Peptide Potential Energy Surfaces and Protein Folding

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Abstract

Motivation. This paper outlines the utility of a 3D→1D transformation of peptide conformation. Although this transformation leads to a linearized notation of protein secondary and tertiary structures that may be used for an objective description and classification of protein folding, nevertheless, the method is intended to be descriptive and is not meant to be predictive.

Method. It is established from first principles that the idealized 2D-Ramachandran potential energy surface must have nine minima. It is therefore an obvious question to ask whether all these nine conformations are actually occurring in proteins. An analysis is carried out on 258 proteins with known X-ray structure. These proteins contain 56 495 amino-acid residues with well-defined ϕ and ψ angles. The minima are identified with the aid of the nine minima of Ac-L-Ala-NHMe determined by ECEPP/2 method allowing a ±40° tolerance in the ϕ and ψ values. All nine conformations do occur in proteins.

Results. *L*-conformation preference varies as: $\varepsilon > \gamma > \alpha >> \delta > \beta = 1$. Pro is the amino acid with the greatest preference for *L*-conformation. *L*-conformation preference varies as: Pro >> Ile > Val > Leu > Thr > Met > Ala > Glu > Phe > Trp > Tyr > Gln > Lys > Ser > Cys > Arg > Asp > His > Asn > Gly. The results relative to achiral Gly shows that the trend-line slope varies as: $\alpha >> \varepsilon > \gamma >> \beta = 0 \approx \delta$. The strong Pro preference is in agreement with its character of strong α-helix and β-sheet breaker, and β-turn and random-coil former.

Conclusions. In XX–XXI centuries, the secondary–tertiary structures of proteins, frequently referred to as protein folding, posed a major problem to medicine, biochemistry, pharmaceutical drug design and related fields. A method is formulated, *via* a 3D→1D transformation, which allows using a qualitative linearized notation for protein 3D structures, which is based on quantitative geometrical data. It appears that with the present objective method, there is no longer any need to refer to a particular protein segment as unordered, and the description–classification of protein secondary–tertiary structures is now within reach of all protein chemists. *L*-conformation preferences vary as: $\varepsilon > \gamma > \alpha >> \delta > \beta = 1$, and as: Pro >> Ile > Val > Leu > Thr > Met > Ala > Glu > Phe > Trp > Tyr > Gln > Lys > Ser > Cys > Arg > Asp > His > Asn > Gly. The Pro preference is in agreement with its strong character of α-helix and β-sheet breaker, and β-turn and random-coil former.

Availability. The original software used in the investigation is available from the author.

Keywords. Peptide potential energy surface; Ramachandran map; peptide conformation; protein folding; protein secondary structure: chirality.

Abbreviations and notations

1D, one dimensional	PEC, potential energy curve
2D, two dimensional	PEHS, potential energy hypersurface
3D, three dimensional	PES, potential energy surface
Ala, alanine	Phe, phenylalanine
C_α, α-carbon atom chiral centre	Pro, proline
ECEPP, empirical conformational energy program for peptides	STD, standard
Gly, glycine	TOP, topological
H-bond, hydrogen bond	β_λ, Betti number
MCA, multidimensional conformational analysis	ϕ, peptide dihedral angle CCNC
N_λ, number of critical points	ψ, peptide dihedral angle NCCN
NA, not assigned	

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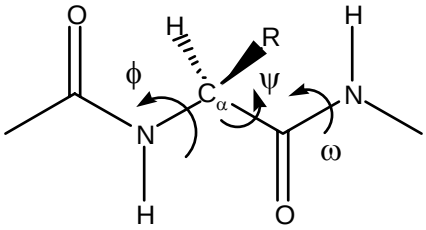
1 INTRODUCTION

Multidimensional conformational analysis (MCA), which is an intuitive conception tool of every organic chemist, allows one to predict from the topology of the component potential energy curves (PEC) the topology of the potential energy surface (PES) if the molecular system is ideal [1–3]. In the case of three-fold periodicity, the $3\times3 = 9$ minima are energetically degenerate. This case is operative for two CH_3 rotors as may be occurring in propane and in molecules with two equivalent CH_3 groups [*e.g.*, CH_3OCH_3, CH_3-$(CH_2)_2$-CH_3, *etc.*]. If, on the other hand, the component PECs continue to have three minima but these minima are energetically non-degenerate then the resultant PES will have nine non-equivalent minima. In the case of the ideal PES, it was possible to make a statement that all nine minima have the same energy value; in the non-ideal case we can make an analogous statement that all nine minima have different energy values. However, we are not in the position to predict what the energy spectrum of these nine minima might be and what the relative stability of these minima could be. Nevertheless, by making an intuitive guess we can suggest an order for the relative stabilities of the diagonal elements:

$$E(0_2) > E(0_1) > E(0_0) \tag{1}$$

What is important to note from the foregoing arguments that the PES for a single peptide unit (Scheme 1)



may be represented as:

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

if ω is constant (usually $\omega = 180°$). Nine minima have been expected to be present on the surface. However, only five out of the nine minima have been recognized earlier in the literature. The minima are labelled as left-handed helix, right-handed helix, extended-like conformation, γ-turn and inverse γ-turn. In Figure 1 both ϕ and ψ vary between zero and 360°.

