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Peptide models XXIV: An ab initio study on N-formyl-L-prolinamide with *trans* peptide bond. The existence or non-existence of α_L and ϵ_L conformations

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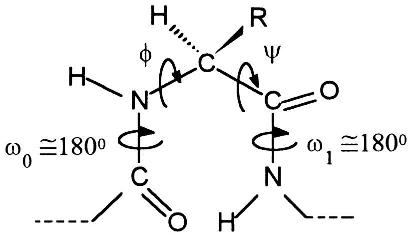
Abstract

N-formyl-L-prolinamide was subjected to geometry optimization at three levels of theory: HF/3-21G, HF/6-31G (d) and B3LYP/6-31G (d). At all three levels of computation the global minimum was γ_L (inverse γ-Turn) backbone conformation with two ring-puckered forms ‘‘UP’’ and ‘‘DOWN’’. At HF/3-21G level of theory three backbone conformations were found γ_L, ϵ_L, and α_L. At higher levels of theory the ϵ_L, and α_L conformations disappeared. The ‘‘UP’’ and ‘‘DOWN’’ ring-puckered forms, in the γ_L backbone conformation, led to practically identical vibrational spectra at the B3LYP/6-31G (d) level of theory.

Keywords: Molecular conformations; N-formyl-L-prolinamide; *Trans*-Peptide bond

1. Introduction

In general N- and C- protected amino acid residues (1), such as they may occur in proteins,



(1)

$$E = E(\phi, \psi) \tag{2}$$

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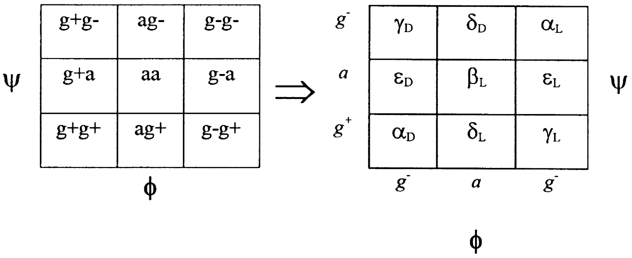


ψ			
	g+g-	ag-	g-g-
	g+a	aa	g-a
	g+g+	ag+	g-g+
	ϕ		

g^-	γ_D	δ_D	α_L
a	ε_D	β_L	ε_L
g^+	α_D	δ_L	γ_L
	g^-	a	g^-

Scheme 1.

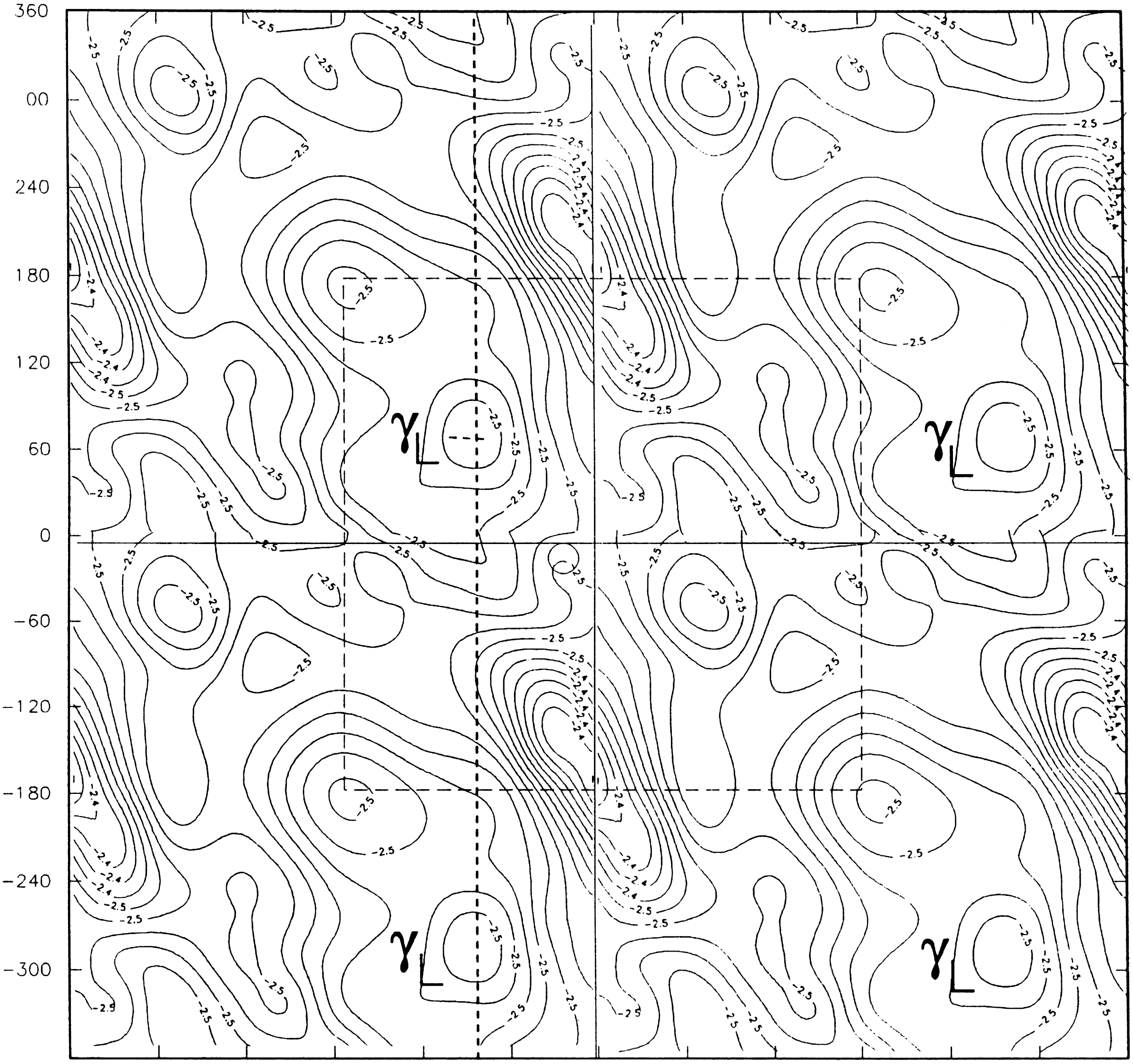


Fig. 1. Ramachandran potential energy surface of HCONH–CHCH$_3$–CONH$_2$. The cross-section used for the protected proline is shown by broken line passing through γ_L.

