# Articles

## The Structure of α-Keratin

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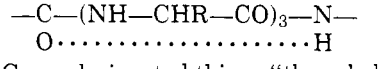
ABSTRACT: Known structural principles (close packing, maximum hydrogen bonding, the tendency of like groups to be surrounded in like manner, and the approximate constancy of interatomic distances and bond angles) are used, with meridional and equatorial x-ray data, to deduce and check the structure pattern for α-keratin. Internally hydrogen-bonded polypeptide helices are grouped into "3-stacks", in which each chain is rotated and shifted vertically a distance equal to the helix pitch (5.15 Å, average), relative to the other two. This shift accounts simply for the meridional x-ray reflection at this spacing. The 3-stack structure repeats after three turns, except for differences in the R groups and a slight twist, required to give satisfaction of both intrachain and interchain forces. The 3-stacks are grouped into 9-stacks and these into 27-stacks (all twisting), giving a crystallographic unit containing 81 chains, with the chain axes spaced approximately like those of close-packed cylinders. When the twisting reaches the limit of stability for good interchain contacting and cross-linking, the residue/turn ratio in each chain helix shifts to another, with twisting in the opposite direction. The twisting reversal mechanism keeps all the helix axes approximately straight, parallel, and in a close-packed arrangement. Interchain distances and orientations are suitable for cystine cross-linking. The dimensions of the 27-stacks agree well with estimates of the "effective radius" of microfibrils. X-ray measurements of spacing changes during fiber extension are explained as due to alternation of zones with much cross-linking and zones with few cross-links.

This paper is an amplification of papers presented at the Tenth International Congress of Crystallography[1] in Amsterdam, August 1975, and the Fifth International Wool Textile Research Conference[2] in Aachen, September 1975.

### Background

On the basis of the principles (1)[3-7] that like atoms or atomic groups tend to be surrounded by close neighbors in like manner and (2)[3,7-11] that groups such as >N–H and O=C< form the maximum number of hydrogen bonds sterically possible, I concluded about 40 years ago that each polypeptide chain in α-keratin has an internally hydrogen-bonded helical structure.

Strong evidence for the correctness of this conclusion was furnished when Pauling and Corey[12] showed that the x-ray data from certain synthetic polypeptides could be explained on the basis of a particular molecular helix of this type: the 13-atom-ring helix[13,14]



(Pauling and Corey designated this as "the α-helix".)

Neither this nor any other simple hydrogen-bonded helical chain structure could account for a meridional spacing, observed in α-keratin, of about 5.1 Å, without introducing an additional assumption, e.g., as to the sequence of the R groups. (Pauling and Corey's explanation was shown by Schomaker to be invalid.[15])

Crick[16] and Pauling and Corey[17] later suggested that this reflection could be accounted for if the axes of the α-helices were distorted so as to follow a long-pitched helix. Two or three molecular helices might be twisted around a common axis, as in a rope. This reasonable model has since been studied extensively by Crick, Fraser and co-workers, and others. For an excellent summary, see Fraser and MacRae.[18]

The rope models, however, seem incapable of explaining satisfactorily the transition to β-keratin, on stretching a fiber in the presence of a hydrogen-bond-breaking agent. It is difficult to imagine any reasonable mechanism for untwisting the ropes. I have therefore looked for (and found) another model for the α-keratin structure, one that appears to conform better with the fundamental principles of crystal structure. As will be shown, this new model satisfactorily explains not only the 5.1 Å reflection, but also other experimental observations not explained by the rope models.