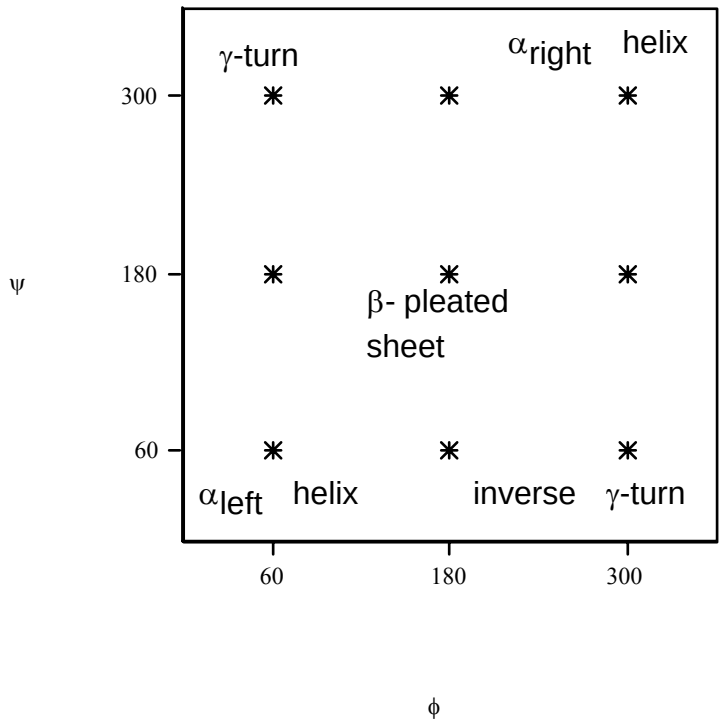


Figure 1. Idealized PES topology for a single amino-acid residue indicating the five minima that already have been identified in the protein literature. (The idealized location of the minima is specified by stars.)

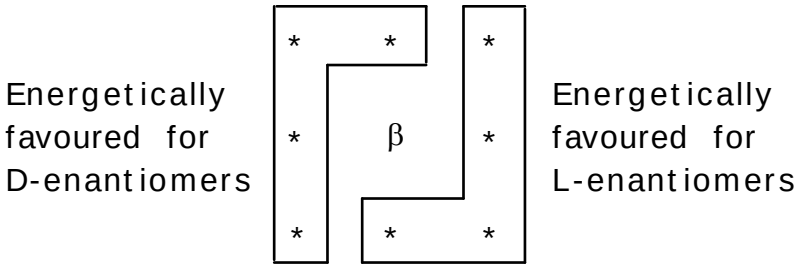
However, protein chemists adopted a range for both ϕ and ψ that runs between –180° and 180° covering both clockwise and counter-clockwise rotations, which may be labelled as standard (STD):

$$-180° \le \phi_{\text{STD}} \le 180° \qquad (3)$$
$$-180° \le \psi_{\text{STD}} \le 180°$$

We feel that our representation is more useful as topological (TOP) relationships can be recognized with a greater ease:

$$0° \le \phi_{\text{TOP}} \le 360° \qquad (4)$$
$$0° \le \psi_{\text{TOP}} \le 360°$$

More important is the fact that apart from the central minimum (the conformation associated with β-pleated sheet) the minima occur in pairs. Thus, the remaining unassigned four minima (*cf*. Figure 1) could be regarded as two pairs of minima. Preliminary study indicated that, apart from the β conformation, the most important, that is the energetically most favoured, conformations for the L-enantiomer are at the *extreme right* and *lower right*, and for the D-enantiomer the most favoured conformations are at the *upper left* and *extreme left*. The topological relationship of these two families is illustrated in Scheme 2.



Consequently, the Greek symbols associated with the *extreme right* are subscripted by *L*, and the Greek symbols associated with the *extreme left* are subscripted by *D*. Thus, instead of saying that the conformation that is capable of producing a right-handed helix we say it is the α_L conformation. Similarly, instead of the conformation that is capable of generating a left-handed helix we might say it is the α_D conformation. In order to refer to the as of yet unassigned conformations, the midpoint at the *top* is labelled as δ_D and the midpoint at the *bottom* is labelled as δ_L. The midpoint at the *left* is labelled as ε_D and the mid-point at the *right* is labelled as ε_L. Utilizing the labels used previously to denote the location of the minima, we obtain the following arrangement (Scheme 3).

