Phase Transitions I.

Preliminary Study of Theophylline Hydrate–Anhydrate System

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The phase transformation of theophylline hydrate to an anhydrous form was measured at a variety of temperatures using X-ray powder diffractometry. The conversion rate appeared to be first order with respect to the amount of hydrate present.

NUMEROUS MEDICINAL AGENTS are capable of existing in the solid state as hydrates and nonhydrated polymorphs. Since the physical chemical properties of many of these modifications of a drug can be markedly different, this may in turn influence its pharmaceutical formulation. In many instances it would therefore be important to understand what factors might influence a solid state transition from a hydrate to an anhydrous form, or *vice versa*, and at what rate this transformation occurs.

The primary purpose of this preliminary study on phase transitions of pharmaceuticals is to demonstrate that by the use of X-ray powder diffractometry, kinetic data for the conversion of a hydrate to its anhydrous state can easily be obtained. The method has the advantage over other techniques in that one is measuring directly the crystal structure transformation. For this study the theophylline system was chosen, since the crystal structure of the hydrate has already been reported (1) and the thermodynamics of dissolution for the system has been investigated (2).

EXPERIMENTAL

Theophylline (U.S.P. grade) was recrystallized from water and then allowed to dry on filter paper at room temperature for a week. The material was then ground in a glass mortar until a fine powder was obtained. Since the particle size was not measured in these experiments, it was necessary to grind all the experimental material at once, so that the particle size distribution from run to run would be fairly constant.

A series of samples weighing approximately 4 Gm. each was distributed evenly on the bottom of Petri dishes by shaking the glass vessels. The dishes were placed in an oven with the temperature previously set. During the experiment, a thermometer recorded the air temperature directly above the sample. Samples were taken from the oven at hourly intervals, without altering the temperature more than a degree or two, and then added to tightly-stoppered vials.

Some of the material was heated at a temperature of 100° for a period of 1 week. Though conversion of the hydrate to the anhydrous form occurred at an extremely rapid rate at this temperature, the week-long heating ensured that all the material was converted to the latter form. X-Ray diffraction powder patterns of the two modifications were measured on a GE XRD-6 diffractometer. There were many diffraction regions in which the two forms had intense peaks which were separated sufficiently to permit quantitative analysis of mixtures of the two, in a manner similar to that described by Azaroff and Buerger (3) and Shell (4). The diffraction peaks utilized were those at 13.2° (2θ) for the hydrate and at 12.6° (2θ) for the anhydrous crystals.

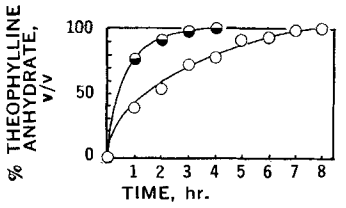

Fig. 1—Anhydrate formation from theophylline hydrate at 40° and 50°. Key: ◒, 50°; O, 40°.

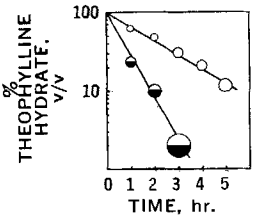

Fig. 2—Conversion of theophylline hydrate to the anhydrate–transformation rates at 40° and 50°. Key: ◒, 50°; O, 40°.

RESULTS AND DISCUSSION

Studies carried out at room temperature (approximately 25°) showed that there was no detectable transformation of the hydrate to the anhydrous form, over a period of 2 months. Above 60° the rate of conversion was so rapid that it was not possible to measure it by the present technique. At 60° the rate was measureable but appeared to be suffering from the lag time necessary for the material to reach the oven temperature. The conversion curves (Figs. 1 and 2) at 40° and 50° gave apparent first-order transformation rates. It is felt that at these temperatures the time necessary for the solid material to reach the oven temperature was probably negligible compared to the initial rate of transformation. Since particle size and humidity were not controlled, it is felt that a detailed analysis of the rate data would be presumptuous. It is interesting to note, however, that the transition temperature for this phase transformation probably lies not too far above room temperature but below 40°. This temperature is considerably lower than that obtained by the solubility method of Shefter and Higuchi (2); where 73° was obtained for the transition temperature in water. This is a direct indication that hu-

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midity probably plays a major role in this phase transformation.

