Structural Studies of the System Na(saccharinate)·$n\,H_2O$: A Model for Crystallization[**]

*Rahul Banerjee, Prashant M. Bhatt, Michael T. Kirchner, and Gautam R. Desiraju**

Saccharin (*o*-sulfobenzimide; Hsac) and its salts have been used as sweeteners for 125 years.[1–3] Current annual worldwide consumption of sodium saccharin dihydrate, Na(sac)·$2\,H_2O$ (**1**, also referred to as soluble saccharin, saccharinum soluble, and crystallose) exceeds 30000 tons. The substance is 500-times sweeter than sucrose and finds extensive use as a noncalorific tabletop sweetener, in foods and beverages, in personal care products, and in a variety of nonfood applications. It is one of the most thoroughly tested of food ingredients and has the approval of the WHO (World Health Organization) after a century of safe use. During the course of recent work on the use of sac in pharmaceutical chemistry,[4] we determined the crystal structure of dihydrate **1**. This complex structure exhibits several unusual features, which could have implications for the mechanism of crystallization and which justify the consideration of crystallization as a supramolecular reaction.

The first unusual feature is that the structure of a highly crystalline small-molecule compound, which was first isolated in 1887, was not determined until 2004. Were earlier attempts made in this direction, and did they prove to be infructuous? Or were no attempts made? Was the structure determined in an industrial laboratory, but not published? It is difficult to examine such questions a posteriori, but it is known that Jovanovski and Kamenar crystallized **1** (prepared from sac and aqueous Na_2CO_3 by the method of Defournel[3]) from EtOH and determined the structure of the resultant triclinic hydrate, $Na_3(sac)_3\cdot 2\,H_2O$ (**2**).[5] Naumov et al., who crystallized **1** from water,[6] according to the method of Jovanovski et al.,[7] and obtained what they termed "another monoclinic form", further stated that "this (monoclinic) hydrate contains more than two molecules of water per formula unit and, therefore, cannot be considered a dihydrate". We obtained **1** routinely by crystallization of the commercial sample from water; indeed the commercial sample is identical to **1**, and crystals could also be selected easily from the commercial sample for X-ray crystallographic studies.

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[*] R. Banerjee, P. M. Bhatt, Dr. M. T. Kirchner, Prof. G. R. Desiraju
School of Chemistry
University of Hyderabad
Hyderabad 500 046 (India)
Fax: (+91) 40-2301-0567
E-mail: gautam_desiraju@yahoo.com

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The monoclinic crystals diffract well, and the structure was determined (Figure 1). Strictly speaking, the material is not even a dihydrate, but rather $Na_{16}(sac)_{16}\cdot 30\,H_2O$, which is equivalent to $Na(sac)\cdot 1.875\,H_2O$. The unit cell is large (15614 Å^3 at room temperature, $P2_1/n$, $Z=4$), and the above formula gives the number of species (362 atoms, 238 non-hydrogen atoms) in the crystallographic asymmetric unit. The asymmetric unit is not the largest reported,[8] but is still of substantial size and complexity. The 64 Na^+ cations, 64 sac^- anions, and 120 water molecules in the unit cell make this crystal structure one of the largest and most complex ever for ions/molecules that are as small and simple as these. Figure 1 shows that the structure may be demarcated into "regular" and "irregular" regions. In the regular domain, the saccharinate anions are nearly parallel and stacked, the Na^+ ions are hexacoordinated with water and sac^-, and the water molecules are efficiently hydrogen bonded. In the irregular region, there is disorder of sac^-, Na^+ (some of which is not necessarily hexacoordinated), and water (some of which is ill-resolved). The solution and refinement of the structure and the modeling of the disorder were not trivial, and we began to appreciate why perhaps this structure had remained undetermined for so long. However, the X-ray data obtained by us were good and extended to high resolution ($2\theta = 52°$), there was no suggestion of modulation or superstructures, and with an R value of 0.045 and a satisfactory modeling of the disorder, we are confident of the quality of our analysis.[9]