γ_D δ_D α_L

ε_D β ε_L

α_D δ_L γ_L

For glycine (Gly) where no chiral centre exists, the β conformation is to be located at the geometric centre. For L-amino acids β becomes β_L and its position is shifted towards the *lower-right* hand corner. For D-amino acids β becomes β_D and its position is shifted towards the *upper-left* hand corner of the idealized topological scheme (*cf*. Scheme 3), which represents only a different cut of the PES as illustrated by the broken lines in Figure 2.

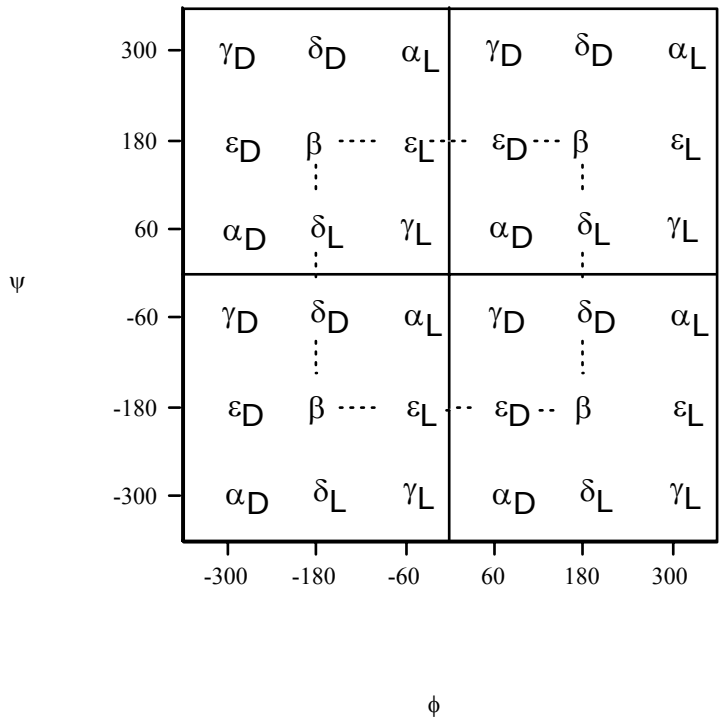


Figure 2. Idealized PES topology for a single amino-acid residue involving two complete cycles of rotation in both ϕ and ψ (the location of the minima are specified by their names in terms of subscripted Greek letters).

In a PES associated with an ideal molecular system, minima, saddle points and maxima occur in a predictable regular pattern. It is customary to denote these critical points with the number of negative eigenvalues of the Hessian matrix, with elements:

$$H_{ij} = \frac{\partial^2 E}{\partial x_i \partial x_j} \tag{5}$$

where $[x_i, x_j]$ are any pair of the total of n variables including $[\phi, \psi]$. The number of negative eigenvalues of the Hessian is usually referred to by the index λ of the critical point. For ordinary surfaces n varies between zero and two ($0 \le \lambda \le 2$):

$$\begin{aligned} \lambda &= 0 \text{ for minima} \\ \lambda &= 1 \text{ for saddle points} \\ \lambda &= 2 \text{ for maxima} \end{aligned} \tag{6}$$

For potential energy hypersurfaces (PEHS):

$$0 \le \lambda \le n \tag{7}$$

for minima $\lambda = 0$, for maxima $\lambda = n$, and in between are located the transition-state points with a variety of indices ranging from one to $n - 1$. Figure 3 again shows an ideal surface as applied to a single peptide residue.

