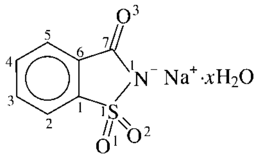
Structure Elucidation

Solid-State Structure and Temperature/Evacuation-Induced Dehydration of Sodium Saccharinate 1.875 Hydrate**

Pance Naumov, Gligor Jovanovski, Orhideja Grupče, Branko Kaitner, A. David Rae, and Seik Weng Ng*

The anion of saccharin[1] is a polyfunctional ligand that binds to a plethora of metal ions.[2,3] The solid hydrate of sodium saccharinate ("sodium saccharin" or "saccharinum soluble"; Scheme 1) is an edible chemical which constitutes more than half of the world's artificial sweeteners, but which is suspected to be carcinogenic.[1] Although the compound has been extensively used for more than 150 years, its exact structure has not been unequivocally established. In most chemical catalogues it is listed as the dihydrate $\mathrm{Na(sac)\cdot 2\,H_2O}$ ($\mathrm{sac} = \mathrm{C_7H_4NO_3S^-}$). An earlier effort to determine its crystal structure failed because of an unusually large monoclinic unit cell[4] and partial dehydration. Air-stable triclinic $\mathrm{Na(sac)}\cdot{}^{2}\!/_{3}\,\mathrm{H_2O}$ is obtained upon recrystallization from ethanol.[5,6] Herein we report the first determination of the structure of the commercial artificial sweetener sodium saccharinate. The relative stability and the mechanisms of isobaric dehydration (heating at constant pressure) and isothermal dehydration (evacuation at constant temperature) of the two hydrates are also revealed.



Scheme 1. The atom-labeling scheme for the monoclinic hydrate of sodium saccharinate.

Recrystallization of sodium saccharinate from different solvents yielded two hydrates. Whereas the physicochemical analysis of the hydrate obtained from 95% ethanol was consistent with the triclinic $\mathrm{Na(sac)}\cdot{}^{2}\!/_{3}\,\mathrm{H_2O}$ described previously,[5,6] the monoclinic hydrate that was obtained from water was identical to the unpurified commercial product. Precise thermoanalytical measurements of the latter showed 1.87 (${}^{15}\!/_{8}$ by diffraction, see below) water molecules per formula unit.

The otherwise stable crystals of $\mathrm{Na(sac)}\cdot{}^{2}\!/_{3}\,\mathrm{H_2O}$ are dehydrated[7] in two well-defined steps when heated under isobaric conditions. The intermediate $\mathrm{Na(sac)}\cdot{}^{4}\!/_{9}\,\mathrm{H_2O}$ exists in the interval 343–389 K (the peaks evident in the differential thermal analysis (DTA) traces are given in parentheses):

$$\mathrm{Na(sac)}\cdot{}^{2}\!/_{3}\,\mathrm{H_2O}\ (338\,\mathrm{K}) \rightarrow \mathrm{Na(sac)}\cdot{}^{4}\!/_{9}\,\mathrm{H_2O}\ (389\,\mathrm{K}) \rightarrow \mathrm{Na(sac)}\ (633\,\mathrm{K})$$

The crystals of $\mathrm{Na(sac)}\cdot{}^{15}\!/_{8}\,\mathrm{H_2O}$ are stable for months if stored in a closed vessel and not allowed to suffer mechanical damage. However, if they are exposed to dry air, placed in an evacuated container, or coarsely ground, they turn opaque. The isobaric dehydration of $\mathrm{Na(sac)}\cdot{}^{15}\!/_{8}\,\mathrm{H_2O}$ (see the Supporting Information) commences above room temperature (>303 K) and proceeds through two intermediates: $\mathrm{Na(sac)}\cdot{}^{9}\!/_{8}\,\mathrm{H_2O}$ (328–373 K) and $\mathrm{Na(sac)}\cdot{}^{2}\!/_{3}\,\mathrm{H_2O}$ or $\mathrm{Na(sac)}\cdot{}^{4}\!/_{9}\,\mathrm{H_2O}$ (the exact formula of the second intermediate could not be identified because of its instability at its formation temperature):

$$\mathrm{Na(sac)}\cdot{}^{15}\!/_{8}\,\mathrm{H_2O}\ (328\,\mathrm{K}) \rightarrow \mathrm{Na(sac)}\cdot{}^{9}\!/_{8}\,\mathrm{H_2O}\ (380\,\mathrm{K}) \rightarrow \mathrm{Na(sac)}\cdot{}^{2}\!/_{3}\,\mathrm{H_2O}\ \text{or}\ \mathrm{Na(sac)}\cdot{}^{4}\!/_{9}\,\mathrm{H_2O}\ (397\,\mathrm{K}) \rightarrow \mathrm{Na(sac)}\ (633\,\mathrm{K})$$