### Packing of Helices

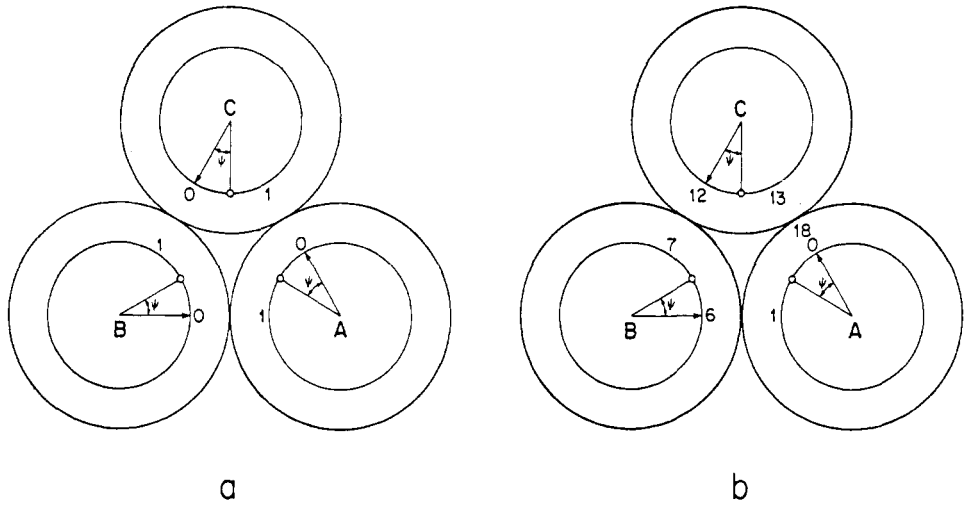
The principle of close packing[3,5,7,10] leads to the conclusion that the molecular helices are stacked, with parallel axes, in an approximately close-packed manner, much like the close packing of cylinders. The sharpness of some meridional and equatorial x-ray reflections is evidence for the essential correctness of this assumption.

The contacting between neighboring chains is determined largely by the following requirements:

(1) Insofar as possible, two contacting chains should be so related, vertically and laterally, as to give the most stable overall contacting.

(2) If possible, all chain helices should be surrounded by other close helices in the same way (at least if differences between the R groups are neglected).

(3) Half-cystine residues in adjacent chains must be so located as to permit disulfide cross-linking,[19] conforming to the approximately known bond length and bond angle requirements.




a b

**Figure 1.** 3-stacks (a) with like residues at the same level and (b) staggered.

### 3-Stacks

No structure is geometrically possible in which the contacts between each chain helix and *all* of its six close neighbors are alike, hence requirement (2) cannot be met. The chains can, however, be grouped into "3-stacks", with like contacts between these stacks.

There are two ways in which contact equivalence within each 3-stack might conceivably be achieved: Corresponding residues in the three chains might all be at the same level (Figure 1a) or at different levels, separated by a distance $P$ (Figure 1b). As will be shown, there is excellent evidence for the correctness of the latter alternative, with $P$ equal to the pitch of the polypeptide helix.

These figures have been drawn on the assumption that the structure repeats exactly after three turns. Departures from this simple idealized relationship will be discussed presently. Each smaller circle in these drawings passes through the projections of the centers of the $C_\beta$ atoms in a regular helix approximating the actual polypeptide chain. The arrows show the directions of the points where the helices intersect an arbitrary base plane. The lead angle ($\psi$) measures the lateral orientation of the beta carbon ($C_\beta$) of residue 1. The numbers give the heights of the closest-approach points on the helices, in units of $P/6$.

Staggered 3-stacks of the kind represented by Figure 1b have previously been proposed[4,20-22] by me for both keratin and collagen.

The structure of Figure 1a is impossible, because it could not give *optimum* contacting between neighbor chains. With like groups at the same level, there would be bad crowding at frequent intervals, when like bulky groups from the three chains all point, at the same level, toward the 3-stack axis. Similar concentrations of three like positive (or negative) groups would also lead to instability.

On the other hand, there is a strong argument in favor of the structure of Figure 1b. Since 5.15 Å is a reasonable value for the average pitch in $\alpha$-keratin, *this structure explains very simply the strong meridional reflection corresponding to this distance.* Whatever the sequence of residues, the pattern of scattering power for x rays in each 3-stack repeats at this interval. Values of the pitch reported for 22 synthetic polypeptides vary from 5.20 to 5.55 Å (Fraser and MacRae,[18] p 214). The disulfide cross-linking in $\alpha$-keratin can reasonably be assumed to decrease the pitch from what it would be without cross-linking.

