The Pattern of Proteins

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ANY theory as to the structure of the molecule of simple native protein must take account of a number of facts, including the following :

(1) The molecules are largely, if not entirely, made up of amino acid residues. They contain —NH—CO linkages, but in general few —NH_2 groups not belonging to side chains, and in some cases possibly none.

(2) There is a general uniformity among proteins of widely different chemical constitution which suggests a simple general plan in the arrangement of the amino acid residues, characteristic of proteins in general. Protein crystals possess high, general trigonal, symmetry.

(3) Many native proteins are 'globular' in form.

(4) A number of proteins[1] of widely different chemical constitution, though isodisperse in solution for a certain range of values of *p*H, split up into molecules of submultiple molecular weights in a sufficiently alkaline medium.

The facts cited suggest that native protein may contain closed, as opposed to open, polypeptides, that the polypeptides, open or closed, are in a folded

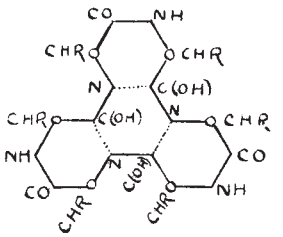
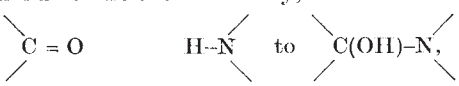


FIG. 1. The 'cyclol 6' molecule.

state, and that the type of folding must be such as to imply the possibility of regular and orderly arrangements of hundreds of residues.

An examination of the geometrical nature of polypeptide chains shows that, *since all amino acids known to occur in proteins are α-derivatives*, they may be folded in hexagonal arrays. Closed polypeptide chains consisting of 2, 6, 18, 42, 66, 90, 114, 138, 162 . . . $(18 + 24n)$ . . . residues form a series with threefold central symmetry. A companion series consisting of 10, 26, 42, 58, 74, 90, 106, 122 . . . $(10 + 16n)$ . . . residues have twofold central symmetry. There is also a series with sixfold central symmetry : others with no central symmetry. Open polypeptides can also be hexagonally folded. The number of free —NH_2 groups, in so far as these indicate an open polypeptide, can be made as small as we please, even zero if we so desire. The hexagonal folding of polypeptide chains, open or closed, evidently allows the construction of molecules containing even hundreds of amino acid residues in orderly array, and provides a characteristic pattern, which in its simplicity and uniformity agrees with many facts of protein chemistry.

The stability of these folded polypeptide chains cannot be attributed to electrostatic attractions between the various CO,NH groups, for the appropriate distance between carbon and nitrogen atoms in these circumstances[2] lies between 2·8 A. and 4·2 A., whereas the distance in our case is at most 1·54 A. By using the transformation* suggested by Frank in 1933 at a lecture given by W. T. Astbury to the Oxford Junior Scientific Society,



which has already proved useful in the structure of α-keratin[3], the situation is at once cleared up and we obtain (Fig. 1) the molecule 'cyclol 6' (the closed

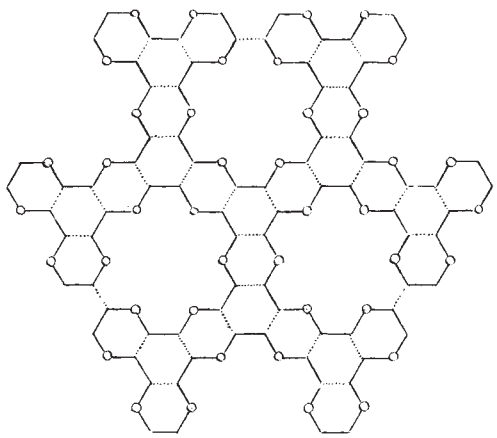


FIG. 2. A 'cyclol 42' molecule.

polypeptide with six residues), 'cyclol 18', 'cyclol 42' (Fig. 2) and so on, and similarly open 'cyclised' polypeptides (Fig. 3).

Hexagonal packing of polypeptides suggests a new *three dimensional* unit, —CHR—C(OH)—N<, which may be used to build three-dimensional molecules of a variety of types. These are now being investigated in detail. At the moment we direct attention only to

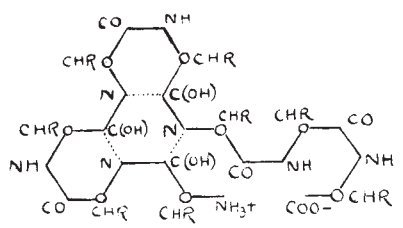


FIG. 3.

single cyclised polypeptides forming hexagons lying approximately in one plane. The cyclol layer molecule is a fabric the thickness of which is one amino acid residue. *Since all naturally occurring amino acids are of lævo type*[4] this fabric is dorsiventral, having a front surface from which the side chains emerge, and a back surface free from side chains. Both front and back carry trios of hydroxyls normal to the surface

* The application of this transformation to these molecules was suggested to me by J. D. Bernal.

in alternating hexagonal arrays. Such a layer molecule and its polymers, formed also by the same transformation, can cover an area of any shape and extent. It offers suggestions as to the structure of the solid protein film when it is one amino acid residue thick. In its most compact form, the cyclol layer molecule gives an area per residue of about 9·9 A.^{2}. Less dense layers can be built, for example, from polymers of cyclol 18 and of cyclol 66 respectively, where the corresponding areas per residue are 13·2 A.^{2} and 16·2 A.^{2} respectively. The figures for unimolecular films of gliadin, glutenin, egg albumin, zein, serum albumin, serum globulin range from $1{\cdot}724 \times 10^{-7}$ gm./cm.^{2} for serum globulin to $1{\cdot}111 \times 10^{-7}$ gm./cm.^{2} for serum albumin[5,6,7]. With an average residue weight of 120, these densities give an area per residue ranging from 11·48 A.^{2} to 18·82 A.^{2}. On the basis of the proposed hexagonal packing of polypeptides I therefore suggest that the upper limit of density of which a protein film is capable without buckling, provided that it is only one amino acid residue thick, is one residue per 9·9 A.^{2}; further, that a higher density implies that the film, though it may still be unimolecular, is more than one amino acid residue thick.