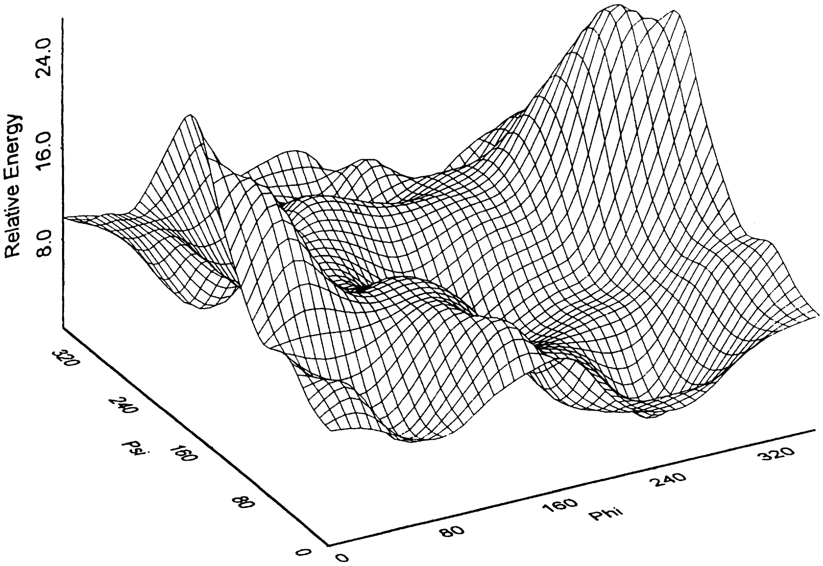


Fig. 2. Pseudo-three-dimensional Ramachandran potential energy surface of HCONH–$CHCH_3$–$CONH_2$ presented in the 0° $\leq \phi \leq$ 360° and 0° $\leq \psi \leq$ 360° range of the independent variables.

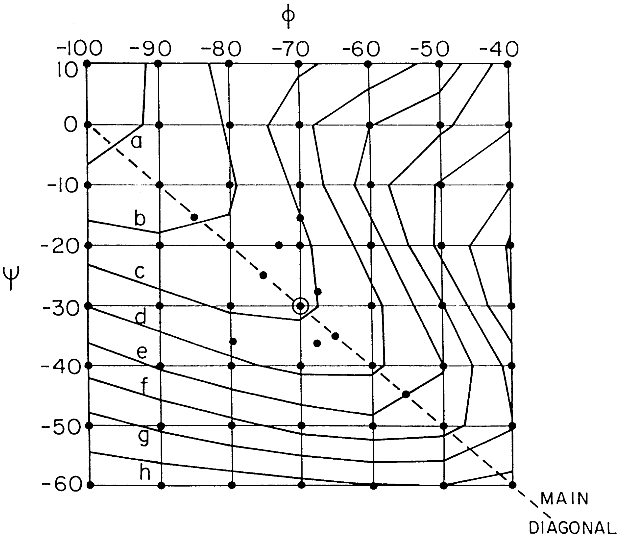


Fig. 3. Energy contour diagram of the potential energy surface in the region of the expected location of the α_L conformation. Computed points are shown as solid circles. a = −412.466841; b = −412.465789; c = −412.464737; d = −421.463684; e = −412.462632; f = −412.461579; g = −412.460526; h = −412.459474.

Table 1
Total energy values of N-formylglycinamide, N-formylpyrrolidine and N-methylformamide computed at various levels of theory at their global minimum structures

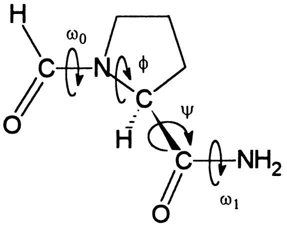
Compound	3-21G	6-31G(d)	
	HF	HF	B3LYP
N-methylformamide	−206.799111	−207.961349	−209.199886
N-methylpyrrolidine	−322.096525	−323.900644	−325.932635
N-methylglycinamide (γ)	−373.648790	−375.747943	−377.852257

have nine discrete conformations [1] since both ϕ and ψ may assume g^+, a and g^- conformations. The pattern of the potential energy surface (PES) (2), frequently referred to as the Ramachandran map, is shown in Scheme 1.

All nine conformation were found in di-amino acid diamides [2,3], such as HCO-L-Ala-L-Ala-NH_2 but most single amino acid diamides, studied so far, such as Ala [4], Val [5], Phe [6,7], did not exhibit the α_L and ϵ_L conformations as minima on the Ramachandran map. This problem was studied extensively [2,3] in the case of N-formyl-L-Alanine-amide and N-acetyl-L-Alanine-methylamide but no minima were located at or near the expected minima of the α_L and ϵ_L conformers. The overall Ramachandran map as well as its landscape representation are presented in Figs. 1 and 2 respectively for For-L-Ala-NH_2. A close-up of the α_L region is shown in Fig. 3.

