TABLE I. Time Course of Warfarin Disappearance from Rat Plasma, Estimated Values of K_d and the Calculated Plasma Warfarin Concentrations

Time (hr)	Plasma concentration ($\mu\text{g/ml}$)	K_d (hr)	Calculated plasma concentration ($\mu\text{g/ml}$)
0.083	1.81	0.974	1.83
0.25	1.40	0.824	1.48
0.50	1.17	0.883	1.23
0.75	1.01	0.804	1.08
1.0	0.971	0.963	0.990
1.333	0.958	1.30	0.906
1.666	0.880	1.23	0.847
2.0	0.819	1.15	0.802
2.5	0.797	1.42	0.751
3.067	0.725	1.22	0.706
3.5	0.647	0.736	0.678
4.033	0.663	1.23	0.648
5.0	0.591	0.868	0.602
7.0	0.524	0.949	0.529
11.0	0.406	a)	0.421
23.0	0.237	a)	0.228
29.0	0.154	a)	0.169
35.0	0.116	a)	0.125
47.25	0.0651	a)	0.0686

Average $K_d = 1.04 \pm 0.21$ (S.E.).a) K_d was not calculated because these data belong to the terminal phase.

tion as a function of time, we attempted to represent the blood concentration *vs.* time profile in terms of a model independent method. The results of a simulation study indicate that this new approach is indeed applicable to the pharmacokinetic analysis of drugs.

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The Properties of Water of Crystallization of Sodium Prasterone Sulfate

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The properties of water of crystallization of sodium prasterone sulfate ($\text{DHA} \cdot \text{SO}_3\text{Na} \cdot 2\text{H}_2\text{O}$) were investigated by thermometric measurements. The anhydrous form ($\text{DHA} \cdot$

SO₃Na) was very hygroscopic, and easily transformed to the dihydrate. The dihydrate was in a stable phase under ordinary storage conditions. If the released water molecules were not effectively exhausted in the dehydration process, a liquefaction phenomenon due to the interaction between water molecules and DHA·SO₃Na was observed.

The activation energy (ΔE) of the dehydration reaction from the dihydrate to the anhydrous form was determined by an isothermal method and a non-isothermal method (Ozawa method) under a constant water vapor pressure, P_{H_2O} = 14.9 mmHg. ΔE obtained by the isothermal method was 31.5 kcal/mol and ΔE obtained by the Ozawa method was 31.3 kcal/mol.

Keywords—sodium prasterone sulfate; water of crystallization; dihydrate; anhydrous form; dehydration; hydration; activation energy

Sodium prasterone sulfate (DHA·SO₃Na·2H₂O) is a drug which softens the birth canal to make delivery easier.¹⁾ In preformulation studies, if a drug has water of crystallization, it is very important to determine its properties. Sodium prasterone sulfate exists as the dihydrate,²⁾ so the present study was carried out to clarify the properties of the water of crystallization of the dihydrate. The dehydration rate of the dihydrate to the anhydrous form was measured and the activation energy of the dehydration reaction was determined by an isothermal method and a non-isothermal method (Ozawa method³⁾). Since it was reported that the dehydration process of water of crystallization was affected by the water vapor pressure in the atmosphere,⁴⁾ the water vapor pressure was kept constant. The hydration of the anhydrous form to the dihydrate and the moisture adsorption of the dihydrate were also studied.

Experimental

Materials—DHA·SO₃Na·2H₂O was prepared as described previously.²⁾ DHA·SO₃Na·2H₂O was twice recrystallized from H₂O–EtOH (1:9) and dried *in vacuo* at 30° for 10 hr. Its water content was 8.49% (by the Karl–Fischer method, Calcd; 8.45%). DHA·SO₃Na·2H₂O was sieved, and the 42–80 mesh portion was used as the test sample.

Dehydration of the Dihydrate—The weight loss due to dehydration was measured by TG using a Shimadzu TG-20 thermal analyser under controlled conditions. The sample (5 ± 0.5 mg) was weighed and N₂ gas was adjusted to P_{H_2O} = 14.9 mmHg by being passed over an NaCl-saturated solution; it was then introduced into the sample chamber at 70 ml/min. After the water vapor pressure in the chamber had reached the desired level, measurements were done at various scanning speeds. The water vapor pressure was monitored with a dewpoint hygrometer which was in a chamber connected to the TG sample chamber. The dehydration temperature and the heat of dehydration were measured by DTA and DSC using Shimadzu DT-20B and DSC-20 thermal analysers, respectively, under the same conditions as for TG measurement. DTA and DSC curves were obtained by using a cell without a seal and with a seal which had some holes, respectively, in order to allow the water to evaporate freely.

Melting Point—The melting point was measured by the capillary method and by hot stage microscopy using a model MP-21 melting point apparatus (Yamato Kagaku Co., Ltd.) and No. 2410 micro melting point apparatus (Yanagimoto Seisakusho Co., Ltd.), respectively.

