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GENERALIZED MATHEMATICAL RELATIONSHIPS FOR POLYPEPTIDE CHAIN HELICES. THE COORDINATES OF THE Π HELIX[*]

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Communicated by J. T. Edsall, June 4, 1953

The formulation of polypeptide chain configurations is concerned principally with intra-chain packing and interactions between atoms in neighboring residue units of the skeletal backbone chain $(—\mathrm{C}\cdot\mathrm{CO}\cdot\mathrm{NH}\cdot—)_n$. The folded or coiled configurations are held together by intra-chain ($\mathrm{CO}\cdot\mathrm{HN}$) hydrogen bonds between residues. In helical configurations the residues are structurally equivalent; they all have identical intra-chain environments (exclusive of amino acid residue variations). Such configurations, therefore, effectively provide maximal intra-chain hydrogen bonding.

Detailed studies depend on the use of precise dimensions for the polypeptide chain. Pauling and Corey have predicted as the fundamental unit a chain residue with dimensions and configuration derived from detailed studies of crystal structure analyses of amides, amino acids, and peptides.[1] On the same basis they have also defined appropriate limits for the hydrogen-bonded oxygen to nitrogen distance and for the angle between the NH and NO vectors.

Only two helical[2, 3] configurations, the α and γ helices, fulfill completely all of the requirements specified by Pauling and Corey. A third helix, the π helix,[4] involves so small a deformation (4°) in the intra-chain α carbon bond angle that it also should probably be considered to fulfill their requirements. Deformations of this order have been observed in amino acid structures.[5]

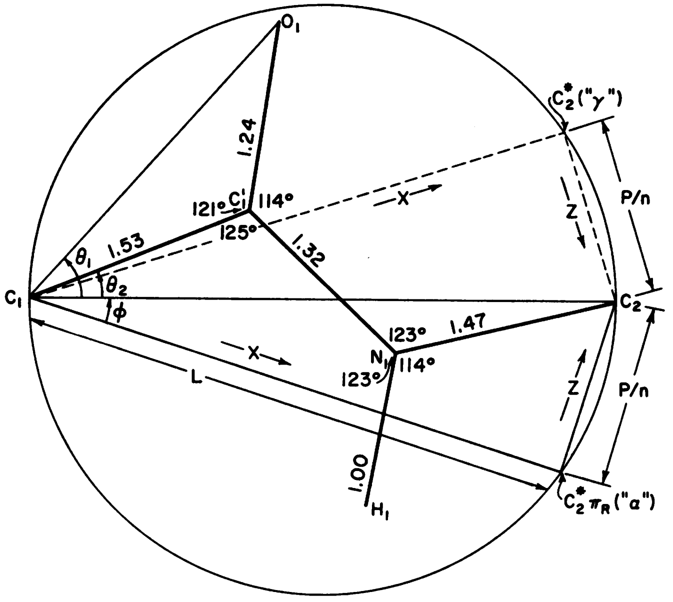


FIGURE 1

Orientation of the chain residues in the "α" and "γ" series. Derivation of the x and z coordinates for the atoms of the first residue. The x and z axial directions in each series are perpendicular and parallel, respectively, to the helical axis.

The π helix was discovered while working with three-dimensional scale models which had dimensions slightly different from the Corey-Donohue[1] dimensions first used by Pauling and Corey. In an attempt to determine the best set of atomic coordinates for this structure, an analytical method was developed. The procedure establishes certain relationships between different polypeptide chain helices which appear to have been confused in the past. The method is rapid and quite general; it may also be useful in the study of non-peptide helical structures where there exists a choice among different values for the independent variables.

In the three helices, α, π, and γ, which satisfy the Pauling-Corey requirements, each residue (—C·CO·NH·C—) is coplanar and lies in one of a zone of planes parallel to and at a common distance from the helical axis. The helices may be described by specifying the carbonyl oxygen to which each NH group is hydrogen bonded. Thus, in the π helix there is a hydrogen bond between one amide group and the fourth amide group beyond it along the chain. This description, however, is inadequate since it overlooks the two fundamentally different ways of coiling a helical structure.

In figure 1 the fundamental dimensions for a single residue $—\cdot C_1 \cdot C_1'O_1 \cdot N_1H_1 \cdot C_2 \cdot —$ have been drawn to scale for the most recently revised set of values[6] and inscribed in a circle of diameter $C_1—C_2$. The residue lies in a vertical plane and if one end (C_1) is kept fixed, the residue may be tilted either up or down. If P is the pitch of the final coil, the vertical translation per complete turn, and n is the number of residues per complete turn, then in a given helix this vertical translation per residue is P/n. If the residue is tilted upward so that $C_1—C_2^*$ (solid line) is its horizontal projection (normal to the helical axis), then the CO and NH groups are almost vertical and parallel to the helical axis. A P/n value of 1.14 A was used to construct this figure and over the range $P/n = 0.9 \rightarrow 1.5$ A deviations from the vertical are not very large. $\tan \phi = P/nL$ where $L = C_1—C_2^*$. The α and π helices are both constructed in this way and we have considered all such helices as belonging to the "α" series.

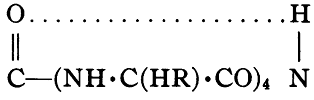
When the residue is tilted downward so that $C_1—C_2^*$ (broken line) is horizontal then the CO and NH groups are both sharply inclined to the helical axis. The $C_1—C_1'$ and $N_1—C_2$ bonds are practically horizontal and parallel to $C_1—C_2^*$ over a wide range. The γ helix is constructed in this way and we have considered all such helices as belonging to the "γ" series.

The residue-unit configurations differ markedly between the two series. Direct transformations between members of different series is impossible. Thus, the early suggestion[7] that the γ-helix might represent supercontracted keratin and supercontraction corresponds to a direct transformation $\alpha \rightarrow \gamma$ is theoretically invalid without reference to the comparative instability of either configuration.