The regular region of the structure consists of ten sac^- anions, which are arranged in a stack of five water-bridged hydrogen-bonded pairs, with an average plane···plane perpendicular distance of 3.69 Å (Figure 1). Two water molecules are involved in each saccharinate pair through strong $O-H\cdots N^-$ hydrogen bonds ($d = 2.85$ Å and $\theta = 165.8°$). Cross-linking of the pairs occurs with octahedrally coordinated Na^+ ions (mean $Na^+\cdots O$ distance: 2.39 Å). The result is a compact, finite arrangement of sac^-, Na^+, and water molecules in the form of three supramolecular cubes and two half-cubes. Further connections with Na^+ and water in an elaborate network of hydrogen bonds and $Na^+\cdots O$ interactions complete the arrangement (see Supporting Information). In the irregular region, the six sac^- anions are no longer parallel. They, along with Na^+ and water, are positionally and/or orientationally disordered (see Supporting Information). There is a variation in the occupancies of these species from crystal to crystal and possibly between one temperature and another. All in all, we carried out structure determinations of four crystals at four different temperatures (total eight data sets collected at 100, 150, 200, and 298 K). The overall conclusion is that there is appreciable mobility of the species in this irregular region which leads to the second unusual feature of this crystal structure: A part of the structure, the regular region, resembles a conventional crystal, but another and adjacent part, the irregular region, has solution-like characteristics. We consider the structure to be in a state of "incipient crystallization".

The third unusual feature of structure **1** is that it can exist in equilibrium with water (Figure 2). When a crystal is placed in the proximity (10–12 mm) of a single drop of water in a

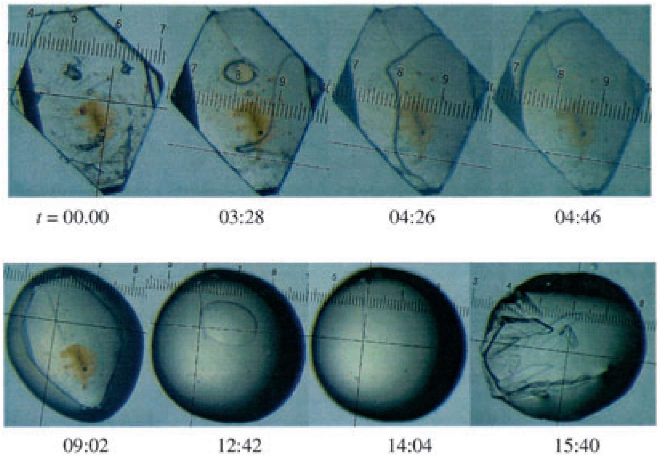

Figure 2. Rapid dissolution and recrystallization of dihydrate **1** in an environment saturated with water vapor (time recorded in minutes after closing the petri dish).

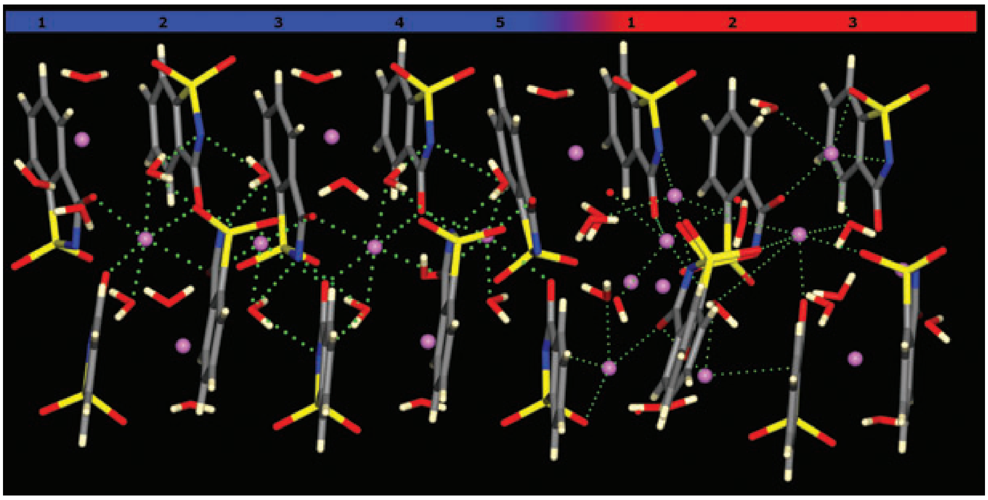

Figure 1. Crystal structure of dihydrate **1** (Na pink, O red, N blue, S yellow, C gray, H cream). The regular regions are on the left side, and the irregular regions are on the right. Note the finite supramolecular cube arrangement. The saccharin residues are numbered.

