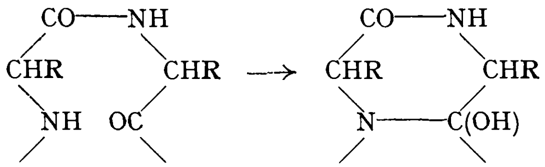
## 110. *The Association of α-Piperidone.*

By G. I. Jenkins and T. W. J. Taylor.

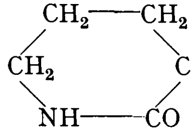
It is becoming increasingly probable that a simple protein should be regarded as consisting essentially of a polypeptide chain folded into some characteristic pattern and held in that arrangement by links between certain points of the chain, and that denaturation of the protein, and possibly also its spreading as a film on a water surface, is a result of an unfolding to give a chain which is not characterised by one particular arrangement of the parts (Wrinch, *Nature*, 1936, **137**, 411; Mirsky and Pauling, *Proc. Nat. Acad. Sci.*, 1936, **22**, 439). Two suggestions have been made as to the nature of the linkages between the groups of the polypeptide chain. The first is a kind of ring-chain tautomerism, in which spatially suitable imino- and carbonyl groups are involved, and it has been pointed out that this could lead to polycyclic folding of the chain (Wrinch, *loc. cit.*; *Nature*, 1936, **138**, 241). In a simple case it can be formulated as follows :

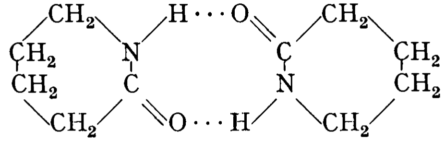


In the second suggestion, the essential mechanism is taken to be hydrogen-bond formation between the same groups and also, possibly, between free amino- and carboxyl groups carried on side chains (Mirsky and Pauling, *loc. cit.*). The two views have been combined in the suggestion that polycyclic assemblies formed in the first manner might associate further by hydrogen-bond formation (Wrinch and Jordan-Lloyd, *Nature*, 1936, **138**, 758).

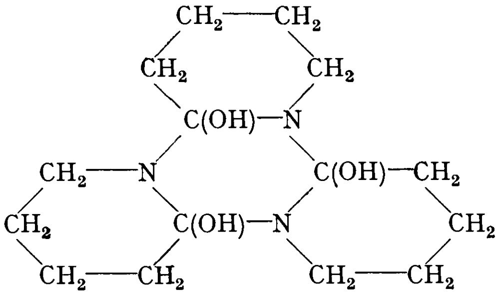
As a consequence of these views, it seemed of interest to establish the type of association in the simple cyclic imide α-piperidone (I), in which the peptide linking -NH-CO- already forms part of a ring. If, as in the first suggestion, there is a tendency for the building up of polycyclic systems, the compound might associate to the trimeric form (II), the structure of which would be very similar to that which Wrinch has postulated as a possible form of a cyclic hexapeptide (III). If, on the other hand, association takes place by hydrogen-bond formation, the polymerised form would presumably be dimeric, with the structure (IV), which is analogous to that of the dimeric form of a carboxylic acid.

(I.)

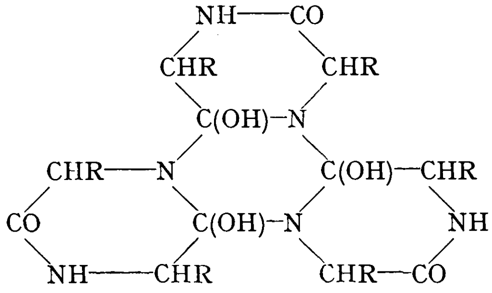




(IV.)



(II.)



(III.)

A trimeric form held together by hydrogen bonds is unlikely; it would contain what would amount to a nine-membered ring, which, because of its small probability of formation, could hardly be present in appreciable quantity in equilibrium with the dimeric and monomeric forms.

The apparent molecular weight of α-piperidone in solution in benzene and in water has been measured by the cryoscopic method. In water the compound shows practically no sign of association at all, presumably because the peptide group is combined with the solvent. In benzene, on the other hand, even at low dilution, the apparent molecular weight is 1·75 times the formula weight, and, as the concentration increases, approaches a value twice that of the formula weight. There is no indication of the existence of a trimeric complex.

The association of several simple amides and anilides has been determined by Meldrum and Turner (J., 1908, **93**, 876) by the boiling-point method. They found practically no indication of association in water, alcohol, or acetone, except possibly with benzamide. Nearly all the compounds were associated in benzene and chloroform. Thus, in general, the behaviour of the cyclic imide resembles that of the amides, and there is the same instability in water of the hydrogen bonds necessary for association. Direct comparison of the boiling-point results with ours is impossible because of the temperature difference, but the amides do not appear to give dimeric molecules at such low concentrations as piperidone does.

## EXPERIMENTAL.

α-Piperidone was prepared by the Beckmann rearrangement of *cyclo*pentanoneoxime (Wallach, *Annalen*, 1900, **312**, 179). It is extremely hygroscopic, and was dried by dissolving it in benzene and removing the solvent in a stream of dry air. It was finally distilled under reduced pressure (b. p. 134—137°/11 mm.), and collected in a glass tube of 7 mm. bore. The rod of solid thus obtained was cut into pellets of suitable size, which were kept in a vacuum over calcium chloride. Freezing-point measurements were made by the ordinary Beckmann method; with benzene as solvent a counter-current of dried air prevented the access of moisture. The benzene was of AnalaR quality, further purified by freezing out, and dried with and distilled from phosphoric oxide in an all-glass apparatus in dry air; its f. p. constant was found to be 52·34° per g.-mol. per 100 g. of solvent, pure naphthalene being used as solute. With both solvents and with all solutions, the amount of supercooling was kept to 0·8° as closely as possible; the aqueous solutions had to be seeded with a small crystal of ice.

α-Piperidone in benzene (formula weight = 99·1).

| Piperidone, mols. %. | Δ. | Apparent mol. wt. | Assoctn. factor. |
|---|---|---|---|
| 1·421 | 0·564° | 169·8 | 1·71 |
| 2·666 | 1·019 | 178·6 | 1·80 |
| 5·142 | 1·944 | 185·3 | 1·87 |
| 7·460 | 2·825 | 189·6 | 1·91 |

α-Piperidone in water.

| Piperidone, mols. %. | Δ. | Apparent mol. wt. | Assoctn. factor. |
|---|---|---|---|
| 0·699 | 0·720° | 100·1 | 1·01 |
| 1·117 | 1·130 | 102·3 | 1·03 |
| 1·786 | 1·770 | 105·1 | 1·06 |
| 2·471 | 2·423 | 106·9 | 1·08 |
| 3·671 | 3·575 | 109·1 | 1·10 |

We express our thanks to Dr. D. Wrinch, who suggested the measurements to us, and to the Rockefeller Foundation for a grant.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, February 9th*, 1937.]