The Nonplanar Peptide Unit. IV. Geometry and Nonplanar Distortions of the *cis*-Peptide Unit

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Synopsis

Semiempirical quantum chemical calculations were carried out using the CNDO/2 and the INDO methods on the model compound *cis*-*N*-methylacetamide in order to get an insight into the problem of possible nonplanar distortions of the *cis*-peptide unit. In addition, the crystal structure data of cyclic peptides containing *cis*-peptide units were analyzed. These studies have indicated that the dihedral angles θ_N and $\Delta\omega$ are correlated approximately by the relation $\Delta\omega = -\theta_N$, whereas θ_C is small and is uncorrelated with $\Delta\omega$, as was found in the case of the *trans*-peptide unit. Both theory and crystal data suggest that out-of-plane distortions at the nitrogen atom of the peptide unit were quite likely to occur and should be included in the conformational calculations. The average geometry for the planar *cis*-peptide unit has also been obtained from the observed examples.

INTRODUCTION

In previous communications of this series,[1-3] we have discussed the results of the calculations made on simple amides using semiempirical quantum chemical methods and an analysis of crystal structure data of simple peptides and amides; these were carried out in order to gain an insight into the problem of possible nonplanar distortions of the peptide units. These nonplanar distortions can be measured in terms of dihedral angles $\Delta\omega$, θ_N, and θ_C, where angle $\theta_N = \theta$ (C_2^α,H:NC) is the angle of rotation when looking from the plane CNC_2^α to CNH, which is positive for a clockwise rotation when looking from C to N, and similarly, $\theta_C = \theta$ (C_1^α,O:CN) is the angle of rotation from the plane NCC_1^α to the plane NCO, which is positive in the clockwise sense looking from N to C. Thus, dihedral angles θ_N and θ_C are measures of out-of-plane motion of N—H hydrogen and carbonyl oxygen atoms, respectively. In other words, the larger the value of these dihedral angles, the larger will be the pyramidal nature of the amide nitrogen or carbonyl carbon atoms. The studies carried out on the peptide unit or amides in the *trans*-conformation have indicated that the nonplanar

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distortions at the amide nitrogen are more easily accomplished as compared with those at the carbonyl carbon of the peptide unit. However, the peptide unit can exist in another stable conformation, namely, the *cis*-conformation. The *cis*-peptide unit, although it occurs rarely in open polypeptide chains, is found frequently in cyclic peptides. Many cyclic peptides are antibiotics, and in general, cyclic peptides make good model compounds for antibiotics. Thus, a knowledge of the possible nonplanar distortions of the peptide units in the *cis*-conformation will play an important role in working out the most probable conformations of these compounds. In fact, the necessity of considering nonplanar distortions of the peptide unit, which was first pointed out by Ramachandran,[4] was based on the observations made on cyclic peptides. Therefore, theoretical studies were carried out on the model compound *cis*-*N*-methylacetamide using semiempirical quantum chemical methods, namely, CNDO/2 and INDO.[5–7] The crystal structure data of cyclic peptides containing *cis*-peptide units have also been analyzed and a comparison has been made between the observed crystal structure data and the results of the theoretical calculations on *cis*-*N*-methylacetamide, as has been done for the *trans*-conformation.

In this connection, in order to have an initial input geometry for the planar peptide skeleton of *cis*-*N*-methylacetamide, an average *cis*-peptide unit geometry was obtained from an analysis of crystal structure data of cyclic peptides. This study has become essential mainly because the standard geometry of the *cis*-peptide unit suggested by Ramachandran and Venkatachalam[8] was derived from crystal data of diketopiperazine,[9] the only structure with *cis*-peptide units available at that time. These studies are discussed briefly in the succeeding sections.

