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Phase transitions of calcium gluceptate

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Summary

Calcium gluceptate (calcium α-glucoheptonate, $CaC_{14}H_{26}O_{16}$) is commercially available as a crystalline hydrate containing 3.5 molecules of water per atom of calcium. A crystalline anhydrate was prepared by dehydration. The transition between the hydrate and the anhydrous phases is reversible, and both phases become X-ray amorphous on grinding. The crystalline phases were characterized by X-ray diffraction, and the crystalline and amorphous forms were subjected to thermal analyses (thermogravimetric analysis, differential scanning calorimetry and hot stage microscopy). Marked differences exist between the apparent water solubilities of these forms at room temperature, and at concentrations greater than the equilibrium solubility of the crystalline hydrate, solutions prepared using the crystalline anhydrate, the X-ray amorphous hydrate and the X-ray amorphous anhydrate are supersaturated, and the stable hydrate crystallizes from solution. A relative humidity (RH)-composition phase diagram shows that the crystalline hydrate and the crystalline anhydrate appear to coexist between 0 and 66% RH (25°C). Various hypotheses for this anomalous behavior were tested. The adsorption of a small amount of water by the anhydrate seems to inhibit further water uptake and prevents the phase transition to the hydrate.

Introduction

Until about 1980, calcium gluceptate (calcium α-glucoheptonate, $CaC_{14}H_{26}O_{16}$) was available commercially as a very water-soluble amorphous anhydrate, III. The material currently available is a sparingly soluble crystalline hydrate, I, containing 3.5 molecules of water of crystallization per atom of calcium. The USP injection is an aqueous solution containing 20.8–23.3% w/v $CaC_{14}H_{26}O_{16}$ and is highly supersaturated with respect to the hydrate. Solutions containing 23% w/v III crystallized within 24 h, but pharmaceutically stable solutions could be prepared provided they were autoclaved at 121°C for 20 min immediately after preparation, which presumably destroys seed crystals of I and thereby prevents heterogeneous nucleation (Suryanarayanan and Mitchell, 1981, 1984). The equilibrium solubility of I was only 3.3% w/v (0.06 molal) at 25.5°C (Suryanarayanan, 1985), and hence this material cannot be used to prepare the USP injection. Since the decrease in water solubility is due to a change in hydration

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and/or crystallinity, it was thought that if I could be made anhydrous and/or amorphous, then the apparent water solubility could be increased. Suryanarayanan and Mitchell (1985) showed that heating I at 60°C under vacuum for 16 h resulted in a crystalline anhydrate. II, which had an apparent water solubility of 1.3 molal at room temperature (≈ 22°C). Since the solubility of I determined under the same experimental conditions was 0.07 molal, its dehydration resulted in about a 19-fold increase in apparent solubility. The USP injection can therefore be prepared using II. The apparent solubility of II was increased further from 1.3 to 5.4 molal by grinding for 2 h. The increase in apparent solubility was due to a decrease in crystallinity and after grinding for 4 h, the material was X-ray amorphous. Decreasing the crystallinity of I by grinding for 1 h resulted in an X-ray amorphous material with an apparent solubility of 0.11 molal at ≈ 22°C. Therefore, changes in the degree of crystallinity have a less marked effect on the apparent solubility of I than of II.

The object of the present work was to examine properties of the various phases of calcium gluceptate in more detail and to investigate their interconversion.

Materials and Methods

Materials

Calcium gluceptate (I) (Pfanstiehl, lot 13313-E) and calcium gluceptate (III) (Pfanstiehl, lot 12953-D) have been described previously (Suryanarayanan and Mitchell, 1985; Suryanaryanan and Mitchell, 1984, respectively). I was dried at 60°C under vacuum (pressure < 133 Pa) for 16 h to give a crystalline anhydrate (II). Room temperature was ≈ 22°C and the relative humidity (RH) was ≈ 35%.