Figure 2 (*a*) shows a perspective drawing of the π helix with 4.4 turns and a pitch $P = 5.02$ A and hence a unit translation per residue $P/n = 1.14$ A. Each succeeding residue, $C_1(CO \cdot NH)C_2$, $C_2(CO \cdot NH)C_3$, etc., lies in a vertical plane parallel to the helical axis and as the plan view, figure 2 (*b*), shows the angle between the two planes is the helical angle $\psi = 360/n$. The angle $180 - \psi$ is the horizontal component of the tetrahedral angle $N_1C_2C_2'$ and so the tetrahedral angle depends on both the number of turns (*n*) in the configuration and the vertical unit residue translation. Both the plan view (in which the nitrogen positions have been omitted at the cross-over points) and the drawing, illustrate that the CO and NH groups are almost vertical and the angle between the NH and NO vectors is small.

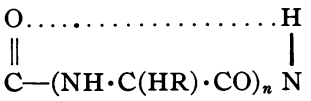
The π helix shown has a right-handed screw axis. The mirror image left-handed helix corresponds to the mirror image of figure 1 with C_1—C_2 plotted from right to left. Looking at the helix upside down corresponds to a horizontal projection C_1^*—C_2 (not drawn) parallel to C_1—C_2^*.

As a helix is wound up, a residue may theoretically form hydrogen bonds with the *n*th amide group beyond it. Figure 2 shows that for the π helix this corresponds to the chemical sequence,



$$\begin{array}{lr} \mathrm{O}\cdots\cdots\cdots\cdots\cdots\cdots & \mathrm{H} \\ \| & | \\ \mathrm{C—(NH\cdot C(HR)\cdot CO)_4} & \mathrm{N} \end{array}$$

read in either direction. For the "α" series the sequence is therefore



$$\begin{array}{lr} \mathrm{O}\cdots\cdots\cdots\cdots\cdots\cdots & \mathrm{H} \\ \| & | \\ \mathrm{C—(NH\cdot C(HR)\cdot CO)_{\mathit{n}}} & \mathrm{N} \end{array}$$

with $3n + 4$ atoms in the hydrogen-bonded loop so formed. Bragg, Kendrew and Perutz[8] have identified helices by symbols which indicate the number of turns in a unit repeat (screw symmetry) with subscript giving the number of atoms in the hydrogen-bonded loop. The π helix[4] would thus be written 4.4_{16}. We have avoided this identification where possible, for it leads to ambiguities; the helices 3.6_{13} and 3.7_{13} are both the α helix,[9] whereas 3.6_{14} is a helix of the "γ" series.

Variations in the number of turns per unit repeat are correlated with changes in the "tetrahedral" angle and hydrogen bond length and angle. Minor revisions are therefore likely to be made from time to time. The right-handed helix π_R in the drawing is shown with two of the β carbons of the amino acid residues drawn in (βC_2, βC_4) at the correct position for naturally occurring L amino acids.[10]

The "γ" series residue unit in figure 1 would lead to left-handed helices. In winding up these units so that a residue may form hydrogen bonds with the *n*th amide group beyond it, the chemical sequence

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Fig. 2 (*a*)—Perspective drawing of the right-handed π_R helix. The link-end carbon atoms are numbered consecutively. The β carbon and hydrogen atom positions for L-amino acids are shown attached to C_2 (α) and C_4 (α). Fig. 2 (*b*)—Plan view of π_R helix. The hydrogen positions are shown with broken lines. Nitrogen positions are omitted at the two cross-over points.

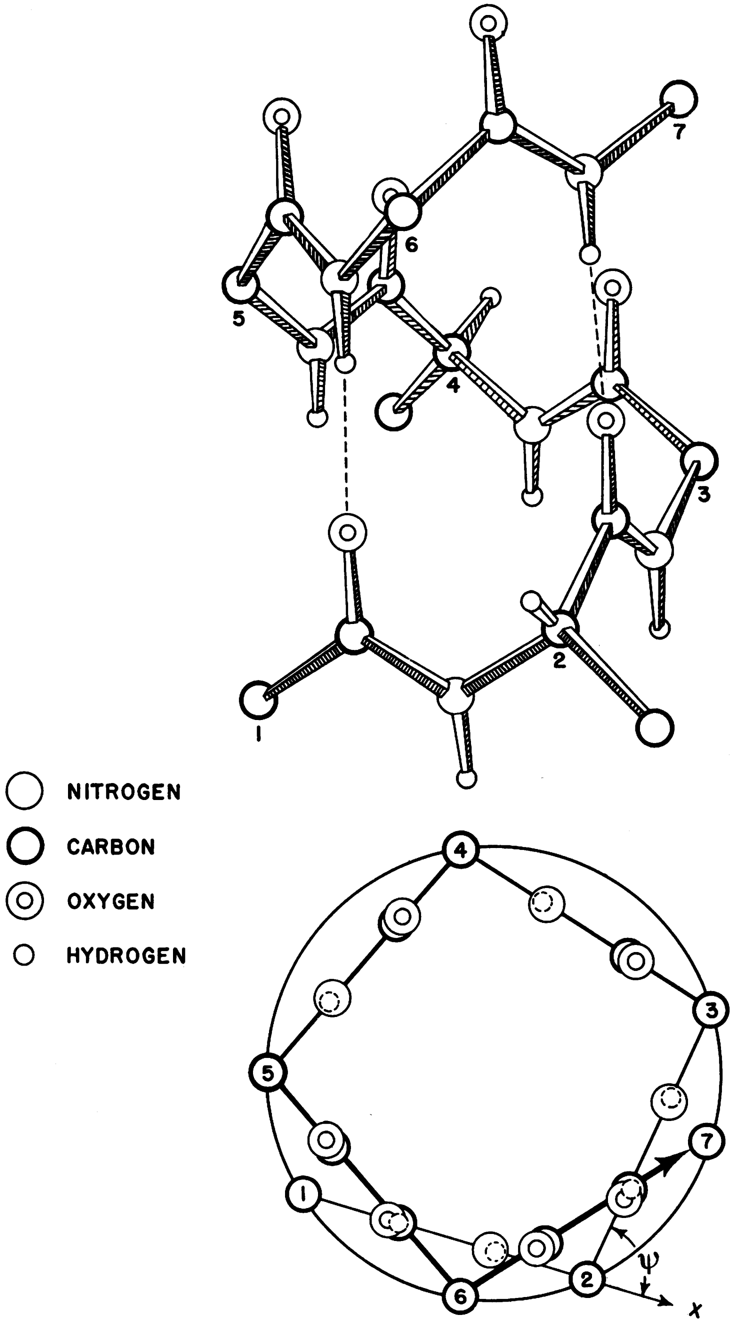
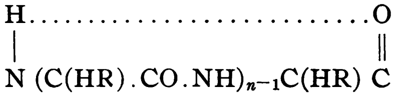


FIGURE 2 (*a*), ABOVE; 2(*b*), BELOW



$$\begin{array}{lr} \mathrm{H}\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots & \mathrm{O} \\ | & \| \\ \mathrm{N}\,(\mathrm{C(HR).CO.NH})_{n-1}\mathrm{C(HR)} & \mathrm{C} \end{array}$$

is obtained. There are $3(n - 1) + 5$ atoms in the hydrogen-bonded loop so formed.