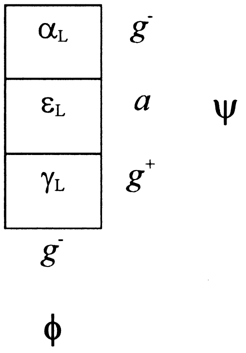
It should be mentioned that the α_L conformation was found in the case of serine (i.e. For-L-Ser-NH_2) owing to side chain/backbone hydrogen bonded interaction [8–12]. However no ϵ_L conformations was reported as yet in the case of any single amino acid diamide studied computationally.

The proline residue is a special case as illustrated by N-formyl-prolinamide (3):



(3)

The pyrrolidine ring will permit only one ϕ value in the vicinity of g^- (i.e. −60°),while ψ may assume three different values in the vicinity of g^+ (i.e. +60°), a (i.e. 180°) and g^- (i.e. −60°). Consequently, instead of nine only three discrete conformers may be expected:



(4)

Note that two out of the three conformers are the ''elusive structures'', namely the α_L and ϵ_L. It is therefore of considerable interest to study the conformations of (3).

2. Computational method

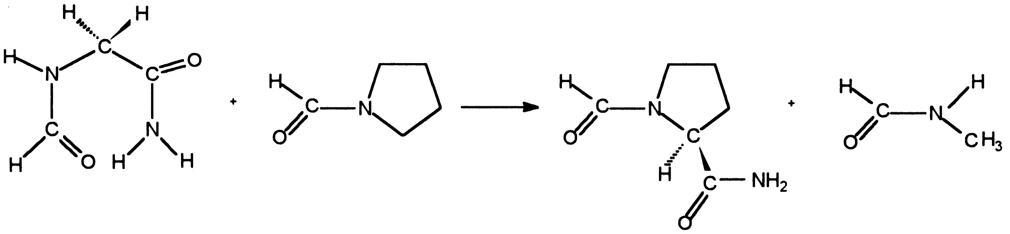
Ab initio Hartree–Fock and density functional geometry optimizations were carried out using the Gaussian 94 program system [13]. Two basis sets 3-21G and 6-31G(d) were employed at the Hartree–Fock (HF) level of theory and the B3LYP type of DFT procedure was applied using only the larger basis set 6-31G(d).

The relative energies (ΔE) were calculated with respect the γ_L conformations. Stabilization enregies (ΔE_{stabil}) were calculated with respect to N-formylglycinamide [14] using the following isodesmic

Table 2
Total energy values of N-formylprolinamide computed at various levels of theories and several geometry optimized backbone (BB) and ring puckered conformations (''UP'' and ''DOWN'' structures are denoted by (U) and (D) respectively)

BB	Puckering	ω_0 (°)	ϕ (°)	ψ (°)	ω_1 (°)	E (hartree)	ΔE (kcal mol^{-1})	ΔE_{stabil} (kcal mol^{-1})
3-21G								
α_L	U (*Syn*)			Not found				—
α_L	D (*anti*)	−173.05	−74.49	−23.44	−179.21	−488.941002	8.37	+3.26
ϵ_L	U (*Syn*)	+175.81	−70.98	150.62	+178.25	−488.943851	6.58	+1.48
ϵ_L	D (*anti*)			Not found				—
γ_L	U (*syn*)	−172.98	−83.28	67.96	−178.84	−488.954348	0.00	−5.11
γ_L	D (*anti*)	−171.71	−82.79	68.77	−178.87	−488.951950	1.50	−3.61
HF/6-31G(d)								
α_L	U (*Syn*)			Not found				—
α_L	D (*anti*)			Not found				—
ϵ_L	U (*Syn*)			Not found				—
ϵ_L	D (*anti*)			Not found				—
γ_L	U (*syn*)	−172.16	−84.90	73.81	−173.09	−491.689586	0.00	−1.47
γ_L	D (*anti*)	−170.46	−83.94	78.83	−171.19	−491.687963	1.19	−0.45
B3LYP/6-31G(d)								
α_L	U (*Syn*)			Not found				—
α_L	D (*anti*)			Not found				—
ϵ_L	U (*Syn*)			Not found				—
ϵ_L	D (*anti*)			Not found				—
γ_L	U (*syn*)	+177.10	−81.01	70.36	−173.55	−494.638904	0.00	−0.06
γ_L	D (*anti*)	−170.01	−81.76	73.56	−171.95	−494.638557	0.22	−0.05

reaction (5):



(5)

The necessary energy components are listed in Table 1.

A total of 7466 Pro residues were collected from 1135 non-homogenous proteins [15,16]. All entries included in this study have high-resolution X-ray structures taken from the 1996 issue of the Brookhaven Protein Data Base (PDB) [17,18].

3. Results and discussion

3.1. Molecular structure and stability

The geometrical and energetic characteristics of N-formyl-prolinamide, as obtained by geometry optimizations at three levels of theory, are summarized in Table 2 and illustrated in Fig. 4. There are a number of points to notice.

1. Ring puckering lead to two isomeric forms. Since the carboxyl group is pointing up the ''UP'' ring puckering means a *Syn* arrangement and a ''DOWN'' puckering means an *anti* arrangement (c.f. Fig. 4).
2. The inverse γ-turn (i.e. the γ_L backbone conformations) occurs at both ''UP'' and ''DOWN'' arrangement at all three levels of theory. The two ring puckered conformers are close in energy ($\Delta E \leq 1.5$ kcal/mol) and one of the two structures represents the global minimum.