The average verticle shifts per residue reported (Fraser and MacRae,[18] p 214) for the synthetic polypeptides vary from 1.30 to 1.525 Å. In $\alpha$-keratin the shift is presumably 1.485 Å, a meridional spacing observed by Fraser, MacRae, and Miller.[23]

### 9-Stacks

Staggered 3-stacks, like the individual polypeptide chains, are helical. It is geometrically impossible to close-pack the 3-stacks so that each makes contact with its six neighbors in just the same way. Three 3-stacks, however, can be grouped into 9-stacks in a way that gives the same contacting of each 3-stack with the others. The actual contacting pattern is presumably that which gives the greatest stability. This might require a vertical shift of each 3-stack relative to its neighbors, but for the present I shall neglect this possibility.

There are two possible ways of orienting 3-stacks within a 9-stack, as illustrated in Figure 2. They differ in the rotation sense of the sequence ABC in the triangle of chains closest to the 9-stack axis. One of these ways is presumably more stable than the other, but I do not know which it is.

### Packing to Form Fibers

9-stacks of either type can be combined to form pseudocrystalline structures in which the polypeptide chain axes are in an arrangement, with hexagonal symmetry, like the arrangement of cylinder axes in a close-packed stack of cylinders, except for relatively small differences between the axis-to-axis distances. I would expect the distances between chain axes in each 3-stack to be slightly shorter than the distance between two chain axes in different 3-stacks (either within a 9-stack or in different 9-stacks), if the effect of cross-linking on these distances can be neglected.

One way of packing the 9-stacks to give a pseudocrystalline structure is illustrated, for the type of 9-stack depicted in Figure 2a, in Figure 3. The crystallographic unit contains just nine chains: one 9-stack. If the 3-stacks all had the ideal staggered structure of Figure 1b and all the R groups were alike, the crystallographic space group would be $P3_1$.

Alternatively, the 9-stacks (of either type) might be grouped around (simple and screw) threefold symmetry axes to give 81-chain units, as pictured in Figure 4 for 9-stacks of the Figure 2b type. The space group is $R3$.

The crystallographic unit, referred to hexagonal axes, contains three groups of 27 chains (each group containing three 9-stacks). The groups might be those around either the right-handed or the left-handed screw axes. (Since the contacts between 9-stacks surrounding a *simple* three-fold axis are between like residues at the same level, they are probably weaker than the contacts between 9-stacks surrounding a threefold *screw* axis.)

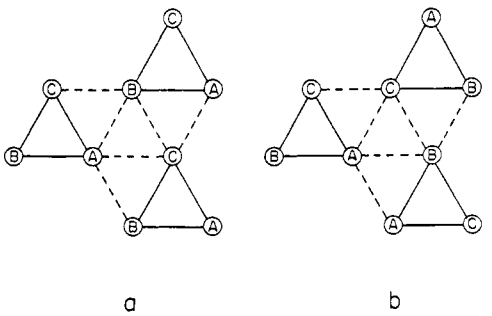


Figure 2. Two hypothetical types of 9-stacks, each composed of three staggered 3-stacks.

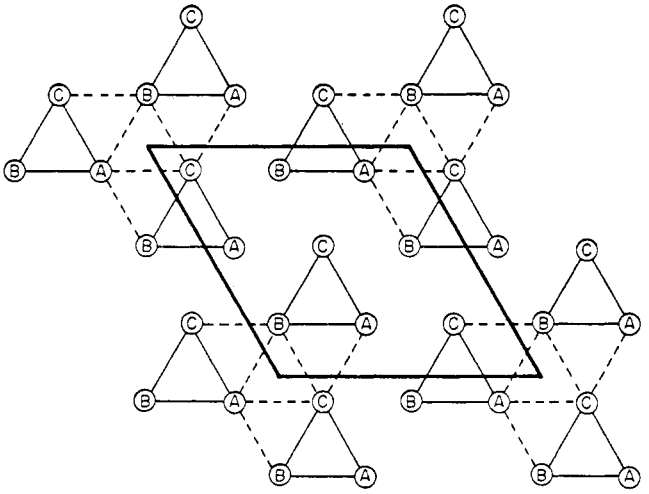


Figure 3. A hypothetical way of packing 9-stacks to form a crystalline arrangement, with the individual chains approximately close-packed. 9-stacks of the type of Figure 2a are represented here.