Atomic coordinates for both series of helices are derived as follows. If the origin of the rectangular coordinate system is taken at C_1 with the x axis along $C_1—C_2^*$ and the z axis parallel to the axis of the helix, the coordinates of atoms in the first residue are calculated from equations of the kind:

$$\begin{aligned} x_{C_1} &= 0 \\ x_{O_1} &= C_1O_1 \cos(\phi + \theta_1) \\ x_{C_1'} &= C_1C_1' \cos(\phi + \theta_2) \qquad (1) \\ x_{C_2} &= C_1C_2 \cos\phi = L \text{ (projected length of the residue)} \end{aligned}$$

$$\begin{aligned} z_{C_1} &= 0 \\ z_{O_1} &= C_1O_1 \sin(\phi + \theta_1) \\ z_{C_1'} &= C_1C_1' \sin(\phi + \theta_2) \\ z_{C_2} &= C_1C_2 \sin\phi = P/n \qquad (2) \end{aligned}$$

In the "γ" series the z axis direction is changed. The same expressions hold except that the signs of the angles θ_1, θ_2, θ_3 and θ_4 are reversed. For all atoms in the first residue $y = 0$ (the residues are both planar and vertical).

The lengths C_1O_1, C_1C_1', and angles θ_1, θ_2, etc., are constants for a given residue model and may be calculated directly. The x and z coordinates for the atoms of the first residue unit are functions of the vertical rise per residue, P/n. In figure 3 (*a*) and (*b*) the atomic coordinates are plotted for the "α" and "γ" series of helices, respectively, over the range of values of P/n from 0.95 to 2.0. They were prepared using Pauling and Corey's most recent set of fundamental residue dimensions. For example, the broken vertical line gives values for α helix with $P/n = 1.48$. Similar expressions for the Corey-Donohue configuration are shown graphically in figures 4 (*a*) and (*b*). There are some marked differences near the limits of the range explored even though the dimensions of the two models are closely similar.

Planes containing successive linked residues are equidistant from the helical axis. The α carbon atoms $C_1C_2C_3$, etc., lie, therefore, on the surface of a cylinder about the helical axis of radius $R = L/(2 \sin \psi/2)$. In horizontal projection they lie, therefore, on the circumference of a circle (Fig. 2 (*b*)). The coordinates of the rth link-end position are:

$$x_{C_r} = L(0 + 1 + \cos\psi + \cos 2\psi \ldots + \cos(r - 2)\psi) \qquad (3a)$$

Fig. 3 (*a*)—Atomic coordinates for the "α" series atom positions plotted as a function of P/n. (Pauling-Corey dimensions.[6])