Methods

The details of grinding, powder X-ray diffraction and thermogravimetric analysis (TGA), have already been described (Suryanarayanan and Mitchell, 1985). Other methods were as follows:

Freeze-drying. About 1 g of I was dissolved in approximately 50 ml of water. The solution was frozen at −76°C (Model UC 105, Kelvinator), dried in a freeze-dryer (Virtis Co.) and stored in a desiccator over phosphorus pentoxide until used.

Thermal analyses. Phase transitions were detected using a differential scanning calorimeter (DSC) with effluent gas analysis (DSC-1B, Perkin-Elmer). About 1–5 mg samples were weighed on an electrobalance (Gram, Cahn Instrument Co.) directly into aluminum sample pans. Scans were made from 30 to 160°C under a stream of dry nitrogen at various heating rates using standard (open) pans, sealed pans and sealed pans with a 0.1–0.2 mm pinhole. Vaporization of the water of crystallization from the standard pans and the sealed pans with a pinhole was detected using the effluent gas analyzer, and was quantitated by weighing the pan after each endothermic peak. The calorimeter was calibrated with indium. In all cases, the peak temperature, i.e. the point on the temperature scale of maximum deviation from the baseline, was determined and this depended on the type of pan used. The values reported (Scheme 1) are the range of peak temperatures at a scanning rate of 10°C · min^{-1} and are based on a minimum of 3 runs. Samples were also mounted dry or in mineral oil on a glass slide, and heated on a hot stage (Mettler, FP2) while being observed under a microscope (Reichert). The temperatures at which transitions occurred were recorded.

Water solubility. Excess of I was added to 20 ml of water contained in 100 ml volumetric flasks. The flasks were mechanically rotated in water baths set at 25.5, 31.5, 34.0 and 37.0°C until equilibrated. Aliquots were drawn into a warm syringe, membrane-filtered (0.20 μm membrane, Nalgene), weighed and diluted with a known weight of water. The density of the diluted solutions was determined in a digital density meter (Model DMA 45, Paar) thermostatically controlled at 25°C, and the concentration determined from a standard curve of the density of various solutions of I against their concentrations in the range 0.009–0.055 molal. The intercept on the y axis, which should be the density of water, was 0.9970 g · cm^{-3}, in agreement with the reported density for water at 25°C of 0.9971 g · cm^{-3} (CRC Handbook, 1984).

II and III are very water-soluble at room tem-

SCHEME 1

TRANSITIONS OF I IN THE DIFFERENTIAL SCANNING CALORIMETER

Pan [a]	Peak	Range of peak maxima (°C) [b]	Reaction [c]
A	1	119–122	$CaG \cdot 3.5H_2O(s) \rightarrow CaG(s) + 3.5H_2O(g)$
	2	144–145	$CaG(s) \rightarrow CaG(\ell)$
B	1	116–119	$CaG \cdot 3.5H_2O(s) \rightarrow xCaG(s) \rightarrow xCaG(so) + H_2O(g)$
C	1	115–124	$CaG \cdot 3.5H_2O(s) \rightarrow CaG(s) + xH_2O(g)$ [d]
D	1	107–118	$CaG \cdot 3.5H_2O(s) \rightarrow CaG(s) + 3.5H_2O(g)$
	2	145–148	$CaG(s) \rightarrow CaG(\ell)$

[a] A = standard pan. B = sealed pan. C = sealed pan with a 0.1 to 0.2 mm pinhole. D = as C but under vacuum.

[b] The range of the peak temperatures is based on 3 or more DSC sample runs at $10°C \cdot min^{-1}$.

[c] CaG = calcium gluceptate; s = solid; g = gas; ℓ= liquid; and so = solution.