One can properly consider a group of three 9-stacks around one of the types of screw axis as a "27-stack", if the net attraction energy between the 9-stacks is significantly greater than the corresponding net attraction energy for the other type of screw axis.

A decision between the 9-chain crystal units and the 81-chain units can be made by studying the equatorial x-ray reflections. Taking the average vertical shift per residue as 1.485 Å (Fraser, MacRae, and Miller[23]), the density as 1.317 g cm$^{-3}$ (Fraser, MacRae, and Simmonds[24]), and the average residue mass as 111 (Fraser, MacRae, and Simmonds[24]), I calculate the edge ($a_0$) of the 81 chain crystallographic unit to be 93.9 Å. This is in excellent agreement (well within the probable errors of the calculation and the x-ray data) with the observed equatorial spacings. See Table I. A nine chain unit could not account for the observed spacings.

The structure arrived at, represented by Figures 1b, 2b, and 4, is similar to one I proposed[4] in 1957. I now think that the closely related 81-chain crystallographic unit in which the 9-stacks are of the type represented by Figure 2a should also be considered.

Approximate dimensions of the 27-stack are readily calculated. Taking the distances between the axes of close chain helices as equal and taking the "radius" of each chain helix as one-half of that distance, the distance from the axis of a 27-stack to its "surface" is 38.8 Å, if the unit cell edge ($a_0$) is 94 Å, and 39.2 Å, if $a_0$ is 95 Å. From the shape of the projection of a 27-stack (see Figure 4), it is obvious that the "effective radius" of this stack must be a few ångström units less than 39 Å. A value of 36 Å would not be unreasonable.

## Microfibrils

The "effective radius" of keratin microfibrils has been estimated by Fraser and MacRae[18,28,29] to be about 36 Å. From the correspondence between this figure and the dimensions of the 27-stack, it seems reasonable to assume that a microfibril is a 27-stack.

## Twisting

The idealized model used for the figures and the discussion up to this point was based on the assumption that the projection of the polypeptide chain structure onto a plane normal to the helix axis repeats exactly after three turns. In other words, it was assumed that the residue/turn ratio is uniformly an integer divided by three. Of course, there must be devia-

