE	-60.0	-23.4	113.8	-69.2	81.0	-68.4	-98.7	96.0
	STD. DEV.	93.2	76.7	63.6	16.3	148.9	154.2	71.2	72.8
	O.F.	25	25	25	28	28	28	39	39

		L-K-N-A	L-K-N-O	Q-K-N-A	Q-K-N-D	B-ADN	G-ADN	C-ADN
1	ACPRLAC 1	-171.7	-5.0	9.3	176.0	.511	-.242	1.036
2	TOSPRHYHR	175.5	-4.3	-2.7	177.4	.328R	-.296R	1.092R
3	DIHYORPRO	90.0*	90.0*	90.0*	90.0*	.637	.041	.658
4	ACTIN BP2	12.7	174.0	-170.8	-9.6	.303	-.292	1.040
5	CY-PR-LEU	6.2	-176.7	-173.3	3.7	.432R	-.114R	.886R
6	CY-PR-GLY	7.3	178.6	-172.6	-1.3	.472R	-.082R	.834R
7	ACTIN P2	12.7	172.8	-168.5	-8.4	.324	-.180	1.120
8	CUBLPR2 1	10.1*	128.1*	-165.5*	-47.6*	.384R	.845R	.991R
9	H-HYP-OH	90.0*	90.0*	90.0*	90.0*	-.078	-.577	1.269
10	ANTAM P8	-3.7	172.2	173.8	-10.3	-.143R	-.598R	1.333R
11	TOSPRHY H	170.6	12.8	-23.4	178.8	-.251R	-.711R	1.197R
12	ANTAM P3	-11.5	171.9	169.6	-6.9	-.199R	-.574R	1.362R
13	Z4BR-GPLG	-174.4	-4.0	8.7	179.1	.153	-.149	1.001
14	CUBLPR2 2	26.3*	138.5*	-149.5*	-37.3*	.809	1.081	.709
15	BOPPPPBL4	179.3	-3.3	2.6	179.6	.165	-.066	1.139
16	LEUPRGL 2	175.2	-3.8	-.6	-179.6	-.280	-.515	1.321
17	BOPPPPBL1	-1.0Z	172.6Z	-177.6Z	-4.0Z	.041R	-.181R	1.246R
18	CY-PPH 2	19.2	178.7	-163.4	-3.9	-.769	-.855	1.451
19	ANTAM P7	-177.0	-2.0	-.4	174.7	.036	-.079	1.313
20	ANTAM P2	177.3	-9.9	4.4	177.2	-.038	.055	1.245
21	AO-PPP P2	171.9	-3.4	-5.4	179.3	-.252	.047	1.331
22	CY-PPH P3	.4	172.8	-179.9	-7.5	-.633R	-.296R	1.449R
23	OL-PROHCL	90.0*	90.0*	90.0*	90.0*	.819	.456	.543
24	AO-PPP P1	-19.5Z	-174.1Z	172.6Z	8.9Z	-.369R	.071R	1.376R
25	TOSPRHY P	-76.3*	63.1*	161.9*	-58.6*	.245	.714	1.283
26	BOPPPPBL3	176.3	2.3	-4.0	-178.1	-.177	.252	1.364
27	BOPPPPBL2	168.6	-3.5	-6.3	-178.4	-.412	.100	1.383
28	CY-PPH 1	1.4	167.0	-178.2	-12.6	-.614R	-.128R	1.458R
29	LEUPRGLY1	175.2	-3.8	-.6	-179.6	-.280	.212	1.321
30	TOSPRHYPR	-77.7*	66.9*	169.2*	-46.2*	.008	.512	1.272
31	AC-PRO-MA	-177.0	-8.4	4.3	172.9	-.198R	.366R	1.276R
32	AO-PPP P3	-179.0	-1.3	1.7	179.4	-.263	.330	1.363
33	ACTIN BP1	18.0	-178.4	-162.6	.9	-.384	.289	1.338
34	ACTIN P1	20.3	-178.4	-162.6	-1.3	-.374	.277	1.313
35	L-PRO-OH	90.0*	90.0*	90.0*	90.0*	-.346R	.317R	1.413R
36	ACPRLAC 2	-171.7	-5.0	9.3	176.0	-.092	.562	1.036
37	TRIENPRCO	101.9*	-22.2*	101.6*	-22.2*	-.381R	-.846R	1.330R
38	Z2BGPLGP1	-168.7	-1.7	12.7	179.6	.348	-.089	1.160
39	BOCPRO-OH	-5.6Z	-179.8Z	174.9Z	.7Z	-.438R	.103R	.812R
40	Z2BGPLGP2	177.8	2.9	-3.1	-178.0	-.380	.179	1.380
	AVERAGE	21.9	29.0	-42.2	42.1	.023	.082	1.175
	STD. DEV.	137.9	107.6	100.2	134.5	.405	.422	.239
	O.F.	28	28	28	28	25	25	25

Table I (*continued*)

		K-NAC	B-NAC	G-NAC	D-NAC	GAMMA	D1	A0	T
1	ACPRLAC 1	-1.01	1.52	1.60	1.06	41.69	2.18	45.93	-4.64
2	TOSPRHYHR	.89	-1.34	-1.56	-1.06	35.28	.22	38.56	-.55
3	OIHYORPRO	-?.14	1.19	1.10	.68	31.66	8.16	40.90	-19.84
4	ACTIN BP2	-.96	1.30	1.47	1.00	34.30	.19	37.03	-.49
5	CY-PR-LEU	.74	-1.22	-1.30	-.86	31.84	3.57	36.48	-9.58
6	CY-PR-GLY	.78	-1.21	-1.26	-.79	31.02	4.53	36.43	-12.20
7	ACTIN P2	-1.02	1.39	1.72	1.12	29.63	1.69	33.46	-4.92
8	CUBLPR2 1	.44	1.25	2.05	1.02	-38.79	-15.65	42.54	38.75
9	H-HYP-OH	-5.14	-1.27	-1.70	-1.25	33.07	-7.84	34.71	22.61
10	ANTAM P8	-1.03	1.34	1.78	1.30	33.29	-8.88	34.74	25.78
11	TOSPRHY H	.81	-1.19	-1.51	-1.14	34.58	-11.16	36.16	31.68
12	ANTAM P3	-1.02	1.35	1.90	1.27	26.81	-8.82	28.79	31.43
13	Z4BR-GPLG	-.99	1.24	1.59	1.00	19.44	-.12	20.91	.56
14	CUBLPR2 2	1.04	1.30	1.93	.72	-30.11	-24.17	45.31	65.17
15	BOPPPPBL4	-.97	1.33	1.77	1.13	14.99	.82	16.40	-4.85
16	LEUPRGL 2	-1.07	1.23	1.65	1.25	19.33	-9.54	22.89	45.17
17	BOPPPPBL1	-1.03	1.35	1.90	1.16	14.77	-1.67	15.02	10.94
18	CY-PPH 2	1.00	-1.33	-2.13	-1.40	17.41	-19.98	34.93	76.73
19	ANTAM P7	-1.09	1.41	2.03	1.26	7.81	-.66	8.08	7.97
20	ANTAM P2	-1.06	1.33	2.02	1.23	-9.19	.29	6.55	184.33
21	AO-PPP P2	-1.07	1.30	2.10	1.27	-17.14	-2.04	19.36	169.97
22	CY-PPH P3	-1.04	1.34	2.25	1.38	-15.02	-10.83	28.55	139.80
23	DL-PROHCL	-.27	1.23	1.27	.56	14.25	-15.86	35.49	170.51
24	AO-PPP P1	-.96	1.30	2.18	1.29	-24.68	-3.13	28.00	169.04
25	TOSPRHY P	1.40	-1.48	-2.41	-1.27	-29.34	10.59	33.84	212.14
26	BOPPPPBL3	-.97	1.23	2.13	1.28	-27.35	.72	28.94	182.44
27	BOPPPPBL2	-1.13	1.36	2.23	1.31	-28.17	-3.12	31.47	170.29
28	CY-PPH 1	-1.03	1.32	2.28	1.39	-24.79	-8.77	34.74	154.56
29	LEUPRGLY1	-1.07	1.23	2.18	1.25	-28.41	-1.00	31.43	176.69
30	TOSPRHYPR	1.46	-1.35	-2.23	-1.22	-32.17	5.77	33.87	196.84
31	AC-PRO-MA	1.11	-1.27	-2.19	-1.25	-34.36	1.95	36.33	185.23
32	AO-PPP P3	-1.09	1.29	2.22	1.30	-35.25	.78	37.54	182.03
33	ACTIN PP1	1.08	-1.25	-2.22	-1.31	-37.73	-1.12	41.66	177.38
34	ACTIN P1	1.10	-1.30	-2.25	-1.34	-36.74	-.81	39.13	177.98
35	L-PRO-OH	-.78	1.28	2.23	1.37	-38.34	-.19	40.96	179.54
36	ACPRLAC 2	-1.01	.99	2.02	1.06	-40.70	4.08	42.76	189.34
37	TRIENPRCO	.82	-1.22	-1.67	-1.35	38.34	-15.59	42.01	39.14
38	Z2BGGLGP1	-1.05	1.45	1.80	1.07	23.86	2.41	26.90	-8.78
39	BOCPRO-OH	-1.01	1.46	1.92	1.19	-30.59	-3.78	35.58	169.58
40	Z2BGPLGP2	-1.03	1.33	2.22	1.38	-34.87	-2.34	38.07	173.99

