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Article

Sodium Aspirin Salts: Crystallization and Characterisation

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Sodium Aspirin Salts: Crystallization and Characterisation

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Abstract

Acetylsalicylic acid (trade name Aspirin) is a well-known drug with antipyretic and analgesic effects. Mixtures that benefit from better solubility of its sodium salt have been sold for almost 90 years. Currently, several drug products are available with sodium aspirin as their active ingredient, but, until now, its crystal structure remained unknown. We have investigated the multicomponent system of sodium acetylsalicylate with the following results: an anhydrate and a dihydrate of a 1:1 salt were identified together with a hemihydrate of a 2:1 salt. Crystal structures of all forms were solved by single-crystal X-ray diffraction. The structural changes upon desolvation were studied by simultaneous TG/DSC supported by X-ray powder diffraction. The crystal structures were compared to those of all up-to-date published crystal structures of aspirin salts. Both of the hydrated sodium salts belong to the same isostructural family, while the anhydrate crystallizes with a unique packing of the acetylsalicylate anions.

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1 Introduction

Acetylsalicylic acid (ASA) has enjoyed the popularity of patients for more than 115 years[1] as the drug product Aspirin®. It belongs to the group of the first-choice drugs. The therapeutic use of acetylsalicylic acid is still widening today. In the beginnings, ASA was administered as an analgesic and antipyretic drug with lower side effects than its predecessor salicylic acid[2]. Other uses of ASA connected to its ability to decrease blood clotting were discovered as well. That resulted in the administration of aspirin in prevention and treatment of cardiovascular diseases, heart attacks and strokes.[3] Nowadays, many scientists are looking for new connections between regular use of acetylsalicylic acid and decreasing risk of cancer, Alzheimer's disease or diabetes.[4–6]

ASA is poorly soluble at the conditions of stomach juice, as the low pH in the stomach impedes the dissolution of ASA. Poor solubility of the drug causes aggregation of insoluble particles in the stomach. These insoluble aggregates promote damage to the gastric mucosa, which lead to side effects such as gastritis and peptic ulcers.[7]

One option how to improve drugs solubility is through crystal engineering. The solid state chemistry is a very important aspect in the pharmaceutical development. Solid forms, such as polymorphs, solvates, salts or co-crystals can modify the physicochemical and resultant biological properties such as solubility, permeability, hygroscopicity, stability, dissolution profile and bioavailability of a drug without any changes in its chemical structure[8,9]. Salt formation (salification) belongs to popular approaches in pharmaceutical development.[10–13] About 50 % of all drugs are used as salts[9]. Many of the new drugs are poorly soluble in water and salification can be an elegant solution for ionizable compounds. Ionizable compounds contain acidic or basic function groups, to which suitable counterions can be bound.[14]

In the literature, we can find that ASA forms many salts with inorganic or organic partners. In the CSD[15], there are 27 unique crystal structures of ASA salts and metallic complexes with Cu, K, Zn, Bi, Ca, Cd, Sn, Ag, Hg, Ni, Li, Ru, Pb, Rb and organic cations. It is worth noting, that some of these structures contain other molecules in addition to ASA and the cation. The full list of these structures can be found in the Figure S1 in SI.

Other ASA salts, for which the crystal structure has not been described, exist as well. Some of them contain the pharmaceutically acceptable partners (e.g. Al, D,L-lysine) and are successfully marketed. For example, the salt with D,L-lysine is known under the trade name Alcacyl® 500 Instant-Pulver or Aspégic®. In this work, we have focused on the Na salt[16], which is the active ingredient in drug products such as Alka-Seltzer®, Catalgine®, TABCIN®, Vida Mia®, Zee-Seltzer®.[17–19]

Even though the sodium acetylsalicylate (sodium aspirin, ASNa) has been known and used by patients for a very long time period[20] (Alka-Seltzer has been on the market since 1931[21]), the crystal structure remained unknown. Therefore, we have focused on the preparation of its diffraction-quality single-crystals and we have been successful in preparation of three forms of this salt and in solving all of their crystal structures.

2 Experimental section

2.1 Materials

Acetylsalicylic acid was purchased from Sigma-Aldrich (purity >99%). Sodium bicarbonate (purity >99%) and propan-2-ol (purity >99.8%) were obtained from Penta.