The transformation of caffeine hydrate to an anhydrous state was also carried out in the same manner. The results obtained for the two purine systems are quite different. Hydrated caffeine had a fairly rapid rate of transformation at room temperature, and the conversion appeared to go through various hydrate intermediates, as evidenced through certain changes in the X-ray powder patterns with time. This latter phenomenon is in agreement with the findings of Waters and Beal (5). The general differences in the transformation processes for the two purine hydrates are consistent with structural studies on the hydrates of the two compounds (1, 6, 7). The hydrogen bonding schemes in the two hydrate crystal structures are markedly different with respect to the waters. It would be tempting to correlate the semiquantitative rate data with the crystal structures of the hydrates; however, such speculations would be premature at this time in view of the lack of structural data on the anhydrous crystals and more detailed phase transformation data.

REFERENCES

(1) Sutor, D. J., *Acta Cryst.*, **11**, 83(1958).
(2) Shefter, E., and Higuchi, T., *J. Pharm. Sci.*, **52**, 781 (1963).
(3) Azaroff, L. V., and Buerger, M. J., "The Powder Method," McGraw-Hill Book Co., New York, N. Y., 1958, p. 200.
(4) Shell, J. W., *J. Pharm. Sci.*, **52**, 24(1963).
(5) Waters, K. L., and Beal, G. D., *J. Am. Pharm. Assoc., Sci. Ed.*, **35**, 12(1946).
(6) Sutor, D. J., *Acta Cryst.*, **11**, 453(1958).
(7) Gerdil, R., and Marsh, R. E., *ibid.*, **13**, 166(1960).

Stereospecific Hydrogenations Using Palladium-on-Poly-L-leucine

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Studies have been conducted concerning the stereospecific nature of catalysts prepared by depositing palladium upon a poly-L-amino acid. The poly-L-amino acid chosen for this study was poly-L-leucine which was prepared from *N*-carboxy-L-leucine anhydride. The substrates employed in this work were α-methylcinnamic acid and α-acetamidocinnamic acid. Hydrogenation of α-methylcinnamic acid catalyzed by palladium-on-poly-L-leucine produced predominately R(−)-dihydro-α-methylcinnamic acid and hydrogenation of α-acetamidocinnamic acid using the same catalyst produced, after hydrolysis, S(−)-phenylalanine.

THE STEREOSPECIFICITY of catalysts prepared from silica gels precipitated in the presence of cinchona alkaloids has been shown by Padgett and Beamer (1). Beamer and Lawson have presented evidence of substrate specificity with similarly prepared gels (2). The silica gel work was based on prior evidence indicating the existence of stereospecific and substrate-specific centers in palladium-on-charcoal catalysts (3). Also, Akabori *et al.* had demonstrated the stereospecificity of palladium-on-silk fibroin (4) and Beckett *et al.* had shown the stereospecificity of adsorption in specially prepared silica gels (5–7).

The present work concerns the observation of stereospecificity in palladium-on-poly-L-amino acids. The poly-L-amino acid chosen for this study was poly-L-leucine which was prepared by polymerization of the *N*-carboxy-α-amino acid anhydride *in vacuo*.

Stereoselection in these catalysts should occur from asymmetric induction arising from stereoselective adsorption to active sites on the catalyst surface followed by *cis*-addition of hydrogen (3).

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EXPERIMENTAL

Reagents—α-Methylcinnamic acid (Aldrich), carbobenzyloxy chloride (Nutritional Biochemicals), L-leucine (Mann Biochemicals).

Poly-L-leucine—This polypeptide was prepared from the *N*-carboxy-α-amino acid anhydride by the Bergman procedure (8) which consisted of preparation of the carbobenzyloxy amino acid (CBZ amino acid) from CBZ chloride and L-leucine. The anhydride was prepared by Leuch's procedure from the CBZ amino acid and thionyl chloride (8). By melting the anhydride under high vacuum (10^{-3} mm. Hg) the polyamino acid was obtained. The yield was 23% of theory (based on L-leucine). Infrared spectra (Nujol mull) of the resulting polyamino acid were identical with those given by Bamford *et al.* (9). Carbon, hydrogen, and nitrogen analyses indicate the product is the hemihydrate and this has been confirmed by drying in an oven. Molecular weight determinations are currently being carried out and will be reported at a later date.

Anal.—Calcd. for $C_6H_{11}NO \cdot {}^1/_2H_2O$: C, 58.99; H, 9.90; N, 11.47. Found: C, 59.66; H, 9.51; N, 11.55.

α-Acetamidocinnamic Acid—This compound was prepared by hydrolysis of the azlactone, 2-methyl-4-benzilideneoxazolin-5-one (10). The product melted from 190° to 191.5° (uncorrected). [Lit. (10) m.p. 191°–192°.]

Preparation of Catalysts—Two methods were used to prepare the catalysts.

Method A—Sixteen milliliters of a 2.5% palladous