Dehydration of Glucuronamide Hydrate. Confirmation of the Predicted Influence of Crystal Packing on Dehydration Reactions

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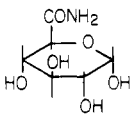
Received April 27, 1982

A number of factors related to the dehydration of glucuronamide hydrate were investigated. Photomicrographic examination of the behavior of crystals of glucuronamide hydrate which were cut and activated with powdered anhydrous compound showed that these crystals lost water of crystallization in a clear front starting from the activated end and moving through the crystal. The threshold temperature for dehydration of glucuronamide hydrate was measured by using thermal gravimetric analysis and compared to the value estimated from published data. This temperature along with the relationship between the threshold temperature and crystal packing which was discussed in the previous paper was used to predict that glucuronamide hydrate should have water tunnels with a relatively small cross sectional area or relatively strong hydrogen bonding of water to the host glucuronamide molecule or both. The crystal structure of glucuronamide hydrate was determined to test this prediction. Crystals of glucuronamide hydrate belong to space group $P2_12_12_1$ with a = 7.426 (3) Å, b = 18.114 (6) Å, c = 6.708 (2) Å and Z = 4. The structure was solved by direct methods, and although it refined to an R factor of 0.033, the variation in equivalent bond lengths suggests that the crystals are of poor quality. Glucuronamide hydrate crystals contain the α anomer of glucuronamide. Analysis of the crystal packing of glucuronamide shows that as predicted it has both a relatively small water tunnel (area = 1.05 Å^2) and three relatively strong hydrogen bonds between water and glucuronamide. Thus, this paper further substantiates the correlation between crystal packing (i.e., tunnel area and hydrogen bonding) and the threshold temperature of desolvation. In addition, the kinetics of dehydration of glucuronamide hydrate at three temperatures were analyzed by measuring the rate of front advancement. The front andvancement followed zero-order kinetics and gave an activation energy of 37.2 kcal/mol. This value compares favorably with the published value which was measured by weight loss.

One test of new correlations involves the use of these correlations as predictive tools. In the previous paper,[1] the crystal packing of crystal hydrates was correlated with the behavior of crystals upon dehydration. It was hypothesized that stable crystal hydrates which have high threshold temperatures for dehydration possess have relatively smaller tunnel areas for dehydration or stronger hydrogen bonding between the host molecule and the water molecule, or both. Glucuronamide hydrate has a relatively high threshold temperature for dehydration[2] and thus the crystal structure of glucuronamide hydrate can be predicted to show one or both of these features.



This paper reports a test of this prediction and indeed shows that glucuronamide hydrate has both water tunnels with a relatively small area and relatively strong hydrogen bonding of the host molecule to the water of hydration.

Experimental Section

Glucuronamide hydrate crystals elongated along the c crystallographic axis were obtained by crystallization from water or an azeotropic mixture of water and dioxane by slow evaporation.

Crystal data: $C_6H_{11}O_6N\cdot H_2O$, M_r = 211.170, orthorhombic, a = 7.426 (3) Å, b = 18.114 (6) Å, c =6.708 (2) Å, V = 902.3 A,^{3} Z = 4, d_c = 1.554 g cm^{-3}, $F(000)$ = 448, Cu Kα radiation (λ = 1.5418 Å), μ = 11.42, space group $P2_12_12_1$ from systematic absences.

Data Collection. The crystal was mounted on a Syntex P3 diffractometer using Cu Kα radiation and a monochromater. The unit cell parameters were determined by least-squares refinement of the 2θ values of 15 reflections. Scans (θ–2θ) through several reflections showed that some reflections were broad and not distinct. Several crystals were examined, and the best one was used for data collection. Data were collected out to a 2θ limit of 135°. The number of independent reflections was 759.