[a] Column headers (see also the figures): C (C_1), A ($C_1\alpha$), B ($C_1\beta$), G ($C_1\gamma$), D ($C_1\delta$), N (N_1), O (O_1), M (N_2), K (C_0), Q (O_0), L ($C_0\alpha$), where subscript 1 designates proline, 0 designates preceding acyl residue, and 2 designates succeeding residue. Bonds are denoted by C–A (C_1–$C_1\alpha$), angles by C–A–B (C_1–$C_1\alpha$–$C_1\beta$), torsions by N–A–B–G (N_1–$C_1\alpha$–$C_1\beta$–$C_1\gamma$); B–ADN signifies distance from $C_1\beta$ to plane ADN ($C_1\alpha$–$C_1\delta$–N_1) and R means that origin and C (C_1) are on same side of the plane; for GAMMA, D_1, A_0, and T see footnotes *b* and *c*. Symbols for compounds:[1] ACPRLAC, Ac-Pro-Lactyl-$NHCH_3$ (1 for "exo" Cγ, 2 for "endo" Cγ), C. Lecomte et al.;[27] AC-PRO-MA, Ac-Pro-$NHCH_3$, Matsuzaki and Iitaka;[28] ACTIN, actinomycin, bis peptide sequences (L-Thr-D-Val-L-Pro-Sar-L-MeVal lactone), P1 and P2 are two prolines, B indicates crystal data from the 7-Br derivative, Jain and Sobell;[29] ANTAM PJ, sodium complex of antamanide analogue, c(Val-Pro-Pro-Phe-Phe-Val-Pro-Pro-Phe-Phe), where J is number of Pro residue, Karle;[30] AO-PPP, amyloxycarbonyl-L-Pro-L-Pro-L-Pro-OH, 1,2,3-Pro unit counting from amino end, G. Kartha et al.;[31] BOPPPPBL, Boc-L-Pro-L-Pro-L-Pro-L-Pro-OBzl, 1,2,3,4-Pro unit counting from amino end, Matsuzaki;[32a] BOCPRO-OH, *t*-Boc-Pro-OH, coordinates reported for C, the carboxyl carbon, are in error, Benedetti et al.;[32b] CUBLPR, bis(*N*-benzyl-L-prolinato)copper(2+), Aleksandrov et al.;[33] CY-PPH, c(L-Pro-L-Pro-L-Hyp) (1 is Pro, 2 is Pro or Hyp, 3 is Hyp), Kartha and Ambady;[34] CY-PR-GLY, c(L-Pro-L-Gly), Von Dreele;[35] CY-PR-LEU, c(L-Pro-L-Leu), Karle;[36] DIHYDRPRO, 2,3-*cis*-3,4-*trans*-3,4-dihydroxy-L-proline, Karle;[37] DL-PROHCL, *dl*-proline hydrochloride, Mitsui et al.;[38] H-HYP-OH, Koetzle;[39] LEUPRGL, H-L-Leu-L-Pro-Gly-OH (1 is C_γ' and 2 is C_γ''), Leung and Marsh;[40] L-PRO-OH, L-proline, Kayushina and Vainshtein;[41] TOSPRHY H, Tos-L-Pro-L-Hyp-OH, R indicates revised calculation of the Fridrichsons and Mathieson data,[42] Sabesan and Venkatesan;[43a] TRIENPRCO, triethylenetetraamineprolinatocobalt(III) cation, Freeman et al.;[43b] Z2BGPLGR, Z(*o*-Br)-Gly-L-Pro-L-Leu-Gly-Pro-OH with H_2O and ethyl acetate of crystallization, only a rather poor crystal was available (1 is internal Pro, 2 is terminal), Ueki et al.;[44a] Z4BR-GPLG, Z(*p*-Br)-Gly-L-Pro-L-Leu-Gly-OH, Ueki et al.[44b] [b] Flags: A, acid; E, ester; Z, alkoxycarbonyl, *, exceptional or nonexistent atom; entries marked with * are to be disregarded. R, unimportant, but means that C (C_1) and origin of crystal coordinates are on same side of the ADN ($C_1\alpha$–$C_1\delta$–N_1) plane. [c] K–NAC, B–NAC, G–NAC, D–NAC are distances of C_0, $C_1\beta$, $C_1\gamma$, and $C_1\delta$ from the plane defined by N_1, $C_1\alpha$, C_1. Distances with same sign are on same side of plane. GAMMA is equivalent to or identical with the Γ of Venkatachalam et al.,[15] and follows their sign convention: negative for $C_1\gamma$ on same side of reference plane as C_1. D_1 is defined in eq 2 and 3. For proline $\chi_i = a_0 \cos [t + 4\pi(i-2)/5]$; eq 4. [d] Averages are based on all unflagged entries in a given column. There are some minor duplications, but these have negligible effect on the averages. The most probable average values for B–G and G–D are 1.53–1.54. The reported short distances are an experimental artifact. See text.

most cases our numbers agree closely with the literature values where available, but we found a few typographical discrepancies. In all cases of discrepancy we rechecked our input data against the crystal coordinates.

Previous summaries of the x-ray data have treated relatively few structures.[25,26] For further data see Table VIII and supplementary material.

The following points are of importance in evaluating proline x-ray data: the mobility of C^β and C^γ and to a lesser extent of C^δ even in the crystal lattice has often caused difficulties in defining ring geometries. Examples are entries 1 and 36, which represent two different calculations for Ac-Pro-lactamide, and entries 16 and 29, which are two treatments of the data for H-Leu-Pro-Gly-OH. The reported geometries must therefore be treated with some caution: the sorts of errors that may be present can be seen by comparing entries 2 and 30, revised calculations for Tos-Pro-Hyp-OH, with the original values, entries 11 and 25. For large molecules the level of uncertainty can be estimated by comparing entries 17 and 34 for actinomycin with entries 4 and 33 for the isomorphous 7-bromoactinomycin. But perhaps the most significant fact to emerge is that proline geometries are relatively constant whether present in salts, metal derivatives, or peptides, or whether the *N*-acyl group is *s*-cis or *s*-trans.

We next consider specific structural elements, first bond distances. Ring bond distances A–B (C^α–C^β), B–G (C^β–C^γ), and G–D (C^γ–C^δ) may have been systematically underestimated. Electron diffraction results for cyclopentane show a C–C distance of 1.546 Å.[4] There are no obvious reasons why proline C–C bonds should depart appreciably from 1.53 to 1.54. Libration corrections on such compounds as caprylolactam raise apparent short C–C bond lengths to normal va-

lues.[45a] Robiette defines various measures of interatomic distances and discusses the effect of bending vibrations on apparent distances.[45b]

Ring bond angles tend to average 104° except for D-N-A (C^{δ}-N-C^{α}), which averages 113° (112.9 ± 1.7°, 33 df, after deleting the seven salts and complexes). The 113° value is reasonable, since depression of the normal value of 115–120° for the C-N-C amide angle (as estimated from N,N-dimethylamides) to 113° parallels the decrease of a normal C-C-C angle (109°) to 104° (Aubry et al.,[46,47] Kitano et al.,[48] Gobillon et al.[49]). Both angle reductions result from ring puckering.