The changes in the IR spectra[3,8] and the final spectra obtained after evacuation and moderate heating of $\mathrm{Na(sac)}\cdot{}^{15}\!/_{8}\,\mathrm{H_2O}$ are nearly identical (Figure 1). This observation indicates that the isobaric dehydration and the initial isothermal dehydration both proceed to give the same product, which was identified by thermal analysis to be $\mathrm{Na(sac)}\cdot{}^{9}\!/_{8}\,\mathrm{H_2O}$. Comparison of the infrared spectra obtained (Figure 2) confirms that the product is not the stable triclinic $\mathrm{Na(sac)}\cdot{}^{2}\!/_{3}\,\mathrm{H_2O}$. Figure 2 also shows that the isothermal dehydration commences more gradually than the isobaric one. The absence of additional spectral changes upon further evacuation indicates that prolonged isothermal evacuation does not affect $\mathrm{Na(sac)}\cdot{}^{9}\!/_{8}\,\mathrm{H_2O}$.

The crystallographic data for the two hydrates and a detailed discussion of the monoclinic structure are given in

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[*] Dr. P. Naumov
International Center for Young Scientists
National Institute for Materials Science
1-1 Namiki, Tsukuba, Ibaraki 305-0044 (Japan)
Fax: (+81) 29-860-4706
E-mail: naumov.pance@nims.go.jp

Dr. P. Naumov, Prof. G. Jovanovski, Prof. O. Grupče
Institute of Chemistry
Faculty of Science
"Sv. Kiril i Metodij" University
P.O. Box 162, MK-1001 Skopje (Macedonia)

Prof. B. Kaitner
Chemistry Department
Laboratory of General and Inorganic Chemistry
Faculty of Science, University of Zagreb
Ul. kralja Zvonimira 8, HR-10002 Zagreb (Croatia)

Prof. A. D. Rae
Australian National University
Research School of Chemistry
Canberra, A.C.T. 0200 (Australia)

Dr. S. W. Ng
Department of Chemistry
University of Malaya, 50603 Kuala Lumpur (Malaysia)

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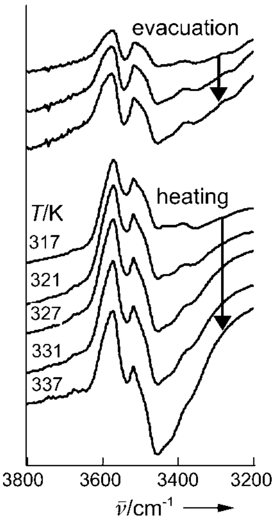

Figure 1. Effects of isothermal (evacuation) and isobaric (heating) dehydration on the ν(OH) region in the difference IR spectrum of $Na(C_7H_4NO_3S)\cdot{}^{15}/_8\,H_2O$. For the isothermal dehydration, the difference spectra were obtained by subtraction of a reference spectrum of Na(sac)$\cdot{}^{15}/_8\,H_2O$ from the spectra of samples evacuated with a rotary oil pump for various times. For the isobaric dehydration, the difference spectra were obtained by subtraction of the initial spectrum of the Na(sac)$\cdot{}^{15}/_8\,H_2O$ from the spectra of the same sample heated at various temperatures.