GEOMETRY OF THE *cis*-PEPTIDE UNIT

Average Values of Bond Lengths and Angles from Crystal Data

The data from the x-ray diffraction studies on single crystals have been used to get the average values of bond lengths and bond angles of the *cis*-peptide unit, except for those involving hydrogen atoms. The values of bond lengths and bond angles, along with their standard deviations, obtained from these data are given in Tables I and II. Since the hydrogen atom attached to the amide nitrogen in every case has not been located precisely, the average values for bond length N—H and bond angles C—N—H and H—N—C_2^α have not been calculated. The weighted average values along with the standard deviations for other bond lengths and bond angles of the peptide unit are given in Fig. 1. In Fig. 1, as well as in the last rows of Tables I and II, the values of bond lengths and bond angles of the

TABLE I
Bond Lengths (in Å) of Peptide Units in the *cis*-Conformation and Their Standard Deviations from Crystal Structure Data of Some Cyclic Peptides

Compound	C_1^α—C	C—O	C—N	N—C_2^α	Ref.
⌐Gly-Gly¬	1.499(7)	1.239(7)	1.325(7)	1.449(7)	9
⌐Gly-Trp¬	1.509(6)	1.238(5)	1.309(6)	1.469(6)	10
	1.523(5)	1.234(4)	1.317(5)	1.451(5)	
⌐L-Ala-L-Ala¬	1.516(3)	1.235(2)	1.329(3)	1.461(3)	11
	1.512(2)	1.239(3)	1.330(2)	1.454(2)	
⌐D-Ala-L-Ala¬	1.509(1)	1.236(1)	1.332(1)	1.454(1)	11
⌐β—Ala—β—Ala¬	1.515(2)	1.239(2)	1.336(2)	1.453(2)	12
⌐L-Pro-L-Leu¬	1.522(6)	1.244(6)	1.341(6)	1.463(6)	13
	1.507(6)	1.228(6)	1.356(6)	1.461(6)	
⌐L-Leu-L-His¬	1.499(4)	1.245(4)	1.332(4)	1.452(4)	14
	1.511(4)	1.237(3)	1.323(3)	1.461(4)	
⌐L-Ser-L-His¬	1.515(3)	1.253(3)	1.313(3)	1.461(4)	15
	1.508(3)	1.232(3)	1.332(3)	1.461(3)	
⌐L-Pro-D-Phe¬	1.508(3)	1.235(3)	1.330(3)	1.454(3)	16
	1.518(3)	1.222(3)	1.331(3)	1.457(3)	
⌐*N*-Me-L-Ala-L-Ala¬	1.516(4)	1.234(4)	1.326(4)	1.468(4)	17
	1.513(4)	1.241(4)	1.335(4)	1.469(4)	
⌐L-Cys-L-Cys¬	1.525(5)	1.247(4)	1.325(5)	1.448(5)	18
Cyclo(Sar_2)	1.506(4)	1.234(3)	1.348(3)	1.455(3)	19
Cyclo(Sar_4)	1.530(5)	1.235(3)	1.352(4)	1.454(5)	20
Cyclo(Sar_5)	1.518(7)	1.227(5)	1.352(6)	1.456(4)	21
	1.517(7)	1.236(6)	1.367(6)	1.455(6)	
	1.537(7)	1.236(6)	1.325(6)	1.433(6)	
Cyclo(Sar_8)	1.536(7)	1.227(5)	1.352(6)	1.454(6)	22
	1.531(7)	1.222(5)	1.340(6)	1.448(6)	
	1.529(7)	1.219(5)	1.350(6)	1.451(6)	
	1.531(7)	1.230(5)	1.338(6)	1.447(6)	
Cyclo(Ala-Sar_4)	1.528(5)	1.224(5)	1.345(5)	1.445(5)	23
	1.528(5)	1.227(5)	1.345(5)	1.448(5)	
	1.523(5)	1.222(5)	1.350(6)	1.455(5)	
Weighted average	1.515(11)	1.235(10)	1.335(13)	1.455(7)	
From Ref. 8	1.53	1.24	1.32	1.47	8

peptide unit as suggested by Ramachandran and Venkatachalam[8] are given. The differences in the two geometries of the *cis*-peptide unit are not significant.

Probable Values of Bond Angles C—N—H and H—N—C_2^α: Results of Quantum Chemical Calculations

In order to get the probable values for bond angles C—N—H and H—N—C_2^α, semiempirical quantum chemical calculations were carried out on the planar *cis*-*N*-methylacetamide molecule using the CNDO/2 and INDO methods. The atomic coordinates of the *cis*-peptide unit were calculated using the parameters from Ref. 8. The methyl group at the

TABLE II
Bond Angles of Peptide Units in the *cis*-Conformation and Their Standard Deviations from Crystal Structure Data of Some Cyclic Peptides