We report values of d_1 (D1) which along with χ_2 (A-B-C-D) and eq 2 reproduce ring torsions χ_1 (N-A-B-G), χ_3 (B-G-D-N), χ_4 (G-D-N-A), and χ_5 (D-N-A-B). For the 160 torsions in Table I the standard deviation of the values calculated from χ_2 and d_1 is about 0.6°. We also report values of a_0 (AO) and t (T) for use in eq 4. These, of course, reproduce the data equally well.

As for planarity of the peptide group, the angle ω is the average of L-K-N-A (C_0^{α}-C_0-N_1-C_1^{α}) and Q-K-N-D (O_0-C_0-N_1-C_1^{δ}) (or equivalently the average of L-K-N-D and Q-K-N-A minus 180). Angles near 180° must both be expressed as positive angles before averaging. The *s*-trans form has an angle near 180°.

Torsions ϕ (K-N-A-C, C_0-N_1-C_1^{α}-C_1) and ψ (N-A-C-M, N_1-C_1^{α}-C_1-N_2) largely determine chain folding, but angles N-K-L (N_1-C_0-C_0^{α}), A-N-K (C_1^{α}-N_1-C_0), C-A-N (C_1-C_1^{α}-N_1), and A-C-M (C_1^{α}-C_1-N_2) are also involved; the 3° variability may be significant in some cases. For the seven *s*-trans derivatives $\phi_{avg} = -66.1$ (±6)° with a range of −57 to −76° and $(\chi_5 - \phi)_{avg} = 62.5$ (±7.4)° with a range from 55 to 80°. For the 11 *s*-cis derivatives $\phi_{avg} = -75.1$ (±23)° with a range of −42 to −110° and $(\chi_5 - \phi)_{avg} = 69.3$ (±7.8) with a range of 59 to 80°. These values lend little support to the hope that ϕ could be predicted sufficiently closely, given the value of χ_5, or vice versa.

In Table I we also report other derived values considered to be of interest. One example is the distance between C_1^{β} and C_1^{γ} and a reference plane defined by C_1^{δ}-N_1-C_1^{α}.[5,25] Another is γ; we have defined γ as the angle between three points: C_1^{γ}, the midpoint of the line joining C_1^{β} and C_1^{δ}, and the midpoint of the line joining N and C_1^{α}. This is intended to correspond to Γ as used by Venkatachalam et al.[14,15] As the reference plane we use N_1, C_1^{α}, and the midpoint of the line joining C_1^{β} and C_1^{δ}. The sign of γ is positive if C_1^{γ} and C_1 are on opposite sides of the reference plane.

Previous Calculations of Conformational Energy of Proline Derivatives. Several studies have examined the effect of ring puckering on overall folding properties of proline-containing peptides and on statistical properties of polyproline and of polyhydroxyproline. These have utilized rather primitive treatments of ring puckering, since the main interest was elsewhere.[50-60] Our calculations provide important information about these relationships, as will be discussed below. Tonelli[61,62] reports calculations for isomerization involving the proline C^{α}-C bond (ψ). Madison[63a] calculated energies for backbone conformations of cyclic (Pro-Gly)$_3$. Madison and Schellman[63b] combined geometric calculations with CD calculations. Young et al.[64] report torsions for minimum energy conformations of c-(L-Pro-L-Pro) based on the Lifson force field:[65,66] χ_1 to χ_4 = 33, 34, −23, 2; $\phi = -16$; $\psi = 26$; $\omega = -10$. Corresponding values for c-(L-Pro-D-Pro) are −37, 36, −22, −1, −6, 5, −14.

The ring conformational energy maps of Venkatachalam et al.[14,15] and earlier calculations of Ramachandran et al.,[67] are discussed below.

New Studies of Conformational Energies of Ac-Pro-OCH$_3$. We have carried out extensive calculations of the energies of ring conformations of Ac-Pro-OCH$_3$ by the methods of molecular mechanics using the force field defined below. Definition of this molecule requires 69 parameters, and all were adjusted except for the two C=O bonds and the one or two constrained parameters required to define the required conformations. The similarity of geometries reported for the various proline derivatives in Table I makes it reasonable to expect that Ac-Pro-OCH$_3$ will be typical of proline rings not subject to special constraints.

Table II. Representative Conformational Energies and Torsions Calculated for Ac-Pro-OCH$_3$

χ_1	46.2	28.7	5.3	−23.1
χ_2	−44.7	−35.0	−5.1	35.1
χ_3	23.0	27.7	2.9	−33.3
χ_4	6.2	−10.3	0.5	20.0
χ_5	−32.2	−11.52	−3.7	1.9
ψ	182.8[a]	157.0	147.3	146.8
ϕ	−89.9	−76.3	−69.0	−61.4
V_s[b]	1.74	0.00[c]	3.61	0.32

[a] For the −180° to 180° range $\psi = -177.2°$. [b] Conformational energy in kcal/mol above the minimum. [c] Conformation A, Table III.

Table II summarizes values of energies, of ring torsions, and of ϕ and ψ for several conformations of *s-trans*-Ac-Pro-OCH$_3$. Table III presents bond lengths, angles, and torsions for two typical conformations. More extensive data, including Cartesian coordinates, are available in the supplementary information which accompanies this article. Results are also summarized in Figures 1 and 2 whose interpretation is discussed below.

In Table IV, we compare the energies for several *s-cis*- and *s-trans*-Ac-Pro-OCH$_3$ conformers. For these low-energy conformers the steric energy V_s for the *s*-cis conformer is about 0.45 kcal/mol larger than for the *s*-trans conformer. On the assumption that $\Delta G \sim \Delta V_s$, ΔG of 0.45 kcal/mol is equivalent to 25% *s*-cis. This corresponds better than could be expected to the 21% *s*-cis observed for Ac-Pro-OCH$_3$ in benzene and 28% in chloroform.[63b]

Figures 1 and 2 serve different and complementary needs. The χ_2, d_1 plot is especially useful as a working diagram, since linear values of χ_2 and d_1 are easily scaled. The a_0, t plot is a polar graph with a_0 radial and t angular (eq 4). It has the important advantage that contours are independent of scale. In order to use these figures it is helpful to understand how they define ring conformations; figures of this type may be applied to all five-membered rings and are thus generally useful. The radial lines at t = 18°, 54°, 90°, . . . in Figure 2 define the loci for the ten possible envelope forms with the indicated atom as the envelope atom; eq 4. There are ten since each ring atom may be either up (+) or down (−) with respect to the average plane.[2-4,7] These envelope loci also appear in Figure 1; they are the diagonals plus the verticals, $\chi_2 = 0$, axis. For cyclopentane itself these lines would be loci for conformations of C_s symmetry. Bisecting each of the above regions, at t = 0°, 36°, 72°, . . . in Figure 2, are loci for the half chair conformations; for cyclopentane these are of C_2 symmetry.

In Figure 2 the radial distance a_0 defines the degree of ring puckering. The phase angle t defines the distribution of the puckering. The origin represents a planar ring. The origin in Figure 1 also represents a planar ring, but the degree of puckering is defined jointly by χ_2 and d_1. In Figure 2 the pseudorotation path for cyclopentane is shown on the circle with $a_0 = 45°$; this is a contour of minimum and almost constant energy.