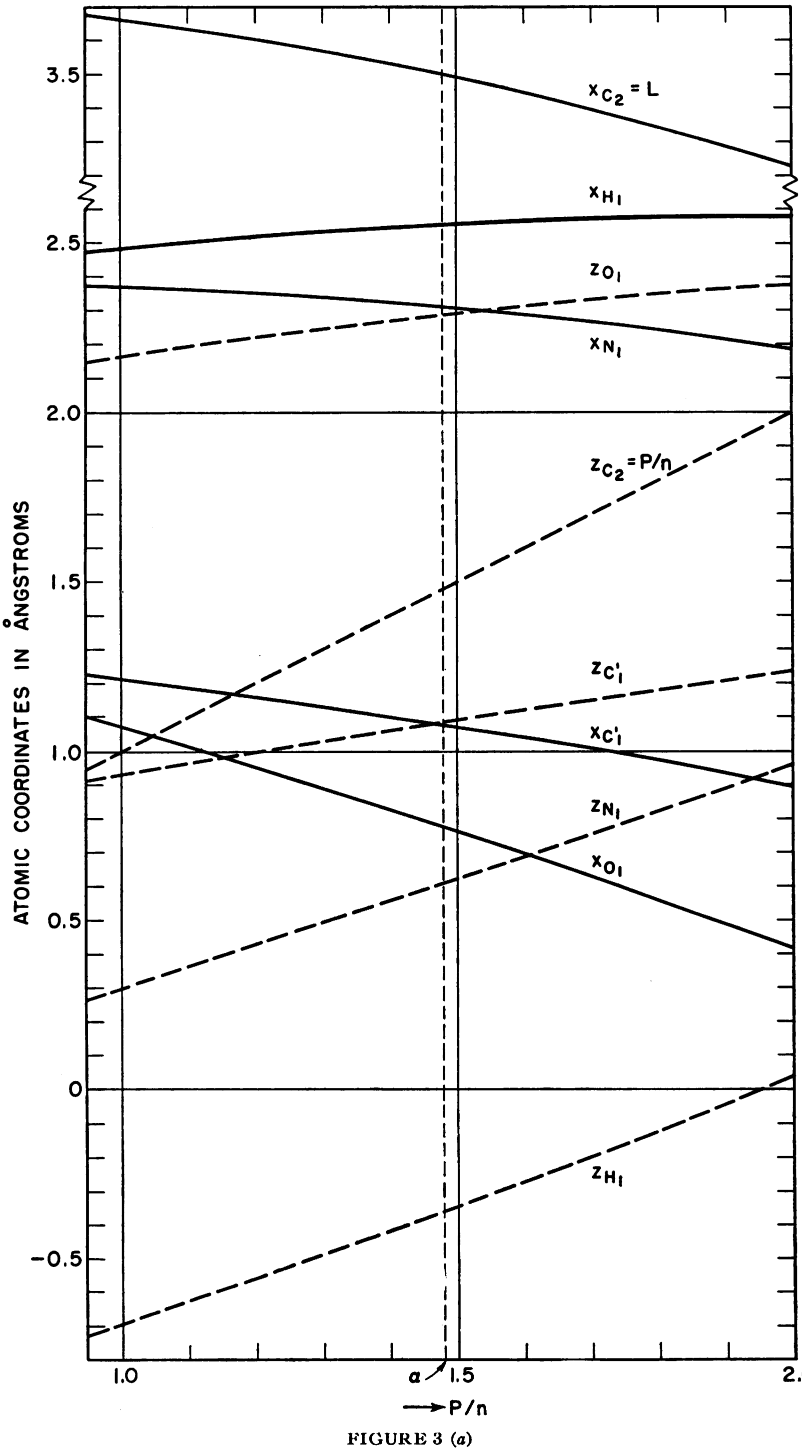

ATOMIC COORDINATES IN ÅNGSTROMS
3.5
2.5
2.0
1.5
1.0
0.5
0
-0.5
$x_{C_2} = L$
x_{H_1}
z_{O_1}
x_{N_1}
$z_{C_2} = P/n$
$z_{C'_1}$
$x_{C'_1}$
z_{N_1}
x_{O_1}
z_{H_1}
1.0
a
1.5
2.0
→P/n

FIGURE 3 (*a*)

$$y_{C_r} = L(0 + 0 + \sin\psi + \sin 2\psi \ldots + \sin(r-2)\psi) \qquad (3b)$$

$$z_{C_r} = (r-1)P/n \qquad (3c)$$

The coordinates of the point P_r in the rth link is given by:

$$x_{P_r} = x_{C_r} + x_{P_1}\cdot\cos(r-1)\psi \qquad (4a)$$

$$y_{P_r} = y_{C_r} + x_{P_1}\cdot\sin(r-1)\psi \qquad (4b)$$

$$z_{P_r} = (r-1)P/n + z_{P_1} \qquad (4c)$$

The equations (3a) and (3b) may be rewritten:

$$x_{C_r} = L\cdot u_r \qquad (5a)$$

$$y_{C_r} = L\cdot v_r \qquad (5b)$$

where u_r and v_r are the unitary coordinates of the link-end positions.

$$u_r = (1 + \cos\psi + \cos 2\psi \ldots + \cos(r-2)\psi) \qquad (6a)$$

$$v_r = (\sin\psi + \sin 2\psi \ldots + \sin(r-2)\psi) \qquad (6b)$$

In figure 5 the unitary coordinates for successive α carbon atoms are recorded for r values of 2 to 6 over the range $n = 3.0$ to 5.5.

The equations (4a) and (4b) may be rewritten:

$$x_{P_r} = L.u_r + A_r\cdot x_{P_1} \qquad (7a)$$

$$y_{P_r} = L\cdot v_r + B_r\cdot x_{P_1} \qquad (7b)$$

where $A_r = \cos(r-1)\psi$ and $B_r = \sin(r-1)\psi$. Values of A_r and B_r for $r = 2$ to 6 are given in figure 6 plotted against n the number of residues per complete turn.

Atomic coordinates of the atoms N_1, C_2, C_2' are required in order to determine the "tetrahedral" angle. The direction cosines of the two vectors N_1C_2 and C_2C_2' may be readily evaluated. The "tetrahedral" angle $N_1C_2C_2' = \chi$ is given by the usual cosine expression. This simplifies to

$$\cos\chi = -\left\{\frac{(A_2\cdot x'_{C_1})\cdot(L - x_{N_1}) + z'_{C_1}\cdot(P/n - z_{N_1})}{N_1C_2\cdot C_2C_2'}\right\} \qquad (8)$$

Similarly the angle τ between the N_r—O_1 and N_r—H_r vectors is given by the equation:

Fig. 3 (*b*)—Atomic coordinates for the "γ" series atom positions plotted as a function of P/n. (Pauling-Corey dimensions.[6])