closed environment (in a covered petri dish), it absorbs water rapidly (1–5 min). Further exposure to the vapor (5–15 min) results in dissolution of the crystal and is followed by rapid recrystallization if the water-saturated environment is absent (cover of petri dish removed). A crystal of **1** for which X-ray data were collected was exposed to water vapor for approximately 10 minutes and then remounted onto the diffractometer for data collection. Although the crystal shape was considerably altered, data collection proceeded normally and the structure obtained was as observed prior to this "watering" treatment. Interestingly, the orientations of the crystal axes before and after treatment with water do not differ by more than 3°, which indicates that this is not a case of dissolution and recrystallization, but rather that the crystal of **1** is bathed in the adhering saturated solution as shown in Figure 2.[10] The very easy solubility of **1** in water, the retention of crystallinity of the "watered" crystal, and the rapid recrystallization of the just-dissolved crystal, when taken along with the high water content of **1** and the presence of the irregular disordered domains in it indicate a crystal that is very close to the dissolution point. We note that the solubility of hydrate **1** at 27 °C is 120.3 g in 100 g water.[11] This is equivalent to a stoichiometry of Na(sac)·13 H_2O. Accordingly, the saturated solution of the substance contains only about seven times the amount of water as crystalline **1**.

The fourth unusual feature of crystalline **1** is that it also loses water readily. It is remarkable that a solid which is so deliquescent in a water-rich environment is so efflorescent in a water-deficient environment (dry N_2 flow, heating, standing in the open in the typically dry Hyderabad climate). TGA (thermogravimetric analysis) and DSC (differential scanning calorimetry) studies of **1** were carried out (see Supporting Information), and water loss was observed to occur in two stages. The first stage begins as low as 35 °C and is essentially complete by 50 °C to yield the Jovanovski–Kamenar hydrate **2**, the structure of which is shown in Figure 3 b. This structure was confirmed by X-ray powder diffraction studies. The second stage (**2** to anhydrate) occurs between 100 and 115 °C. The crystal structure of the anhydrate has not been reported hitherto. We obtained crystals by cooling a melt of the commercial sample, but these crystals were small and poorly diffracting, and the structural model we obtained (Figure 3 d) is of necessarily limited accuracy ($R = 0.19$). However, this model was confirmed with Rietveld refinement of the coordinates obtained in the single-crystal study against the X-ray powder spectrum of the anhydrate (see Supporting Information).[12] The resemblance of the packing of the anhydrate to that of hydrate **2** also provides confirmation of its structure.

A mixed Na/K water-deficient hydrate, $NaK_2(sac)_3·H_2O$ (**3**) has also been reported (Figure 3 c).[13] This structure has not been obtained for sodium saccharinate, but adopting the idea of a packing landscape,[14] we believe that it is a good model for the putative $Na_3(sac)_3·H_2O$. Finally, we obtained a potassium saccharinate salt $K_3(sac)_3·2.33\,H_2O$ (**4**) when we crystallized a mixture of sac and K_2CO_3 from water.[15] The structure of **4** is shown in Figure 3 a, and in keeping with the theme of a packing landscape for the system Na(sac)·$n\,H_2O$, it would be a very good model for a water-rich pseudopolymorph of hydrate **2**. In summary, the four structures listed