Structure Analysis. The structure was solved by application of the MULTAN program (1978 version).[3] The first E map revealed the positions of all of the heavy atoms in the sugar moiety but not the position of the oxygen atom of the water of hydration. Two cycles of least-squares refinement and a difference map revealed the position of the oxygen atom of the water of hydration. Several cycles of least-squares refinement first with isotropic temperature factors and then anisotropic temperature factors reduced the R factor to 0.065. A difference map revealed the positions of all hydrogen atoms. Four more cycles of least-squares refinement with isotropic temperature factors for the hydrogen atoms and anisotropic temperature factors for the nonhydrogen atoms gave a final R factor of 0.033. All of the hydrogen atoms were in reasonable positions except for HO_4 which had an O–H bond length of 0.514. A final difference map showed at least four peaks of 1 e/Å^3; however, these peaks were not in chemically reasonable positions. Efforts to explain these peaks in terms of disorder failed.

Optical Goniometry. The interfacial angles on a well-formed crystal of glucuronamide hydrate were measured by using a Huber optical goniometer. These angles were compared to the calculated angles by using a computer program. The assigned faces were confirmed by using precission photography. Figure 1 shows the Miller indices of the crystal faces of this habit.

Solid-State Reactions. Reactions were usually run on a Mettler FP5 or FP52 hot stage and photographed with a Zeiss microscope.

Thermal Gravimetric Analysis. The dehydration of glucuronamide was studied by using a Perkin-Elmer TGS-2 with a heating rate of 6 °C/min and a purge-gas (N_2) flow rate of 10 mL/min. The powder diffraction pattern of dehydrated crystals was not measured. The threshold temperature was defined as the temperature at which 2% of the solvent is lost. The estimated error in this measurement was ±1.0°.

(1) Perrier, P. R.; Byrn, S. R. *J. Org. Chem.*, previous paper in this issue.
(2) Horikoshi, I.; Himuro, I. *Yakagaku Zasshi* **1966**, *86*, 319.
(3) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. B* **1970**, *26*, 274.

0022-3263/82/1947-4677$01.25/0

Table I. Atomic Parameters for Glucuronamide Hydrate ($\times 10^4$; for H, $\times 10^3$) with Estimated Standard Deviations in Parentheses

atom	a	b	c
C1	6396 (6)	3550 (2)	2221 (6)
C2	8392 (5)	3405 (2)	3163 (6)
C3	8221 (6)	3445 (2)	5182 (6)
C4	7180 (5)	4150 (2)	5774 (5)
C5	5205 (5)	4197 (2)	4782 (5)
C6	4104 (5)	4917 (2)	5202 (6)
O1	5124 (4)	2950 (1)	2518 (5)
O2	9118 (4)	2694 (1)	2624 (6)
O3	10185 (4)	3436 (2)	5973 (5)
O4	6752 (5)	4154 (2)	7642 (5)
O5	5539 (4)	4216 (1)	2884 (3)
O6	4836 (4)	5520 (1)	4805 (4)
N1	2364 (5)	4838 (2)	6009 (5)
OW	2088 (5)	3148 (2)	0201 (5)
HCl	641 (4)	361 (2)	079 (5)
HC2	942 (6)	382 (2)	274 (7)
HC3	737 (7)	303 (3)	564 (6)
HC4	792 (5)	461 (2)	550 (5)
HC5	433 (5)	375 (2)	509 (5)
HO1	427 (12)	286 (5)	108 (16)
HO2	973 (12)	258 (6)	137 (16)
HO3	1052 (7)	303 (3)	649 (7)
HO4	734 (10)	425 (4)	813 (8)
HW1	253 (8)	292 (3)	912 (8)
HW2	166 (8)	355 (4)	967 (9)
HN1	180 (6)	442 (3)	−369 (6)
HN2	152 (6)	524 (2)	−349 (6)

Table IV. Rate Constants for Front Advance in Glucuronamide Hydrate

temp, °C	$10^3(1/T)$, K^{-1}	10^3k, mm h^{-1}	ln k
60	3.002	107.00	4.67
65	2.957	212.00	5.36
70	2.914	556.00	6.32

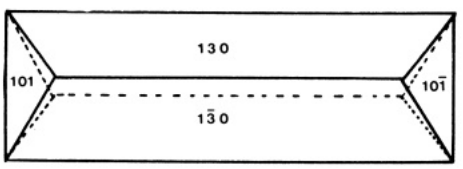


Figure 1. Schematic diagram of a typical crystal of glucuronamide hydrate showing the Miller indices of the crystal faces.