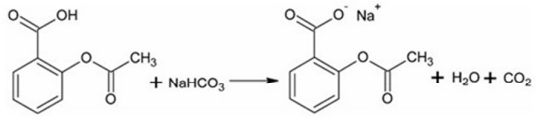
2.2 General Salt Preparation Route

The general principle of the aspirin sodium salt synthesis is based on careful neutralization of ASA. Suitable neutralization agents can be weak bases e.g. carbonates or bicarbonates (Scheme 1a). Unlike for the potassium aspirin salt, using strong basis is inappropriate, because the formed salt hydrolyses in basic environment (Scheme 1b).

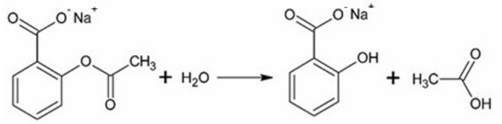
First, we have attempted the reproduction of ASNa preparation according to available patents[20], but with limited success only. Therefore, we optimized parameters like amount of water, combination of water and solvent for initiating the reaction and the conditions of the crystallization. Our optimized preparation process is as follows: ASA is reacted with sodium bicarbonate in the presence of a small amount of water that initiates the reaction. Additional water is produced as a side product, which keeps the reaction running. The end of the reaction is indicated by the extinction of the CO_2 bubbles. Then, propan-2-ol is added and the solution is filtered. The crystallization of the individual forms depends on the different crystallization conditions.

It is worth noting that we observed that the success rate and the yield of our experiments improved over time, even for the experiments with seemingly identical procedures and conditions. This lead us to believe that, for the successful crystallization of sodium aspirin, the 'contamination' of the environment with its crystallization nuclei[22] is essential.

a)



b)



Scheme 1. a) The ASNa salt preparation route, b) hydrolysis of the salt

2.3 Preparation of the Solid Forms.

Single crystals of ASNa dihydrate were prepared by mixing ASA with small amount of water, and, then, sodium bicarbonate was added. The mixture immediately began to react. After the reaction, which took about 20 hours, propan-2-ol was poured into the reaction mixture, which was filtered subsequently. The pure solution was stored in a freezer. Plate−like crystals were grown within a few hours.

Crystals of ASNa anhydrate were successfully prepared in two ways - direct synthetic route and by the dehydration of the dihydrate form. 1) ASA was mixed with small amount of water and sodium bicarbonate. The mixture was left to react for approximately 20 hours and then cold propan-2-ol was added. The solution was filtered and allowed to crystallize under reduced pressure in a vacuum oven at room temperature. A static vacuum was applied. The starting pressure level was 0.3 kPa, slowly increasing to 5 kPa. 2) ASNa dihydrate, prepared according to the process above, was dehydrated in vacuum drying oven. The dehydration was carried out under reduced pressure (about 0,1 kPa) during about 36 hours. A powder material suitable for XRPD was prepared this way.
A hemihydrate of the 2:1 salt was prepared using a mixture of water and propan-2-ol (2:1 v/v) to initiate the reaction between ASA and sodium bicarbonate. Crystals were obtained after the end of the reaction. No additional solvent was added.

2.4 Differential Scanning Calorimetry/Thermogravimetric Analysis (DSC/TG).

A combined analysis of DSC/TG was measured on a simultaneous thermoanalyser TG-DSC Sensys Evo. The device is equipped with a Calvet 3D sensor. Samples were measured in air atmosphere. The temperature range was 20 - 300 °C with the heating rate of 10 °C/min. The samples were measured in non-hermetically sealed Al pans.

2.5 Powder X-Ray Diffraction (PXRD).

For preliminary analysis a X'Pert3 Powder PANalytical diffractometer with CuK$\alpha_{1,2}$ radiation (wavelength 1.54180 Å) was used at 40 kV and 30 mA. The samples were measured on the silicon wafer and scanned within a range of 5.013 - 39.983° 2Θ with a step size of 0.026° 2Θ and a step time of 21.32 s. The evaluation of samples was done by the software HighScore Plus[23].