Contour energies in Figures 1 and 2 are shown relative to the conformation of minimum energy. This is located near $\chi_2 = -36$, $d_1 = -1$ (designated as region B by Ramachandran

Table III. Bond Lengths, Angles, and Torsions Calculated for Ac-Pro-OCH_3[a]

		A	B			A	B
$C^{\beta}-C^{\gamma}$	(3-5)	1.527	1.524	$O_2-C_2^{\alpha}-H_2^{\alpha 2}$	(28-29-32)	110.3	110.2
$C^{\beta}-C^{\alpha}$	(3-22)	1.532	1.538	$O_2-C_2^{\alpha}-H_2^{\alpha 1}$	(28-29-33)	109.1	109.1
$C^{\gamma}-C^{\delta}$	(5-9)	1.526	1.524	$H_2^{\alpha 3}-C_2^{\alpha}-H_2^{\alpha 2}$	(31-29-32)	109.6	109.6
$C^{\delta}-N$	(9-13)	1.458	1.459	$H_2^{\alpha 3}-C_2^{\alpha}-H_2^{\alpha 1}$	(31-29-33)	108.8	108.8
$N-C_0$	(13-14)	1.346	1.347	$H_2^{\alpha 2}-C_2^{\alpha}-H_2^{\alpha 1}$	(32-29-33)	108.8	108.8
$N-C^{\alpha}$	(13-22)	1.461	1.467	$H^{\beta 1}-C^{\beta}-C^{\gamma}-H^{\gamma 2}$	(2-3-5-7)	197.5	286.7
C_0-O_0	(14-16)	1.240	1.240	$H^{\beta 1}-C^{\beta}-C^{\gamma}-H^{\gamma 1}$	(2-3-5-8)	318.6	49.3
$C_0-C_0^{\alpha}$	(14-17)	1.519	1.518	$H^{\beta 1}-C^{\beta}-C^{\gamma}-C^{\delta}$	(2-3-5-9)	81.6	166.1
$C^{\alpha}-C$	(22-25)	1.520	1.519	$H^{\beta 2}-C^{\beta}-C^{\gamma}-H^{\gamma 2}$	(4-3-5-7)	318.3	48.8
$C-O$	(25-27)	1.240	1.240	$H^{\beta 2}-C^{\beta}-C^{\gamma}-H^{\gamma 1}$	(4-3-5-8)	79.4	171.3
$C-O_2$	(25-28)	1.373	1.373	$H^{\beta 2}-C^{\beta}-C^{\gamma}-C^{\delta}$	(4-3-5-9)	202.4	288.2
$O_2-C_2^{\alpha}$	(28-29)	1.457	1.457	$C^{\alpha}-C^{\beta}-C^{\gamma}-H^{\gamma 2}$	(22-3-5-7)	80.9	165.5
$C^{\beta}-H^{\beta 1}$	(3-2)	1.103	1.103	$C^{\alpha}-C^{\beta}-C^{\gamma}-H^{\gamma 1}$	(22-3-5-8)	201.9	288.0
$C^{\beta}-H^{\beta 2}$	(3-4)	1.102	1.102	$C^{\alpha}-C^{\beta}-C^{\gamma}-C^{\delta}$	(22-3-5-9)	325.0	44.9
$C^{\gamma}-H^{\gamma 2}$	(5-7)	1.103	1.103	$H^{\beta 1}-C^{\beta}-C^{\alpha}-N$	(2-3-22-13)	272.4	298.7
$C^{\gamma}-H^{\gamma 1}$	(5-8)	1.103	1.101	$H^{\beta 1}-C^{\beta}-C^{\alpha}-H^{\alpha}$	(2-3-22-24)	30.8	324.1
$C^{\delta}-H^{\delta 1}$	(9-11)	1.102	1.102	$H^{\beta 1}-C^{\beta}-C^{\alpha}-C$	(2-3-22-25)	152.5	86.7
$C^{\delta}-H^{\delta 2}$	(9-12)	1.101	1.103	$H^{\beta 2}-C^{\beta}-C^{\alpha}-N$	(4-3-22-13)	151.8	87.0
$C_0^{\alpha}-H_0^{\alpha 2}$	(17-19)	1.100	1.100	$H^{\beta 2}-C^{\beta}-C^{\alpha}-H^{\alpha}$	(4-3-22-24)	270.1	202.4
$C_0^{\alpha}-H_0^{\alpha 1}$	(17-20)	1.100	1.100	$H^{\beta 2}-C^{\beta}-C^{\alpha}-C$	(4-3-22-25)	31.8	325.0
$C_0^{\alpha}-H_0^{\alpha 3}$	(17-21)	1.101	1.101	$C^{\gamma}-C^{\beta}-C^{\alpha}-N$	(5-3-22-13)	28.7	330.2
$C^{\alpha}-H^{\alpha}$	(22-24)	1.103	1.102	$C^{\beta}-C^{\beta}-C^{\alpha}-H^{\alpha}$	(5-3-22-24)	147.0	85.6
$C_2^{\alpha}-H_2^{\alpha 3}$	(29-31)	1.100	1.100	$C^{\gamma}-C^{\beta}-C^{\alpha}-C$	(5-3-22-25)	268.7	208.3
$C_2^{\alpha}-H_2^{\alpha 2}$	(29-32)	1.100	1.100	$C^{\beta}-C^{\gamma}-C^{\delta}-H^{\delta 1}$	(3-5-9-11)	271.4	197.4
$C_2^{\alpha}-H_2^{\alpha 1}$	(29-33)	1.100	1.100	$C^{\beta}-C^{\gamma}-C^{\delta}-H^{\delta 2}$	(3-5-9-12)	149.6	74.5
$C^{\beta}-C^{\gamma}-C^{\delta}$	(3-5-9)	103.1	101.1	$C^{\beta}-C^{\gamma}-C^{\delta}-N$	(3-5-9-13)	27.7	318.0
$C^{\beta}-C^{\alpha}-N$	(3-22-13)	103.0	102.5	$H^{\gamma 2}-C^{\gamma}-C^{\delta}-H^{\delta 1}$	(7-5-9-11)	155.9	76.8
$C^{\beta}-C^{\alpha}-C$	(3-22-25)	111.5	110.8	$H^{\gamma 2}-C^{\gamma}-C^{\delta}-H^{\delta 2}$	(7-5-9-12)	34.1	313.9
$C^{\gamma}-C^{\beta}-C^{\alpha}$	(5-3-22)	104.6	102.2	$H^{\gamma 2}-C^{\gamma}-C^{\delta}-N$	(7-5-9-13)	272.2	197.4
$C^{\gamma}-C^{\delta}-N$	(5-9-13)	104.6	100.8	$H^{\gamma 1}-C^{\gamma}-C^{\delta}-H^{\delta 1}$	(8-5-9-11)	34.4	314.0
$C^{\delta}-N-C_0$	(9-13-14)	123.7	123.9	$H^{\gamma 1}-C^{\gamma}-C^{\delta}-H^{\delta 2}$	(8-5-9-12)	272.6	191.1
$C^{\delta}-N-C^{\alpha}$	(9-13-22)	112.7	112.1	$H^{\gamma 1}-C^{\gamma}-C^{\delta}-N$	(8-5-9-13)	150.7	74.6
$N-C_0-O_0$	(13-14-16)	121.1	121.1	$C^{\gamma}-C^{\delta}-N-C_0$	(5-9-13-14)	174.3	208.1
$N-C_0-C_0^{\alpha}$	(13-14-17)	119.9	119.9	$C^{\gamma}-C^{\delta}-N-C^{\alpha}$	(5-9-13-22)	349.7	24.5
$N-C^{\alpha}-C$	(13-22-25)	111.8	114.0	$H^{\delta 1}-C^{\delta}-N-C_0$	(11-9-13-14)	291.4	325.9
C_0-N-C^{α}	(14-13-22)	123.4	123.9	$H^{\delta 1}-C^{\delta}-N-C^{\alpha}$	(11-9-13-22)	106.8	142.3
$O_0-C_0-C_0^{\alpha}$	(16-14-17)	119.1	118.9	$H^{\delta 2}-C^{\delta}-N-C_0$	(12-9-13-14)	53.4	90.0
$C^{\alpha}-C-O$	(22-25-27)	120.6	120.4	$H^{\delta 2}-C^{\delta}-N-C^{\alpha}$	(12-9-13-22)	228.8	266.4
$C^{\alpha}-C-O_2$	(22-25-28)	116.9	117.0	$C^{\delta}-N-C_0-O_0$	(9-13-14-16)	176.5	173.5
$C-O_2-C_2^{\alpha}$	(25-28-29)	118.6	118.5	$C^{\delta}-N-C_0-C_0^{\alpha}$	(9-13-14-17)	356.0	354.8
$O-C-O_2$	(27-25-28)	122.4	122.5	$C^{\alpha}-N-C_0-O_0$	(22-13-14-16)	1.6	357.4
$H^{\beta 1}-C^{\beta}-H^{\beta 2}$	(2-3-4)	108.7	109.0	$C^{\alpha}-N-C_0-C_0^{\alpha}$	(22-13-14-17)	181.1	178.8
$H^{\beta 1}-C^{\beta}-C^{\alpha}$	(2-3-22)	109.3	112.6	$C^{\delta}-N-C^{\alpha}-C^{\beta}$	(9-13-22-3)	348.5	3.2
$H^{\beta 1}-C^{\beta}-C^{\gamma}$	(2-3-5)	108.7	113.1	$C^{\delta}-N-C^{\alpha}-H^{\alpha}$	(9-13-22-24)	229.9	246.1
$H^{\beta 2}-C^{\beta}-C^{\gamma}$	(4-3-5)	113.1	110.0	$C^{\delta}-N-C^{\alpha}-C$	(9-13-22-25)	108.3	123.0
$H^{\beta 2}-C^{\beta}-C^{\alpha}$	(4-3-22)	112.3	109.9	$C_0-N-C^{\alpha}-C^{\beta}$	(14-13-22-3)	163.9	179.7
$H^{\gamma 2}-C^{\gamma}-C^{\beta}$	(7-5-3)	108.7	112.8	$C_0-N-C^{\alpha}-H^{\alpha}$	(14-13-22-24)	45.3	62.6
$H^{\gamma 2}-C^{\gamma}-C^{\delta}$	(7-5-9)	109.3	112.7	$C_0-N-C^{\alpha}-C$	(14-13-22-25)	283.7	299.4
$H^{\gamma 2}-C^{\gamma}-H^{\gamma 1}$	(7-5-8)	108.7	109.4	$N-C_0-C_0^{\alpha}-H_0^{\alpha 2}$	(13-14-17-19)	293.8	313.1
$H^{\gamma 1}-C^{\gamma}-C^{\beta}$	(8-5-3)	113.4	110.2	$N-C_0-C_0^{\alpha}-H_0^{\alpha 1}$	(13-14-17-20)	55.9	75.4
$H^{\gamma 1}-C^{\gamma}-C^{\delta}$	(8-5-9)	113.4	110.5	$N-C_0-C_0^{\alpha}-H_0^{\alpha 3}$	(13-14-17-21)	174.9	194.3
$H^{\delta 1}-C^{\delta}-C^{\beta}$	(11-9-5)	109.7	110.1	$O_0-C_0-C_0^{\alpha}-H_0^{\alpha 2}$	(16-14-17-19)	113.3	134.5
$H^{\delta 1}-C^{\delta}-H^{\delta 2}$	(11-9-12)	109.9	110.2	$O_0-C_0-C_0^{\alpha}-H_0^{\alpha 1}$	(16-14-17-20)	235.4	256.8
$H^{\delta 1}-C^{\delta}-N$	(11-9-13)	108.6	113.9	$O_0-C_0-C_0^{\alpha}-H_0^{\alpha 3}$	(16-14-17-21)	354.4	15.7
$H^{\delta 2}-C^{\delta}-C^{\gamma}$	(12-9-5)	111.2	111.8	$C^{\beta}-C^{\alpha}-C-O$	(3-22-25-27)	90.9	324.5
$H^{\delta 2}-C^{\delta}-N$	(12-9-13)	112.7	109.7	$C^{\beta}-C^{\alpha}-C-O_2$	(3-22-25-28)	271.7	146.9
$H_0^{\delta 1}-C_0^{\alpha}-C_0$	(19-17-14)	110.4	110.9	$N-C^{\alpha}-C-O$	(13-22-25-27)	336.2	79.5
$H_0^{\delta 1}-C_0^{\alpha}-H_0^{\alpha 1}$	(19-17-20)	109.9	110.1	$N-C^{\alpha}-C-O_2$	(13-22-25-28)	157.0	261.9
$H_0^{\delta 1}-C_0^{\alpha}-H_0^{\alpha 3}$	(19-17-21)	107.9	107.6	$H^{\alpha}-C^{\alpha}-C-O$	(24-22-25-27)	213.7	202.4
$H_0^{\alpha 1}-C_0^{\alpha}-C_0$	(20-17-14)	111.0	110.4	$H^{\alpha}-C^{\alpha}-C-O_2$	(24-22-25-28)	34.5	24.8
$H_0^{\alpha 1}-C_0^{\alpha}-H_0^{\alpha 3}$	(20-17-21)	107.8	107.9	$C^{\alpha}-C-O_2-C_2^{\alpha}$	(22-25-28-29)	179.5	179.2
$H_0^{\alpha 3}-C_0^{\alpha}-C_0$	(21-17-14)	109.9	109.7	$O-C-O_2-C_2^{\alpha}$	(27-25-28-29)	0.3	1.7
$H^{\alpha}-C^{\alpha}-C^{\beta}$	(24-22-3)	110.9	110.7	$C-O_2-C_2^{\alpha}-H_2^{\alpha 3}$	(25-28-29-31)	299.3	299.1
$H^{\alpha}-C^{\alpha}-N$	(24-22-13)	110.6	108.3	$C-O_2-C_2^{\alpha}-H_2^{\alpha 2}$	(25-28-29-32)	60.5	60.2
$H^{\alpha}-C^{\alpha}-C$	(24-22-25)	109.0	110.3	$C-O_2-C_2^{\alpha}-H_2^{\alpha 1}$	(25-28-29-33)	179.9	179.7
$O_2-C_2^{\alpha}-H_2^{\alpha 3}$	(28-29-31)	110.2	110.3				