Compound	C_1^α—C—O	C_1^α—C—N	O—C—N	C—N—C_2^α
⌐Gly-Gly¬	118.5(3)	118.9(3)	122.6(3)	126.0(3)
⌐Gly-Trp¬	116.0(3)	119.5(3)	124.5(3)	127.4(3)
	117.8(4)	120.7(4)	121.4(4)	125.1(4)
⌐L-Ala-L-Ala¬	120.2(2)	116.8(2)	123.0(2)	125.9(2)
	120.6(2)	116.9(2)	122.5(2)	126.2(1)
⌐D-Ala-L-Ala¬	118.4(1)	118.6(1)	123.0(1)	127.9(1)
⌐β—Ala-β—Ala¬	119.9(1)	119.0(1)	121.1(1)	125.5(1)
⌐L-Pro-L-Leu¬	123.9(3)	113.9(3)	122.2(3)	123.5(3)
⌐L-Pro-L-Leu¬	123.9(3)	113.9(3)	122.2(3)	123.5(3)
	122.8(3)	114.0(3)	123.2(3)	123.0(4)
⌐L-Leu-L-His¬	119.2(3)	119.3(3)	121.4(3)	126.5(2)
	118.8(2)	119.0(3)	122.2(3)	126.6(2)
⌐L-Ser-L-His¬	119.3(3)	118.8(3)	121.8(3)	126.8(3)
	117.6(3)	120.1(3)	122.3(3)	126.2(3)
⌐L-Pro-D-Phe¬	118.9(2)	117.3(2)	123.8(2)	126.8(3)
	119.7(2)	117.2(2)	123.1(2)	127.0(3)
⌐*N*-Me-L-Ala-L-Ala¬	119.3(2)	117.6(2)	123.0(2)	125.1(2)
	118.8(2)	118.6(2)	122.4(2)	123.3(2)
⌐L-Cys-L-Cys¬	118.0(1)	120.0(1)	121.9(2)	127.6(2)
Cyclo(Sar_2)	118.3(2)	118.1(2)	123.6(2)	124.6(2)
Cyclo(Sar_4)	119.2(3)	119.1(2)	121.7(3)	123.9(3)
Cyclo(Sar_5)	121.9(4)	116.1(4)	122.0(4)	123.6(4)
	121.7(5)	116.1(5)	122.2(5)	120.8(5)
	117.9(5)	121.0(5)	121.1(5)	124.1(5)
Cyclo(Sar_8)	120.9(5)	117.2(5)	121.9(5)	125.0(5)
	120.7(5)	116.2(4)	122.9(5)	122.7(4)
	120.5(5)	117.4(4)	121.9(5)	123.6(4)
	120.6(5)	117.7(4)	121.8(5)	123.8(4)
Cyclo(Ala-Sar_4)	120.7(5)	117.8(5)	122.3(4)	123.6(5)
	121.5(4)	117.4(4)	122.5(5)	124.3(5)
	119.8(5)	116.0(4)	120.5(6)	120.5(6)
Weighted average	119.4	118.1	122.4	125.3
	(1.7)	(1.7)	(0.9)	(1.9)
From Ref. 8	119.0	118.0	123.0	126.0

carbonyl carbon atom was fixed such that one of the C_1^α—H bonds eclipses the C=O bond. The other methyl group was fixed to the nitrogen atom with its hydrogens in the staggered conformation with respect to the N—H bond. Our calculations on the planar *cis*-*N*-methylacetamide molecule with the above geometry have suggested these orientations of methyl groups. The bond angles τ_4(C—N—C_2^α) and τ_5(C—N—H) were varied from the initial values by ±2.5°, and the energy of the planar *cis*-*N*-methylacetamide molecule was calculated. The changes in the values of τ_4 and τ_5 from the initial values are represented by $\Delta\tau_4$ and $\Delta\tau_5$, respectively. The change in energy values of the molecule, calculated for different values of $\Delta\tau_4$ and $\Delta\tau_5$, are given in Table III. It is clear from the ΔE values