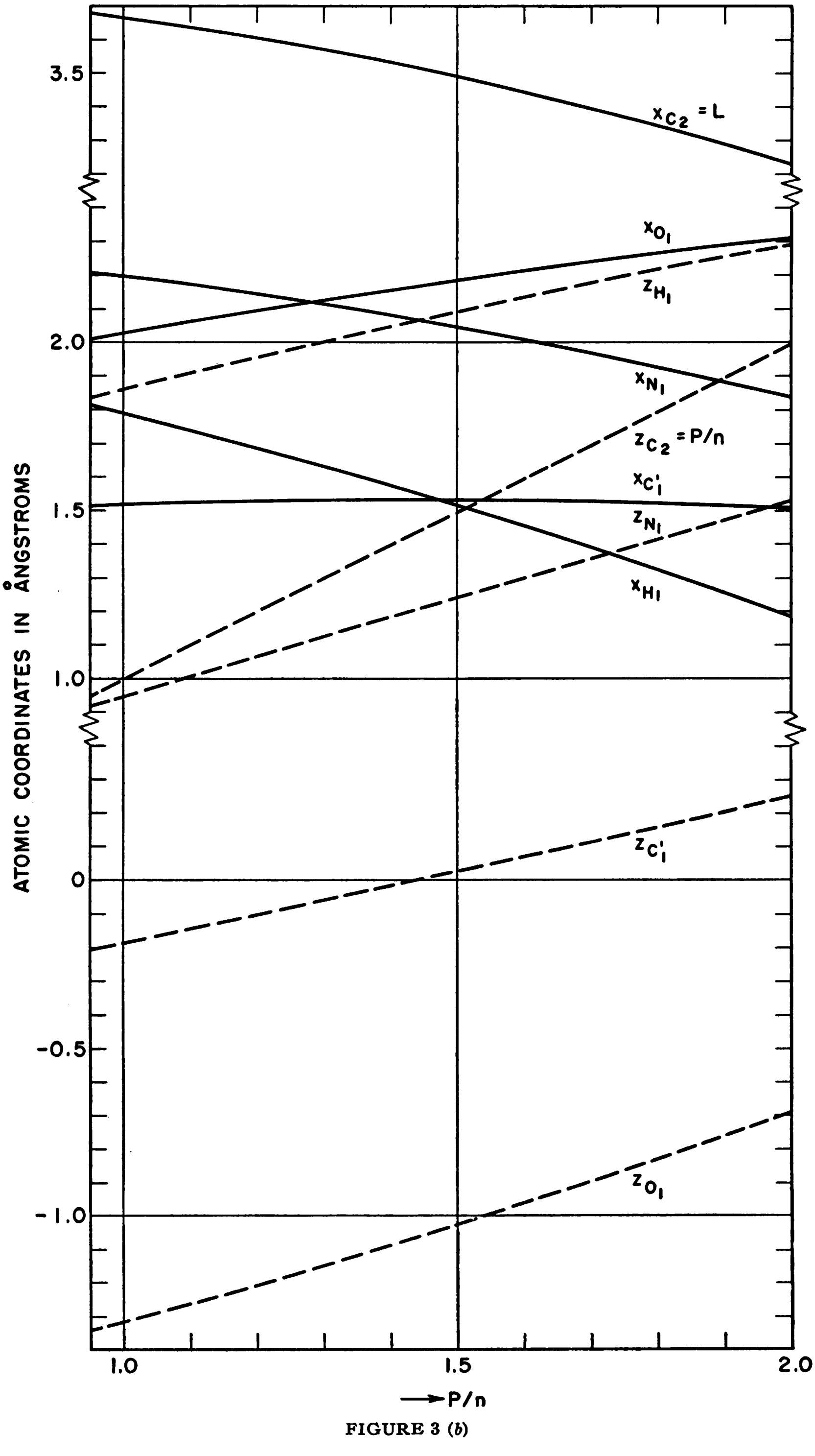

3.5
2.0
1.5
1.0
0
-0.5
-1.0
1.0
1.5
2.0
ATOMIC COORDINATES IN ÅNGSTROMS
→P/n
$x_{C_2} = L$
x_{O_1}
z_{H_1}
x_{N_1}
$z_{C_2} = P/n$
$x_{C'_1}$
z_{N_1}
x_{H_1}
$z_{C'_1}$
z_{O_1}

FIGURE 3 (*b*)

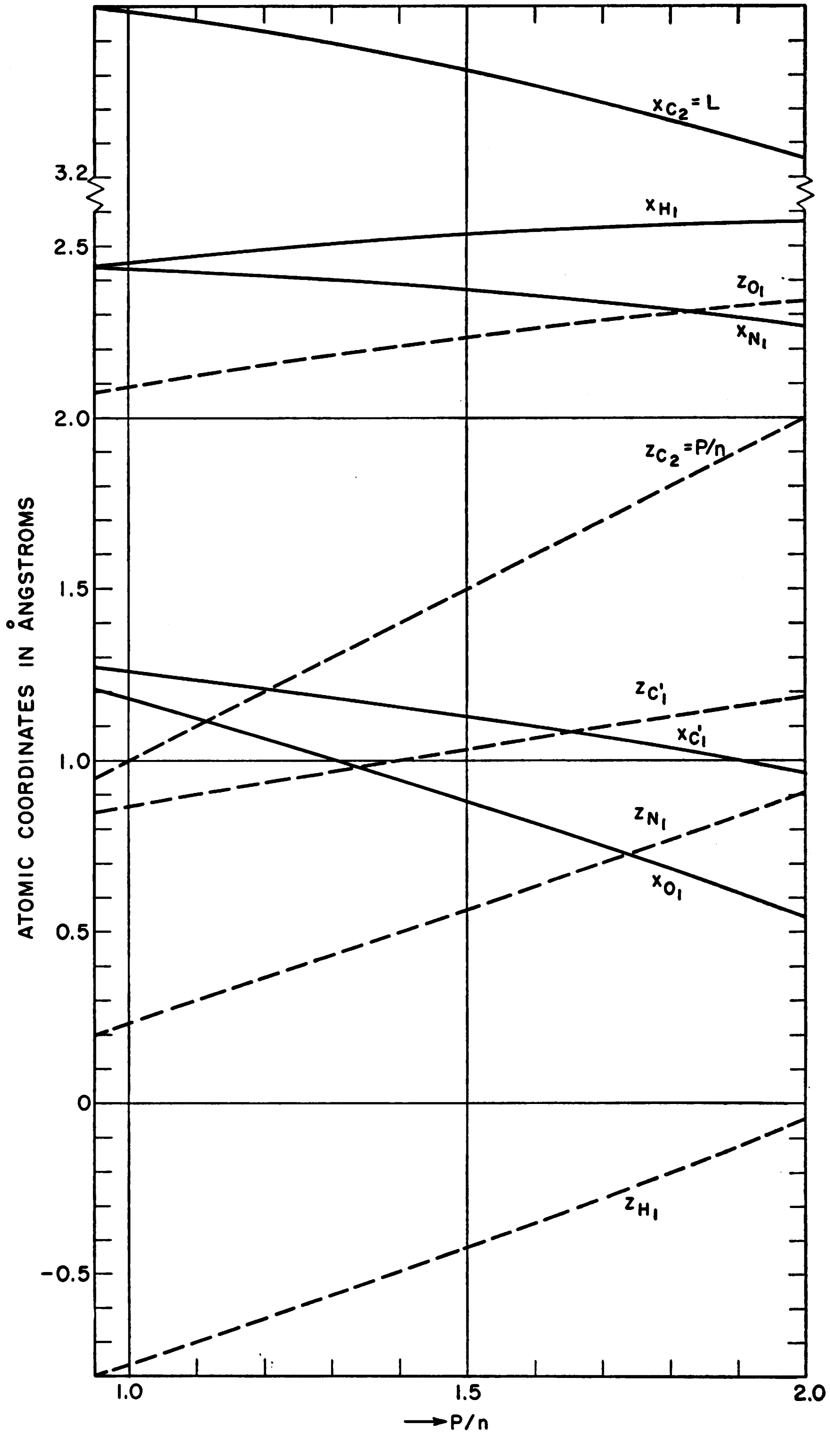


FIGURE 4 (*a*)

Atomic coordinates for the "α" series atom positions plotted as a function of *P/n*. (Corey-Donohue dimensions.[1])