[d] In sealed pan with a pinhole, there is incomplete removal by vaporization of the liberated water of crystallization.

perature, but the maximum solubilities could not be estimated because the solutions were supersaturated with respect to the stable hydrate, I, which crystallized very rapidly from solution. An apparent solubility was determined for II (Suryanarayanan and Mitchell, 1985). The apparent solubility is a complex parameter depending on both the dissolution rate of II and the rate of crystallization of I. The apparent solubility of III could not be determined because the increase in viscosity hindered dispersion and dissolution of additional solid, but was > 4 molal.

Relative humidity–composition diagrams. Accurately weighed amounts of I, II and II were stored in desiccators over phosphorus pentoxide or various saturated salt solutions at 25°C (Isotemp Incubator, Fisher) to give relative humidities of 0, 9, 20, 33, 43, 52, 66, 68, 79 and 90%. Weight changes were monitored until constant weights were obtained. The weight changes were complete within a month, and no significant further changes were detected after storage for a year.

Results and Discussion

Table 1 lists, in a condensed form, the powder X-ray diffraction data of some solid phases of calcium gluceptate. Diffractograms of I and II and the X-ray data of the dried precipitate from solutions of III have been published earlier (Suryanarayanan and Mitchell, 1984, 1985). The diffraction pattern of I corresponds closely with that of the precipitate obtained from aqueous solutions of II and III, indicating that the precipitate in both cases is the crystalline hydrate, I. Removal of the water of crystallization from I by heating under vacuum results in collapse and recrystallization of the crystal lattice to give the anhydrate, II. Similarly, dehydrating the precipitate from aqueous solutions of II and III usually resulted in material with an X-ray diffraction pattern corresponding to II. Occasionally, however, even after rigorous drying, only the most intense peaks of II were apparent in the diffraction pattern of the precipitate, while the overall pattern was the same as I. It is apparent that removal of water of crystallization from the hydrate does not always lead to lattice collapse and recrystallization of the anhydrate throughout the entire sample. Thus, Table 1 includes an example where the major interplanar spacings of a precipitate from a solution of III dried under vacuum at 80°C for 46 h are those of I while only the interplanar spacings of 4.57 Å and 4.87 Å are characteristic of II.

Sample III and the freeze-dried material were X-ray amorphous, while both I and II could be made X-ray amorphous by grinding for 1 h and 4 h, respectively (Scheme 2).

Scheme 1 summarizes the sequence of dehydra-

TABLE 1

INTERPLANAR SPACINGS CALCULATED FROM THE 8 MOST INTENSE PEAKS OF SOME SOLID PHASES OF CALCIUM GLUCEPTATE

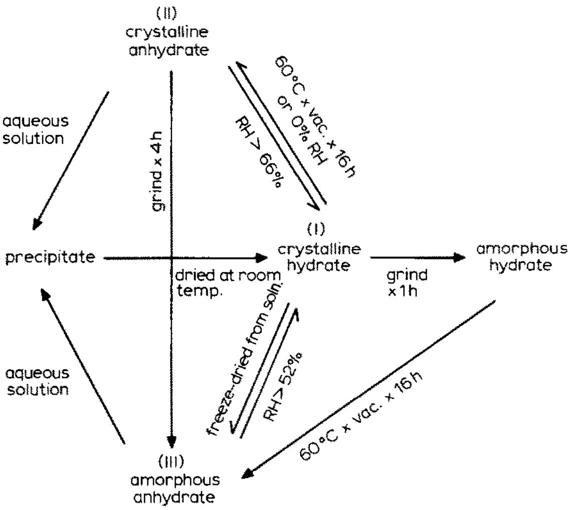
I		II		Precipitate [a]		Precipitate [b]		Precipitate [c]	
d	I/I_0	d	I/I_0	d	I/I_0	d	I/I_0	d	I/I_0
2.43	28	3.06	22	2.43	28	3.04	27	2.43	28
2.97	21	3.29	19	2.97	22	3.25	23	3.34	34
3.35	32	3.69	22	3.35	34	3.66	26	3.83	56
3.85	51	4.23	51	3.83	46	4.21	62	4.11	47
3.90	24	4.38	100	3.90	18	4.35	100	4.31	100
4.13	48	4.60	71	4.13	34	4.57	76	4.57	35
4.33	100	4.91	64	4.31	100	4.89	58	4.87	34
5.34	39	6.55	34	5.33	33	6.56	31	5.34	36

d = interplanar spacing (Å). I/I_0 = relative intensity (%).