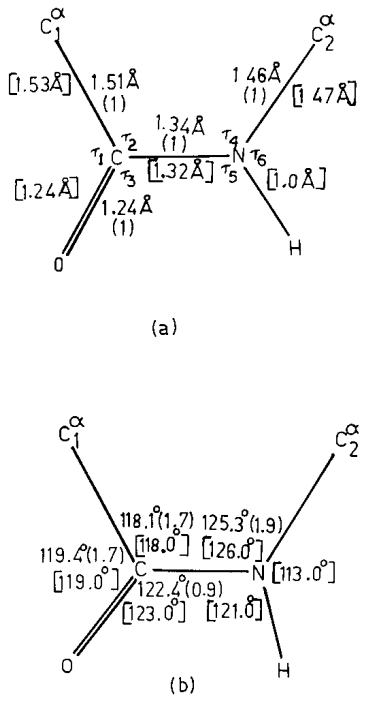


Fig. 1. Weighted average values, obtained from the crystal structure data of cyclic peptides of bond lengths (a) and bond angles (b) of the *cis*-peptide unit along with their standard deviations. Parameters from Ref. 8 are given in square brackets.

that the energy is minimum for the initial structure. Since there are no significant changes in the values of other bond angles and bond lengths obtained from crystal structure data and the values from Ref. 8, further quantum chemical calculations were carried out for the molecule of *cis*-*N*-methylacetamide using the parameters of Ref. 8.

TABLE III
Energy Values (in kcal/mol) Obtained from CNDO/2 and INDO Methods for *N*-Methylacetamide in the *cis*-Conformation[a]

	$\Delta\tau_5$		
$\Delta\tau_4$	−2.5°	0.0°	+2.5°
	A. CNDO/2		
−2.5°	+0.51	+0.26	+0.33
0.0°	+0.09	+0.0	+0.23
+2.5°	+0.03	+0.11	+0.50
	B. INDO		
−2.5°	+0.52	+0.10	+0.34
0.0°	+0.09	0.0	+0.24
+2.5°	+0.02	+0.10	+0.52

[a] $\Delta\tau_4$ and $\Delta\tau_5$ are variations of bond angles τ_4 and τ_5 from values as given in Fig. 1(b). Energy of the molecule of *N*-methylacetamide having equilibrium geometry was assumed to be 0.0 kcal/mol.

NONPLANAR DISTORTIONS OF *cis*-*N*-METHYLACETAMIDE: QUANTUM CHEMICAL CALCULATIONS

As mentioned in the earlier communication of this series,[1] nonplanar distortions at the amide nitrogen of the peptide unit can be described in terms of two dihedral angles, namely, $\Delta\omega$ and θ_N. Therefore, these dihedral angles $\Delta\omega$ and θ_N were varied at intervals of 5° from 0° to 20° and 0° to 40°, respectively. It should be mentioned that the value of bond angle H—N—$C_2^\alpha(\tau_6)$ not only depends on the values of bond angles C—N—$C_2^\alpha(\tau_4)$ and C—N—H(τ_5), but also on the value of the dihedral angle θ_N. Thus, the value of τ_6 is uniquely fixed by the values of τ_4, τ_5, and θ_N. Therefore, in order to see the effect of in-plane distortions on out-of-plane distortions, the molecular energy was calculated by varying the parameters τ_4 and τ_5 in addition to the parameters $\Delta\omega$ and θ_N. These bond angles were varied at intervals of 2.5° around their respective initial values, namely, 126.0° and 121.0°. The energy of the molecule having a planar *cis*-conformation was assumed to be 0.0 kcal/mol. For each ($\Delta\omega$,θ_N), the energy was minimized with respect to τ_4 and τ_5. These energy values, obtained using the CNDO/2 and the INDO methods and after minimization with respect to τ_4 and τ_5, are used to draw isoenergy contours in the ($\Delta\omega$,θ_N)-plane at intervals of 0.5 kcal/mol, as shown in Fig. 2.

It can be seen from Fig. 2(a) that the CNDO/2 method gives a global minimum at $\Delta\omega = 15°$ and $\theta_N = -25°$ (for $\Delta\tau_4 = 0.0°$ and $\Delta\tau_5 = -2.5°$). The global minimum position is marked in Fig. 2(a) by a cross (×). However, the energy differences between the global minimum and the planar