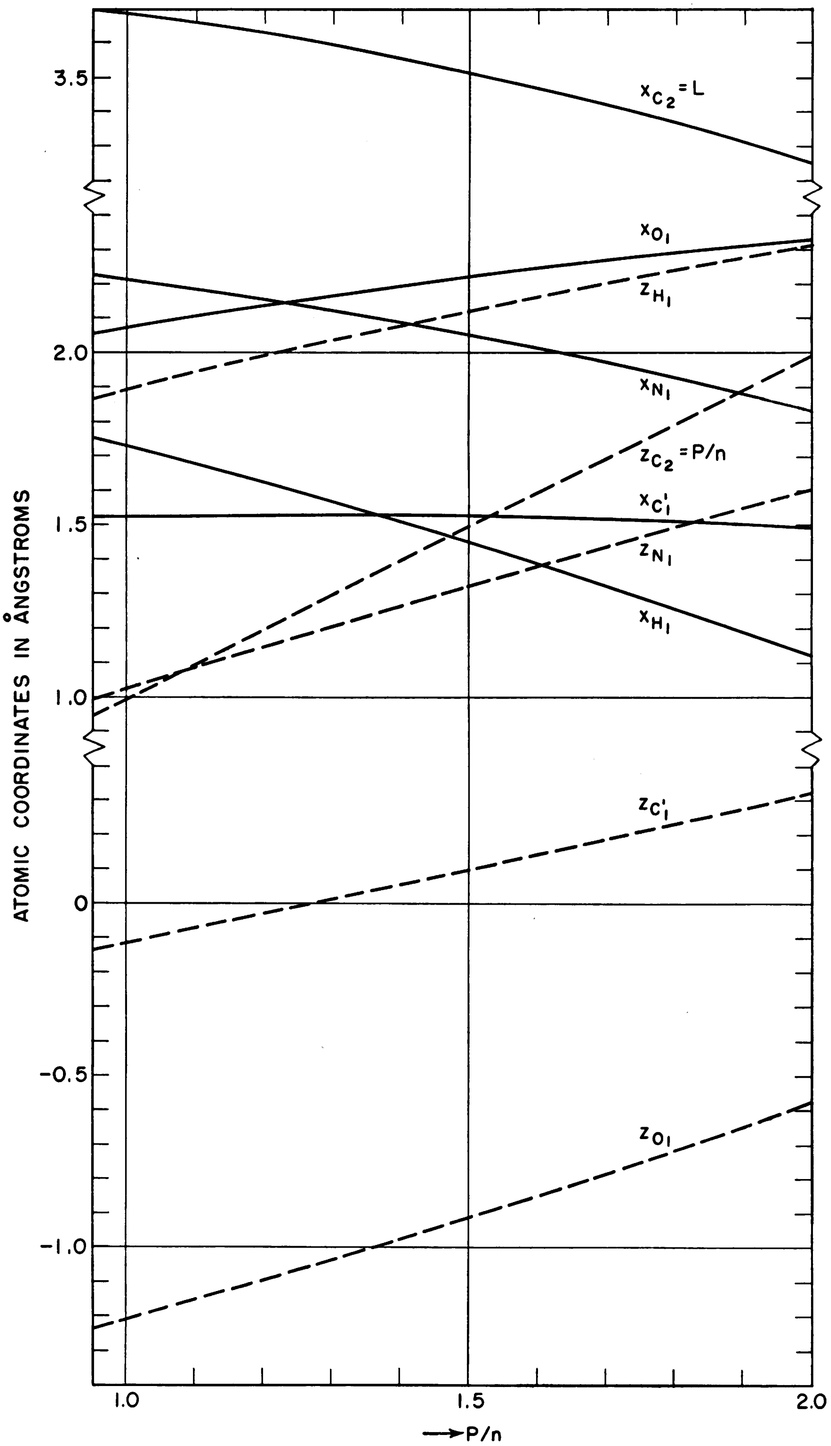


FIGURE 4 (*b*)

Atomic coordinates for the "γ" series atom positions plotted as a function of P/n. (Corey-Donohue dimensions.[1])