Results and Discussion

Mechanism of Dehydration

DTA and TG curves of DHA·SO₃Na·2H₂O obtained at various scanning speeds (2, 5, 10, 15°/min) at 14.9 mmHg water vapor pressure are shown in Fig. 1. In the DTA curves, the endothermic peaks due to dehydration shifted toward higher temperature as the scanning speed increased. DTA curves gave one peak for dehydration at a scanning speed of 2°/min, but two peaks at higher scanning speeds. Since the two peaks appeared more clearly at higher scanning speeds, they might not be due to loss of the two water molecules of the dihydrate at different temperatures. Sekiguchi *et al.*⁵⁾ and Niazi⁶⁾ reported that the hydrate or solvate produced a liquid phase during dehydration or desolvation by heating when the hydrate or solvate was rapidly heated and water or solvent vapor was not effectively exhausted, and the

Fig. 1. DTA and TG Curves of DHA·SO₃Na·2H₂O at P_{H₂O} = 14.9 mmHg
Scan speed (°C/min); a, 2; b, 5; c, 10; d, 15.

corresponding DTA curves gave at least two peaks under such conditions. The dehydration mechanism described above was supported by the results of the following experiments. When DHA·SO₃Na·2H₂O packed in a capillary tube of 1 mm diameter was heated at 3°/min in an oil bath, a liquefaction phenomenon was observed at 125–128°, but in a hot stage micrograph, the liquefaction at 125° was not observed and only decomposition at 157° was observed. It was considered that water vapor was less effectively exhausted in the capillary method than in the hot stage micrograph method, so that interaction between water vapor and DHA·SO₃Na occurred in the capillary and the liquefaction phenomenon at 125° was observed.

This dehydration mechanism involves decomposition of the hydrate to the anhydrous form and the formation of a solution, followed by the evaporation of the water molecules. The second endothermic peak in DTA curves which appeared at higher scanning speeds was considered to be due to the formation of a solution and/or to the evaporation of the water molecules. The temperature at which the liquefaction described above occurs may be misunderstood as the melting point; however, these two liquefaction phenomena must be distinguished from one another.

Activation Energy of the Dehydration Reaction

1) **Isothermal Method**—The dehydration rate of DHA·SO₃Na·2H₂O at constant temperature was measured at P_{H₂O} = 14.9 mmHg and the activation energy for the dehydration reaction was determined. As Horikoshi^{7a)} reported previously, Jander's equation^{7b)} can be applied to the dehydration curves in order to calculate the activation energy of the dehydration reaction. Fig. 2 shows the Jander's equation plots. A good correlation was established for the dehydration reaction of DHA·SO₃Na·2H₂O. The slopes obtained by the least-squares method were used to prepare an Arrhenius plot. The fits were good. The activation energy determined was 31.5 kcal/mol.

2) **Non-isothermal Method (Ozawa Method)**—The activation energy of dehydration can be determined by a non-isothermal method. Several non-isothermal methods have been reported.⁸⁾ Among them, the one proposed by Ozawa, which was applied to griseofulvin desolvation by Sekiguchi *et al.*,⁵⁾ was applied to DHA·SO₃Na·2H₂O dehydration. As shown in Fig. 3, a good linear relationship between the logarithm of heating rate and the reciprocal of temperature was obtained at P_{H₂O} = 14.9 mmHg. The activation energy calculated from the slopes within the range of residual fraction from 30% to 90% was 31.3 ± 4.9 kcal/mol. Large values of ΔE were obtained at 10% and 20% residual fraction, and these values were omitted. The value of ΔE determined by the Ozawa method was similar to that obtained by the isothermal method.

Fig. 2. Jander's Equation Plots

○, 82°; ●, 91°; ▲, 103°; △, 109°.

Fig. 3. Plots of the Logarithm of Scan Speed *versus* the Reciprocal of Absolute Temperature for the Indicated Conversions of the Dehydration of $\text{DHA} \cdot \text{SO}_3\text{Na} \cdot 2\text{H}_2\text{O}$ at $P_{\text{H}_2\text{O}} = 14.9$ mmHg

The heat of dehydration per mole of H_2O determined from DSC curves at a scanning rate of $5^\circ/\text{min}$ was 9.0 ± 0.2 kcal/mol.

Hydration and Moisture Sorption

When 0.5 ± 0.05 g of $\text{DHA} \cdot \text{SO}_3\text{Na} \cdot 2\text{H}_2\text{O}$ in a weighing bottle was placed in a desiccator adjusted to the appropriate water vapor pressure at 21° , the percentages of weight increase after 3 weeks' exposure were 0.08% at $P_{\text{H}_2\text{O}} = 8.7$ mmHg (44% R.H.), 0.28% at $P_{\text{H}_2\text{O}} = 14.9$ mmHg (75% R.H.) and 0.4% at $P_{\text{H}_2\text{O}} = 18.6$ mmHg (94% R.H.). When the anhydrous form (5 ± 0.5 mg), which was formed by the dehydration of $\text{DHA} \cdot \text{SO}_3\text{Na} \cdot 2\text{H}_2\text{O}$ at 60° under reduced pressure, was placed in the TG sample chamber and exposed to N_2 gas adjusted to the appropriate water vapor pressure at 21° , it adsorbed water rapidly and transformed into the dihydrate. The times required to reach the dihydrate state were 25, 30 and 90 min at $P_{\text{H}_2\text{O}} = 8.7$, 14.9 and 18.6 mmHg, respectively. These results show that the anhydrous form is unstable to humidity and that the dihydrate is the most stable form under normal conditions.

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