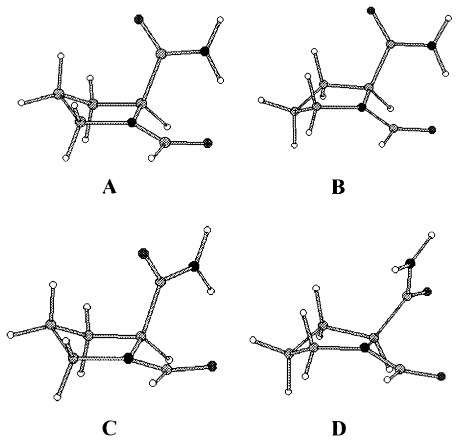
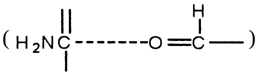
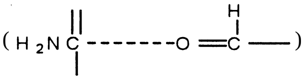


Fig. 4. Molecular structures of the optimized conformations of N-Formyl-L-Prolinamide.
(A) γ_L (*syn*): r (O···HN) = 1.98 Å; ∠ (NHO) = 143.1°.
(B) γ_L (*anti*): r (O···HN) = 1.96 Å; ∠ (NHO) = 143.3°.
(C) ϵ_L (*syn*): r (



$H_2N\overset{\|}{\underset{|}{C}}\text{-------}O{=}\overset{H}{\overset{|}{C}}\text{—}$) = 3.12 Å.
(D) α_L (*anti*): r (



$H_2N\overset{\|}{\underset{|}{C}}\text{-------}O{=}\overset{H}{\overset{|}{C}}\text{—}$) = 3.17 Å.
N: black; O: heavily shaded; C: highly shaded;
H: open circle.

3. At HF/3-21G level of theory there is a ''DOWN'' (or *anti*) ring puckering structure for the α_L-backbone conformation. Likewise, at the same level of theory, there exist a ''UP'' (or *Syn*) ring puckered structure for the ϵ_L backbone conformation. Since this was the first time an ϵ_L conformation was located for a single aminoacid diamide these two backbone conformations (α_L and the ϵ_L) were reoptimized at the HF/3-21G level of theory at ''tight'' condition and each were subjected to a frequency calculation. Both structures turned out to be a minimum. The ''tight'' optimization yielded energy values, which were the same as the ''normal'' optimization within 0.0000005 hartree. The computed differences in torsional angles are shown in bold in Table 3. All frequencies were positive. The lowest frequencies were rather small: 43.1 and 32.1 cm^{-1} for the α_L and ϵ_L conformations respectively indicating that both minimums are rather shallow. However, without any shadow of doubt the α_L and ϵ_L minima do exist at the HF/3-21G level of theory.
4. Two sets of scan, along torsional angle ψ, were carried out (along the broken vertical line shown in Fig. 1) incorporating the global minimum, i.e. the γ_L backbone conformation. One of the two sets were for the ''UP'' or (*Syn*) puckered ring (Fig. 5) while the other one was for the ''DOWN'' or (*anti*) puckered ring (Fig. 6). The two scans in Fig. 5 are identical, as expected, eventhough the curve on which the points are denoted by solid circles started from the γ_L while the set of computed points (open circles) associated with the other curve have started with the ϵ_L backbone conformation. In contrast to that described before, in Fig. 6 (depicting the ''DOWN'' or *anti* ring pucked structure) the two curves are not identical. The

Table 3
A comparison of the ''tight'' (T) and ''normal'' (N) optimization on molecular geometry and energy of N-formly-L-prolinamide, with ''UP'' (U) and ''DOWN'' (D) ring puckering. Computed at HF/3-21G level of theory

BB	Puckering	Opt	ω_0^a	ϕ (°)	ψ (°)	ω_1^a	E (hartree)
α_L	U (*Syn*)	N			Not found		
		T			Not found		
α_L	D (*anti*)	N	173.05	−74.49	−23.44	−179.21	−488.941002
		T	−17**1.38**	−74.**52**	−23.41	−179.27	−488.941002
ϵ_L	U (*Syn*)	N	+175.81	−70.89	15062	+178.25	−488.943851
		T	+175.8**0**	−70.**94**	150.**58**	+178.2**6**	−488.943851
ϵ_L	D(*anti*)	N			Not found		
		T			Not found		
γ_L	U (*Syn*)	N	−172.98	−83.28	67.96	−178.84	−488.954348
		T	−172.**64**	−83.27	67.9**4**	−178.8**2**	−488.954348
γ_L	D (*anti*)	N	−171.71	−82.79	68.77	−178.87	−488.951950
		T	−171.**82**	−82.**80**	68.72	−178.8**4**	−488.951950

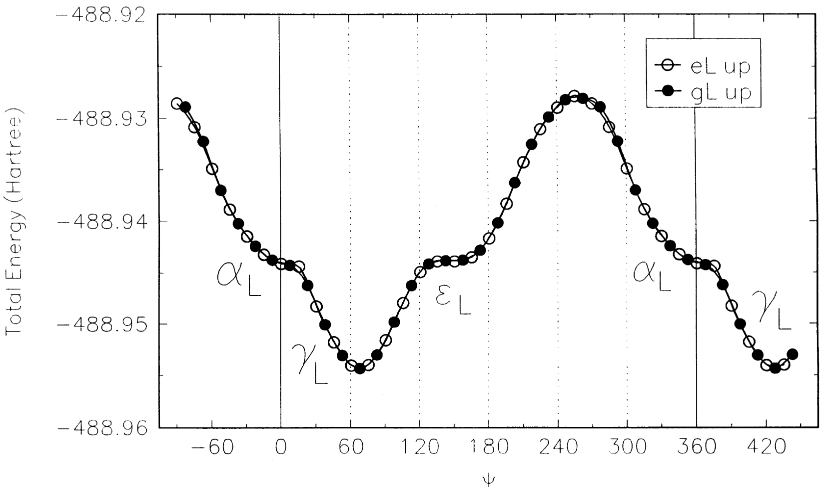


Fig. 5. Potential energy curve $E = E(\psi)$ cross-section of the conformational PES for the ‘‘UP’’ (*Syn*) ring puckered N-formyl-L-prolinamide.

hysteresis like deviation, in the vicinity of the α_L and ϵ_L region, is owing to the change in ring puckering. In other words, eventhough the scan was started with ‘‘DOWN’’ or *anti* structure the CH_2 group the flipped from ‘‘DOWN’’ to ‘‘UP’’ and back along the change in ψ.