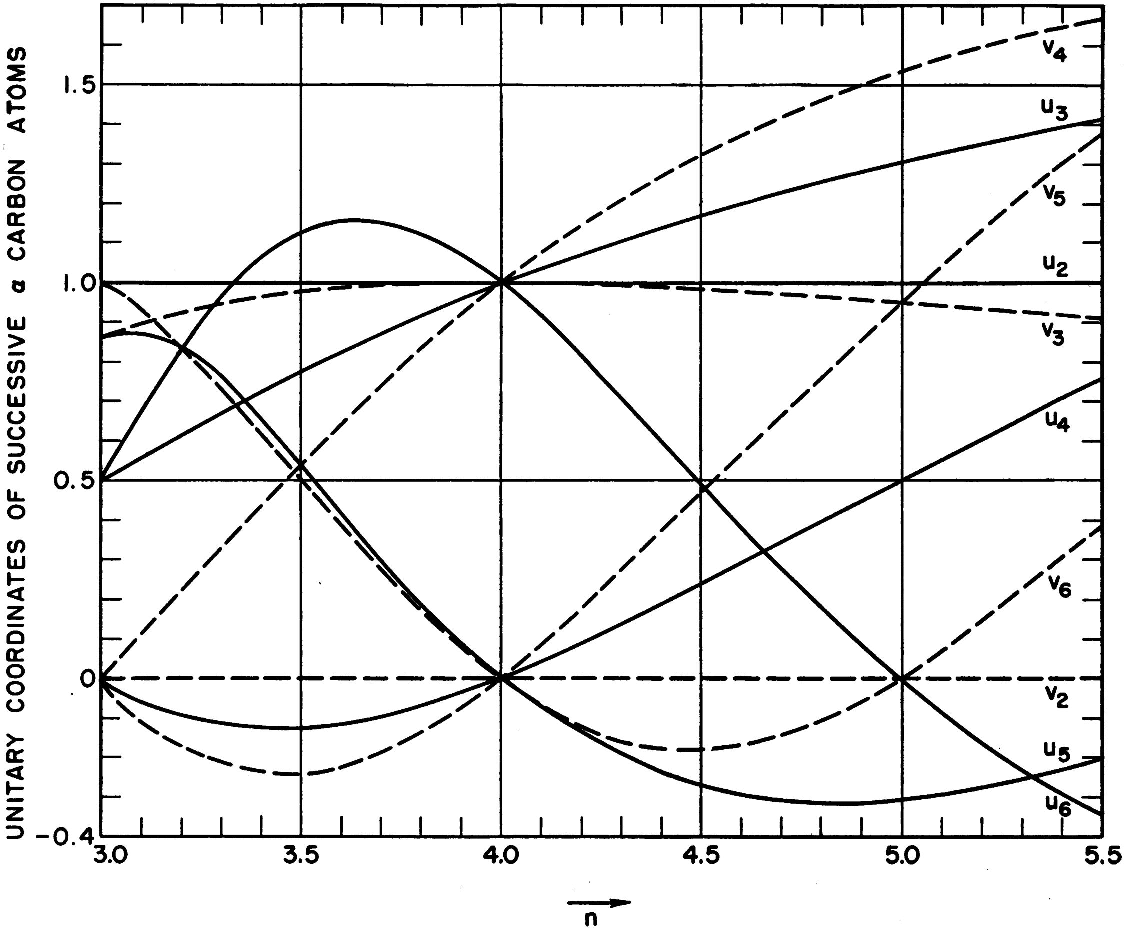


FIGURE 5

Unitary coordinates for successive α carbon atoms.

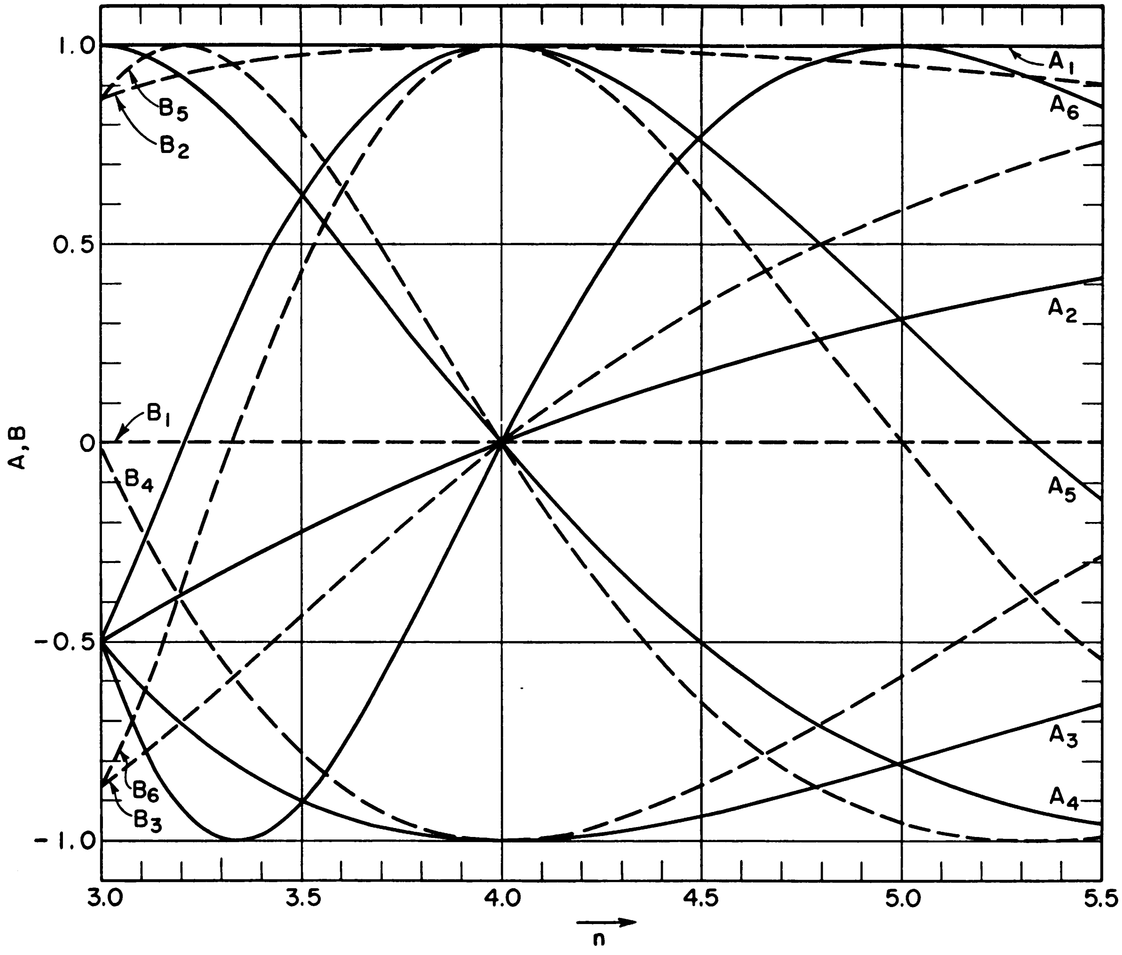


FIGURE 6

Values of $A_r = \cos (r - 1)\psi$ and $B_r = \sin (r - 1)\psi$.

$$\cos \tau = \frac{(x_{N_r} - x_{O_1})(x_{N_r} - x_{H_r}) + y_{N_r}(y_{N_r} - y_{H_r}) + (z_{N_r} - z_{O_1})(z_{N_r} - z_{H_r})}{N_rH_r \cdot N_rO_1} \qquad (9)$$

where

$$N_r - O_1 = \sqrt{(x_{N_r} - x_{O_1})^2 + (y_{N_r})^2 + (z_{N_r} - z_{O_1})^2} \qquad (10)$$

If the helical axis is taken as the origin of the coordinate system (the most convenient form for calculation of the radial distribution function) cylindrical coordinates[3] (ρ, δ) of the atoms may be readily evaluated. Thus for example

$$\rho_{N_1} = \sqrt{(x_{N_1})^2 + R^2 - x_{N_1}L} \qquad (11a)$$

$$\delta_{N_1} = \sin^{-1}\left(\frac{x_{N_1} \cdot \cos \psi/2}{\rho_{N_1}}\right) \qquad (11b)$$

Coordinates for the β carbon atom may be easily derived once the $N_1C_2C_2'$ angle has been evaluated.