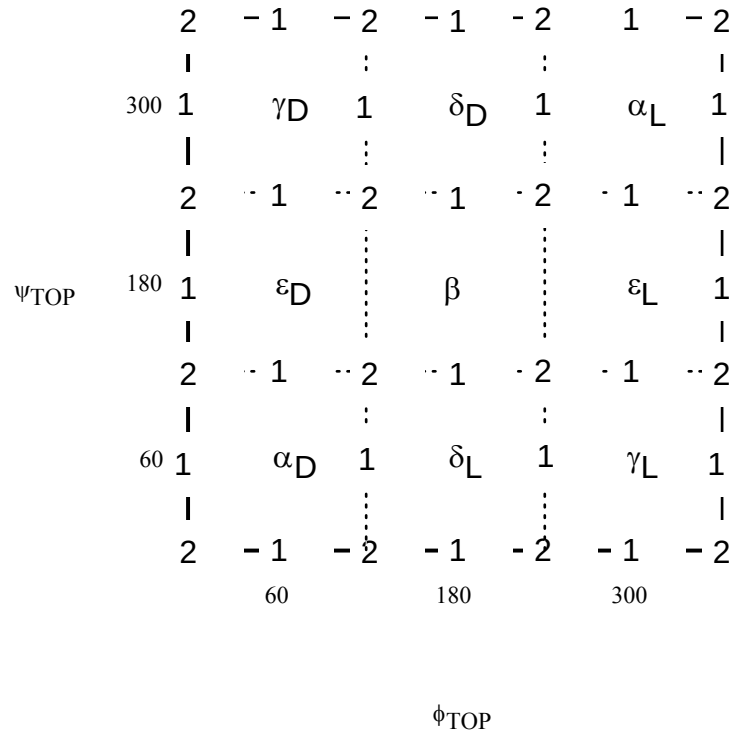


Figure 3. The topology of an idealized two-dimensional (2D) Ramachandran map containing the *a priori* predicted nine minima for a single amino-acid residue (…–CONH–CHR–CONH–…). The horizontal and vertical dashed lines represent low lying mountain ridges that separate the nine distinctly different catchment regions labelled by the Greek letters. (Note that the topologically (TOP) useful regions of ϕ and ψ are given in a 0–360° range.) Numerals indicate the expected location of saddle points ($\lambda = 1$) and maxima ($\lambda = 2$).

In Figure 3 the minima are not labelled by 0 but by the Greek letters introduced earlier α_L, β, γ_L, *etc*., but critical points of higher indices are denoted by their λ values: 1 and 2. There are two points to note about Figure 3. (1) The minima are separated from each other by mountain ridges containing maxima and saddle points. Each valley contains a single minimum and these valleys are normally referred to, after Mezey [4], as catchment regions. (2) In Figure 3, the indices of the PES may be calculated from the indices of the appropriate PEC if Mezey's criteria are fulfilled:

$$\lambda(x_1, x_2) = \lambda(x_1) + \lambda(x_2) \tag{8}$$

or

$$\lambda(\phi, \psi) = \lambda(\phi) + \lambda(\psi) \tag{9}$$

It is well known from topology, at is has been noted earlier [4–6], that the Betti numbers (β_λ) for a conformational problem:

$$\beta_\lambda = \binom{n}{\lambda} \tag{10}$$

represent the minimal number of critical points of index λ for PEC ($n = 1$), for PES ($n = 2$) and for PEHS ($n \geq 3$), and they follow an alternating sum rule, according to Morse theory [7]:

$$\sum_{\lambda=0}^{n}(-1)^{\lambda}\beta_{\lambda}=0 \tag{11}$$

just like the actual number of critical points (N_λ):

$$\sum_{\lambda=0}^{n}(-1)^{\lambda}N_{\lambda}=0 \tag{12}$$

where

$$N_{\lambda}\geq\beta_{\lambda} \tag{13}$$

On the basis of the foregoing for an ideal surface, one might expect that the Betti numbers, β_λ (that originate from mathematics), and the actual number of critical points N_λ (that incorporates chemistry) may be functionally related to each other:

$$N_{\lambda}=f(\beta_{\lambda}) \tag{14}$$

The full functional relationship introduced by Mezey [8,9] may be written as:

$$N_{\lambda}=\left(\prod_{i=1}^{n}m_{i}\right)\beta_{\lambda} \tag{15}$$

Each m_i may be associated with the number of bonds eclipsing during a full cycle (*i.e.*, from 0° to 360°) of internal rotation (torsion). For a couple of CH_3 rotations or for that matter, rotation about a chiral centre (C_α) of a peptide residue (*i.e.*, about ϕ and ψ), $m = m_1 = m_2 = 3$:

$$N_{\lambda}=\left(\prod_{i=1}^{2}m_{i}\right)\beta_{\lambda}=m^{2}\beta_{\lambda}=3^{2}\beta_{\lambda}=9\beta_{\lambda} \tag{16}$$

2 MATERIALS AND METHODS

A molecular system, of course, is not always ideal. Sometimes N_λ cannot be calculated as simply as Equation (16) implies. In general, we might say that whenever excessive attractive or excessive repulsion interactions occur we may anticipate deviation from ideal behaviour. It is generally observed that excessive attractive interactions and excessive repulsive interactions may create or annihilate critical points. Our accumulated experience indicates that hydrogen bonding (H-bond) do not qualify as excessive attractive interactions therefore in peptide conformations new minima are never created (an H-bond may only stabilize an otherwise legitimate minimum). However, repulsive interactions in peptides may be excessive enough to annihilate certain minima. For the annihilation of critical points, the selection rules for annihilation are those as published earlier [10] and illustrated schematically in Figure 4. The upshot of all of this is that in the case of peptides and proteins $N_0 = 9$, which appears to represent an upper bound for the number of possible minima for a single amino acid residue.