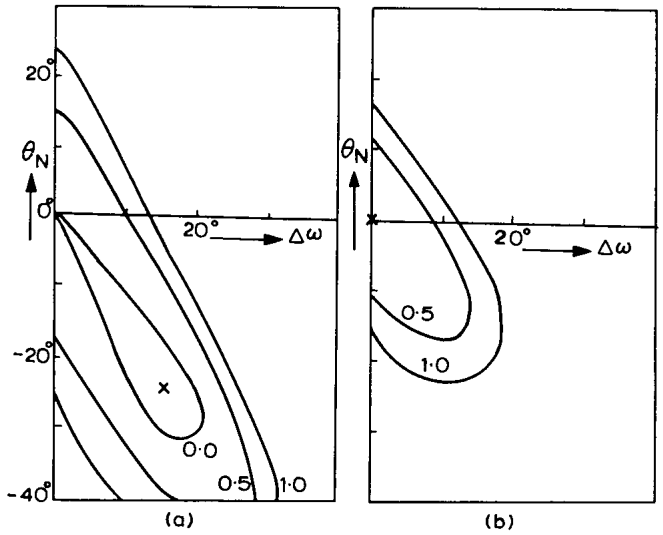


Fig. 2. Isoenergy curves at intervals of 0.5 kcal/mol in the ($\Delta\omega$,θ_N)-plane for *N*-methylacetamide having the *cis*-conformation obtained using the CNDO/2 (a) and the INDO (b) methods. The minimum-energy position is marked by the cross (×).

conformation is only 0.1 kcal/mol. Thus, all the conformations lying in the region enclosed by the 0.0. kcal/mol energy contour will be equally probable.

The INDO method gives a shallow energy minimum around the planar conformation. Thus, the results presented in Fig. 2(b) indicate that distortions from planarity for $|\Delta\omega|$ up to 10° and $|\theta_N|$ up to 15° can occur without appreciable change in energy.

ANALYSIS OF CRYSTAL STRUCTURE DATA FOR NONPLANARITY IN THE *cis*-PEPTIDE UNIT

The data from the crystal structures of peptides containing the *cis*-peptide unit were used to calculate the values of the parameters $\Delta\omega$, θ_N, and θ_C. The values of these parameters are listed in Table IV. Inspection of Table IV shows that *cis*-peptide units are generally distorted from planarity, in particular at the nitrogen atom, and $\Delta\omega$ and θ_N vary over a range of 0°–19.0° and 0°–23.8°, respectively. The values of $\Delta\omega$ and θ_N from Table IV are plotted in Fig. 3(a). Similarly, in Fig. 3(b), the values of θ_C and $\Delta\omega$ from the crystal structures are plotted. It can be seen from Fig. 3(b) that the values of θ_C generally lie in the range of −5° to +5° and are equally distributed on either side of the $\Delta\omega$ axis, similar to our observation on the *trans*-peptide unit.[3] This indicates that possible nonplanar distortions at the carbonyl carbon atom are very small as compared with those at the nitrogen atom of the *cis*-peptide unit, and are uncorrelated to $\Delta\omega$, while there is a strong correlation between $\Delta\omega$ and θ_N, shown by the dashed diagonals in Fig. 3(a).

DISCUSSION

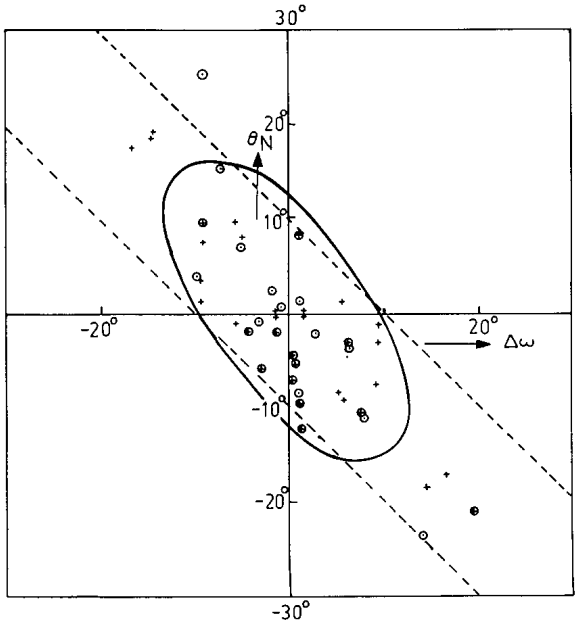
In deriving the averaged geometry of the planar *cis*-peptide unit, data from molecules such as actinomycin, ilamycin B_1, antamanide, and cyclo-(Pro-Pro-Hyp) or cyclo(Pro_3) are not used mainly because these structures are not as accurate as those considered here. However, the inclusion of bond lengths and bond angle values from these structures does not alter the dimensions given in this paper. The values of the dihedral angle θ_C, as obtained from the crystal structure data of various cyclic peptides for *cis*-peptide units (Table IV) and the distribution of points in the $(\Delta\omega,\theta_C)$-plane [Fig. 3(b)], are very similar to those reported in our earlier communication[3] for *trans*-peptide units. This suggested that the constraint of cyclization, as such, has very little effect on nonplanar distortions at the carbonyl carbon atom. However, the observed values of $(\Delta\omega,\theta_N)$ which are plotted in the Fig. 3(a) indicate that constraints due to cyclization may get released to some extent by nonplanar distortions of the peptide unit. The distortions result with the expense of very little energy, which can be seen from the fact that most of the observed $(\Delta\omega,\theta_N)$ values lie within the 0.5 kcal/mol contour for *cis*-*N*-methylacetamide, as calculated using the INDO method.