[a] A (LSX8D5B1) $\chi_2 = -35$, $d_1 = -0.5$, minimum energy. B (LSX8C56) $\chi_2 = 44.9$, $d_1 = -6.1$, 0.89 kcal above minimum. Bond lengths are given in angstroms, angles in degrees.

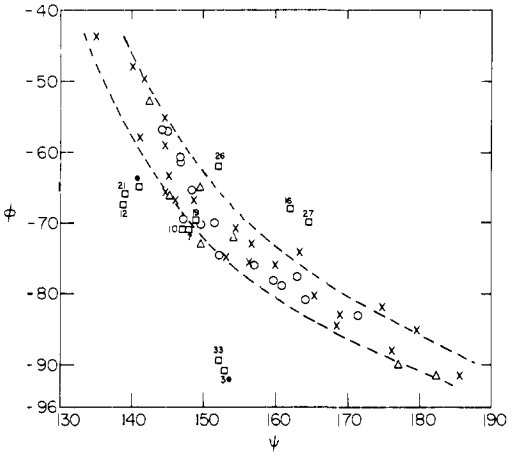


Figure 3. ϕ-ψ values found for *s-trans*-Ac-Pro-OCH_3 at the energy minima for various constrained ring conformations. It is not a ϕ-ψ energy contour plot. The band represents a range of energies; it includes *all* conformations within the 3.0-kcal contours of Figure 1. The numbered squares are x-ray data from Table I; several of these are well off the band, yet represent energies less than 0.5 kcal above the minimum. As shown by this figure, ring conformations limit but do not control ϕ and ψ. Symbols: O, ring conformations less than 1.0 kcal above global minimum; Δ, from 1 to 2; x, greater than 2.

et al.[67]). There is a second region of minimum energy, region A, located near $\chi_2 = 36$, $d_1 = -4$. The contours are drawn every 0.5 kcal/mol above the minimum; the region A minimum is 0.3 kcal/mol above the region B minimum. The energy barrier lies near $\chi_2 = -5$, $d_1 = -7$; this is a flat saddle about 2.7 kcal above the minimum. In these diagrams the carboxyl is "up" with respect to the average plane of the ring. The noticeable lack of symmetry is caused by the carboxyl group.

Contours at $\chi_2 = 0$ and at $t = 90$ or 270° show that envelope forms with nitrogen as the envelope atom have relatively high energies; such conformations would require the C-N-C amide bond to decrease to 100–105°, a considerable distortion from the unstrained value of about 118–120°.