[a] Precipitate from a solution of II dried at room temperature, ≃ 22°C.

[b] Precipitate from a solution of II dried at 80°C under vacuum for 5 h.

[c] Precipitate from a solution of III dried at 80°C under vacuum for 46 h.



Scheme 2. Interconversions of calcium gluceptate.

tion reactions of I as determined by thermal analyses. The DSC thermogram in standard pans showed endotherms at 119–122°C and 144–145°C. The weight loss after the first endotherm was 11.2% w/w compared with 11.3% w/w found by TGA and the theoretical value of 11.4% w/w for the complete dehydration of calcium gluceptate · $3.5H_2O$. Since the first endotherm was also accompanied by an effluent gas peak, it is evidently due to the dehydration of I and simultaneous vaporization of the water of crystallization. Hot stage microscopy confirmed that the second endotherm corresponded with melting of the anhydrate. When heated in a sealed pan, I gave a single endotherm at 116–119°C. The water liberated on dehydration cannot escape from a sealed pan, and after the reaction, the system will include the solid anhydrate, an aqueous solution and water vapor (Scheme 1, B) [1]. In a sealed pan with a pinhole, the endotherm at 115–124°C was accompanied by a weight loss of between 10 and 11% w/w, indicating incomplete removal by vaporization of all the liberated water of crystallization. In neither the sealed pan nor sealed pan

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[1] An approximate estimate of the solubility of II at 120°C can be obtained from the van't Hoff equation:

$$\log\frac{\alpha_2}{\alpha_1} = \frac{\Delta H(T_2 - T_1)}{2.303R\,(T_1 \cdot T_2)}$$

where α_1 and α_2 are the solubilities at temperatures T_1 and T_2, respectively and ΔH is the enthalpy change accompanying solution of one mole. The ΔH for II at ≃ 22°C is 13800 $J \cdot mol^{-1}$ (Suryanarayanan and Mitchell, 1985) and α_1 for II at T_1 ≃ 22°C is 1.3 molal (Suryanarayanan and Mitchell, 1985), then α_2 at T_2 = 120°C is 5.3 molal. 1 mol of II (molecular weight 490.4) requires 189 g of water to give a 5.3 molal solution at 120°C. But 1 mol of I (molecular weight 553.4) liberates only 63 g of water of crystallization on dehydration. Hence the amount of water evolved on dehydration of I to II is insufficient to completely dissolve II and some will remain as solid.

with a pinhole was dehydration followed by a melting endotherm. However, when the scan using a sealed pan with a pinhole was repeated under reduced pressure, the thermogram was similar to that found using standard pans with endotherms at 107–118°C and 145–148°C (Scheme 1, D). It is suggested that some of the water vapor evolved following the dehydration of I is adsorbed by the anhydrate and prevents its subsequent melting. Further confirmation for this unusual behavior was obtained by scanning I at atmospheric pressure in a sealed pan with a pinhole up to the baseline departure of the dehydration endotherm. The temperature was then held constant for 5 min while vacuum was applied, and the scan continued under reduced pressure. The melting endotherm reappeared at ≃ 145°C, thus confirming that adsorbed water prevents melting since vacuum applied at the dehydration endotherm will remove the water of crystallization as it is evolved.