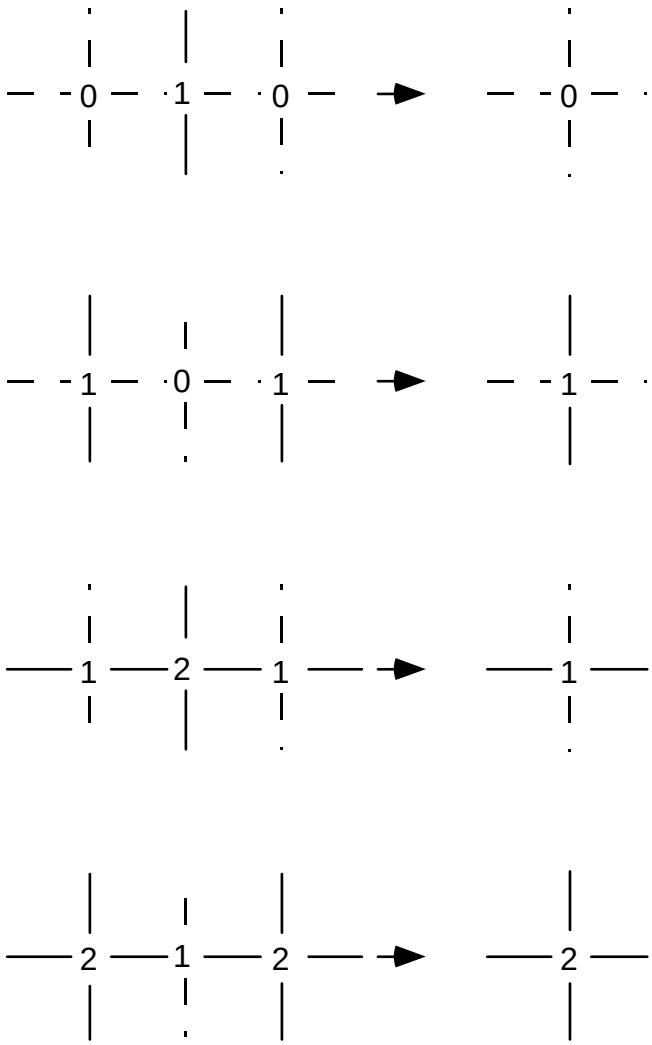


Figure 4. Selection rules for the collapse of three critical points to one.

It has been established from first principles that the idealized 2D-Ramachandran PES (*cf*. Figure 4) must have nine minima. It is therefore an obvious question to ask whether all these nine conformations are actually occurring in proteins. Perczel *et al*. [11] carried out an analysis of 258 proteins with known X-ray structure [12,13]. These proteins contained 56 495 amino-acid residues with well-defined ϕ and ψ angles. The minima were identified with the aid of the nine minima of Ac-L-Ala-NHMe determined by ECEPP/2 method allowing a ±40° tolerance in the ϕ and ψ values. Perczel *et al*. [14] drew a number of conclusions. (1) The *not-assigned* (NA) conformations are quite large indicating that Ac-L-Ala-NHMe may not be as good a model to mimic a single amino-acid residue in a protein than hitherto might have been believed. (2) Gly has the greatest number of NA cases implying that the alanine (Ala) derivative, which has a side chain, may be a much better model to all amino-acid residues with side chains than to Gly, which have no side chain; (perhaps Gly should be modelled with Gly). (3) Since Gly is achiral, instead of nine only five unique conformations occur. This means to say that the α_L conformation must be the same as α_D and that similarly might be expected for the other three pairs: $\gamma_L = \gamma_D$, $\delta_L = \delta_D$ and $\varepsilon_L = \varepsilon_D$. The actual finding is not all that far from expectation: $\alpha_L = 850$, $\alpha_D = 631$, $\gamma_L = 79$, $\gamma_D = 160$, $\delta_L = 62$,

$\delta_D = 45$, $\varepsilon_L = 388$ and $\varepsilon_D = 324$. Undoubtedly, the actual degeneracy is lost in the 1799 NA conformations. (4) Phenylalanine (Phe) has no γ_D conformation and proline (Pro) has no ε_D and γ_D conformations. All other amino-acid residues do occur in all the possible nine conformations.

3 RESULTS AND DISCUSSION

It is important to emphasize, nevertheless, that all nine conformations do occur in proteins as demonstrated by Table 1. In general, the preference for the *L* conformation varies in the order $\varepsilon > \gamma > \alpha >> \delta > \beta = 1$. In particular, Pro is the amino acid with the greatest preference for the *L* conformation. For the different amino acids, there is, in general, a preference for the *L* conformation, which varies in the order: Pro >> Ile > Val > Leu > Thr > Met > Ala > Glu > Phe > Trp > Tyr > Gln > Lys > Ser > Cys > Arg > Asp > His > Asn > Gly. As Gly is achiral, the energy of any *L* conformer is equal to that of its corresponding *D* enantiomer: $\alpha_L = \alpha_D$,… Therefore, Gly relative frequencies of occurrence are close to one, *e.g.*, $\text{total}_L/\text{total}_D = 1.189$.