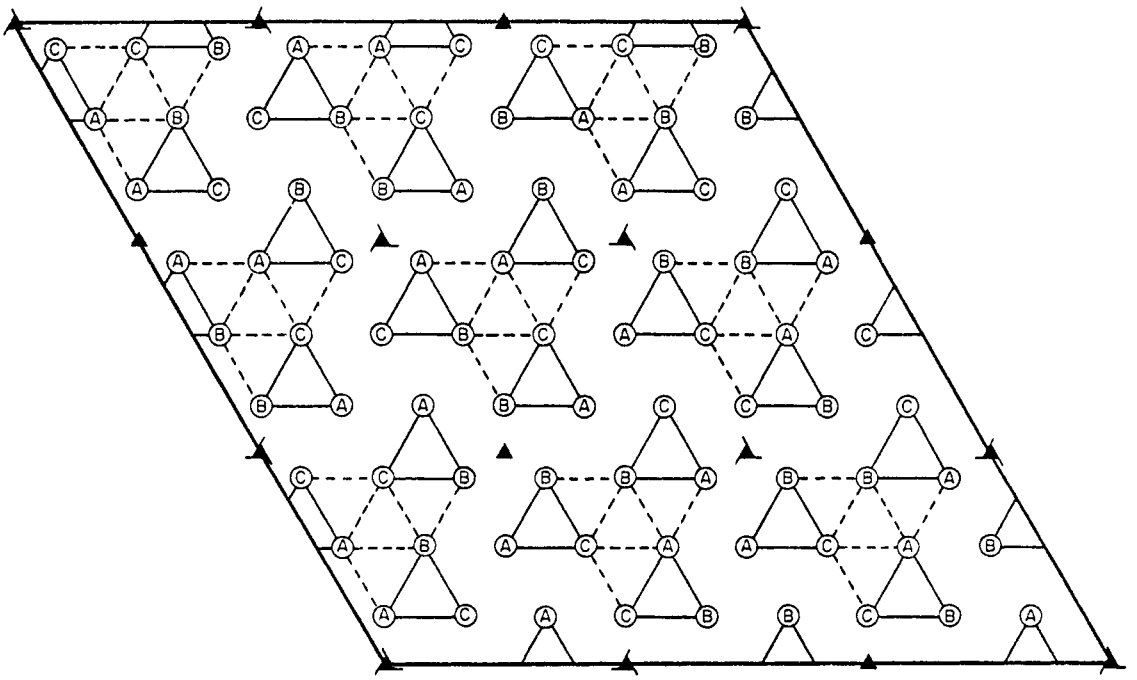


Figure 4. Packing of 9-stacks (of the type of Figure 2b) to give a crystalline arrangement with 81 approximately close-packed chains per crystallographic unit.

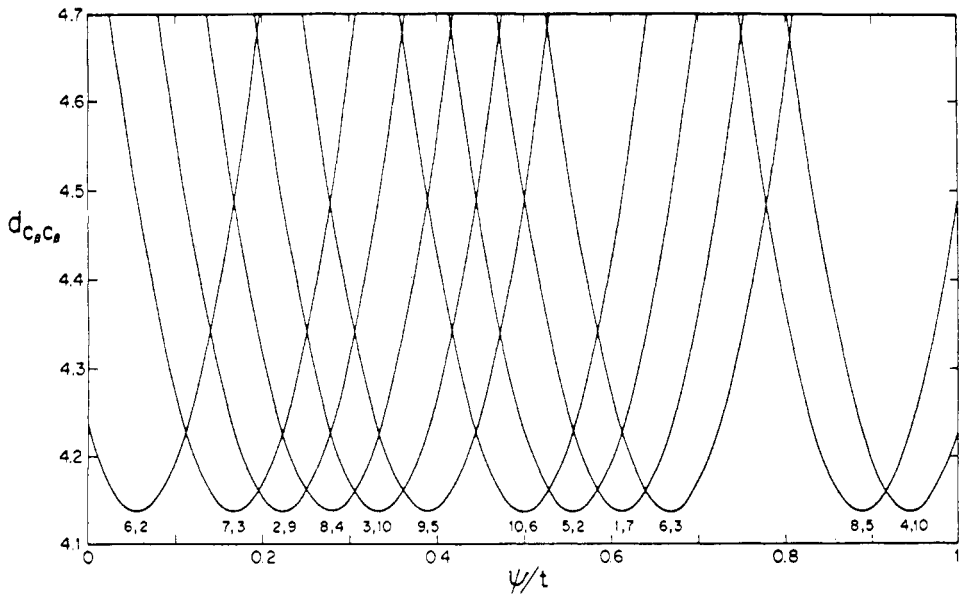



**Figure 5.** Calculated approach distances ($d_{C_\beta C_\beta}$), as functions of the ratio of $\psi$ (the lead angle) to $t$ (the change of lateral orientation per residue).

tions from this ratio, due to differences between the R groups, cross-linking, and other types of interaction between neighboring helices, etc. Neglecting the random deviations, let us now consider possible regular deviations that might persist for considerable distances in the axial direction.

There is nothing about the structure of a hydrogen-bonded helix to require (or favor) a residue/turn ratio that is integral or a ratio of simple integers.[3] Certain ratios of simple integers, however, do give better *inter*chain stability, especially for the hexagonal packing that has been deduced.

Pauling and Corey, from assumptions and approximations about the internal structure of the $\alpha$-helix, first[30] calculated a residue/turn ratio of about 3.7 (hence 11.1 residues per three turns). Then,[12] to give better hexagonal packing, they assumed 18 residues in five turns (or 10.8 residues in three turns). For the 22 synthetic polypeptides (all assumed to have the $\alpha$-helix structure) listed by Fraser and MacRae[18] (p 214), the "twist angles per residue" vary from 90 to 102.9°, corresponding to residues per three turns between 10.5 and 12. There is of course no reason to believe that the average residue/turn ratio in $\alpha$-keratin, with its many disulfide (and probably other) cross-links and many R groups quite different from those in the synthetic polypeptides that have been carefully studied, should be close to the residue/turn ratios observed in those polypeptides.