In a reasonably unrestricted system such as a standard DSC sample pan, a hydrate can lose water over a range of temperatures. The endotherm with a maximum at ≃ 120°C obtained on heating I in standard pans was much broader than the single endotherm obtained on heating I in sealed pans with or without a pinhole. In sealed pans with a small pinhole, the rate of vapor loss becomes appreciable only when the vapor pressure within the pan has sufficiently increased so as to exceed atmospheric pressure. Moreover, the restricted escape route (0.1–0.2 mm pinhole), could bring the water vapor and the dehydrated material into intimate contact, facilitating adsorption of water by the anhydrate.

The DSC thermograms of III, irrespective of the type of pan used, showed neither exothermic nor endothermic peaks between 25 and 160°C, indicating that the material was anhydrous as received, and did not undergo any phase transitions in this temperature range. The absence of a melting endotherm in the thermogram of the amorphous anhydrate, III, suggests the possibility that the anomalous thermal behavior of I may be due to the fact that it dehydrates to an amorphous anhydrate if the liberated water of crystallization is not removed (Scheme 1, B and C). This seems unlikely, however, since, as shown in Scheme 2, a combination of dehydration and prolonged grinding is necessary to convert I to III.

Thermograms of II, obtained immediately after preparation by dehydrating I, showed a single endotherm at ≃ 140°C, irrespective of the type of pan used. There was no appreciable weight loss, and hot stage microscopy showed that the endotherm corresponded to melting. Exposing II to the atmosphere under ambient conditions (≃ 35% RH and 22°C) for 15 min led to a small weight increase (≃ 2% w/w), and on heating in a sealed pan, a very small endotherm appeared at ≃ 118°C and the melting endotherm disappeared from the thermogram. The weight increase on exposing II to ambient atmosphere is indicative of moisture adsorption. If the adsorbed moisture dissolves some of the anhydrate, the solution would likely be supersaturated with respect to the stable hydrate and could result in precipitation of the hydrate on the surface of the crystals of the anhydrate. The small endotherm occurring at ≃ 118°C is most likely due to dehydration of this surface hydrate. Since the pan was sealed, the liberated water vapor cannot escape. It can therefore be readsorbed by II and prevent subsequent melting as found for I in sealed pan with or without a pinhole.

The thermal behavior of a freeze-dried solution of I was similar to that of III, in that no endothermic or exothermic peaks occurred between 25 and 160°C. Since the X-ray diffraction pattern showed it to be non-crystalline, it is concluded that the freeze-dried material is an amorphous anhydrate. Due to the low aqueous solubility of I, freeze-drying is not a convenient method of preparing III. Dehydrating I to II and then grinding for 4 h gave III (Suryanarayanan and Mitchell, 1985), but a more efficient pathway for converting I to III was to grind I until X-ray amorphous (about 1 h) and then to dehydrate the amorphous hydrate by heating at 60°C under vacuum or by storing in a desiccator over phosphorous pentoxide, both to constant weight (Scheme 2).

Fig. 1a shows the water content of II and I after storage at various RH to constant weight. The water content of II increased non-stoichiometrically to a value of 3.2% w/w at 66% RH followed by a sharp increase at higher RH to