Table 1. Relative Frequency of Occurrence of the Backbone Conformations of Various Amino Acids in Proteins

Entry	Amin. acid	α_L/α_D	γ_L/γ_D	δ_L/δ_D	$\varepsilon_L/\varepsilon_D$	$\text{Total}_L/\text{total}_D$	α_L/α_D rel. Gly	γ_L/γ_D rel. Gly	δ_L/δ_D rl. Gly	$\varepsilon_L/\varepsilon_D$ rel. Gly	Tot_L/tt_D rel. Gly
1	Ala	48.019	4.083	1.814	66.083	24.903	35.647	8.270	1.317	55.183	20.949
2	Arg	12.911	21.800	5.700	101.000	16.108	9.584	44.152	4.137	84.340	13.550
3	Asn	3.028	13.750	4.833	41.667	4.814	2.248	27.848	3.508	34.794	4.050
4	Asp	18.309	14.333	3.106	37.167	14.446	13.592	29.030	2.255	31.036	12.152
5	Cys	25.421	25.333	0.800	64.600	17.346	18.871	51.308	0.581	53.944	14.591
6	Gln	21.357	14.333	2.000	62.167	19.333	15.855	29.030	1.452	51.912	16.263
7	Glu	53.538	7.929	1.481	33.417	24.608	39.744	16.058	1.075	27.905	20.700
8	Gly	1.347	0.494	1.378	1.198	1.189	1.000	1.000	1.000	1.000	1.000
9	His	11.962	15.200	4.167	48.500	12.241	8.880	30.785	3.024	40.500	10.297
10	Ile	69.714	55.500	2.333	183.000	49.500	51.753	112.405	1.694	152.814	41.639
11	Leu	42.333	26.727	2.649	68.071	31.009	31.426	54.131	1.922	56.843	26.084
12	Lys	24.915	9.095	2.200	51.583	18.521	18.496	18.421	1.597	43.075	15.580
13	Met	28.077	58.000	1.857	69.000	24.957	20.843	117.468	1.348	57.619	20.993
14	Phe	25.419	∞	2.778	196.000	23.950	18.870	∞	2.016	163.670	20.146
15	Pro	936.000	∞	3.000	∞	1111.000	694.842	∞	2.177	∞	934.561
16	Ser	24.329	6.321	3.286	39.667	17.503	18.060	12.803	2.385	33.124	14.723
17	Thr	83.467	12.500	1.327	63.667	25.067	61.962	25.316	0.963	53.165	21.086
18	Trp	130.667	4.000	2.250	158.000	23.731	97.001	8.101	1.633	131.938	19.962
19	Tyr	15.694	48.667	5.067	146.333	21.509	11.651	98.565	3.677	122.196	18.093
20	Val	115.714	46.000	1.057	113.375	35.554	85.901	93.165	0.767	94.674	29.908

As Gly is achiral, the results for all the amino acids relative to Gly are also calculated (*cf.* Table 1). The comparative frequency of occurrence of for the *L* conformation relative to Gly is shown in Figure 5.

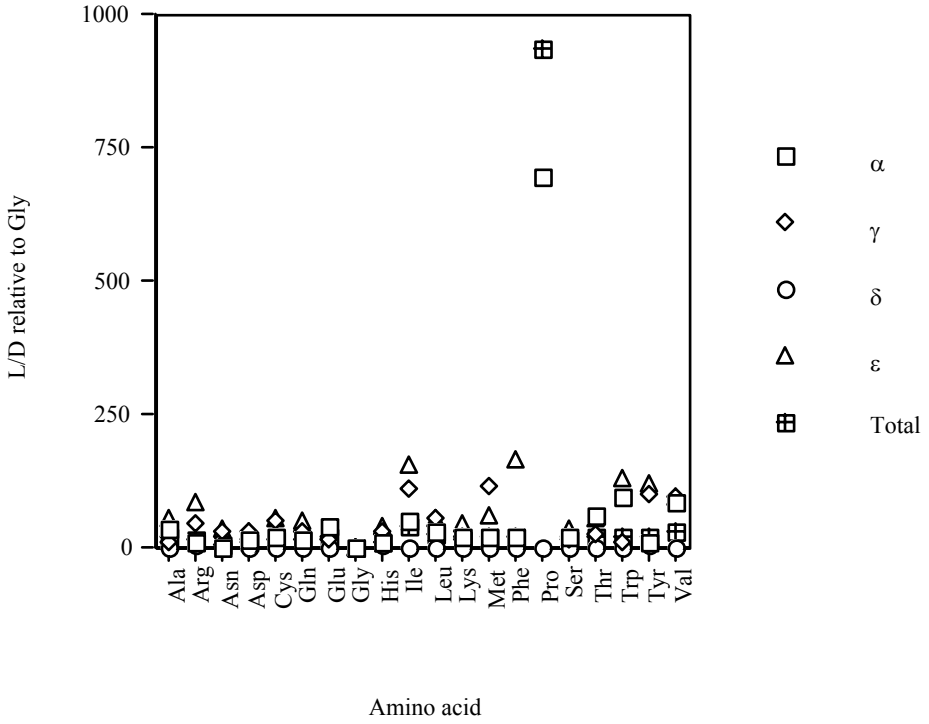


Figure 5. Comparative frequency of occurrence of the backbone conformations of various amino acids relative to Gly.