Elleman[31] has reported that some high-sulfur fractions from wool show approximate repetition of a ten residue unit. Perhaps, in regions of the $\alpha$-keratin structure where the concentration of cystine cross-links is high, there are about ten residues per three turns.

The actual average structure, in a region of $\alpha$-keratin, is presumably that having the lowest overall Gibbs energy. The residue/turn ratio should be a compromise between that favored by the *intra*helix forces and that giving the best *inter*helix stability. Since the kinds and distributions of the R groups vary in different parts of the structure, we should expect the average residue/turn ratio to vary correspondingly.

I propose that the *intra*chain forces in a helix having R groups corresponding to the average composition of an average $\alpha$-keratin favor a residue/turn ratio intermediate between two ratios (perhaps 10/3 and either 11/3 or 18/5), each of which would give good *inter*chain stability. Good interchain stability depends on the accommodation (without crowding) of bulky side chains, a stable distribution of the ionic and hydrogen-bond-forming groups, and especially on the possibility of forming cystine cross-links (with stable bond lengths and bond angles) from the cysteine residues originally in the chains (at locations that are not now known).

If these ideas are correct, the actual residue/turn ratio in some regions of the structure is a little larger than the smaller of the two intermolecularly favored ratios (perhaps 10/3 = 3.33) and in other regions a little smaller than the larger of the two intermolecularly favored ratios (perhaps 11/3 = 3.67 or 18/5 = 3.60).

Because of the differences between the actual (average) ratios and the simple ratios giving lateral repetition of the structure after three turns, a slight twist in one direction or the other would be added to the structure of each chain helix depicted in Figure 1b. The interactions between the R groups in different chain helices of each 3-stack would then produce a (smaller) twist, in the opposite direction, of the whole 3-stack around its axis. There would similarly be a slight twist in each 9-stack and each 27-stack.

At some level the structure is presumably ideal, corresponding to the drawings in the figures. As the height above or below that level increases, the *total* angles of twist around the 3-stack, 9-stack, and 27-stack axes increase. Deviations of the atoms and groups from their locations in the ideal structure increase. The stresses produced by the twisting are probably especially large where interchain cross-links are stretched and where the irregular outer surfaces of adjacent 27-stacks (moving in opposite directions) rub together.

When the summation of these stresses becomes large enough, the residue/turn ratio in each helix is forced to change to the equilibrium value near the other intermolecularly favored ratio. This reverses the direction of the twist. Presumably the twist reversal process continues throughout the structure. It furnishes a mechanism for keeping the chain axes nearly straight and for keeping the arrangement of chain axes close to that for close-packed cylinders.

I have previously speculated and written[20,22] about slow twisting of polymer structures from an ideal intermolecularly favored structure, as a result of the interaction of intermolecular and intramolecular forces, concluding that when a stability limit is reached there is some kind of sudden alteration of the structure, followed by another region of twisting. I consider $\alpha$-keratin to be a fine example of this "new principle of polymer structure". In this case the structural change is one

**Table I**
**Spacings of Equatorial Reflections (Å)**

| | Calcd | | Exptl | | |
|---|---|---|---|---|---|
| *hi*.0 | $a$ = 94 Å | $a$ = 95 Å | Mac-Arthur[25] | Bear and Rugo[26] | Spei[27] |
| 10.0 | 81.4 | 82.3 | 81 | 83 | 82 |
| 20.0 | 40.7 | 41.1 | 41 | 45 | 42 |
| 30.0 | 27.1 | 27.4 | 27 | 28 | 27 |
| 63.0 | 10.3 | 10.4 | 10.5 | | |
| 80.0 | 10.2 | 10.3 | | 9.8 | 9.8 |
| 90.0 | 9.0 | 9.1 | 9.2 | | |

that produces a reversal of the twisting direction. I predict that many more examples will be found. The structure changes must produce observable changes in the x-ray diffractions and other properties. Why do not polymer scientists design and make synthetic polymers that will behave in the same way?