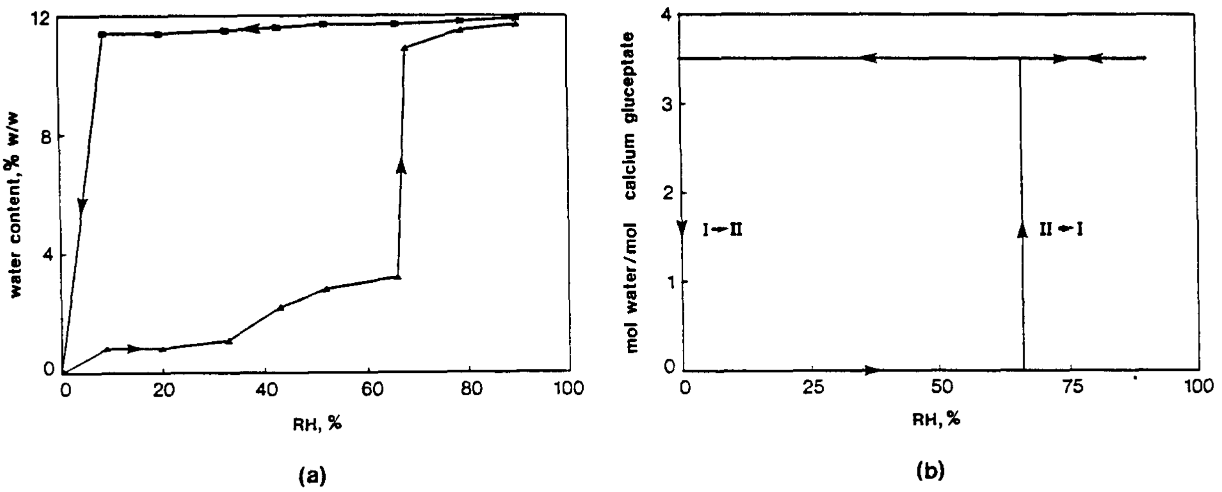

Fig. 1. Relative humidity–composition diagrams of calcium gluceptate at 25°C. a: water content following storage of II (▲) and I (■). b: phase transitions of I and II.

≃ 11.4% w/w which corresponds to the 3.5 hydrate, I. However, the dehydration of I to II occurred only at 0% RH and there were no weight losses from 66% through 9% RH. The phase changes corresponding to Fig. 1a are given in Fig. 1b which is based on: (i) percent weight change after storage; (ii) identification of the solid phase by powder X-ray diffractometry; and (iii) quantitation by TGA of the number of molecules of water of crystallization.

Fig. 1b shows that between 0% and 66% RH, neither I nor II undergo interconversion (even after storage for one year). This observation is contrary to the phase rule according to which I and II cannot coexist in stable equilibrium over a range of vapor pressures at a constant temperature. Therefore, between 0% and 66% RH, either the phase changes occur very slowly or some factor(s) is inhibiting the transition reaction. Apart from similar behavior reported for griseofulvin and its chloroform solvate (Sekiguchi et al., 1968) and for sodium sulfamethomidine and its hydrate (Takahashi and Sato, 1960) such marked hysteresis effects appear to be rare. Various hypotheses for this unusual behavior are discussed below.

(a) Mitrevej and Hollenbeck (1983) suggested the existence of an "hydrophobic field" around aspirin crystals which inhibited the condensation of water from a humid atmosphere in the vicinity of the crystals. When mixed with certain hydrophilic excipients such as colloidal silicon dioxide, water readily condensed on the aspirin crystals. A similar "field" created around crystals of II on dehydrating I could possibly explain its apparent stability up to 66% RH, with the water vapor pressure overcoming this field leading to rehydration at higher RH. To test this suggestion, samples of II were mixed with 1% and 5% w/w colloidal silicon dioxide, and these mixtures were stored at various RH. However, the II to I transition still occurred only at RH > 66%.

(b) Another possibility is that of an energy barrier to the dehydration (I to II) and rehydration (II to I) reactions. The energy of activation, E_a, for the dehydration of I to II was estimated by DSC using the following relationship (Kissinger, 1957):

$$\frac{d\left[\ln(\phi/T_m^2)\right]}{d(1/T_m)} = -\frac{E_a}{R} \qquad (1)$$

where ϕ is the heating rate (°C · min^{-1}), T_m is the temperature (°K) at which peak enthalpic deflection occurs, and R is the gas constant. A plot of ln (ϕ/T_m^2) versus $1/T_m$ gives the activation energy without any assumptions about the reaction mechanism. Samples of I were heated a 2.5, 5, 10, 20 and 40°C · min^{-1} in a DSC using standard pans, and the temperature of peak enthalpic deflection (the peak due to dehydration and vaporization of water at $\simeq 121°C$, Scheme 1, A) was noted. The energy of activation for dehydration of I calculated from the Kissinger plot was 93 $kJ \cdot mol^{-1}$ (Fig. 2). The energy of activation for the dehydration of I is not unusually high when compared with the activation energies for the dehydration of some other pharmaceutical hydrates listed in Table 2, and suggests that an energy barrier to the dehydration of I to II is unlikely.

