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Short Communications

On the Solubilisation of C_{21}-Steroids

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In 1949, Ekwall and Sjöblom [1] established that aqueous solutions of association colloids are able to solubilise steroid hormones. Since then considerable data on the solubilisation of steroids have accumulated,[2-3] but they do not permit any reliable conclusions about the solubilisation mechanism involved. With the intention of elucidating this mechanism, solubilisation studies have now been continued systematically. For this purpose, the solubilities of several series of structurally related steroids differing from each other in the number and position of hydrophilic substituents and double bonds in different association colloid solutions have been determined. The present paper is a brief summary of the results obtained with ten corticosteroids and their derivatives in solutions of sodium dodecyl sulphate, tetradecyltrimethylammonium bromide, and a polyoxyethylene sorbitan monolaurate (Tween 20).

The experimental technique was essentially the same as that described previously,[3] using the ultra-violet absorption of the steroids for the solubility determinations. As previously noted with other solubilised compounds,[2-4] the maxima for the steroids in aqueous solutions were somewhat shifted and depressed as compared with those recorded with ethanol as the solvent. This effect was most pronounced in solutions containing the nonionic colloid.

A few of the solubility curves obtained are shown in Figs. 1–2. The solubilisation begins near the CMC above which the

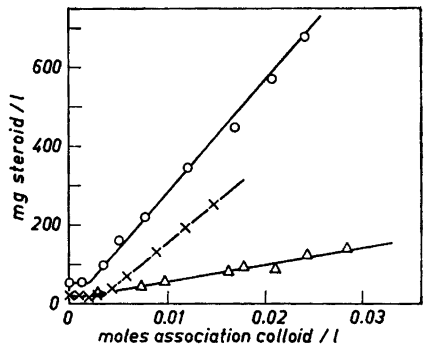

Fig. 1. The solubility of cortisone-21-acetate in aqueous association colloid solutions. Sodium dodecyl sulphate at 40°C (O), tetradecyltrimethylammonium bromide at 20°C (×), and Tween 20 at 20°C (△).

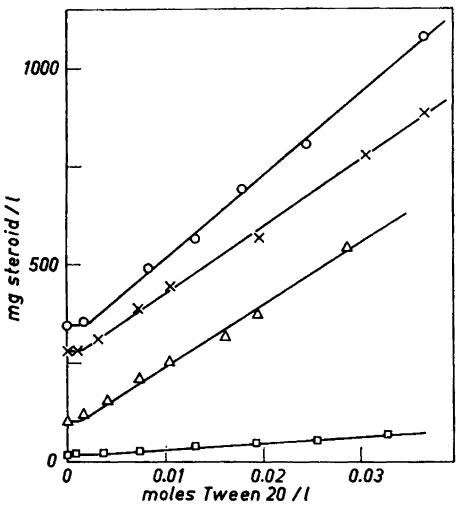

Fig. 2. The solubilities of some hydrocortisone derivatives in aqueous solutions of Tween 20 at 20°C. Hydrocortisone (O), Δ^1-hydrocortisone (×), 9-fluoro-16-methyl-Δ^1-hydrocortisone (△), and hydrocortisone-21-acetate (□).

solubility increases linearly with the colloid concentration. From the slopes of the solubility curves the saturation capacity of the micellar substance for the different steroids was calculated. These values are collected in Table 1.

Table 1. Maximum solubilisation powers of association colloids for different C_{21}-steroids. NaDS = sodium dodecyl sulphate (40°C), TDTM = tetradecyltrimethylammonium bromide (20°C), Tw 20 = Tween 20 (20°C).

Steroid	Mole steroid per mole micellar substance		
	NaDS	TDTM	Tw 20
11-Desoxycorticosterone	0.38		0.11
—„— -21-acetate	0.16	0.070	0.013
Cortisone	0.20	0.14	0.023
—„— -21-acetate	0.071	0.050	0.0090
Δ^1-Cortisone	0.23	0.27	0.036
—„— -21-acetate	0.087		0.012
Hydrocortisone	0.30	0.32	0.057
—„— -21-acetate	0.026	0.025	0.0043
Δ^1-Hydrocortisone	0.22	0.21	0.047
9-Fluoro-16-methyl-Δ^1-hydrocortisone	0.16	0.27	0.041

At first, it may be noted that the amounts solubilised vary about two powers of ten. In solutions of each colloid the most soluble of the steroids (11-desoxycorticosterone) is solubilised in more than ten times greater amounts than the least soluble (hydrocortisone-21-acetate). With a few exceptions, the order of solubility of the steroids was the same in all of the colloid solutions studied. However, the solubilities in solutions of the non-ionic colloid (Tween 20) are five to ten times lower than the solubilities in the solutions of the two ionic colloids, which are of the same order of magnitude. The much lower saturation capacity of the non-ionic micelles as compared with the saturation capacities of the ionic micelles may be due either to differences in micellar structure or to different solubilisation mechanisms. A difference between these two types of colloids regarding the solubilisation of C_{21}-steroids is also supported by the above mentioned solvent effect on the ultraviolet absorption.