The breadth of the low-energy regions indicates that there are several low lying vibrational energy levels. If the energy differences are equated to ΔG, there are predicted to be roughly twice as many molecules with conformations in the B class as in the A class. The relative areas inside the 0.5-kcal contours of Figure 2 predict a 0.77:0.23 ratio. At present there is no experimental evidence which bears directly on the ratios, but possibly some of the NMR data on coupling constants would repay reinterpretation. Such small differences in these effectively gas-phase enthalpies could be overridden by small differential solvation effects.

The squares in Figure 1 designate the conformations of the 40 proline rings numbered as in Table I. Of these, 27 fall in regions whose energies are less than 1.5 kcal/mol and nine are within 2.0 kcal above the minimum. The four outside this region may represent strained molecules (due to ring closure) or may point to problems in the x-ray values. Points 19 and 20 are for the antamanide analogue molecule for which it may be technically difficult to obtain details of ring conformations with high precision. It is also of interest to compare the older[42] and the newer[43a] calculations of Tos-Pro-Hyp-OH discussed above. Thus point 11 (original) became point 2 (recalculated) for the Hyp ring, while point 25 (original) became point 30 (recalculated) for the Pro ring. We conclude that the x-ray data are closely consistent with the energy contours of Figures 1 and 2.

We now comment briefly on two other results. Bond lengths are nearly independent of conformation; the data in Table III are typical. Use of fixed bond lengths would thus be a very good approximation.

Table IV. Energy Difference *s-cis*- vs. *s-trans*-Ac-Pro-OCH_3

χ_2	d_1	$\Delta V_{s\text{-trans}}$	$\Delta V_{s\text{-cis}}$	$\Delta\Delta V$
−35.02	−2.73	0.08	0.51	0.43
−35.31	15.65	2.79	3.22	0.43
−5.11	0.55	2.73	3.21	0.48
34.80	9.63	2.21	2.65	0.44
34.96	0.095	0.67	1.08	0.41

The amide group is almost but not quite planar in the calculated conformations and for most of the examples in Table I. Small departures from planarity do not cost much energy. Torsions labeled 22-13-14-16 and 9-13-14-17 in Table III are torsions Q-K-N-A (O_0-C_0-N_1-$C_1{}^\alpha$) and L-K-N-D ($C_0{}^\alpha$-C_0-N_1-$C_1{}^\alpha$) in Table I. Two different molecular motions may contribute to nonplanarity about an sp^2 atom; one is a bending mode in which the angle sum about a nominally planar atom departs from 360°, the other a twisting mode about a bond joining the sp^2 atom to another atom (Winkler and Dunitz,[45a] Ermer and Lifson[68]).

Comparisons with Previous Calculations. The minimum energy conformation reported by Young et al.[64] for c-(L-Pro-L-Pro) (and cited above) has $\chi_2 = 34$ and $d_1 = 5$, that for (L-Pro-D-Pro) has $\chi_2 = 36$ and $d_1 = 7.5$. These are about 1.3–1.8 kcal/mol above the global minimum, and are comparable to the x-ray results. The molecules may be strained.

Venkatachalam et al.[15] present energy contour diagrams based on Γ and θ which compare roughly with ours; they indicate roughly similar locations of the energy minima, but there are differences in details of the contours that may prove significant for some applications. There are also differences in the torsion angles for the minimum energy conformations reported in Table I of Venkatachalam et al.[14] and those summarized in our Figure 1.

In a much earlier study Ramachandran et al.[67] tried out several simple force fields. They did not publish energy contours, but the data in their Tables II and III fall fairly well on the contours in our Figure 1. We conclude that the general features of the energy contours are rather insensitive to appreciable differences in force fields.

Relationship between Ring Torsions and ϕ. Venkatachalam et al.[15] have considered in some detail the relationship of ϕ and ψ to ring torsions. Their study assumed that ϕ could be defined by one of the ring torsions, χ_5, an assumption that is true only within about ±15°.

We did not carry out computations to prepare an energy contour map for ϕ and ψ. The points in the ϕ-ψ plot shown in Figure 3 are a by-product of the calculations used to prepare Figures 1 and 2. In these calculations all internal parameters including ϕ and ψ were minimized for selected values of χ_2 and d_1. The curve then illustrates what control, if any, ring conformations exert over ϕ and ψ. The data fall on a rather narrow band in a pattern which is pretty much independent of the overall conformational energy. We have also included in Figure 3 those proline derivatives from Table I whose ϕ-ψ values are in this general range. There is another minimum near $\psi = -30$ which we did not explore. Points 33 and 34, for example, lie off the band even though the ring conformational energy is near the minimum value. These results show clearly that ring conformations have little control over ϕ (or ψ); rather, the flexibility of the ring serves to increase the area enclosed by the contour for a given ϕ-ψ energy.

Results from NMR Studies. Most NMR studies of proline conformations fall into one of three classes: those which estimate *s*-cis-*s*-trans ratios of *N*-acyl groups, those which evaluate average dihedral angles via a Karplus relationship, and those which estimate ring mobility in terms of ^{13}C T_1 values. See Deslauriers and Smith for a review.[70]

Table V. Typical *s*-Cis–*s*-Trans Acylproline Ratios[a]

Ac-Pro-OH	D_2O pH 1.3	19% *s*-cis[b]
	D_2O high pH	45% *s*-cis[b]
	"crystal"[c]	All *s*-trans[d]
	Me_2SO-d_6	29% *s*-cis[b]
	Me_2SO-d_6	25% *s*-cis[f]
	D_2O	50% *s*-cis[g]
	H_2O, 0.1 M H_2SO_4	25% *s*-cis[h]
	H_2O, pH 9	50% *s*-cis[h]
	$CHCl_3$	20% *s*-cis[h]
	45% C_6H_6–$CHCl_3$	11% *s*-cis[h]
Ac-Pro-OCH_3	H_2O	16% *s*-cis[h]
	$CHCl_3$	28% *s*-cis[h]
	C_6H_6	21% *s*-cis[h]
Other examples (46 of these)		Mostly 10–40% cis

[a] This is an abstract of the complete table available in the supplementary material for this paper. The complete table presents data for 48 compounds. Abbreviations (IUPAC-IUB):[1] Iva, isovaleryl; Ibu, isobutyryl; Piv, pivaloyl = trimethylacetyl; Ahy, Allohydroxyproline; Glp, pyroglutamyl (= 4-ketopyrrolidine-2-carbonyl); Boc, *tert*-butoxycarbonyl; Han, homoanthranoyl = 2-aminophenylacetyl; Mma, methylmethacrolyl. [b] Bedford and Sadler.[72] [c] Conformation in "crystalline" state is based on NMR spectrum taken shortly after dissolution in CD_3OD at −60 °C. Peaks for *s*-cis appeared on warming. [d] Thomas and Williams.[73] [e] Thomas and Williams.[74] [f] Nishihara et al.[75,76] [g] Voelter et al.[77,78] [h] Madison and Schellman.[63b]

Table V summarizes the data on cis–trans populations. The complete table is presented in the supplementary material. Most determinations have been based on relative areas of the *s*-trans and *s*-cis sets of ^{13}C lines; it is not always clear whether pulsing rates have been chosen properly so as to minimize complications due to nuclear Overhauser effects, but there is a general consistency in the results. In several cases ^1H NMR were used, but peak overlap often causes difficulties.

For simple acylproline derivatives in equilibrium in solution the amounts of *s*-cis conformer range from about 10% to 40% (omitting the extremes), corresponding to a $\Delta\Delta G[= \Delta G(s\text{-cis}) - \Delta G(s\text{-trans})]$ range of 1.4 to 0.3 kcal/mol. Such an energy difference is sufficiently small to allow an acylproline to conform readily to environmental constraints. Direct solvent effects are of some significance, ranging from $\Delta G \approx 0.25$ kcal/mol for Ac-Pro-NH_2 to 0.7 kcal/mol for Ac-Pro-OH. An overall average $\Delta\Delta G$ of 0.7 kcal/mol corresponding to 25% cis may tentatively be adopted as a measure of the intrinsic stability of the *s*-trans acylproline conformation over the *s*-cis in D_2O and Me_2SO-d_6, and probably in other solvents.