The energy of activation for the transition of II to I was also estimated. The heat of solution of I calculated from the slope of a van't Hoff plot of log molar solubility as a function of the reciprocal of absolute temperature was $+40\ kJ \cdot mol^{-1}$, while the heat of solution of II at $\simeq 22°C$ determined by solution calorimetry was $+14\ kJ \cdot mol^{-1}$ (Suryanarayanan and Mitchell, 1985). The difference in the heats of solution, ΔH_d, is the heat change accompanying the dehydration reaction, and has a value of $+26\ kJ \cdot mol^{-1}$ (Fig. 3). The energy of activation for the dehydration of I, E_a, estimated from the Kissinger plot was 93 $kJ \cdot mol^{-1}$. Since the change from I to II is a reversible process, the energy of activation for the transition of II to I, E_b, can be estimated from (Glasstone and Lewis, 1982):

$$E_a - E_b = \Delta H_d \qquad (2)$$

whence $E_b = 67\ kJ \cdot mol^{-1}$. The low value of E_b suggests that an energy barrier for the transition of II to I is unlikely.

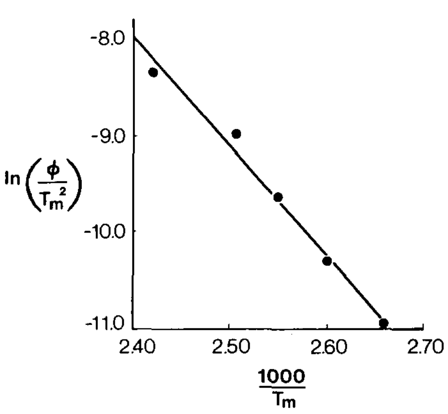

Fig. 2. Kissinger plot for calculating the activation energy of dehydration of I. T_m = peak temperature (°K); ϕ = heating rate ($°C \cdot min^{-1}$).

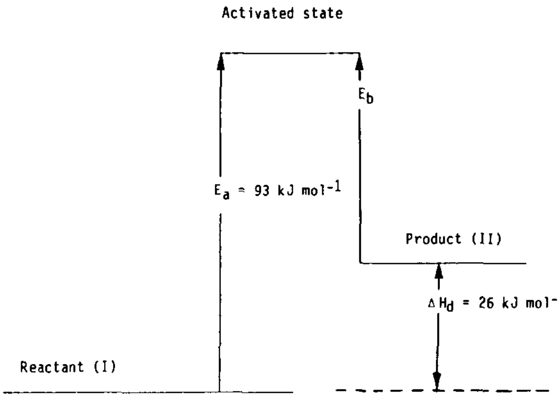

Fig. 3. Estimation of energy of activation, E_b, for the transition from II to I (the figure is not to scale; see text for the limitations of this estimation).

Some limitations of the above estimations are: (i) small errors in the measurement of T_m can lead to large errors in the value of E_a estimated using Kissinger's method (Cunningham and Wilburn, 1970); (ii) a thermal lag, which increases with heating rate is an intrinsic characteristic of the DSC apparatus. Therefore, Kissinger's method tends to underestimate the value of E_a (Pope and Judd, 1977); and (iii) since the dehydration of I occurs at temperatures above 100°C, E_a was estimated under conditions of negligible water content. On the other hand, ΔH_d was determined from reaction in water. The effect of differences in water activity on the values of E_a and ΔH_d is therefore neglected in Fig. 3 and in the calculation of E_b using Eqn. 2. In spite of these limitations, the values of E_a and E_b provide a useful but approximate estimate of the energies involved and the low values suggest that an energy barrier is not the limiting factor in the dehydration/rehydration reactions.