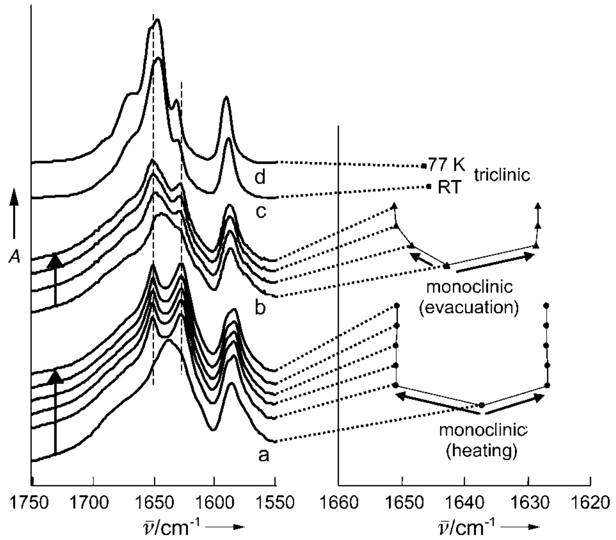

Figure 2. Changes (left) and temporal profiles of the positions (right) of the carbonyl stretching bands in the IR spectrum of $Na(C_7H_4NO_3S)\cdot{}^{15}/_8\,H_2O$ with isobaric (monoclinic: a, ●) and isothermal (monoclinic: b, ▲) dehydration. The spectra and values for $Na(C_7H_4NO_3S)\cdot{}^{2}/_3\,H_2O$ (■) at 298 K (c, RT) and 77 K (d) are also plotted for comparison.

the Supporting Information. The structure of the triclinic hydrate at 78 K is identical to the structure determined at room temperature.[5] The crystal of the monoclinic $P2_1/n$ hydrate $Na_{64}(C_7H_4NO_3S)_{64}\cdot 120\,H_2O$ ($Na(C_7H_4NO_3S)\cdot{}^{15}/_8\,H_2O$, $a = 18.6998(1)$, $b = 28.5277(1)$, $c = 29.2257(3)$ Å, $\beta = 93.582(1)^\circ$, $V = 15\,560.4(2)$ Å^3, $Z = 64$, $T = 95(2)$ K) may be regarded as an occupational and displacive modulation of an idealized (i) structure with $C2/m$ $Z = 8$ symmetry whereby $a_i = a$, $b_i = b/4$, and $c_i = c/2$. The large number of structurally different water molecules is confirmed by the matrix-isolation spectra of the partially deuterated compound.[9] As shown in Figure 3, a large fraction of the structure can be described as a displacive modulation of the saccharinate anions away from the hypothetical idealized $C2/m$ structure in which all but the sulfonyl oxygen atoms of the saccharinate anions would lie on mirror planes and consequently strictly parallel to each other. Two sodium atoms (Na12 and Na13, see the Supporting Information) take the positions of two water molecules (O16 and O23) in the idealized structure. The resulting structural misfit results in three sodium atoms (Na12, Na15, Na16), four water molecules (O1, O2, O15, O23), and one saccharinate anion (**I**) being disordered over two positions with occupancies 0.334(2) and 0.666(2). The displacive modulations allow all the sodium atoms to be surrounded by six oxygen or nitrogen atoms, and all the water molecules to be at reasonable contact distances to the saccharinate anions. The ranges of the shortest distances of the ligands to the metal atoms are compiled in Table 1.

The crystal structure of Na(sac)$\cdot{}^{9}/_8\,H_2O$ obtained by dehydration of Na(sac)$\cdot{}^{15}/_8\,H_2O$ could not be determined because of reduced crystallinity. However, the splitting of the ν(CO) mode in the IR spectra (1651, 1627 cm^{-1}; Figure 2) indicates that the saccharinate ions differentiate into two structural groups upon dehydration, with average[3a] C–O