Results

The crystal structure of glucuronamide hydrate has been determined, and the solid-state dehydration of this hydrate was studied by using photomicrography and thermal gravimetric analysis.

Crystal Structure of Glucuronamide Hydrate. Glucuronamide crystallizes in space group $P2_12_12_1$, and a stereoscopic drawing of the molecule is shown in Figure 2.

Glucuronamide exists in solution as a mixture of the α and β anomers. Figure 2 shows that the α anomer is present in crystals of the hydrate. Table I lists the final atomic positions and Table II (supplementary material) lists the bond lengths and angles in glucuronamide hydrate.

Table III (supplementary material) lists the intramolecular contacts less than or equal to the sum of the covalent radii plus 2 Å for the nonhydrogen atoms. This table also describes the hydrogen bonding of the water of hydration and H···O distances of the hydrogen atoms involved in hydrogen bonds.

The glucuronamide molecules are held together by O–H···O and N–H···O hydrogen bonds. The shortest of these are $HO_3\cdots O_1$ distance of 1.92 Å and the $HN_2\cdots O_5$ distance of 2.04 Å. The water molecules are held in the crystal by a complex set of O–H···O hydrogen bonds. The strongest of these are the $HO_1\cdots O$ bond (1.80 Å), the $O_2\cdots HW_1$ bond (2.00 Å), and the $HW_2\cdots O_6$ bond (2.03 Å). Figure 3 shows the crystal packing of glucuronamide hydrate.

Solid-State Reaction of Glucuronamide Hydrate. The solid-state dehydration of glucuronamide hydrate was studied by using photomicrography and thermal gravimetric analysis (TGA). A TGA trace showed that glucuronamide hydrate had lost 2% of its water of hydration at 82 (1) °C. Photomicrographic studies of the dehydration showed that the reaction proceeded from the ends toward the middle in a clear front. In addition, cutting and dusting the hydrate crystals with powdered anhydrous compound was found to nucleate and initiate the reaction as discussed in the previous paper. For example, if dehydrated powder were scratched on one end of a cut glucuronamide hydrate crystal, then the reaction proceeded from that end of the crystal in a well-defined front. Such a reaction is shown in Figure 4. Crystals which were not activated by cutting and dusting with the dehydrated powder were more stable.

Activated crystals were photographed while reacting at 60, 65, and 70 °C. The photographs were then projected on a screen and the front advance was measured at various times.[4] A millimeter scale was photographed under

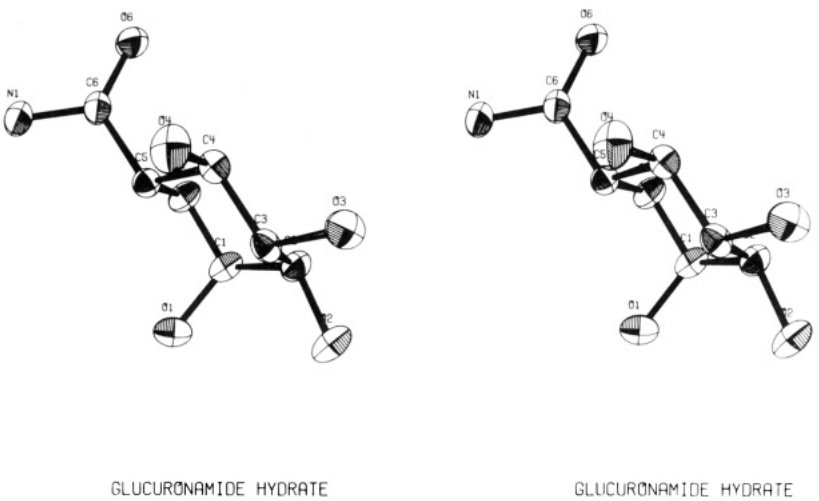


Figure 2. Stereoscopic drawing of the structure of the glucuronamide molecule in the hydrate.