(c) Byrn (1982) has shown that the desolvation of certain hydrates may be initiated by inoculation with the desolvated material. If it were similarly possible to initiate the dehydration of I, the reaction might proceed at $RH > 0\%$. To test this, samples of I were initially stored at 0% RH and as soon as they began to dehydrate to II (which was

TABLE 2

ACTIVATION ENERGIES FOR SOME DEHYDRATION REACTIONS

Compound	Energy of activation ($kJ \cdot mol^{-1}$)	Reference
Cefamandole sodium monohydrate → anhydrate	71	Pikal et al., 1983
Ampicillin monohydrate → anhydrate	95	Shefter et al., 1973
Sodium prasterone sulfate dihydrate → anhydrate	131	Nakagawa et al., 1981
Theophylline monohydrate → anhydrate	140	Shefter et al., 1973
Sulfaguanidine monohydrate → anhydrate	Between 67 and 168 depending on crystallinity of the samples as well as environmental factors	Sekiguchi et al., 1984
Mercaptopurine monohydrate → anhydrate	Between 191 and 264 depending on the method of determination	Niazi, 1978

evident from a loss in weight), they were transferred to chambers at 9, 33 and 52% RH. The samples did not continue to lose weight, indicating that I and II could apparently coexist at these humidities. Similarly, the conversion of II to I by inoculation with I was attempted: samples of II were initially stored at 79% RH, and when they began to gain weight and change to I, they were transferred to chambers at 9, 33 and 52% RH. The samples did not continue to gain weight, again confirming that II and I could apparently coexist at these humidities.

(d) Though samples of II stored in the range of 0–66% RH did not undergo a transition to I, the water content of the samples ranged from 0.83% w/w at 9% RH to 3.2% w/w at 66% RH (Fig. 1a). As postulated earlier, if the adsorbed moisture dissolves some of the anhydrate, the solution would likely be supersaturated with respect to the stable hydrate and could result in precipitation of the hydrate on the surface of the anhydrous crystals. It is suggested that this hydrated layer hinders the diffusion of water vapor, thus inhibiting the conversion of II to I below 66% RH. The hydrated layer therefore delays the attainment of equilibrium. When stored at RH > 66%, the water vapor pressure is presumably high enough to overcome the resistance of the hydrated surface layer and transition to I occurs. The suggested role of adsorbed moisture is supported by the DSC studies which revealed the dramatic effect of traces of adsorbed moisture on the thermal behavior of II after being exposed to the atmosphere.

Interconversions of the various phases of calcium gluceptate are summarized in Scheme 2. While the transition of II to I occurred at RH > 66%, the transition of III to I occurred at RH > 52%, showing that the highly energetic amorphous form required a lower RH for the transition. The United States Pharmacopeia (USP XXI, 1985) suggests that calcium gluceptate can exist as a hydrate containing 2 molecules of water per atom of calcium, but this form was not encountered during these studies.

Conclusions

(1) Calcium gluceptate occurs both as a hydrate and as an anhydrate and each phase can exist in either a crystalline or an X-ray amorphous form.

(2) The transition between the crystalline hydrate and the crystalline anhydrous phases is reversible, and on grinding, both phases become X-ray amorphous.

(3) There are marked differences in the apparent water solubilities of these forms and at concentrations greater than the equilibrium solubility of the crystalline hydrate, solutions prepared using the crystalline anhydrate, the X-ray

amorphous hydrate, and the X-ray amorphous anhydrate are supersaturated and the stable hydrate crystallizes out.

(4) The crystalline hydrate and crystalline anhydrous phases can coexist between 0 and 66% RH. Within this range, the adsorption of a small amount of water by the anhydrate seems to inhibit further water uptake and prevents both melting and the phase transition to the hydrate.

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