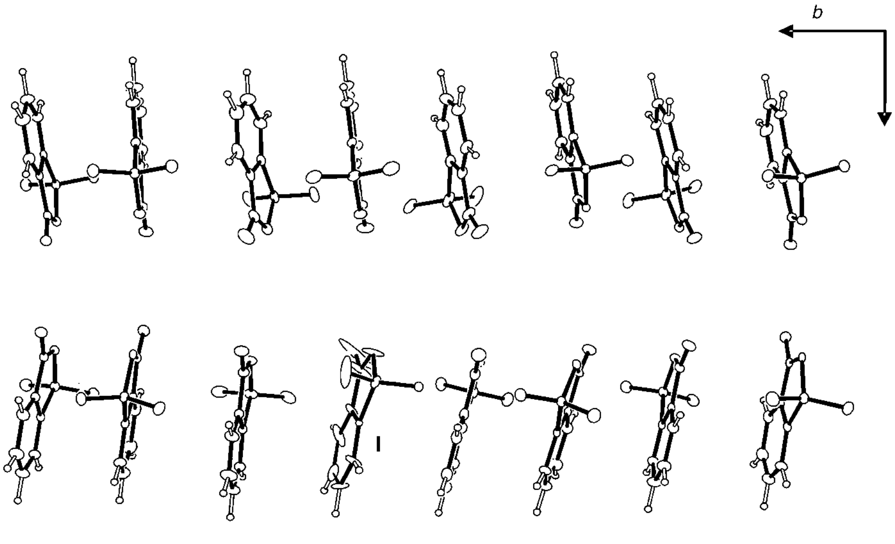

Figure 3. The positions of the 16 independent saccharinate anions relative to each other as viewed approximately normal to the *bc*-plane. Only the major part (occupancy 0.666(2)) of the disordered saccharinate ion **I** is shown.

Table 1: Ranges of the metal-to-ligand distances in the structure of $Na(C_7H_4NO_3S)\cdot{}^{15}/_{8}\,H_2O$.

Parameter[a]	Range [Å]
Na···O1,2	2.289(12)–2.940(3)
Na···O3	2.214(2)–3.081(8)
Na···N1	2.435(3)–3.062(3)
Na···O(water)	2.200(6)–2.862(4)

[a] The atom labels refer to Scheme 1.

bond lengths of 1.222 and 1.238 Å. Moreover, the shift of the ν(CO) modes of Na(sac)$\cdot{}^{9}/_{8}\,H_2O$ relative to Na(sac)$\cdot{}^{15}/_{8}\,H_2O$ reveals[3] that upon dehydration the saccharinate residues of one group correspond more to the 1,2-benzisothiazol-3-one form while those of the other group are closer to the 1,2-benzisothiazolyl-3-olato form.

In the initial structure, the saccharinate ions are stacked into columns running parallel to the b-axis (Figure 4). The metal ions and the water molecules fill up the space between the saccharinate columns. On the basis of the above findings and the structure of Na(sac)$\cdot{}^{15}/_{8}\,H_2O$, we suggest the following scenario for its initial dehydration: Removal of the loosely bound 48 water molecules from the unit cell during the first step, induced either by heating or by evacuation, causes the saccharinate ions to slide out of the stacks, presumably in the direction of their sulfonyl functional groups and towards the voids produced by the leaving water molecules. The sliding results in differentiation of the saccharinate ions into two groups, which differ in their distances to the metal ions and their ionicity, which is recorded as a splitting of the carbonyl band.

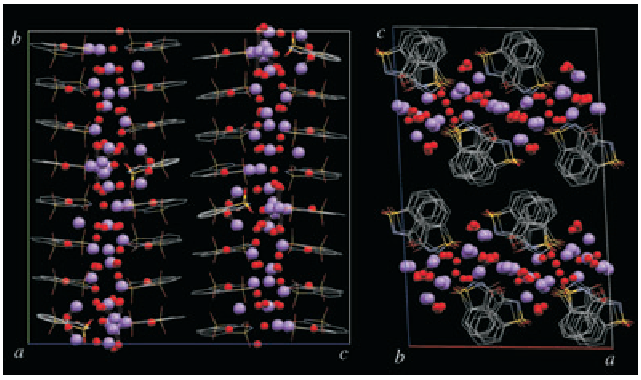

Figure 4. Ball-and-stick representation of the packing in the structure of $Na(C_7H_4NO_3S)\cdot{}^{15}/_{8}\,H_2O$. Water oxygen atoms and the sodium ions are colored red and purple, respectively. The hydrogen atoms are omitted for clarity.

Experimental Section

Recrystallization of commercial sodium saccharinate (Merck, purity $>99\,\%$) from water by slow evaporation at ambient temperature yielded large colorless monoclinic crystal blocks of centimeter dimensions. The cell parameters corresponded with the compound prepared by neutralization of an aqueous solution of saccharin with sodium carbonate or sodium hydroxide[10] and recrystallized from water. The purity of the sample before and after the recrystallization was checked by elemental analysis and inductively coupled plasma/atomic emission spectroscopy (ICP-AES). The contents of the most likely impurities, potassium (62 and 11 ppm by ICP-AES) and ethanol (below the detection limit of 0.1 ppm by HS-GC/MS), were insignificant for the purposes of this study. The diffraction measurements were carried out on a $0.45\times0.25\times0.20\,mm^3$ specimen obtained by partial dissolution of a larger crystal in water. The triclinic compound was obtained in the form of smaller colorless crystals by recrystallization from 95 % ethanol.