TABLE IV
Values of Dihedral Angles $\Delta\omega$, θ_N, and θ_C (in deg) Calculated for Peptide Units in the *cis*-Conformation from X-Ray Diffraction Data of Some Cyclic Peptides

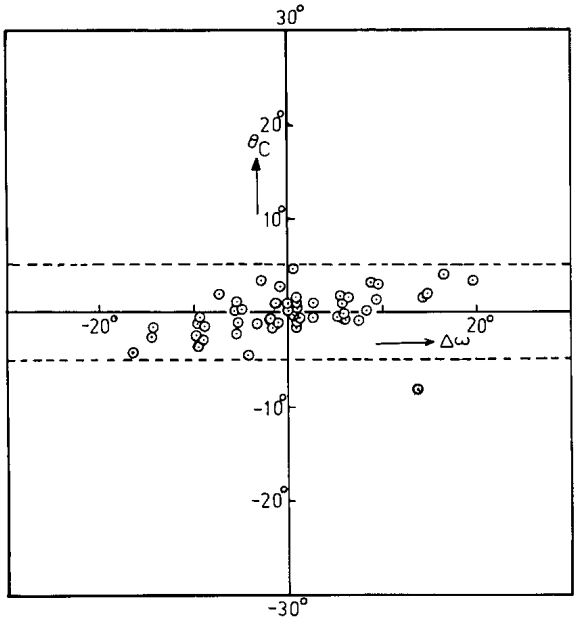
Compound	$\Delta\omega$	θ_N	θ_C
┌Gly-Trp┐	+2.7	−2.3	+1.0
┌L-Ala-L-Ala┐	+8.2	−11.1	+0.2
	+0.8	−8.6	−1.4
┌D-Ala-L-Ala┐	−3.2	−0.9	−1.1
┌β-Ala-β-Ala┐	+0.9	+1.2	+1.2
┌L-Pro-L-Leu┐	+6.4	−3.8	+1.6
	+6.2[a]	−2.9	−0.5
┌L-Leu-L-His┐	−9.2	+25.2	−1.1
	−9.5	+4.0	−2.5
┌L-Ser-L-His┐	−1.9	+2.4	−0.2
	−0.8	+0.5	+2.8
┌L-Pro-D-Phe┐	2.7	—	−0.1
	+0.7[a]	+8.3	−0.3
┌*N*-Me-L-Ala-L-Ala┐	−9.3[a]	+9.9	−0.1
┌L-Cys-L-Cys┐	−5.2	+7.1	+1.4
	−7.2	+15.3	+2.2
Cyclo(Sar_4)	+9.4[a]	−1.3	+3.2
	−5.5[a]	−1.0	−2.1
Cyclo(Sar_5)	−9.4[a]	+3.4	−1.4
	−1.2[a]	+0.2	+1.0
	+14.2[a]	−18.8	+1.5
Cyclo(Sar_8)	+9.1[a]	−7.6	+2.9
	−1.1[a]	−0.4	−1.0
	+16.5[a]	−17.2	+4.2
	+5.6[a]	−9.8	−0.1
Cyclo(Ala-Sar_4)	−14.4[a]	+19.0	−2.3
	−4.9[a]	+8.2	+0.2
Cyclo(Pro-Pro-Hyp)[b]	−5.4[a]	+9.2	−1.1
	+19.5[a]	−21.0	+3.1
	+0.0[a]	−7.1	+0.8
	+1.0[a]	−12.4	−0.9
Cyclo(Pro_3)[b]	+0.4[a]	−5.1	+4.8
	−1.5[a]	−2.5	−1.5
	+0.8[a]	−9.7	+1.3
	+14.0[a]	−23.7	−8.0
	+7.5[a]	−10.4	−0.6
	+0.1[a]	−5.0	+0.4
Li-Antamanide[c]	−4.3[a]	−1.9	−4.5
	−2.9[a]	−6.0	+3.3