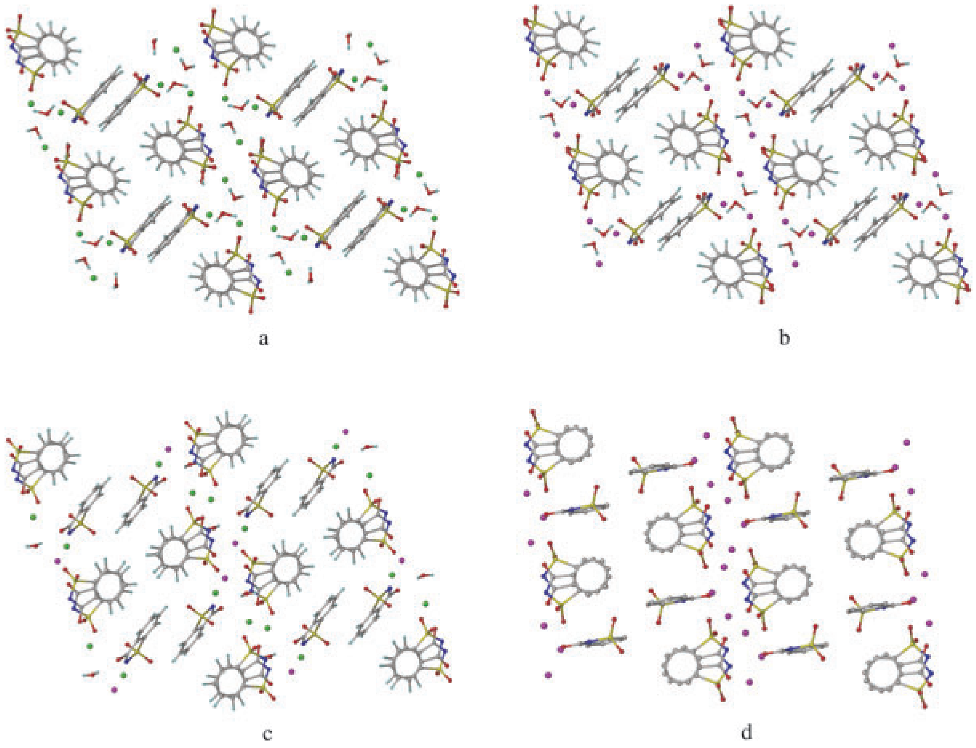

Figure 3. Packing landscape in the system (Na/K)(saccharinate)·$n\,H_2O$: a) Water-rich $K_3(sac)_3·2.33\,H_2O$ (**4**), b) Jovanovski–Kamenar hydrate, $Na_3(sac)_3·2\,H_2O$ (**2**), c) water-deficient $NaK_2(sac)_3·H_2O$ (**3**), and d) anhydrate Na(sac). Note the similarity in packing in these cases. Na^+/K^+ ions are shown as pink/green solid spheres.

above (**2**, **3**, **4**, and anhydrate) are all very similar. In every case, the positions of Na^+/K^+ and sac^- ions are nearly the same and there are variable amounts of water, ranging from 0.78 molecules of water per formula unit of metal saccharinate in **4**, to 0.66 H_2O in hydrate **2**, to 0.33 H_2O in the mixed Na/K hydrate **3**, to zero in the anhydrate. The structure of dihydrate **1**, which has 1.875 formula units of water per formula unit of sodium saccharinate, is quite different from these four structures, which constitute a related set. Therefore, the transformation of structural significance is the loss of water from **1** to give the Jovanovski–Kamenar hydrate **2**.

Inspection of the crystal structures of **1** and **2** (Figure 3 and Figure 4) shows that while the sac^- residues in **1** are all nearly parallel, those in **2** occur in two groups that are perpendicular to each other. The stacking of residues in the infinite stack down [001] bears a close resemblance to that in the regular domains of hydrate **1**. The residues that occur as discrete dimers in **2**, perpendicular to the infinite stack, are in a stoichiometry that is half that of the residues in the infinite stack. This 2:1 stoichiometry of residues in **2** is reminiscent of the 5:3 demarcation of sac^- residues in the regular and irregular regions of dihydrate **1** and suggests a possible mechanism for the conversion **1**→**2**.[16] Water loss from the infinite channels in water-rich **1** would allow for relative motion between stacks. While the regular domains are largely conserved,[17] the residues in the irregular domains might move into the empty regions created by the loss of water and also assume a perpendicular geometry. The cartoon depiction of events (Figure 5) is a good possibility because we propose that maximum movement of residues occurs in those regions of **1** where the arrangement is the least regular and where molecular motion is already expected to be facile.[18] Furthermore, we note that selected supramolecular synthons in dihydrate **1** are retained in the Jovanovski–Kamenar hydrate. The stacked synthons in the regular domains of **1** are preserved as mentioned above. Hydrogen-bonded synthons in the irregular domains of **1** are also conserved in **2** (Figure 6). The fact that these synthons are carried over into **2**, even as there is much structural reorganization, is in keeping with the idea of synthons as kinetically significant units that are preserved through all stages of crystallization.[19]

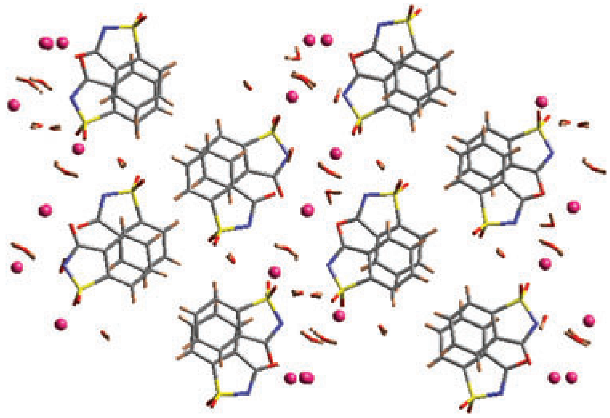

Figure 4. Crystal structure of dihydrate **1** looking down the stacking direction.