5. Larger basis set and the inclusion of electron correlation altered substantially the PES, as certain conformations were annihiliated [20]. This was observed in the case of the α_L as well as the ϵ_L conformation.
6. The geometrical arrangements are illustrated in Fig. 4. In the case of the two γ_L conformations the seven member ring with the dominant N–H···O=C hydrogen bonding is clearly seen. However, in the case of the α_L and ϵ_L conformation no evidence was seen for the existence of any possible (hydrogen bonding or charge transfer) interactions; the relevant interatomic separations are longer than 3 Å.
7. The energetics of the ring inversion are presented in Table 4. The barrier to ring flips on going from γ_L ‘‘UP’’ to γ_L ‘‘DOWN’’ is relatively low. It turned out to be 3.08 and 2.13 kcal/mol at the HF/3-21G and B3LYP/6-31G(d) levels of theory respectively. The schematic inversion potentials are shown in Fig. 7.
8. The stabilization energy, ($\Delta E_{\mathrm{estabil}}$), as computed according to Eq. (5) for the global minimum: γ_L ‘‘UP’’ (or *Syn*) is −5.11 kcal/mol. This value positions N-formyl-prolinamide, at the HF/3-21G level of theory, in between serine and valine as shown

Table 4
Ring puckering energetics[a] for N-formly-L-Prolinamide computedat two levels of theory

	HF/3-21G		B3LYP/6-31G(d)	
	E (hartree)	E_a or ΔE (kcal mol^{-1})	E (hartree)	E_a or ΔE (kcal mol^{-1})
γ_L ‘‘UP’’ (*Syn*)	−488.954348	0.00	−494.638905	0.00
TS	−488.949437	3.08	−494.635558	2.13
γ_L.’’DOWN’’ (*anti*)	−488.951950	1.50	−494.638558	0.22

[a] See Fig. 7 for illustration.

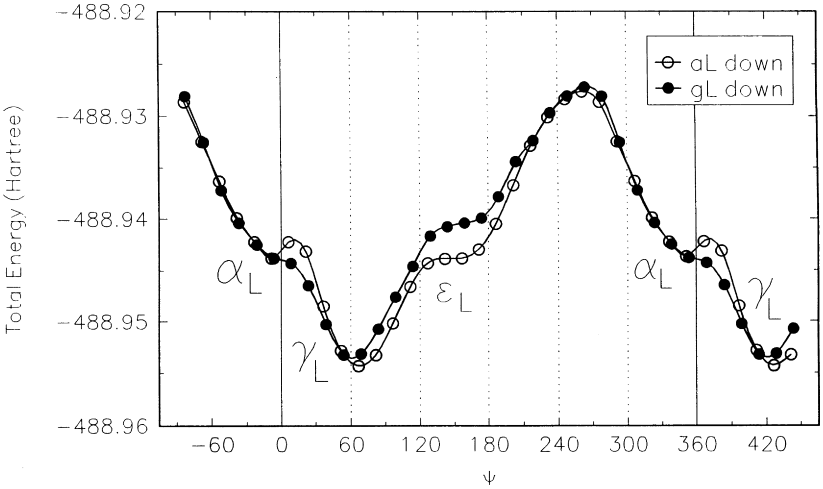


Fig. 6. Potential energy curve $E = E(\psi)$ cross-section of the conformational PES for the ''DOWN'' (*anti*) ring puckered N-formyl-L-prolinamide.

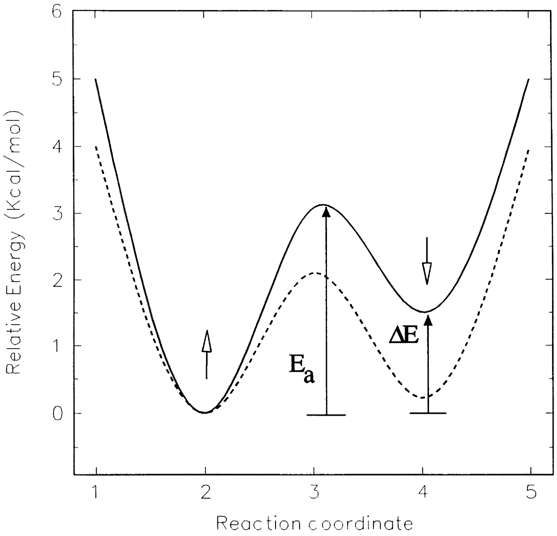


Fig. 7. A schematical potential energy function of ring puckering for the γ_L backbone conformation of N-formyl-L-prolinamide ($\gamma_{L(\uparrow)} \leftrightarrow$ TS $\leftrightarrow \gamma_{L(\downarrow)}$).