Less work has been done on acyloxycarbonyl derivatives. The three examples in Table V for *tert*-butoxycarbonyl and for *tert*-amyloxycarbonyl are *s*-cis. One ^1H NMR study reports that *Z*-Pro-ONP (*p*-nitrophenyl ester) is 50% *s*-cis in Me_2SO-d_6.[71]

Several groups have attempted to establish proline ring conformations in solution by calculating ring torsions from vicinal coupling constants with use of the Karplus relationship. The approach is promising, but there are great technical difficulties. Available results are summarized in Table VI. The general conclusion is that solution results more or less correspond to the regions of minimum energy shown in Figures 1 and 2.

In several examples the proline ring cannot be assigned any single conformation (nor single averaged conformation), but the data must be treated by averaging the coupling constants predicted for two or more conformations. These cases are indicated by paired sets of conformational angles for a given compound. Equilibration between conformers is to be expected to be fast on the NMR time scale, since the predicted barrier between the energy minima in Figures 1 and 2 is only about 2.7 kcal/mol.

In early work Abraham et al.,[101] Abraham and McLauchlan,[102,103] and Abraham and Thomas[104] interpreted coupling constants of $^+H_2$-Hyp-O^- in D_2O in terms of a conformation similar to that found by x-ray crystallography,[39] although the estimated solution puckering is larger. Abraham and Thomas[104] (1964) stated that for H-Hyp-O^- and for H-Ahy-O^- (allohydroxyproline) the coupling data could be interpreted consistently only by assuming that there was a population of at least two conformers, and these were of equal energy, for the ratio did not change with temperature. This observation was most perceptive and accords excellently with subsequent studies. However, the numerical values assigned to the torsions

Table VI. Torsion Angles from Coupling Constants[a]

		χ_1	χ_2	χ_3	χ_4	χ_5
H-Hyp-O^-	D_2O	−10.2[c]	16.5[c]	(−16.5)[d]	(10.2)[d]	0
		−43.3[c]	72.2[c]	(−73.5)[d]	(46.8)[d]	(1.1)[d]
$^+H_2$-Hyp-O^-[b]	D_2O	−32.0[c]	52.3[c]	(−52.6)[d]	(32.3)[d]	0
H-Aly-O^-[b]	D_2O	15	−61	87	−78	37[e]
		−31	−6	40	−61	57
$^+H_2$-Hyp-O^-[f]	D_2O			43	72	0
$^+H_2$-Pro-OH[g]		10	−35			18.3
		−30	35			1.7
H-Pro-O^-[g]			−30			
			20			
Cyclic (Pro-Pro)[h]	$CDCl_3$	−30	42	−21		
Cyclic (Pro-D-Pro)[h]	$CDCl_3$	−40	29	−12		
Cyclic (Pro-Pro-Hyp)[i]	$CDCl_3$	30	−10	−5	25	
Glp-His-Pro-OH[j]			−30			
Poly-Hyp[h]	D_2O	−25	45	−45	25	
Poly-Pro[i]	D_2O	−25	35	−35	25	
		25	−35	35	−25	
trans-4-F-H_2^+-Pro-OH[k]	D_2O	−30.3	51.5	−52.7	36.6	−4.0
cis-4-F-H_2^+-Pro-OH[k]	D_2O	17.0	−49.4	51.5	−48.1	21.1

[a] Abbreviations, footnote a, Table V. [b] Abraham and Thomas.[104] [c] χ_1 and χ_2 from Table I of Abraham and McLauchlan.[103] The listed constants are illustrative of paired conformations that are consistent with the coupling based on values of θ constants. [d] Calculated from χ_1 and χ_2. [e] Sign reversed in the paper. [f] Abraham and McLauchlan.[103] [g] Pogliani, et al.[107] [h] Torchia.[105] [i] Torchia.[106] [j] Haar et al.[86] [k] Gerig and McLeod[108] reported single conformer torsions for *trans*-4-fluoroproline; $\chi_2 = 53$ and $d_1 = -12$; the cis isomer values are rather inconsistent and show roughly $\chi_2 \approx -45$ and $d_1 \approx -19$. Both sets define conformations of improbably high energies. The reported torsions do not follow the current sign conventions and do not obey eq 2 very well.

Table VII. Force Field

The Schleyer 1973 Alkane Force Field[a,b]

Stretch	Ref	FC
C-C	1.52	4.40
C-H	1.10	4.60

Torsion	Ref	10^3 barrier
H-C-C-H	60.0	1.617 (9)[d]
H-C-C-C	60.0	1.617 (9)
C-C-C-C	60.0	1.037 (9)

Bend	Ref	10^4 FC	10^6 FCC[c]
C-C-H (P)[e]	109.5	1.2185	−1.17
C-C-H (S)	109.0	1.2185	−1.17
C-C-H (T)	109.2	1.2185	−1.17
H-C-H (P)	109.2	1.0052	−0.96
H-C-H (S)	109.1	1.0052	−0.96
C-C-C (S)	110.4	1.7363	−1.67
C-C-C (T)	110.1	1.7363	−1.67
C-C-C (Q)	109.5	1.7363	−1.67

Nonbonded

$V = a \exp(-br) - cr^{-6}$

	a	b	c
H···H	45.25	3.750	0.5970
H···C	33.85	3.582	0.5880
C···C	107.40	3.117	4.2981

Additions to the Alkane Force Field to Treat Peptides[f]

Stretch	Ref	FC
C3-N	1.45	4.40
C2-N	1.32	4.40
C2=O2	1.24	(Fixed)
C2-O3	1.36	4.40
C2-C3	1.51	4.40
C3-O3	1.45	4.40

Bend	Ref	10^4 FC
C3-N-C2	121.	3.
C3-N-C3	118.	3.
C3-C2-O2	121.	3.
N-C2-O2	121.	3.
N-C2-C3	118.	3.
C3-C2-O3	118.	3.
O3-C2-O2	121.	3.

Torsion	Ref	10^3 Barrier
X-C3-N-X	60.0	1.03 (6)[d]
X-C3-C2-O	60.0	0.518 (6)
X-C3-C2-N	60.0	0.518 (6)
X-C2-N-C3	0.0	34.7 (4)
O-C2-O-C3	0.0	29.57 (4)

Coulombic charges (electrons)

Amide N2	−0.503
Amide O2	−0.704
Amide C2	1.207
Ester O2	−0.348
Ester O3	−0.174
Ester C2	0.522

Nonbonded:
H···N, H···O same as H···C
C···N, C···O, N···O same as C···C

Dielectric constant 4

[a] Engler et al.[118] [b] Energy units for force constants are mdyne-angstroms per molecule, with distances in angstroms, angles and torsions in degrees, coulombic charges in fractions of an electron. [c] Cubic correction. [d] We partition the barrier into the number of parts indicated in parentheses. Total barrier is $9 \times 1.617 \times 10^{-3}$, etc. [e] P primary, S secondary, T tertiary, Q quaternary. [f] C3-N means sp^3 carbon to nitrogen, C2-O3 is sp^3 carbon to alkyl oxygen of ester, designated as sp^3 oxygen. Note: 1 mdyn-Å/molecule = 143.8 kcal/mol.

for most of these compounds are well outside of any energetically allowed limits.

Later torsion estimates computed with energy considerations as guides fall within acceptable ranges. In one example solution values may be compared with crystal values. Cyclic Pro-Pro-Hyp as the benzoate ester has been analyzed in careful detail.[90] The crystal[34] shows three sets of torsion values, none of which corresponds to the solution values. The solution values do correspond roughly to the average of the x-ray data, but the significance is not entirely clear, since Hyp is found in only two of the three proline sites in the crystal and the average of these two does not correspond to the solution values.

^{13}C spin-lattice relaxation times (T_1) have been reported for many proline derivatives and have been interpreted in terms of mobilities of the carbon atoms; Torchia and Lyerla,[97] Deslauriers et al.,[109] Komoroski et al.,[110] Fossel et al.[111] X-ray data indicate generally high mobility for C^β and C^γ in crystals, but mobility is relative. Torchia and Lyerla[97] carried out a detailed analysis of mobilities in poly(Pro), poly(Hyp), poly(Pro-Gly), poly(Hyp-Gly), and poly(Gly-Gly-Pro-Gly) in a relatively successful effort to sort out the contributing factors. Pertinent conclusions were: backbone mobility of C and C^α is relatively lower for polymers with larger proline fractions, but even in poly(Pro) the C and C^α mobility is very much higher than found in the ordered ribonuclease backbone.[112] Net mobilities for C^β and C^γ are appreciably larger than for C^δ (Table VI of Torchia and Lyerla[97]). Fossel et al.[111] report T_1 values and correlation times for several dipeptides containing glycine and proline which give similar ordering of ring atom mobilities. Komoroski et al.[110] report T_1 values for the proline rings of gramicidin; the T_1 values show trends similar to other proline derivatives.