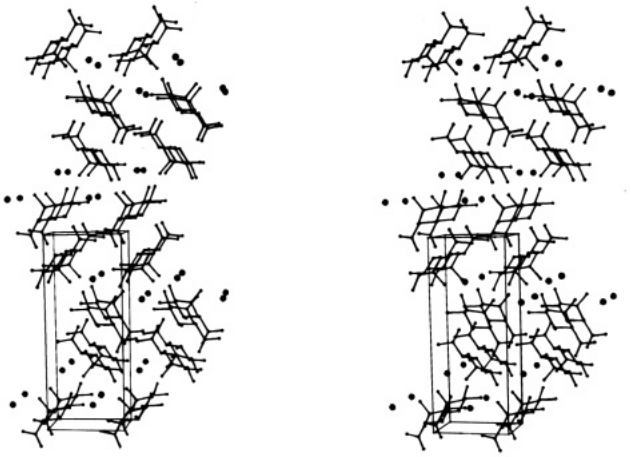


Figure 3. Stereoscopic view of the crystal packing of glucuronamide hydrate. The origin is at the bottom left corner with *a* across, *b* vertical, and *c* out of the plane of the paper.

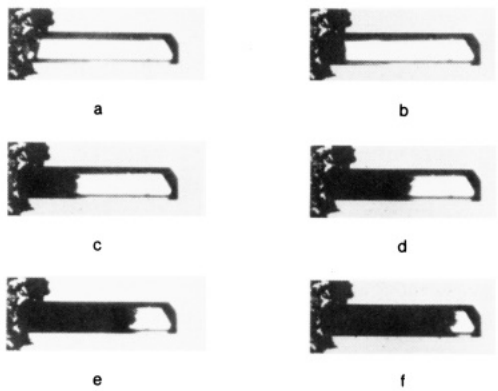


Figure 4. Dehydration reaction of a single crystal of glucuronamide hydrate at 65 °C: (a) at $t = 0$, (*b*) after 29 min, (c) after 73 min, (d) after 105 min, (e) after 135 min, (f) after 149 min. The (001) face was artifically created by cutting with a scalpel and activated by the dehydrated compound.

identical conditions and projected so that actual distances could be measured. The rate of front advance was linear as shown in Figure 5.

The rate constants for the desolvation at 60, 65 and 70 °C are shown in Table IV.

These rate constants were plotted according to the Arrhenius equation as shown in Figure 6 and gave an activation energy of 37.2 kcal/mol.

Discussion

A number of factors related to the dehydration of glucuronamide hydrate are reported in this paper. Photomicrographic examination of the behavior of crystals of glucuronamide show that a clear front advancement for dehydration occurred when the end of the crystal was removed with a scalpel and activated with powdered anhydrous compound. This behavior is completely consistent with the behavior of the hydrate crystals discussed in the previous paper.

Thermal gravimetric analysis (TGA) studies show that the threshold temperature for dehydration is approximately 82 (±1) °C. This is higher than the value of about 70 (±5) °C which can be estimated from the TGA trace shown in the paper of Horikoshi and Himuro.[2] This difference may be due to instrumental factors since these

(4) Stout, G. H.; Jensen, L. H. "X-ray Structure Determination"; Macmilla Co.: New York, 1965; p 303.