Table 5
Calculated frequencies for the ''UP'' (*Syn*) and ''DOWN'' (*anti*) puckering of the γ_L conformation of N-formyl-L-prolinamide. Computed at the B3LYP/6-31G(d) level of theory

Syn			*Anti*		
U[a]	S[b]	I[c]	U	S	I
62.29	59.88	2.63	63.74	61.27	3.39
94.89	91.22	3.67	83.69	80.45	3.03
149.53	143.74	0.81	131.6	126.50	1.06
203.34	195.47	6.61	213.81	205.54	6.55
233.03	224.01	4.69	239.77	230.49	6.89
270.76	260.28	4.85	293.11	281.77	21.34
310.62	298.60	21.53	310.24	298.23	2.04
365.55	351.40	13.13	377.02	362.43	11.74
410.91	395.01	11.35	403.18	387.58	5.99
503.28	483.80	84.72	527.00	506.60	12.56
513.42	493.55	131.07	535.46	514.74	192.03
558.41	536.8	22.32	586.44	563.74	24.55
643.27	618.38	25.88	606.89	583.40	18.63
664.49	638.77	20.95	667.52	641.69	40.29
734.89	706.45	13.52	720.11	692.24	31.84
753.96	724.78	14.19	748.30	719.34	7.40
820.60	788.84	2.23	826.27	794.30	4.59
885.28	851.02	2.92	888.16	853.79	4.86
904.46	869.46	4.80	918.00	882.48	1.16
931.84	895.78	0.93	927.64	891.74	2.93
936.38	900.14	2.69	940.67	904.27	4.40
998.48	959.84	3.64	993.33	954.89	1.58
1023.09	983.50	0.62	1019.81	980.35	0.50
1066.56	1025.28	2.53	1051.41	1010.72	2.76
1114.24	1071.12	1.58	1125.32	1081.77	7.15
1162.35	1117.37	0.18	1163.90	1118.86	6.57
1176.47	1130.94	19.48	1179.65	1134.00	18.86
1210.46	1163.61	18.16	1203.04	1156.48	21.03
1214.75	1167.74	2.39	1223.30	1175.96	3.61
1278.46	1228.98	6.29	1265.59	1216.61	9.13
1306.76	1256.19	26.14	1299.43	1249.15	15.31
1328.46	1277.05	18.88	1333.02	1281.43	17.14
1351.17	1298.88	5.75	1353.27	1300.90	33.22
1363.51	1310.74	28.41	1361.06	1308.39	4.60
1367.67	1314.74	6.85	1381.39	1327.93	1.88
1409.25	1354.71	32.18	1408.61	1354.10	26.74
1415.64	1360.85	122.60	1418.96	1364.05	100.50
1448.63	1392.57	26.64	1456.64	1400.27	48.25
1508.17	1449.80	8.21	1521.55	1462.66	3.21
1527.13	1468.03	14.72	1530.61	1471.38	8.05
1550.39	1490.39	4.18	1545.43	1485.62	1.11
1652.71	1588.75	191.38	1655.70	1591.63	195.28
1758.98	1690.91	275.01	1757.49	1689.47	285.51
1800.82	1731.13	331.15	1806.87	1736.95	324.72
2994.85	2878.95	72.13	2999.41	2883.33	77.47
3036.89	2919.36	55.04	3042.46	2924.71	38.94
3067.97	2949.24	14.04	3065.59	2946.95	26.90
3082.01	2962.74	21.28	3071.19	2952.34	7.91
3085.81	2966.39	12.56	3091.04	2971.41	15.74
3099.20	2979.26	30.90	3113.67	2993.17	23.66
3135.87	3014.51	26.78	3122.23	3001.40	25.89
3160.25	3037.95	4.35	3139.85	3018.34	16.64
3480.80	3346.09	129.62	3475.71	3341.20	133.99
3664.03	3522.23	68.15	3659.68	3518.05	66.71

[a] U: Unscaled frequencies (cm^{-1}).

[b] S: Scaled frequencies (cm^{-1}), scaling factor (0.9613) from Ref. [21].

[c] I: IR intensities ($\mathrm{K\,m\,mol}^{-1}$).

in (6):

$$\begin{array}{l} \mathrm{Gly} > \mathrm{Ser}(g^-g^+) > \mathrm{Pro(``UP")} > \mathrm{Val}(a) \\ 0.00 > -5.08 \qquad > -5.11 \quad > -5.40 \\ > \mathrm{Ala} > \mathrm{Phe}(g^-) > \mathrm{Phe}(a) \\ > -5.60 > -5.74 > -6.82 \\ > \mathrm{Phe}(g^+) \\ > -8.33 \end{array}$$

3.2. Vibrational characteristics

Since the γ_L conformation represents the global minimum and the ''UP'' and ''DOWN'' ring puckering structure are very close in energy ($\Delta E = 0.2$ kcal/mol at the DFT level of theory) we have subjected these two structures to vibrational analysis. The frequencies were computed for the ''UP'' (i.e. *Syn*) and the ''DOWN'' (i.e. *anti*) structures at the B3LYP/6-31G(d) level of theory and the results are summarized in Table 5.

The frequencies were scaled using an accepted [21] frequency factor of 0.9613. These scaled values are also tabulated in Table 3 together with the computed intensities. The spectroscopic differences between the ''UP'' (*Syn*) and ''DOWN'' (*anti*) ring seem very small as can also be judged from Fig. 8(a) and (b). Consequently one cannot expect to see the super-