[a] Denotes that the hydrogen atom attached to the nitrogen atom in the peptide residue is replaced by C (as in imido group)
[b] Data derived from Refs. 24 and 25.
[c] Private communication from Prof. Karle.

Second, the conformations plotted in Fig. 3(a) also lie within the area enclosed by the diagonals, which are parallel to a straight line having the equation $\theta_N = -\Delta\omega$ and passing through the $\Delta\omega$ axis at +10° and −10°. The distribution of points in this figure indicates that $\Delta\omega$ and θ_N are cor-



(a)



(b)

Fig. 3. (a) The plotted values of $(\Delta\omega,\theta_N)$ from Table IV. The diagonals are parallel to a straight line $\theta_N = -\Delta\omega$ and cut the $\Delta\omega$ axis at $\Delta\omega = \pm 10°$; enclosing the observed points, they indicate a correlated variation of $\Delta\omega$ and θ_N. Note that most of the observed points lie inside the 0.5 kcal/mol contour obtained using the INDO results for *cis*-*N*-methylacetamide. (b) Distribution of points in the $(\Delta\omega,\theta_C)$-plane for the *cis*-peptide units. The data used are from Table IV and indicate that θ_C is rarely greater than 5° and is uncorrelated with $\Delta\omega$. +, Gly with H substituted. ⊙, Non-Gly. ⊕, Non-Gly with H substituted.

related approximately by the relation $\Delta\omega = -\theta_N$, thus indicating a close correspondence between theory and observation. These results are very similar to those discussed in our earlier communication[3] for *trans*-peptide units.

The results of energy calculations carried out using the INDO method for the parameters τ_4,τ_5, in addition to $\Delta\omega$, and θ_N, indicate that the energy required to bring nonplanar deformations of the order of 10°–15° is nearly the same as that required to vary the bond angles τ_4 and τ_5 by ±2.5° from their equilibrium values. These energy values also point out that for higher values of θ_N (which decrease the bond angle H—N—C_2^{α}), the energy reaches a minimum when the value of the bond angle τ_5 (C—N—H) decreases. This is in good agreement with the usual physical picture that the hydrogen atom, being lightest, should more easily adopt in-plane, as well as out-of-plane, deformations, as compared to the methyl group attached to the nitrogen atom.

Here, only the INDO results are discussed, mainly because in the previous paper of this series[3] it has been pointed out that the INDO results are in better agreement with experimental observations than those obtained using the CNDO/2 method. However, it should be noted that the results obtained for *cis*-*N*-methylacetamide using the CNDO/2 method are not very different from those obtained using the same method for the *trans*-conformer.

CONCLUSIONS

The foregoing results and discussion lead to the following conclusions:

1. The weighted average values obtained for bond lengths and bond angles of the *cis*-peptide unit from crystal structure data of cyclic peptides mentioned here should be used in conformational calculations of cyclic peptides.

2. The influence of the constraint of cyclization on nonplanar distortions is very little, in particular at the carbonyl carbon atom. $|\theta_C|$ values are found to be small ($|\theta_C| \leqslant 5°$), and the dihedral angles $\Delta\omega$ and θ_C are uncorrelated, as in the case of *trans*-peptide unit.

3. The nonplanar distortions at the nitrogen atom having values of $|\Delta\omega|$ and $|\theta_N|$ up to 10° and 15°, respectively, are very likely. The dihedral angles $\Delta\omega$ and θ_N are approximately related by the relation $\Delta\omega = -\theta_N$. Thus, in conformational energy calculations on cyclic peptides or polypeptides containing *cis*-peptide units, these distortions should also be included.

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