It seems likely that the chain helices throughout the structure are of the 13-atom-ring (α-helix) type, but this is not a necessary requirement of my theory.

## Cross-Linking

To study the cross-linking possibilities in the structures of Figures 3 and 4 I have calculated the closest distances between $C_\beta$ atoms in neighboring chains and compared them with the maximum possible value, computed from $d_{CS}$ = 1.87 Å, $d_{SS}$ = 2.04 Å, ∠CSS = 103° as reported by Yakel and Hughes[32] for *N,N'*-diglycyl-L-cystine dihydrate crystals. These data yield $d_{C_\beta C_\beta,max}$ = 4.69 Å. For the theoretical distance calculations I have taken the distance between neighboring chain axes as 95 Å/9 = 10.56 Å and the distance of each $C_\beta$ from its chain axis as 3.294 Å, the value computed for poly(L-alanine) by Arnott and Dover.[33]

Most of these calculations have been made for a regular helix with a residue/turn ratio of 10/3. For this ratio I find that the structure of Figure 3 has all approach distances ($d_{C_\beta C_\beta}$) larger than 4.85 Å, regardless of the lead angle. Note that this distance is somewhat larger than the assumed $d_{C_\beta C_\beta,max}$. For the structure of Figure 4, on the other hand, I calculate much smaller values of $d_{C_\beta C_\beta}$, down to 4.14 Å at certain values of the lead angle. See Figure 5.

The numbers below each curve minimum in Figure 5 indicate the pairs of residue sequence numbers having the approach distances shown by the curve. Thus, 6,2 represents the pairs A6-B2, B6-C2, and C6-A2. A, B, and C designate chains in the 3-stack, for which (see Figure 1b) one can deduce the heights and orientations of each $C_\beta$ atom in the (untwisted) structure. Twisting the helix from the regular helix for which the calculations were made is equivalent to changing the value of the lead angle.

Because of the crossing of the curves, there are, at any given value of the lead angle (or the twist), from two to five pairs of residue numbers (like 6,2) having approach distances short enough for disulfide cross-links. (It is of course not necessary for *all* of the close pairs to be connected by bridges.) Obviously, many pairs of cysteine groups (with sequence numbers not too far apart) could interact to form cystine cross-links with little or no distortion of the structure. When the residue sequences become known, it may be possible to predict the locations of the disulfide bridges and the atoms in them. Then one can relate the structure more quantitatively to the x-ray diffraction data.

I have made similar calculations for helices with 11 residues per three turns and some for residue/turn ratios of 7/2 and 18/5, with results similar to those described and illustrated for 10/3, but differing in details. All yield many short approach distances, if the Figure 5 structure is assumed.

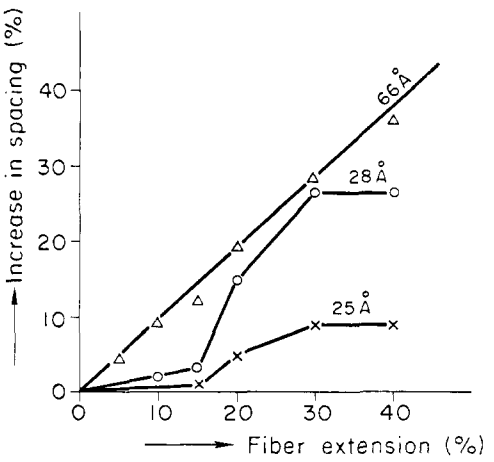



**Figure 6.** Variation of the spacing of certain meridional x-ray reflections from mohair fibers (after treatment with trifluoroethanol) with stretching of the fiber. From Spei.[30] Reproduced by courtesy of Melliand Textilberichte KG.

These cross-linking calculations thus confirm the conclusion reached from an analysis of the equatorial x-ray reflections, that the crystallographic unit is that containing 81 chains, not that containing 9 chains.

Many of the close approach pairs, if connected by disulfide bridges, would require some cys-cys sequences in the chains. This can explain the fact that such sequences frequently occur in keratins (Lindley and Haylett[34]).