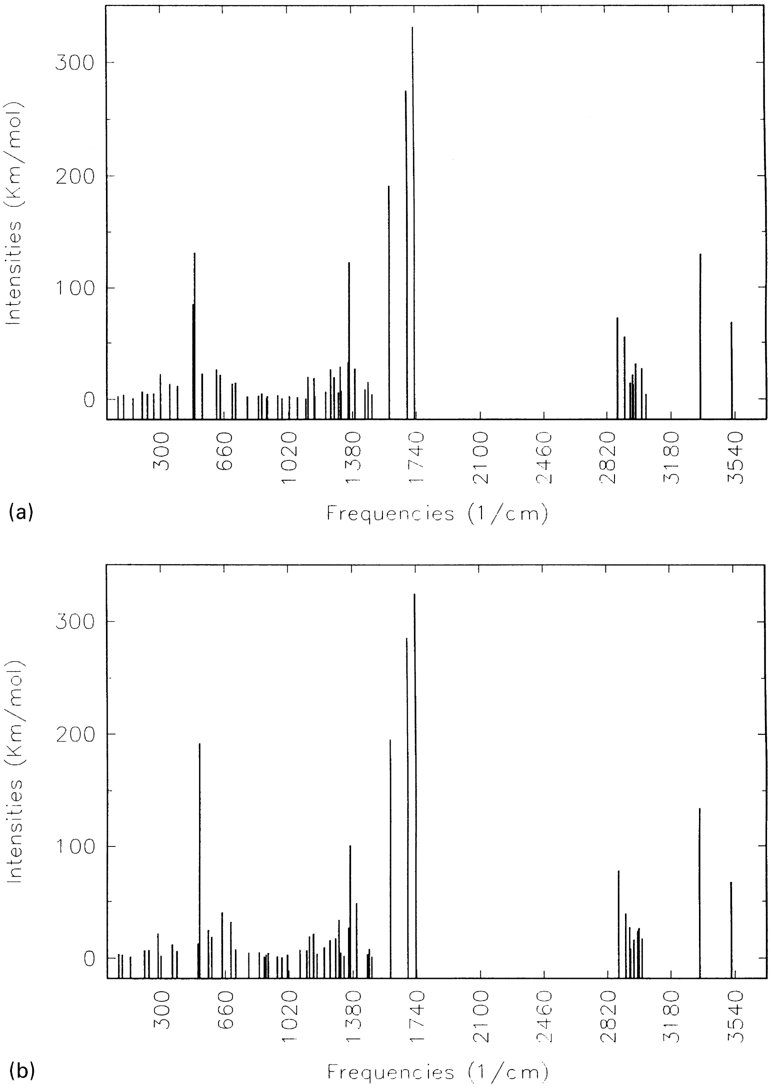


Fig. 8. (a) Scaled vibrational spectrum of N-formyl-L-prolinamide in the $\gamma_{L(\uparrow)}$ conformation. (b) Scaled vibrational spectrum for N-formyl-L-prolinamide in the $\gamma_{L(\downarrow)}$ conformation.

imposition of two sets of lines in the experimental spectra. These results can now be compared with experimental observations.

3.3. Statistical analysis of protein structure

Using the backbone dihedral parameters (ϕ and ψ), all of the 7466 Proline residues were plotted on a ϕ, ψ map (Fig. 9). The number of proline conformations (Nψ) is shown as a function of ψ in Fig. 10(a) and Fig. 10(b) shows

$$+\ln[N_\psi/N_{\mathrm{total}}]$$

as a function of ψ.Fig. 10(c) shows

$$-\ln[N_\psi/N_{\mathrm{total}}].$$

This latter figure is analogous to a potential energy

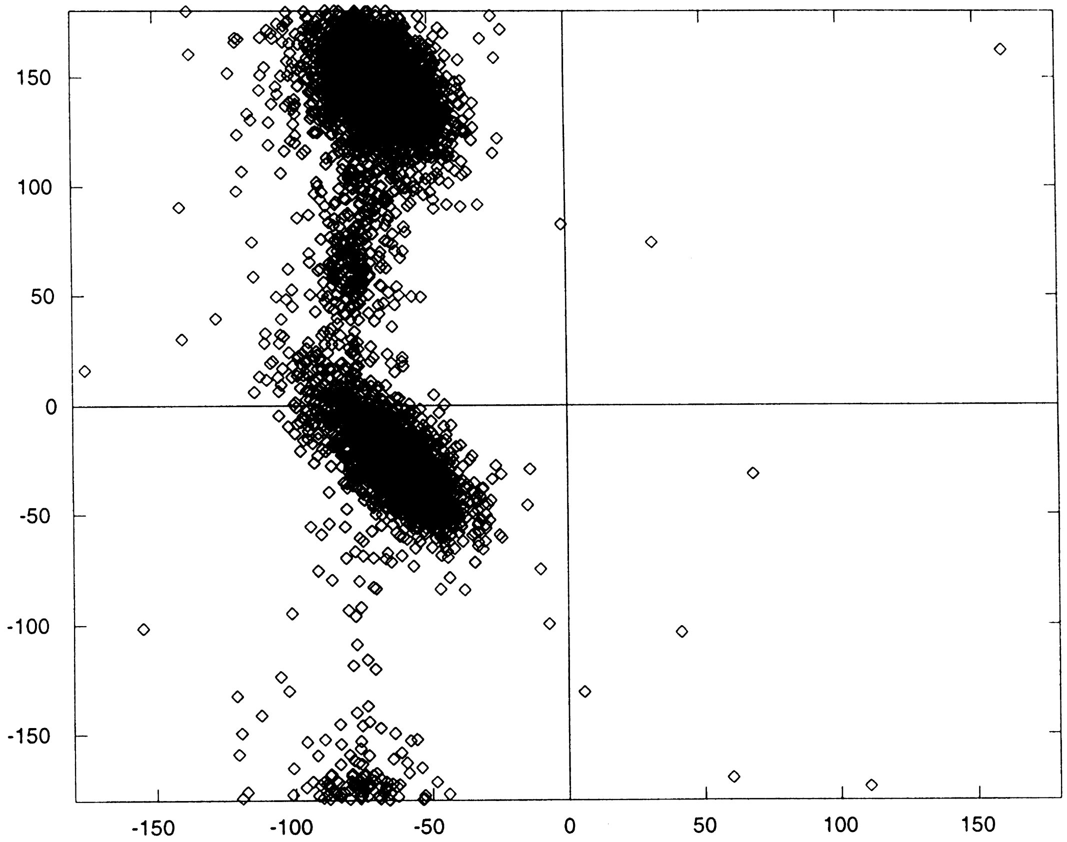


Fig. 9. Distribution of proline residue backbone conformations taken from 1135 non-homogeneous protein from the Brookheve PDB.