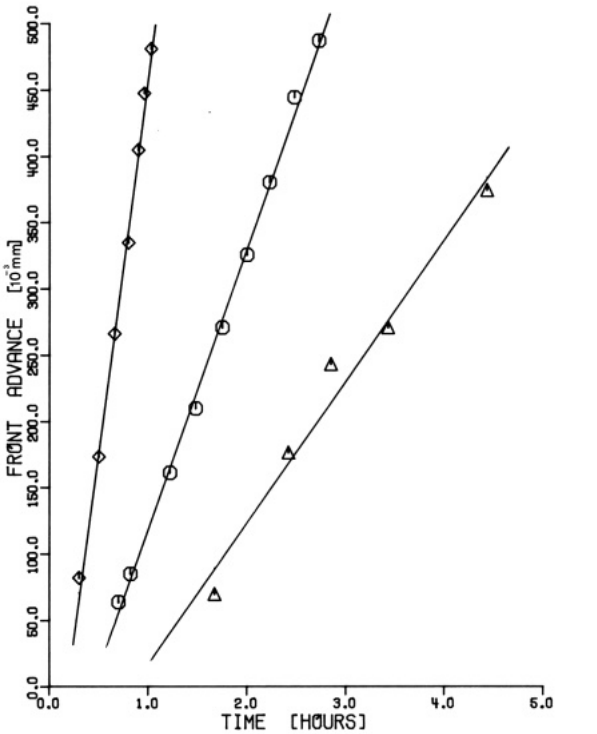


Figure 5. Plot of the front advance vs. time for the dehydration of glucuronamide hydrate. The squares are for 70 °C, the circles for 65 °C, and the triangles for 60 °C.

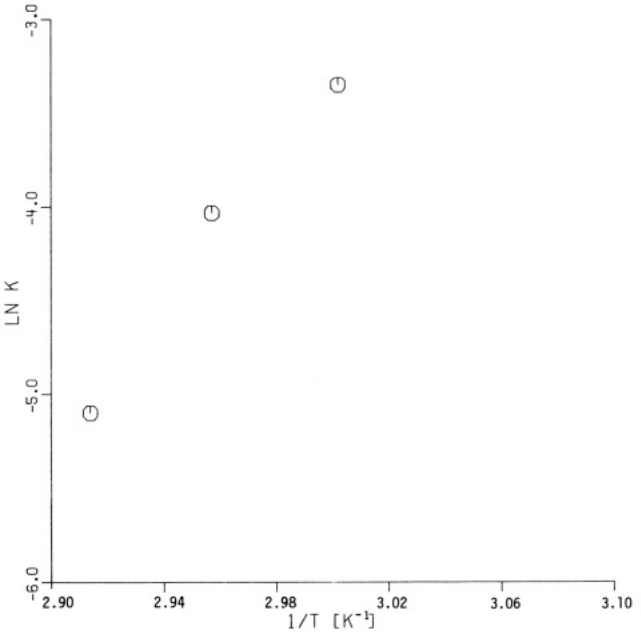


Figure 6. Plot of the rate constant for dehydration vs. temperature for glucuronamide hydrate.

data were measured at different heating rates, at different purge-gas flow rates, and on different instruments or to differences in sample history.

This threshold temperature for dehydration is quite consistent with crystal packing. The results of the previous paper lead to the hypothesis that crystals with a relatively high threshold temperature for desolvation such as glucuronamide hydrate would have either a small tunnel area for water escape or relatively strong hydrogen bonding of the host to the water molecules, or both. Indeed, the tunnel area of glucuronamide is a relatively small 1.05 Å^2, and there are three relatively strong water–glucuronamide hydrogen bonds with O···O distances of 2.762, 2.816, and

2.861 Å (bifurcated). This result further substantiates the hypothesis that the threshold temperature for desolvation is related to the crystal packing.

Glucuronamide hydrate also dehydrates anisotropically in a manner similar to the hydrates discussed in the previous paper. Glucuronamide hydrate crystallizes in needles, and analysis of the crystal packing shows that the water molecules of crystallization are arranged in tunnels parallel to the needle axis as shown in Figure 3. Cutting crystals of glucuronamide hydrate perpendicular to the needle axis and activation of the cut end with powdered anhydrous compound shortened the incubation period for dehydration and produced a clear front advance. This behavior is entirely consistent with the crystal packing which shows water tunnels parallel to the needle axis and with previous studies on the anistropic desolvation of crystal hydrates.[1]

The clear front advancement shown in Figure 4 allowed the measurement of the rate of front advance at 60, 65, and 70 °C. The rate of front advance followed zero-order kinetics, and rate constants at these temperatures gave an activation energy of 37.2 kcal/mol. This favorably compares with the published value of 38.6 kcal/mol which was determined by application of the Avrami-Erofeev equation to weight loss data.[2]