For Entries in Table 1, the trend line of comparative frequency of occurrence of for the *L* conformation relative to Gly is shown in Figure 6. Two data for Pro have been eliminated to obtain better detail. The slope of the trend line varies in the order: $\alpha >> \varepsilon > \gamma >> \beta = 0 \approx \delta$.

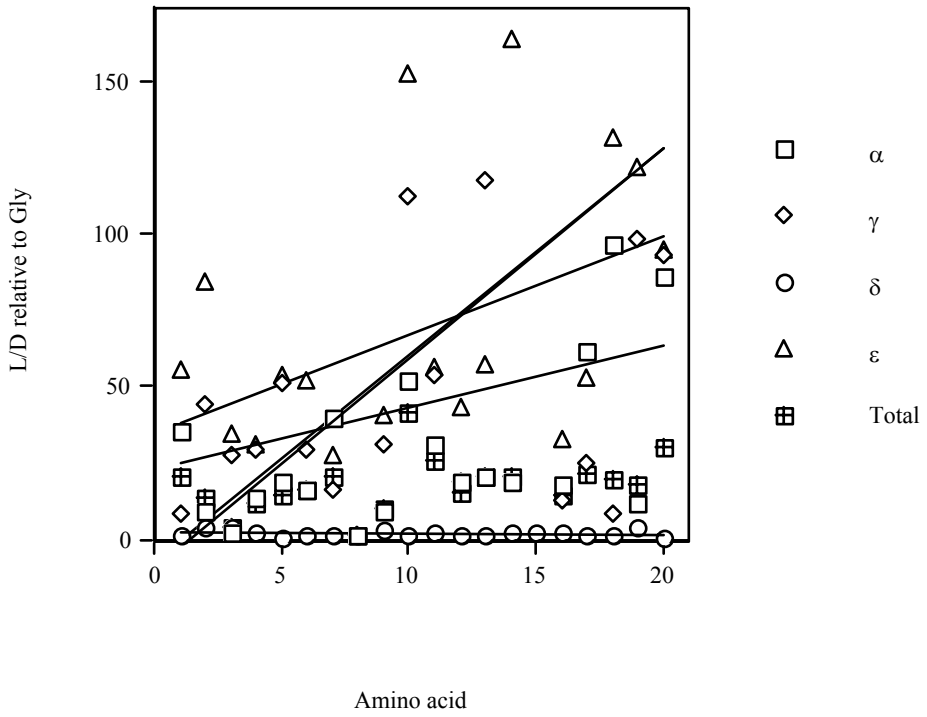


Figure 6. Trend line of comparative frequency of occurrence of the backbone conformations relative to Gly.

Using the known structure of 29 proteins as determined *via* X-ray crystallography, Chou and Fasman calculated the probabilities of α-helix, β-*sheet* [15], β-turn [16] and random coil [17]. The conformational parameters P_α, P_β, P_t and P_c were defined as the frequency with which a particular residue is found in a structure relative to the average frequency for all amino acids being found in that structure. The hydropathy index P_h was developed by Kyte and Doolittle [18]. The conformational parameters are tabulated in Table 2.

Table 2. Conformational Parameters of the Backbone Conformations of Various Amino Acids in Proteins

Amino acid	P_α [a]	P_β [b]	P_t [c]	P_c [d]	P_h [e]	$-P_\alpha-P_\beta+P_t+P_c$	P_α rel. Gly	P_β rel. Gly	P_t rel. Gly	P_c rel. Gly	P_h rel. Gly	$-P_\alpha-P_\beta+P_t+P_c$ rel. Gly
Ala	1.42	0.83	0.66	0.66	1.8	-0.93	2.491	1.107	0.423	0.465	-4.500	-0.560
Arg	0.98	0.93	0.95	1.20	-4.5	0.24	1.719	1.240	0.609	0.845	11.250	0.145
Asn	0.67	0.89	1.56	1.33	-3.5	1.33	1.175	1.187	1.000	0.937	8.750	0.801
Asp	1.01	0.54	1.46	1.09	-3.5	1.00	1.772	0.720	0.936	0.768	8.750	0.602
Cys	0.70	1.19	1.19	1.07	2.5	0.37	1.228	1.587	0.763	0.754	-6.250	0.223
Gln	1.11	1.10	0.98	0.79	-3.5	-0.44	1.947	1.467	0.628	0.556	8.750	-0.265
Glu	1.51	0.37	0.74	0.87	-3.5	-0.27	2.649	0.493	0.474	0.613	8.750	-0.163
Gly	0.57	0.75	1.56	1.42	-0.4	1.66	1.000	1.000	1.000	1.000	1.000	1.000
His	1.00	0.87	0.95	0.92	-3.2	0.00	1.754	1.160	0.609	0.648	8.000	0.000
Ile	1.08	1.60	0.47	0.78	4.5	-1.43	1.895	2.133	0.301	0.549	-11.250	-0.861