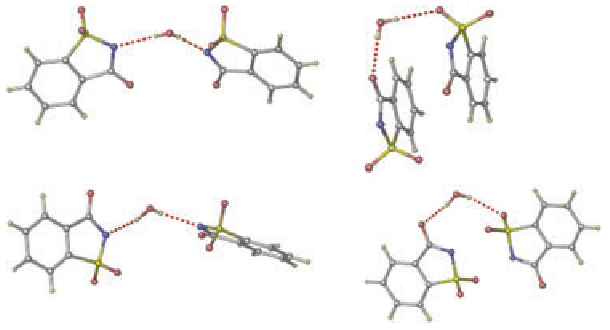

Figure 6. Conserved supramolecular synthons in dihydrate **1** (top) and the Jovanovski–Kamenar hydrate **2** (bottom).

Crystallization may be viewed as a supramolecular reaction, with nucleation likened to the transition state. The formation of a crystal from solution exemplifies a shift of the enthalpy–entropy balance. From the entropy-dominated situation in solution, order enters the putative crystal through the formation of a liquidlike cluster of solvent and solute.[20] The nucleation step is presumably accompanied by a critical increase in order and an entropically driven expulsion of solvent from the cluster into the bulk solution to yield the first crystals. Such a model explains why the majority of crystals of organic molecules do not contain solvent molecules of crystallization, unless there are specific enthalpic reasons

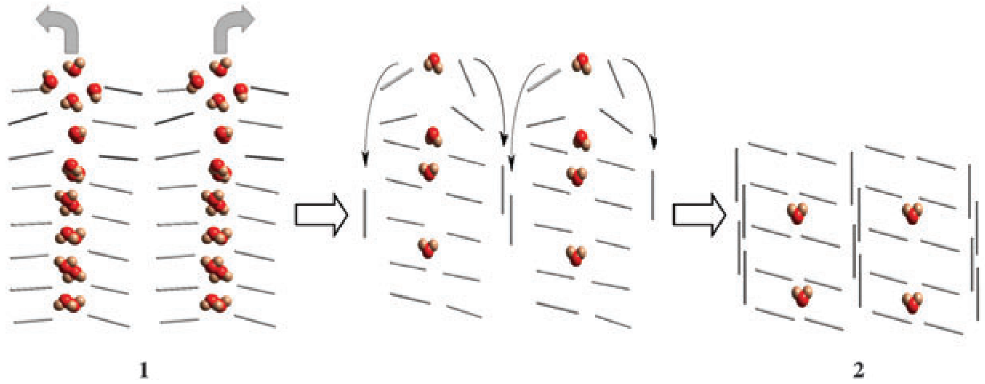

Figure 5. Transformation between hydrates, **1**→**2**. Note that all sac^- anions are nearly parallel in **1**, whereas they adopt two orientations in **2**.

(hydrogen bonds, close packing) for solvent inclusion.[21] A crystal, in turn, represents the optimization of enthalpic factors through favorable intermolecular interactions. The appearance of certain robust interaction patterns, or supramolecular synthons, in crystal structures suggest that these patterns are kinetically favored, and they make their appearance even in the early stages of crystallization. It is instructive to view the crystal structure of **1** from the above viewpoint.