Atomic coordinates for two variations of the π helix are given in table 1. When the helix is constructed with 4.3 residues per turn the strain in the tetrahedral angle is minimized, but the $O_1N_5H_5$ angle is larger than that shown in figure 2. Series of atomic coordinates have been calculated using (*a*) the original scale model dimensions,[11] (*b*) the Corey-Donohue[1] dimensions, and (*c*) the Pauling-Corey dimensions.[6] From these, values of the tetrahedral angle and hydrogen bond dimensions have been derived. For values of $P/n = 1.14$ to 1.15 and $n = 4.3$ to 4.4 (i.e., $P = 4.9$ to 5.06), the following range of values was obtained.

$\angle N_1C_1C_2'$	113.5° → 115.5°
$O_1 - N_5$	2.75 A → 2.83 A
$\angle O_1N_5H_5$	3.5° → 18°

No attempt has been made to develop differential functions; however, the x and z coordinates in the graphs, figures 3 and 4, are the differentials of each other.

$$\frac{\delta}{\delta x} A \cos x = -A \sin x$$

For a given residue configuration the pitch P and the number of residues per turn, n, may be varied independently. Once a set of values has been chosen it is obvious what type of adjustment is needed to improve the solution. A graphical method[12] has also been devised which permits extremely rapid trial and error determinations of the three critical variables.

Four helices of the "α" class have been described. "α"$_{n=1}$ corresponds to the 2_7 or α_{11} configuration proposed by Huggins,[13] Zahn,[14] and Mizushima.[15] Examination of figure 1 shows that in this helix the $O_1N_2H_2$ angle will be large for the values of P/n required. "α"$_{n=2}$ corresponds to the 3.0_{10} helix suggested by Taylor[16] and Huggins. "α"$_{n=3}$ is the α

TABLE 1

ATOMIC COORDINATES, AND VALUES FOR $N_1C_2C_2'$, N_5—O_1, AND $O_1N_5H_5$; x, y and z in A

	x	y	z
	$n = 4.3$, $P = 4.90$, $P/n = 1.14$		
C_1	0	0	0
C_1'	1.18	0	0.98
O_1	0.99	0	2.20
N_1	2.36	0	0.39
H_1	2.51	0	−0.60
C_2	3.62	0	1.14
Helical axis	1.81	2.02	..
	$\angle N_1C_2C_2'$	113.5°	
	N_5—O_1	2.79 A	
	$\angle O_1N_5H_5$	17.5°	
	$n = 4.4$, $P = 5.06$, $P/n = 1.15$		
C_1	0	0	0
C_1'	1.18	0	0.98
O_1	0.98	0	2.21
N_1	2.36	0	0.40
H_1	2.51	0	−0.59
C_2	3.62	0	1.15
Helical axis	1.81	2.09	..
	$\angle N_1C_2C_2'$	115°	
	N_5—O_1	2.80 A	
	$\angle O_1N_5H_5$	10.5°	
	"α"$_{n=5}$, $n = 5.2$, $P = 4.95$, $P/n = 0.95$		
C_1	0	0	0
C_1'	1.23	0	0.91
O_1	1.10	0	2.15
N_1	2.38	0	0.27
H_1	2.48	0	−0.73
C_2	3.68	0	0.95
Helical axis	1.84	2.66	..
	$\angle N_1C_2C_2'$	122°	
	N_5—O_1	2.93 A	
	$\angle O_1N_5H_5$	17°	

helix and "α"$_{n=4}$ is the π helix. "α"$_{n=5}$ has been studied by us. The horizontal component of the $N_1C_2C_2'$ angle is $180-360/(5 + \delta)$ where δ is fractional, and is, therefore, itself of the order of 110°. In the "α" series the vertical component of this angle is considerable. For $n = 5.2$, $P =$

4.95, and the Pauling-Corey model, figure 1, the $N_1C_2C_2'$ angle is 122° (table 1). This deformation is large. However, as the range of values for the helix shows, slight changes in the model and in the values for P and n, may lead to considerable differences in the tetrahedral angle derived. Hydrogen bond length and angle are reasonable for the structure. All the members of the group "α"$_{n=1}$ → "α"$_{n=5}$ are acceptable if the restrictive criteria are somewhat relaxed. Transformation between different configurations may be accomplished by simultaneously decreasing or increasing the wind up angle, and either reducing or increasing the vertical tilt per unit residue.

Four helices of the "γ" series have been described. In this series the angle $N_1C_2C_2'$ is almost equal to its horizontal component $180 - \psi$. "γ"$_{n=2}$ (2_8)[13] and "γ"$_{n=3}$ (the 11 atom ring)[17] are therefore completely excluded for the coplanar configuration. In "γ"$_{n=4}$ this angle is still rather small. For the variant with 4.3[18] residues per turn the horizontal component is 96.3°. "γ"$_{n=5}$ is the γ helix. "γ"$_{n=6}$ and higher members of this series give "tetrahedral" angles which are much too large.

The relative stabilities of polypeptide chain helices have been evaluated in terms of structural features which are not considered here. Pauling and Corey[19] have estimated, for the α and γ helices, the strain involved in possible "unfavorable orientation" about the N_1C_2 and C_2C_2' bonds, and incomplete van der Waals' stabilization.[9] Robinson and Ambrose[20] and more recently Donohue[18] have both made further estimates of the qualitative or semiquantitative agreement between certain helices and a wide range of restrictive criteria. The fundamental residue dimensions used are not specified in detail for either study. Both groups of investigators have used models different from the Pauling-Corey residue unit, and considerable latitude, including the introduction of slight distortions from the planar amide configuration, has been permitted in adjusting the residue dimensions to improve the agreement with their theoretical requirements.

The graphs reproduced in this paper permit the rapid variation of helical configurations based on a particular model, but must be redrawn for each new residue model. The amount of variation to be expected is illustrated by comparison of Figs. 3 and 4. These graphs are for a residue lying wholly in one vertical plane parallel to the helical axis. While this restriction can be easily relaxed in any particular case, once values of P/n and n have been chosen, systematic allowance for lack of coplanarity would involve the construction of families of graphs. This elaboration did not appear justified at this time.

Acknowledgment.—We are grateful to Professor J. T. Edsall for his critical interest in this study.

* This work was supported by the Eugene Higgins Trust, by grants from the Rockefeller Foundation, the National Institutes of Health, by contributions from industry and by funds of Harvard University; and, one of us (H. J. G-W.), by ONR Contracts N5ori-07801 and N5ori-07858. All inquiries concerning this paper should be addressed to Dr. Low.

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