Leu	1.21	1.30	0.59	0.66	3.8	-1.26	2.123	1.733	0.378	0.465	-9.500	-0.759
Lys	1.16	0.74	1.01	1.05	-3.9	0.16	2.035	0.987	0.647	0.739	9.750	0.096
Met	1.45	1.05	0.60	0.61	1.9	-1.29	2.544	1.400	0.385	0.430	-4.750	-0.777
Phe	1.13	1.38	0.60	0.81	2.8	-1.1	1.982	1.840	0.385	0.570	-7.000	-0.663
Pro	0.57	0.55	1.52	1.45	-1.6	1.85	1.000	0.733	0.974	1.021	4.000	1.114
Ser	0.77	0.75	1.43	1.27	-0.8	1.18	1.351	1.000	0.917	0.894	2.000	0.711
Thr	0.83	1.19	0.96	1.05	-0.7	-0.01	1.456	1.587	0.615	0.739	1.750	-0.006
Trp	1.08	1.37	0.96	0.82	-0.9	-0.67	1.895	1.827	0.615	0.577	2.250	-0.404
Tyr	0.69	1.47	1.14	1.19	-1.3	0.17	1.211	1.960	0.731	0.838	3.250	0.102
Val	1.06	1.70	0.50	0.66	4.2	-1.6	1.860	2.267	0.321	0.465	-10.500	-0.964

[a] P_α: conformational parameter for the α-helix.
[b] P_β: conformational parameter for the β-sheet.
[c] P_t: conformational parameter for the β-turn.
[d] P_c: conformational parameter for random coil.
[e] P_h: hydropathy parameter.

It can be seen from the conformational parameters (*cf*. Table 2) that Pro is a strong α-helix breaker, strong β-sheet breaker, strong β-turn former and strong random-coil former. This strong character of Pro is in agreement with the strong frequency of occurrence of the conformations (*cf*. Table 1). A new parameter is proposed: $P_{\text{global}} = -P_\alpha - P_\beta + P_t + P_c$. In particular, Pro is the amino acid with the greatest value of P_{global}. For the different amino acids P_{global} varies in the order: Pro > Gly > Asn > Ser > Asp > Cys > Arg > Tyr > Lys > His > Thr > Glu > Gln > Trp > Ala > Phe > Leu > Met > Ile > Val.

4 CONCLUSIONS

From the precedent results and discussion, the following conclusions can be drawn.

1. It is fair to say that in our century, among others, the secondary and tertiary structural of proteins, frequently referred to as *protein folding* posed a major problem to medicine, biochemistry, pharmaceutical drug design and to related fields. We have now formulated a method, *via* a 3D→1D transformation, which allows one to use a qualitative linearized notation for protein 3D structures, which is based on quantitative geometrical data. It appears that with the present objective method, there is no longer any need to refer to a particular protein segment as *unordered* and the description and classification of protein secondary and tertiary structures is now within reach of all protein chemists.

2. All nine conformations do occur in proteins. In general, the preference for the *L* conformation varies in the order $\varepsilon > \gamma > \alpha >> \delta > \beta = 1$. Pro is the amino acid with the greatest preference for the *L* conformation. The preference for the *L* conformation varies in the order: Pro >> Ile > Val > Leu > Thr > Met > Ala > Glu > Phe > Trp > Tyr > Gln > Lys > Ser > Cys > Arg > Asp > His > Asn > Gly. The results relative to achiral Gly shows that the slope of the trend line varies in the order

$\alpha >> \varepsilon > \gamma >> \beta = 0 \approx \delta$. The strong preference of Pro is in agreement with its character of strong α-helix breaker, strong β-sheet breaker, strong β-turn former and strong random-coil former.

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Biography

Francisco Torrens is lecturer of physical chemistry at the Universitat de València. After obtaining a Ph.D. degree in molecular associations in azines and macrocycles from the Universitat de València, Dr. Torrens undertook postdoctoral research with Professor Rivail at the Université de Nancy I. More recently, Dr. Torrens has collaborated on

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