The structure of **1** is a good model for nucleation in the crystallization of the Jovanovski–Kamenar hydrate from water. Note that direct observation of a crystal nucleus through static diffraction methods will be difficult. A nucleus (like a transition state) is a high-energy intermediate, and it will only be possible to deduce ideas about its structure indirectly. However, there is enough in the structure of **1** that is unusual for us to believe that it represents as good an approximation of what a crystal nucleus looks like, as can be obtained presently. First, the unit cell and asymmetric unit are large. A large unit cell, in itself, is unexceptional, but for crystals in which the building blocks (molecules, ions, and solvent) are so small, such a large unit cell is noteworthy. A similar situation is obtained in the giant molybdate clusters studied by Müller and co-workers,[22] and one of us has stated elsewhere that the isolation of these structures provides a closer look at crystallization events.[23] We searched the Cambridge Structural Database for large unit cells and found 592 hits for which the volume of the unit cell is greater than 10000 Å^3. Of these, only a handful correspond to cases in which small molecules adopt low-symmetry space groups (typical examples are MACCID02, QOWDIP, and QULKOX). Dihydrate **1**, is therefore distinctive.

Second, the contents of the entire unit cell are not neatly organized, and there are regular and less-regular domains. One could even describe the irregular regions as "messy". The combination of these two events (large unit cell, regular and irregular domains) and also the excessive amount of solvent in the crystal is very suggestive of a crystallization reaction still in progress. Third, dihydrate **1** is evenly poised between solution and hydrate **2**. To our knowledge, there is no other reported example of a substance that gains and loses solvent so very easily. There is not much difference in water content between crystalline **1** and the saturated solution. Amazingly, the same compound loses water at 35 °C, and the resulting hydrate **2** does not gain water when exposed to the vapor. Once again, easy gain or loss of water would, in itself, be unexceptional. When it occurs for the same substance, it becomes significant and suggests that **1** is a bridge between the saturated solution and the stable Jovanovski–Kamenar hydrate; in other words, it is closer to the crystal nucleus of **2** than either of the extremes.

It is useful to consider just why this complex structure is even isolated. The finite supramolecular cube arrangement and the variation in the cube edges (2.312–2.595 Å) provide a hint. It is possible that the geometrical requirements for stacking of aromatic residues are not exactly in accord with the octahedral coordination of Na^+ ions (Figure 1), but it is clear that both these unconnected events are required to sustain the cube architecture. Accordingly, the regular domain cannot extend infinitely (if it did, **1** would become an ordinary, even somewhat commonplace, crystal). In trying to maintain the ring stacking, the Na^+ coordination is compromised or vice versa and the result is a blend of regular and irregular regions.[24] The regular regions, however, become the major portion of crystalline **2**, while the irregular regions undergo further evolution. This is a thermodynamic argument. On the kinetic side, it could be asserted that the main reason that one even observes a structure such as **1** is because the solvent involved is water. Enough has been said elsewhere about the ability of this remarkable solvent to sustain elaborate patterns of molecular recognition.[25] We have noted here that it plays a significant, even crucial, role in the supramolecular interactions in **1**. The energetics of these water interactions, to both sac^- and Na^+, may be sufficient to stabilize this essentially metastable species.

The liquidlike cluster of solvent and solute that precedes nucleation should contain solvent–solvent, solvent–solute, and solute–solute interactions. We note, however, that dihydrate **1** does not contain a single hydrogen bond between two water molecules. In keeping with the idea of crystallization as a supramolecular reaction and our description of dihydrate **1** as a supramolecular transition state, or at least a high-energy reaction intermediate, we apply the Hammond Postulate and conclude that **1** is an example of a late transition state. Large regions of **1** resemble the structure of **2**, and there are no solvent–solvent interactions. Elements of order have entered the crystal nucleus, the important supramolecular synthons are in place, if not exactly in the correct locations, and the product of crystallization (hydrate **2**) is a kinetic product. It is still a matter of conjecture that early transition-state crystal nuclei will have solution-like character and that they will lead to thermodynamic products (perhaps hydrate **3** or the anhydrate).

In conclusion, we have determined the crystal structure of the long-known sodium saccharinate dihydrate (**1**). This metastable structure relates both to solution and to the more-stable crystalline sodium saccharinate hydrates **2**–**4** and the anhydrate. It is truly ironic that a substance as unusual as **1** has been available on a scale of hundreds of tons for over a century, but has remained structurally uninvestigated until now. It is exceptional that a species which is in such delicate equilibrium with the solution is able to diffract so well. We believe that this property is because of the rigidity that is imparted to the system by several hydrogen bonds and $Na^+\cdots O$ interactions formed by water.[26] Indeed, the very existence and easy observation of this unique structure owe to the presence of the large excess of water in the crystal. We suggest that some degree of long-range order, essential for crystallinity, is already present in crystal nuclei, at least in those that correspond to late supramolecular transition states. In summary, dihydrate **1** appears to be a good model for the structure of a nucleus in the crystallization reaction.[27]