The most marked change in the solubilisation is effected by esterification of the hydroxyl group at C_{21}. *E.g.*, hydrocortisone-21-acetate is solubilised in about twelve times smaller amounts than the unesterified steroid. With 11-desoxycorticosterone, cortisone, and Δ^1-cortisone a similar, but slightly less striking, effect is observed. The decrease in solubility resulting from the esterification is of the same order of magnitude in the solutions of all the colloids studied and indicates that the free hydroxyl group at C_{21} actively enhances the solubilisation of the steroids in some way. The free hydroxyl group is, however, not essential for solubilisation, since the 21-acetoxy-steroids are still solubilised in considerable amounts. In the latter, the side chain at C_{17} seems to be of minor importance, since the amounts of the 21-acetoxy-steroids solubilised are of the same order of magnitude as the amounts of oestrone and oestradiol,[3] which both lack this side chain.

Besides the esterification of the C_{21}-hydroxyl group, other alterations in the steroid molecule have less uniform effects on the solubilisation. The influence of hydroxyl groups at C_{11} and C_{17} and an oxo group at C_{11} is illustrated by the solubilities of 11-desoxycorticosterone, cortisone, and hydrocortisone as well as the corresponding 21-acetoxy compounds. Of the unesterified steroids mentioned, cortisone is the least soluble in all the colloid solutions studied. When the oxo group at C_{11} in cortisone is replaced by a hydroxyl group (hydrocortisone), the solubility increases markedly. However, a similar effect is obtained when both oxygen atoms at C_{11} and C_{17} are removed (11-desoxycorticosterone). In this respect considerable quantitative differences between the solubilisation by different colloids are observed. When the corresponding 21-acetoxy compounds are compared, it is found that they behave quite differently. Hydrocortisone-21-acetate, which contains two free hydroxyl groups, is the least soluble in all the colloid solutions employed, whereas 11-desoxycorticosterone-21-acetate with no free hydroxyls is the most soluble. This suggests that different solubilisation mechanisms apply in the case of the free steroids and their 21-acetoxy derivatives.

The introduction of a second double bond between C_1 and C_2 has no uniform effect on the solubilisation. In the case of cortisone the double bond slightly increases the solubility, but in the case of hydrocortisone an opposite effect is noted. In this respect also considerable quantitative differences are observed with different colloids. Furthermore, the data for Δ^1-cortisone and Δ^1-hydrocortisone are less reliable than those for the other steroids, since turbid solutions were often formed around the CMC. This phenomenon is possibly due to the formation of a mesomorphous phase, as in the case of cholesterol and association colloid solutions.[5] As with all the other steroids studied perfectly clear solutions were obtained at all colloid concentrations, it may be suggested that a double bond in certain positions of the steroid skeleton contributes to the formation of a mesomorphous phase.

At last, the solubility values for 9-fluoro-16-methyl-Δ^1-hydrocortisone indicate, that the methyl group and fluorine are of little importance for the solubilisation.

The systematic investigations of the solubilisation of steroids is being continued and the results presented here will be discussed later in more detail together with other data.

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1. Ekwall, P. and Sjöblom, L. *Acta Chem. Scand.* **3** (1949) 1179.
2. Ekwall, P. and Sjöblom, L. *Acta Endocrinol.* **4** (1950) 179; Ekwall, P., Lundsten, T. and Sjöblom, L. *Acta Chem. Scand.* **5** (1951) 1383; Ekwall, P., Sjöblom, L. and Olsen, J. *Ibid.* **7** (1953) 347.
3. Sjöblom, L. *Acta Acad. Aboensis, Math. Phys.* **20** (1956) No. 14; **21** (1958) No. 7.
4. Ekwall, P., Setälä, K. and Sjöblom, L. *Acta Chem. Scand.* **5** (1951) 175.
5. Ekwall, P., Baltscheffsky, H. and Mandell, L. *Ibid.* **15** (1961) 1195; Mandell, L. *Finska Kemistsamfundets Medd.* **72** (1963) 49.

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Favorsky Rearrangements

II. Attempts to Rearrange Pentabromoacetone

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Recently it has been found that the reaction between di-, tri- and tetrahalo ketones and weak bases such as carbonates or bicarbonates give good yields of Favorsky rearranged products. In most cases the reaction showed geometric specificity.[1-6] Continuing these studies it appeared interesting to study the effect of the same weak bases on the related pentabromo ketones. In this connection Wagner, Kloosterziel and Bickel found that small amounts of Favorsky rearranged products were isolated from the reaction between penta- and hexachloroacetone and sodium trichloroacetate.[7]

Since only α-haloketones having at least one α-hydrogen can undergo the Favorsky rearrangement [8] it was necessary to use pentabromoacetone. Accordingly pentabromoacetone was treated with excess aqueous bicarbonate and the reaction mixture was extracted with ether, acidified and then once again extracted with ether. From the acidic extract an acid could be isolated. However, it was not the expected 2,2,3-tribromoacrylic acid but dibromoacetic acid. This acid could be isolated in 64 % yield. The basic extract was distilled and from this extract bromoform could be isolated in 67 % yield. The reaction is probably an example of a haloform reaction and it can be visualized in the following way, *cf.* Ref.[9]

$$CBr_3COCHBr_2 + OH^- \rightleftharpoons CBr_3-\underset{\displaystyle OH}{\overset{\displaystyle O^-}{\underset{|}{\overset{|}{C}}}}-CHBr_2 \rightleftharpoons$$

$$CBr_3^- + CHBr_2COOH \rightleftharpoons CHBr_3 + CHBr_2COO^- \quad \text{(I)}$$

Attempts to use water, a still weaker base, instead of bicarbonate for the reaction (at 80°C for 4 days) resulted in the isolation of small amounts of crude materials, which consisted partly of dibromoacetic acid and bromoform.