

described a substance in this situation which, on account of its property of contraction in weak acids, he referred to as the cementing substance. He considered the substance to be a mucin. Recently¹, I have shown that its chief characteristics are those of a protein. Following what has been said above, it should be added that this protein reacts strongly with water.

According to modern theory^{3,4}, the degree of hydration of a protein at different concentrations of hydrogen ions will depend upon the ionization of the NH_3^+ and COO^- radicals of the side-chains. Near the iso-electric point, a maximal number of the side-chains will be oppositely charged. The attraction of opposite charges will bring the side-chains together and result in a more compact structure with exclusion of water. On the alkaline side of the iso-electric point there will be suppression of charge on the cationic centres of the protein. A large proportion of side-chains will therefore come to possess the same negative charge and their mutual repulsion will open up the structure and lead to swelling. Theoretically, therefore, the properties of connective tissue described above are those of a protein having an iso-electric point in the region of pH 4.5.

Schade and Menschel⁵ have shown that neutral salts may cause swelling of connective tissue. I have found that this effect is morphologically identical with that which occurs in conditions of reduced hydrogen ion concentration, and also that the reaction involved has the following features: (1) At neutrality the smallest concentrations of various salts necessary to cause swelling lie between $M/5$ and $M/20$. (2) While swelling, the tissue withdraws salt ions from the surrounding solution. (3) The capacity of a salt to cause swelling is greater with reduction of hydrogen ion concentration from the iso-electric point. (4) Although, in general, the actions of salts and hydrogen ions on the hydration of connective tissue are opposite and reversible, salts have no capacity to 'unlock' tissue which has become shrunken by prolonged treatment at a pH value near the iso-electric point.

It is clear that the hydration of connective tissue by the action of neutral salts is accompanied by some sort of union of salt with the protein. Probably the salt ions combine in some manner with protein side-chains. To do so, such side-chains must be available and not involved in electrovalent links with oppositely charged side-chains. Perhaps this is why salt has only a feeble 'unlocking' effect on tissue constricted by treatment near the iso-electric point of the inter-fibrillary protein, and also why, with decrease in hydrogen ion concentration away from this iso-electric point, the hydrating effect of the salt is so much greater.

It is apparent that salts exert a hydrating influence on connective tissue in physiological concentrations. This fact alone must be a matter of considerable importance not only to biological science but also to clinical medicine.

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March 21.

¹ Day, T. D., *Nature*, **159**, 100 (1947).

² Flemming, W., *Arch. micr. Anat.*, **12**, 391 (1876).

³ Höber, R., "Physical Chemistry of Cells and Tissues", 296 (Churchill, London, 1945).

⁴ Lloyd, D. J., and Phillips, H., *Trans. Farad. Soc.*, **29**, 132 (1933).

⁵ Schade, H., and Menschel, H., *Kolloid-Zeitschr.*, **31**, 171 (1922).

Tetrahydrofuran Hydroperoxide

A STUDY has recently been made in these laboratories of the liquid-phase oxidation of ethers. The products of oxidation may be satisfactorily accounted for by the formation of an intermediate hydroperoxide and its subsequent decomposition. As with the hydroperoxides of hydrocarbons, those of ethers are apparently often too unstable for isolation; but in the case of tetrahydrofuran the hydroperoxide has been isolated in the pure state.

The hydroperoxide obtained by the removal of unchanged tetrahydrofuran at low pressure from a sample which had undergone oxidation by prolonged exposure to air during storage was a liquid (n_D^{20} 1.6933) at room temperature. The product gave on analysis C 46.0, H 7.9 per cent (required, C 46.1, H 7.7 per cent) and liberated the theoretical quantity of iodine from acidified potassium iodide. The hydroperoxide was completely miscible with water and soluble in the common organic solvents (acetone, methanol, acetic acid), and strongly catalysed the polymerization of styrene and methyl methacrylate. The onset of thermal decomposition occurred in the range 70–80° C., and rapid heating to 100° C. did not cause detonation, though the decomposition became more violent at still higher temperatures. The normal reagents for the destruction of peroxides (ferrous sulphate, sodium hydroxide, etc.) were equally efficacious in the case of tetrahydrofuran hydroperoxide, the chief product of both the thermal and catalysed decompositions being γ -butyrolactone. The formation of γ -butyrolactone may be accounted for by loss of water:



though the fact that tetrahydrofuran hydroperoxide is a polymerization catalyst indicates that some homolytic decomposition also occurs, probably by fission of the O—O bond.

A complete account of this work will be published elsewhere.

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March 17.

Benzimidazole Analogues of Pteric and Pteroylglutamic Acids

IN the course of experiments on the relationship of structure to biological activity in the folic acid series of growth factors, we have examined the benzimidazole analogues of pteric acid and of pteroylglutamic acid¹.

The compound (I), m.p. 281° (decomp.), in which the 2-amino-4-hydroxypteridyl residue (numbering according to the "Ring Index", Reinhold, New York, 1940) of pteric acid is replaced by a benzimidazole ring, was prepared from 2-chloromethylbenzimidazole² and *p*-aminobenzoic acid in boiling alcohol, or *via* its ethyl ester, from ethyl *p*-aminobenzoate (found: C, 66.8; H, 4.7; $\text{C}_{15}\text{H}_{13}\text{O}_2\text{N}_3$, requires C, 67.4; H, 4.7 per cent). The benzimidazole analogue of pteroylglutamic acid was obtained as a