Cyclol layers may also be used to build molecules and molecular aggregates with extension in three dimensions, since they may be linked front to front by means of the side chains, in particular, by cystine bridges, and back to back by means of hydroxyls[8]. The single-layer cyclol is a fabric capable of covering a two-dimensional area of any shape and extent; a three-dimensional array can then be built, layer upon layer, the linkage being alternately by means of side chains and hydroxyls. The idea that native proteins consist largely, if not entirely, of cyclised polypeptides therefore implies that some native proteins, including those of 'globular' type, may have a layer structure.

Linkage by means of hydroxyls recalls the structures of graphitic oxide and montmorillonite, etc. Such a structure suggests a considerable capacity for hydration, an outstanding characteristic of many proteins. Further, since alternate layers are held together by means of hydroxyls, and contiguous molecules may also be held together in the same way, a protein molecular aggregate will, on this theory, necessarily be sensitive to changes in the acidity of the medium; in particular, a sufficiently high *p*H will cause such an aggregate to dissociate into single-layer units or into two-layer units joined by cystine bridges or side chains in covalent linkages. Svedberg's results, according to which a number of different native proteins break up into smaller molecules with sub-multiple molecular weights[1], here find a simple interpretation. The particular sub-multiples which occur may be regarded as affording evidence as to the type of symmetry possessed by the layers out of which the molecular aggregates are built.

The hypothesis that native proteins consist essentially of cyclised polypeptides thus takes account of the facts mentioned in (1), (2), (3), (4) above. Further, it derives support from the case of α-keratin, for with Astbury's 'pseudo-diketopiperazine' structure[9] the polypeptides may be regarded as partially cyclised since they are cyclised at regular intervals, one out of every three (CO,NH) groups being involved. It is also suggestive in relation to a variety of other facts belonging to organic chemistry, X-ray analysis, enzyme chemistry and cytology. I cite the following:

(1) The rhythm of 18 in the distribution of amino acids in gelatin found by Bergmann[9], and the suggestion of Astbury[10] that in gelatin "the effective length of an amino acid residue is only about 2·8 A.".

(2) The low molecular weight not exceeding 1,000 found by Svedberg[11] for the bulk of the material from which lactalbumin is formed.

(3) Secretin[12], a protein with molecular weight of about 5,000, containing no open polypeptide chains.

(4) The nuclear membrane, which, consisting of proteins and lipoids, plays an important part in mitosis on account of its variable permeability.

(5) Bergmann's findings[13] with respect to dipeptidase; these suggest that the dipeptide substrate, upon which this enzyme acts, has a hexagonal configuration.

Finally, the deduction from the hypothesis of cyclised polypeptides, that native proteins may consist of dorsiventral layers, with the side-chains issuing from one side only, suggests that immunological reactions are concerned only with surfaces carrying side-chains. Hence, such reactions depend both on the particular nature and on the arrangement of the amino acids.

Full details of the work, which is to be regarded as offering for consideration, a simple *working hypothesis*, for which no finality is claimed, will be published in due course.

[1] Svedberg, *Science*, **79**, 327 (1934).
[2] International Tables for the Determination of Crystal Structure.
[3] Astbury and Woods, *Phil. Trans. Roy. Soc.*, **232**, 333 (1933).
[4] Jordan Lloyd, *Biol. Rev.*, **7**, 256 (1932).
[5] Gorter, *J. Gen. Phys.*, **18**, 421 (1935); *Amer. J. Diseases of Children*, **47**, 945 (1934).
[6] Gorter and van Ormondt, *Biochem. J.*, **29**, 48 (1935).
[7] Schulman and Rideal, *Biochem. J.*, **27**, 1581 (1933).
[8] Bernal and Megaw, *Proc. Roy. Soc.*, A, **151**, 384 (1935).
[9] Bergmann, *J. Biol. Chem.*, **110**, 471 (1935).
[10] Astbury, Cold Spring Harbor Symposia on Quantitative Biology, 2, 15 (1934).
[11] Sjogren and Svedberg, *J. Amer. Chem. Soc.*, **52**, 3650 (1930).
[12] Hammersten *et al.*, *Biochem. Z.*, **264**, 272 and 275 (1933).
[13] Bergmann *et al.*, *J. Biol. Chem.*, **109**, 325 (1935).

Association of Technical Institutions

Annual Meeting in London

THE annual meeting of the Association of Technical Institutions was held in the Goldsmiths' Hall, London, on February 28–29. The Right Hon. Lord Plender was installed as president for 1936. In his presidential address he surveyed such changes in the structure of the business world as the development of large stores, the grouping of railways and the general trend towards amalgamation of small units of business. He referred especially to costing and its scientific application which have been so useful to industry, and he emphasised the need for skilled persons in such branches as accountancy, foreign exchange, advertising, etc.

In a paper on "Technology and the Community" Councillor Wright Robinson touched a question already adumbrated in the recent "Report on Policy