## Zones

In regions where the number of cys residues is relatively large, the chains must be tied together to form a quite rigid structure, incapable of easy extension, even after treatment with a hydrogen-bond-breaking solvent. Spei[27] has observed that, on stretching mohair fibers after treatment with trifluoroethanol, the spacing of the 66 Å meridional reflection increases in proportion to the fiber extension; whereas, up to about 15% extension, the 25 and 28 Å reflections increase their spacings only slightly. See Figure 6.

This behavior suggests an alternation of zones in the fiber direction: zone I, containing many cross-links, and zone II, containing few. Speculating, I tentatively suggest that each zone I extends for about 28 Å and each zone II for about 38 Å (in the unstretched fiber), giving a pseudorepeat distance of about 66 Å. This would account simply both for the strong reflection at that distance and for Spei's observations. The actual structure may be more complex. Further research in this field is obviously needed.

It is tempting to speculate that each zone I is a region in which the average residue/turn ratio approaches the smaller value (perhaps 10/3) giving interchain stability, and that each zone II is a region in which the average ratio approaches the larger value (perhaps 11/3 or 18/5) giving interchain stability. This is not a necessary consequence of the theory, however.

## The Residue Sequence and Meridional Reflections

There have been many attempts to index the meridional reflections on the basis of a unit distance, $c_0$. As more and better experimental data become available, it becomes necessary to go to larger and larger values of $c_0$. A probably related fact is that, as more is learned of the order of residues in the polypeptide chain, the more likely it appears that there is no repeating unit. If so, there is no crystallographic unit distance in the fiber direction. The keratin fiber is not a true crystal. The meridional (and other) spacings and intensities must depend in a complicated way on the residue sequence, the distribution of cross-links, the helix pitch (and perhaps its

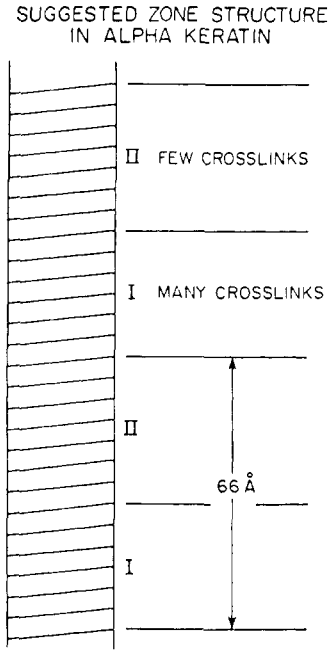



**Figure 7.** A simple zone structure that would explain the results illustrated in Figure 6.

variation), the residue/turn ratios, the pattern of twist reversals, the zone structure, etc.

It seems likely that little further progress can be made toward a quantitative understanding of the meridional data until much more is known about the residue sequence, at least. It may be helpful, perhaps necessary, to study simpler synthetic polymer fibers with similar structure patterns first.

## Future Research

The last sentence can also be applied to other aspects of the structure–property relationships in keratin and related materials. Research specifically designed to check and extend the basic concepts of this theory is obviously needed. Such research can probably best be done using appropriate synthetic polymers. We need polymers with mers (e.g., amino acid residues) in a regular sequence that differs in the two directions, a requisite for forming staggered 3-stacks. There should be bulky or polar or cross-linkable side chains that will produce *inter*chain forces (favoring some lateral orientations over others) comparable with the *intra*chain forces favoring a particular residue/turn ratio. We need such polymers with alternating blocks (e.g., many cross-linkable groups in one kind of a block and few in the other kind).

In $\alpha$-keratin there are many local irregularities related to the irregularities in the residue sequence. Also, as I have pointed out, there are several kinds of systematic irregularities. $\alpha$-Keratin can be considered a paracrystalline material, as defined by Hosemann.[35] Bonart and Spei[36] have dealt with some aspects of the irregularity problem. I hope that these scientists and others will study the types of irregularities that exist in $\alpha$-keratin and will develop new methods for dealing, experimentally and theoretically, with these types.

**Acknowledgments.** Finally, I want to acknowledge my great indebtedness to W. T. Astbury and the other scientists whose experimental results I have used and to R. D. B. Fraser and T. P. MacRae, whose book[18] and other publications I have found very helpful.

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