The thermogravimetry/differential scanning calorimetry (TG/DSC) curves were recorded in the 298–723 K range on a Rigaku ThermoPlus analyzer at a heating rate of $2\,K\,min^{-1}$ using non-pulverized, freshly prepared crystals. The IR spectra were recorded on a Perkin–Elmer System 2000 interferometer (KBr pellets) using a low-temperature cell. The pellets were prepared under minimum dehydration. Diffraction measurements on the two crystals were carried out at 95 K on a Siemens CCD area-detector diffractometer equipped with the Rigaku low-temperature system.[11] The triclinic structure was determined by direct phase determination[12] and refined[13] to $R=0.0298$ for 4943 $I>2\sigma(I)$ reflections ($wR_2=0.0805$) and $R=0.0336$ for all 5570 ($wR_2=0.0823$) reflections (GOF = 1.080). For the monoclinic compound, the sphere of 246589 reflections measured to $2\theta=55°$ ($-24<h<24$, $-36<l<36$, $-37<l<37$) consisted of 35542 independent reflections. The structure was determined with SHELXS-97[14] and refined with RAELS00.[15,16] The structure (see the Supporting Information) is presented as an ORTEP[17] diagram in Figure 3. CCDC 242403 and 242404 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.

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[8] The difference IR spectra in the ν(OH) region were employed to avoid overlap with the strong bands of the reactant. The ν(CO) mode of Na(sac)$\cdot{}^{15}\!/_8\,H_2O$ which splits into a doublet was found to be very sensitive to dehydration.

[9] As the pronounced structural disorder precludes accurate location of the hydrogen atoms by X-ray diffraction, the structure of the stoichiometric water was additionally investigated with the isotopic matrix-isolation method (examples: a) G. Jovanovski, P. Naumov, O. Grupče, B. Kaitner, *Eur. J. Solid State Inorg. Chem.* **1998**, *35*, 231–242; b) P. Naumov, G. Jovanovski, *Solid State Sci.* **2000**, *2*, 249–256) from spectra of partially deuterated Na(sac)$\cdot{}^{15}\!/_8\,(H,D)_2O$ with low deuterium content ($x_D < 5\,\%$). The isotopically isolated HDO isotopomers exhibit a complex spectrum in the 2660–2280 cm^{-1} region (see the Supporting Information), to which 30 mixed Gaussian–Lorentzian component ν(OD) bands with different intensities were fitted. This result indicates the structural dissimilarity of at least 30 structurally different water OH groups.

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[16] The use of refinable coordinates defined relative to local orthonormal axial systems (a) A. D. Rae, *Acta Crystallogr. C* **1975**, *31*, 560–570; b) A. D. Rae, *Acta Crystallogr. C* **1975**, *31*, 570–574) allowed all the saccharinate anions in the asymmetric unit to be exactly the same and have exact local mirror symmetry. The thermal motion of each molecule was described by its own *TLX* parameterization (T is the translation tensor, L is the libration tensor, and X is the origin of libration), 15 variables per molecule. Both components of the disordered anion **I** were set to belong to the same *TLX* parameterization with the T value constrained to be isotropic. The remaining non-hydrogen atoms were refined as isolated anisotropic atoms. Hydrogen atoms were re-included in expected geometric positions after each refinement cycle and were given thermal parameters defined by those of the atoms to which they are attached. Some 792 variables were used to describe the refinement of 245 non-hydrogen atom sites and 132 hydrogen atom sites. In the final refinement cycle (see Supporting Information), the maximum Δ/σ value was 0.10. min./max. electron density: $-3.3/3.4\ e\text{Å}^{-3}$ when all reflections were used. An uncorrelated 4 % error in $|F(\mathrm{h})|$ was included along with a counting statistic error for evaluating weights $w = [\sigma(F)^2 + (0.04F)^2]^{-1}$. The errors quoted for bond lengths and angles are conditional on the appropriateness of the various constraints and restraints.

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