curve owing to the following linear relationship [12,19]:

$$\Delta E = -|m|\ln[N_{\psi}/N_{\text{total}}]+b.$$

4. Conclusions

Proline represent a special case among the most common naturally occurring amino acids. Owing to the relatively narrow margin of variation in ϕ the proline residue may have only three discrete conformations: γ_L, ϵ_L and α_L. Since, in most amino acid residues the ϵ_L and α_L conformation were annihilated in the Ramachandran map it was observed with great interest that both ϵ_L and α_L conformation were found by geometry optimization at the HF/3.-21G level of theory. These conformations disappeared at higher levels of theory.

The pyrrolidine ring showed that the ‘‘UP’’ and ‘‘DOWN’’ ring puckered structures were energetically very close to each other and they had only a couple of kcal/mol barrier heights for ring inversion.

The calculated vibrational spectra for the ‘‘UP’’ and ‘‘DOWN’’ isomers were practically identical.

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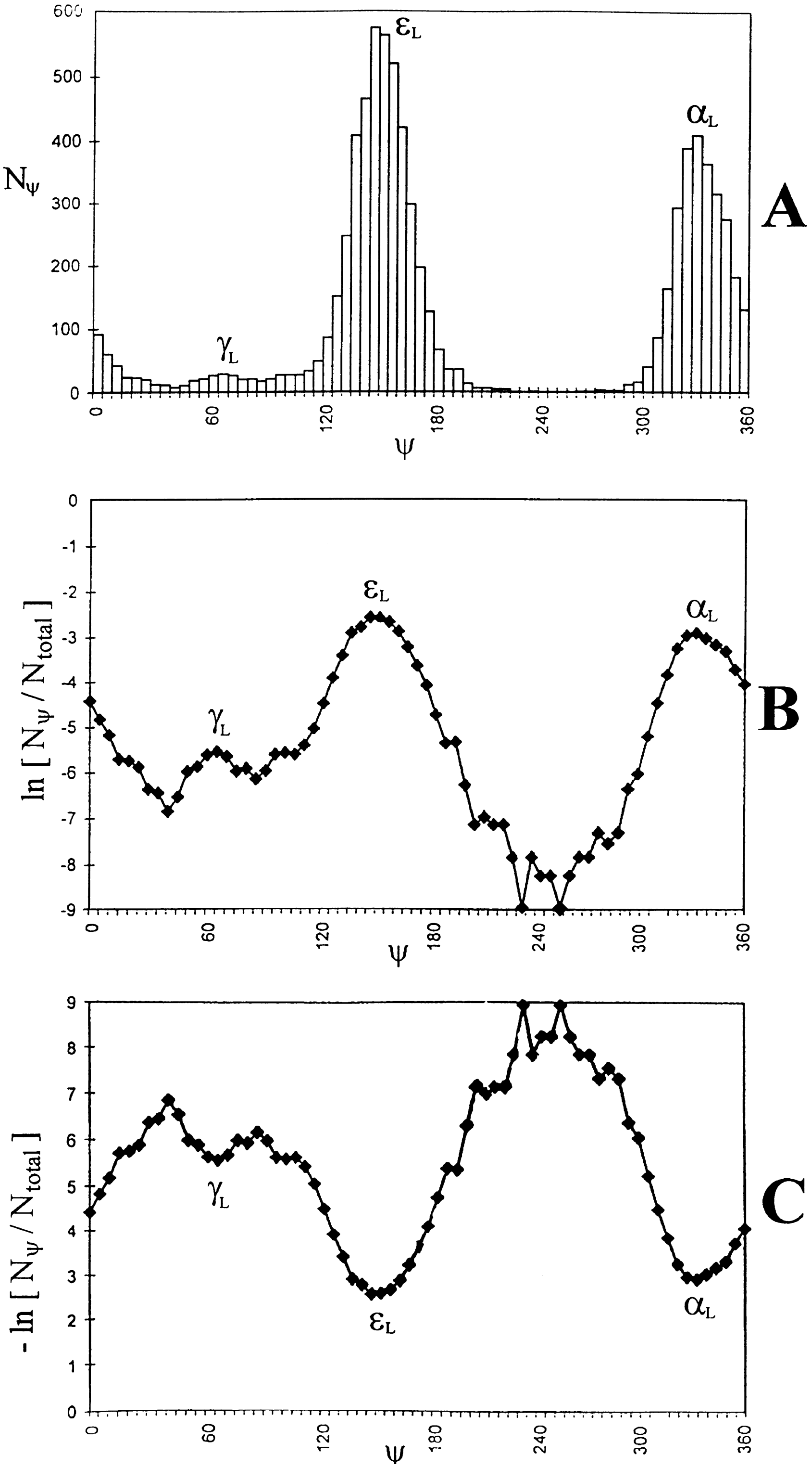

Fig. 10. (a) Number (N_ψ) of proline residues as a function of ψ. (b) Natural log of relative number $\ln[N_\psi/N_{\text{total}}]$ of proline residues as a function of ψ. (c) Negative of the natural log of XXX$-\ln[N_\psi/N_{\text{total}}]$.

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