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Keywords: hydrogen bonds · nucleation · saccharin · transition states · water

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[9] Crystal data: Hydrate **1**, $Na_{16}(C_7H_4NO_3S)_{16}(H_2O)_{30}$, monoclinic, $P2_1/n$, $a = 18.5918(11)$, $b = 28.3628(16)$, $c = 29.0562(16)$ Å, $\beta = 93.560(2)°$, $V = 15291.7(15)$ Å^3, $Z = 4$, $T = 100(2)$ K, $\mu = 0.381$ mm^{-1}, 105833 reflections measured, 30081 independent, 21746 observed ($I > 2\sigma(I)$), 2385 parameters, $R1 = 0.0448$, $wR2 = 0.0719$ (for $I > 2\sigma(I)$). Hydrate **4**, $K_3(C_7H_4NO_3S)_3(H_2O)_{2.33}$, triclinic, $P\bar{1}$, $a = 7.6104(5)$, $b = 12.3049(8)$, $c = 15.4936(10)$ Å, $\alpha = 72.2780(10)$, $\beta = 86.5810(10)$, $\gamma = 81.2290(10)°$, $V = 1365.75(5)$ Å^3, $Z = 2$, $T = 298$ K, $\mu = 0.794$ mm^{-1}, 22602 reflections measured, 5369 independent, 5029 observed ($I > 2\sigma(I)$), 410 parameters, $R1 = 0.0312$, $wR2 = 0.0879$ (for $I > 2\sigma(I)$). Intensity data were collected on a Bruker Nonius Smart Apex CCD with graphite monochromated $Mo_{K\alpha}$ radiation at 100 K and 298 K. The structures were solved by direct methods and refined anisotropically by full-matrix least-squares method using the Shelxtl 6.14 software package. CCDC 258588 and 258589 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] In hindsight, it is not clear if Naumov et al.[6] had examined (inadvertently) “watered” crystals when they stated that the dihydrate contains more than two molecules of water in the formula unit.

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[15] We performed this experiment to ascertain if a potassium analogue of dihydrate **1** could be obtained. It is hardly surprising that we could not and adds to the body of evidence which suggests that the structure of **1** is truly unusual. The water stoichiometry of 2.33 in this potassium salt, **4**, contrasts with the results of Jovanovski et al. (G. Jovanovski, B. Kaitner, O. Grupce, P. Naumov, *Cent. Eur. J. Chem.* **2004**, *2*, 254), who report the structure of $K_3(sac)_3{\cdot}2H_2O$.

[16] In hindsight, it would appear that recrystallization of the commercial compound from EtOH by Jovanovski and Kamenar caused partial dehydration to **2**.

[17] Careful inspection of the packing diagrams will show that the registry of molecules in the stack changes in the conversion **1**→**2**, such that paired molecules in **1** have the SO_2 groups on the same side, while in **2** each pair has an SO_2 and a CO group on the same side. However, there is much reorganization in the transformation and we believe that such a registry change can be easily accomplished.

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[24] Our failure to obtain the potassium analogue of **1** supports this notion, but it is hardly proof. One might suggest that the K analogue occurs en route to crystals of **4**, and that it is a true transition state in contrast to **1**, which could be viewed as a high-energy reaction intermediate.

[25] Selected references include: a) L. J. Barbour, G. W. Orr, J. L. Atwood, *Nature* **1998**, *393*, 671; b) L. Infantes, J. Chisholm, S. Motherwell, *CrystEngComm* **2003**, *5*, 480; c) R. Ludwig, *Angew. Chem.* **2001**, *113*, 1856; *Angew. Chem. Int. Ed.* **2001**, *40*, 1808.

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[27] *Note added in proof:* While this paper was being refereed, the crystal structure of dihydrate **1** was published independently by another group, see: P. Naumov, G. Jovanovski, O. Grupèe, B. Kaitner, A. D. Rae, S. W. Ng, *Angew. Chem.* **2005**, *117*, 1277; *Angew. Chem. Int. Ed.* **2005**, *44*, 1251. The details of the crystal structure are essentially the same in both studies. However the remarkable aspect of the structure is that it touches upon the nature of what a supramolecular transition state might look like, and this interpretation is particular to our work.