It is clear from Table II that bond lengths of equivalent bonds in glucuronamide hydrate are quite different. In addition, these bond lengths show much more variation than the corresponding bond lengths in anhydrous glucuronamide.[5] In anhydrous glucuronamide the C-C bond lengths vary vrom 1.508 to 1.541 Å, and the C-O single bond lengths vary from 1.394 to 1.431 Å. In glucuronamide hydrate, the C-C bond lengths vary from 1.362 to 1.632 Å, and the C-O bond lengths vary from 1.293 to 1.552 Å. The bond angles in glucuronamide hydrate also show much more variation than those in anhydrous glucuronamide. In glucuronamide hydrate, the tetrahedral bond angles vary from 100.1° to 116.4°, while in anhydrous glucuronamide these angles vary from 107.0° to 113.3°.

The variation in equivalent bond lengths and angles of glucuronamide hydrate and the differences between the bond lengths of glucuronamide hydrate and glucuronamide indicate that the real standard deviations in bond lengths and angles are much larger than those obtained from the least-squares refinement. Attempts to find crystals which refined to give more consistent bond lengths and angles failed because of the poor quality of the crystals. In addition, the large peaks in the final difference map could not be interpreted in terms of disorder. Thus, the variations in bond lengths and angles are probably the result of the poor quality of the crystals. However, the low R factor and reasonable crystal packing and intermolecular distances leave little doubt that the structure is approximately correct.

In conclusion, the data for glucuronamide are completely consistent with the hypothesis that the water tunnel area and hydrogen bonding are the main factors which control the threshold temperature for dehydration.

Acknowledgment. We are thankful to the Fonds National Suisse de la Recherche Scientifique, to the National Institutes of Health (Grant GM21174), and to Eli Lilly Co., Lilly Research Laboratories, which have partly supported this research.

Registry No. Glucuronamide hydrate, 83232-07-9.

Supplementary Material Available: temperature factors; Table II, bond lengths and angles; Table III, intermolecular contacts and hydrogen bonds (6 pages). Ordering information is given on any current masthead page.

(5) Clarke, T. A.; Thomas, J. M. *J. Chem. Soc. A* **1969**, 2227.
(6) Flippen, J. L.; Gilardi, R. D. *Acta Crystallogr., Sect. B* **1974**, *30*, 537.

On the Sulfonation Positional Reactivity Order of Arenesulfonic Acids[1]

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Received March 23, 1982

Available isomer distributions of the sulfonation (sulfodeprotonation) of the arenemonosulfonic acids and some of their methyl, *tert*-butyl, and phenyl derivatives have been compiled. The observed positional reactivity orders for the sulfonic acids of the aromatic hydrocarbons have been analyzed in terms of three factors, viz., (i) the differences in the localization energies of the positions under scrutiny of the corresponding aromatic hydrocarbon, containing all the substituents except the sulfo group, (ii) the (electronic) directing effect of the sulfonic acid substituent, and (iii) the difference in steric hindrance for the introduction of the (second) sulfonic acid group. It appears that each of these three factors is decisive for the positional reactivity order if the two other factors are nondiscriminating.

Some time ago it was reported that the positional reactivity order for sulfonation of monosulfonic acids of a given dimethylnaphthalene (DMN) roughly follows the reactivity order, as predicted by the localization energies (L) calculated for the various positions of the unsubstituted DMN with due observance of steric factors.[2] On the basis of this argument it would be expected that the main product of the disulfonation of 1,8-dimethylphenanthrene would be the 2,7-disulfonic acid, L_2 and L_3 being 2.3628

(1) Aromatic Sulfonation. 83. For part 82, see H. Cerfontain, A. Koeberg-Telder, K. Laali, and H. J. A. Lambrechts, accepted for publication in *J. Org. Chem.*

(2) K. Lammertsma and H. Cerfontain, *J. Chem. Soc., Perkin Trans. 2*, 673 (1979).

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