The Force Field. During the past dozen years there have been extensive calculations of peptide conformations; in general these have concentrated on effects of variation of torsions. Lifson's group seems to have proposed the only fairly comprehensive peptide force field (Hagler et al.,[69] Hagler and Lifson,[113] Karplus and Lifson,[66] Schellman and Lifson,[65] Warshel et al.[114]). For other approaches see Ramachandran[116] and Scheraga.[117] The problem of parameterizing the necessary set of constants is formidable. Fortunately, it is possible to get useful results even with rather crude force fields; with careful ad hoc choices we may expect good geometries, and even rather good specifications of the energy contours near the minima.

For example, Schleyer's group has extended his alkane force field (Engler et al.[118]) to treat developing carbon cations and has achieved excellent results in predicting steric effects on solvolysis reactions (Slutsky et al.,[119] Fry et al.,[120] Bingham and Schleyer[121]). We have successfully used other extensions of the Schleyer force field to treat steric hindrance in ester hydrolysis (DeTar and Tenpas[122]).

Because a major part of the steric energy of most molecules depends on alkane types of interactions, it is especially pertinent to use a good alkane force field as the basis for elaboration. We have chosen the Schleyer 1973 force field, whose general validity has been established.[118,122] There are other good alkane force fields, but most are rather more complex and afford no clear advantages.

Table VIII. Summary of Observed and Calculated Proline Bond Lengths and Angles

Bonds	Obsd[a]	Calcd[b]	Angles	Obsd	Calcd
C^{α}-C	1.52 (0.02)	1.52	C-C^{α}-C^{β}	111 (3)	111
C^{α}-C^{β}	1.54 (0.04)	1.53	C-C^{α}-N	111 (3)	112
C^{β}-C^{γ}	1.51 (0.04)	1.53	C^{β}-C^{α}-N	103 (2)	103
C^{γ}-C^{δ}	1.52 (0.03)	1.53	C^{α}-C^{β}-C^{γ}	105 (3)	104
C^{δ}-N	1.49 (0.03)	1.46	C^{β}-C^{γ}-C^{δ}	106 (4)	103
N-C^{α}	1.48 (0.03)	1.46	C^{γ}-C^{δ}-N	103 (2)	105
C=O	1.24 (0.02)	1.24	C^{δ}-N-C^{α}	113 (2)	113
C-N	1.33 (0.03)	1.35	C_0-N-C^{α}	122 (3)	123
			C_0-N-C^{δ}	124 (3)	124
			O_0-C_0-N	121 (2)	121
			C_0^{α}-C_0-N	118 (3)	120
			C_0^{α}-C_0-O	121 (3)	119

[a] From averages of 25-40 values of x-ray coordinates. The standard derivation of a given value from the average is given in parentheses. [b] Typical values calculated for Ac-Pro-OCH_3.

Minimal treatment of peptides requires more than double the constants used for alkanes. In fact, treatment of peptides in the same detail would require several hundred force constants, reference distances, van der Waals terms, Coulombic constants, and hydrogen bond functions.

Our force field is summarized in Table VII. Since this may not suffice to reproduce our calculations we include a detailed printout summary in the supplementary material. In lieu of parameterization against reference molecules, which we have not yet done, we have adopted the following: for all bond lengths we have chosen a reference length which with the C-C force constant yields reasonably correct bond distances. For C=O we have used fixed values. It probably would be immaterial whether we allowed bond distances to vary so long as the same procedure was followed for all conformations. The reference angles about sp^2 carbons sum to 360° (planarity) and represent the general trend that angles flanking the double bond are roughly equal and slightly greater than 120°. The force constant 3×10^{-4} (mdyn-Å molecule^{-1} deg^{-2}) is roughly twice the C-C-C bending constant.

We customarily partition torsion barriers into nine parts in order to assure that the energy is independent of the description of the molecule. Warshel and Lifson[115] have reported a similar practice. Torsions across nitrogen have a sixfold partition (for a threefold barrier), across an amide O=C—N—C fourfold, and across an ester O=C-O-C twofold (for a twofold barrier). For χ_4 and χ_5 we used the C-C-C-C barrier per interaction, and this results in two-thirds of the C-C-C-C barrier or about 0.9 kcal/mol. For the C^{α}-C′ barrier we used half this value; see Lowe.[123] For the amide cis-trans rotational barrier we used 20 kcal/mol and for the ester C-O 8.5 kcal/mol.

Carbon van der Waals constants were applied also to N and O. For the present molecule the attractive part of the function plays a minor role, and the disregard of van der Waals radii is more apparent than real. Unfortunately there are no accepted ways to choose proper values for the several dozens of possible pairwise interactions.

The assignment of electron fractions (Coulombic charges) to the amide and ester groups reproduce the dipole moments: 3.7 D for the amide; 3.8 D for dimethylacetamide (Kumler and Porter[126]); other amides 3.5-3.9 D (McClellan[125]); 1.7 D for the ester methyl acetate 1.68 (Zahn,[124] McClellan[125]). The ratios of negative charges are in accord with those used by others and are derived from approximate quantum mechanical calculations.[56a,b,69] Within-group 1,3 Coulombic interactions are omitted, since the total 1,3 interactions have been incorporated into the force constants and reference angles. All between-group Coulombic interactions are included, however, since the purpose of the point charges is to describe the dipole moments. In actual fact calculations of proline conformations with Coulombic forces are not greatly different from those without. Other workers have chosen to assign Coulombic charges to alkane carbon atoms and hydrogen atoms.[56a,69] This is, of course, conceptually more realistic than assuming neutrality and is supported by approximate quantum mechanical calculations. However, force fields work successfully both with (Lifson and Warshel[127]) and without these detailed Coulombic charge distributions (Jacob et al.,[128] Allinger,[129] Engler et al.,[118] and many others), and the relative merits of the two approaches have not yet received careful comparison.

Typical calculated values of bond lengths and angles for acetylproline methyl ester are compared with averages of x-ray data in Table VIII. Agreement is satisfactory, and could be improved slightly by further adjustment of reference values. Since we are calculating relative steric energies of conformations, small changes in standard bond lengths and angles turn out to have only a minor effect. Calculations made with a force field which gave considerably larger departures than shown in Table VII produced nearly the same trends in conformational energies.

Calculations. The molecular mechanics calculations were performed with the program MOLMEC, described earlier.[122] Sample output is included in the supplementary material. Steric energies V_s were in the 13 kcal/mol range; adjustments were iterated until ΔV_s, the change in V_s per iteration, dropped below 1 part in 10 000. According to our algorithms, final V_s values will always be slightly higher than the minimum defined by the force field. We estimate that for the 1 part in 10 000 per iteration convergence limit V_s will be a maximum of 0.05 kcal/mol high; use of broader limits such as 1 part in 1000 gives somewhat larger but usable maximum errors of about 0.15-0.20 kcal/mol.

Probable errors for bond lengths due to breaking off iterations are effectively zero (0.0001 or less); the change in the angles between values found at 1 part in 1000 per iteration convergence and values at 1 part in 10 000 is a maximum of 0.3°, for most angles much less; the improvement in torsions was 0.6° or less.

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Supplementary Material Available: The crystal coordinate input used to prepare Table I (including transformation to the corresponding Cartesian coordinates); input Cartesian coordinates of the heavy atoms for representative calculated minimum energy conformations of Ac-Pro-OCH_3; table of heavy atom internal coordinates just like Table I, but calculated from the above Cartesian coordinates of calculated minimum energy conformations of Ac-Pro-OCH_3; complete Cartesian coordinates, including all hydrogen atoms, for representative minimum energy conformations of Ac-Pro-OCH_3; complete Table V; typical MOLMEC output showing force field (94 pages). Ordering information is given on any current masthead page.

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