2.6 Single Crystal X-Ray Diffraction (SXRD).

ASNa anhydrate crystallized as colourless needles. Quality crystals were obtained from the mother liquor, directly mounted to the goniometer head and cooled down. The analyses were conducted using the four-circle RTG diffractometer Bruker D8 Venture. The diffractometer is equipped with Incoatec IμS micro-focus source (high brilliance multilayer optics), CuKα radiation with the wavelength of 1.5418 Å, and CMOS detector Photon 100. Data collection, unit cell refinement and data reduction was done by Bruker SAINT software[24]. Single crystals of ASNa dihydrate were crystallized from propan-2-ol and of ASNa hemihydrate from propan-2-ol : water (1:2 v/v). CuKα diffraction data of both crystals were collected on four-circle RTG diffractometer Xcalibur PX. Data collection, unit cell refinement and data reduction was done by CrysAlisPro CCD.[25] Twin laws in all structures were searched for by ROTAX[26] and no twinning was found. All structures were solved by direct methods by Sir92[27]. Program CRYSTALS[28] was used to refine structure and analyze absolute configuration. The positional and anisotropic thermal parameters of all non-hydrogen atoms

were refined. The hydrogen atoms were located in a Fourier difference map and refined riding with their pivot atoms. Molecular graphics were prepared in Mercury[29] and Discovery Studio.[30]

3 Results and Discussion

By a crystallization of acetylsalicylic acid with sodium bicarbonate, three crystalline forms of a sodium salt were prepared and their structures were solved. They included the anhydrate and the dihydrate of sodium acetylsalicylate (ASNa) and the hemihydrate of the 2:1 salt.
All structures were solved by single-crystal diffraction. The data collection and refinement details are described in Table 1. Distances and angles between Na and carboxylic oxygen atoms can be found in Table S1 in Supporting information.

Table 1. Crystallographic data of the sodium acetylsalicylate forms

Form	**ASNa anhydrate**	**ASNa dihydrate**	**ASNa 2:1 hemihydrate**
Empirical formula	C9 H7 Na1 O4	C9 H11 Na1 O6	C9 H8.5 Na0.5 O4.5
Formula weight	202.14	238.17	200.16
Crystallographic system	trigonal	monoclinic	monoclinic
Space group	*R* 3*c*	*P* 2_1/*c*	*C* 2/*c*
a (Å)	39.7168(13)	15.2144(3)	25.3326(17)
b (Å)	39.7168(13)	6.86391(14)	7.8837(6)
c (Å)	6.0865(2)	10.4770(3)	10.6356(8)
α (°)	90	90	90
β (°)	90	104.639(2)	109.174(6)
γ (°)	120	90	90
V (Å^3)	8314.7(3)	1058.60(3)	2005.46(15)
Z, calculated density (g/cm^3)	36, 1.450	4, 1.494	8, 1.326
F(000)	3726	496	832
R_{obs} /R_{all}	0.0841/0.0843	0.0404/0.0437	0.0462/0.0621
w R_{obs} / *w* R_{all}	0.2280/0.2284	0.1115/0.1130	0.0886/0.1074
Radiation	Cu K_α	Cu K_α	Cu K_α
Wavelength	1.54184 Å	1.54184 Å	1.54184 Å
Temperature	180 K	180 K	293 K
Crystal size (mm)	0.058 x 0.136 x 0.452	0.214 x 0.480 x 0.530	0.095 x 0.313 x 0.475
No. of measured reflections	22386	19996	13348
Independent reflections (R_{int})	3365 (0.032)	2199 (0.051)	1799 (0.047)
Data/parameters	3362/254	2198/158	1799/162
GoF	0.9420	1.0000	0.9637
Res. el. dens. (e Å^{-3})	-0.67, 0.91	-0.24, 0.22	-0.20, 0.20
CCDC No	1840789	1840790	1840788

3.1 ASNa anhydrate

ASNa anhydrate crystallizes in the trigonal system with the *R* 3*c* space group, which is rather unusual for organic crystals (0.08 % in CSD[15]). Two molecules of acetylsalicylate and two sodium cations are present in the asymmetric unit (Figure 1a). The unit cell then contains 36 of each species (Figure 1b). The structure is made up of sodium ion channels, onto which the acetylsalicylate ions are bound. The channels run along the *c*-axis direction (Figure 1c). Four molecules of acetylsalicylate are bonded to each sodium ion. There are no classical H-bonds in the molecular packing. All Na-O bond distances shorter than 2.5 Å and the corresponding angles for ASNa anhydrate are shown in Table S1 in Supporting information. The comparison of the bond distances reveals that the bond distances are considerably shorter in the ASNa anhydrate than in the other two structures. Also, the variation of the values is small, which well corresponds with the higher stability of this form. The Na1 and Na11 surroundings differ significantly. Na11 is coordinated with 5 oxygen atoms, while there are only four O atoms in the closer vicinity of Na1.

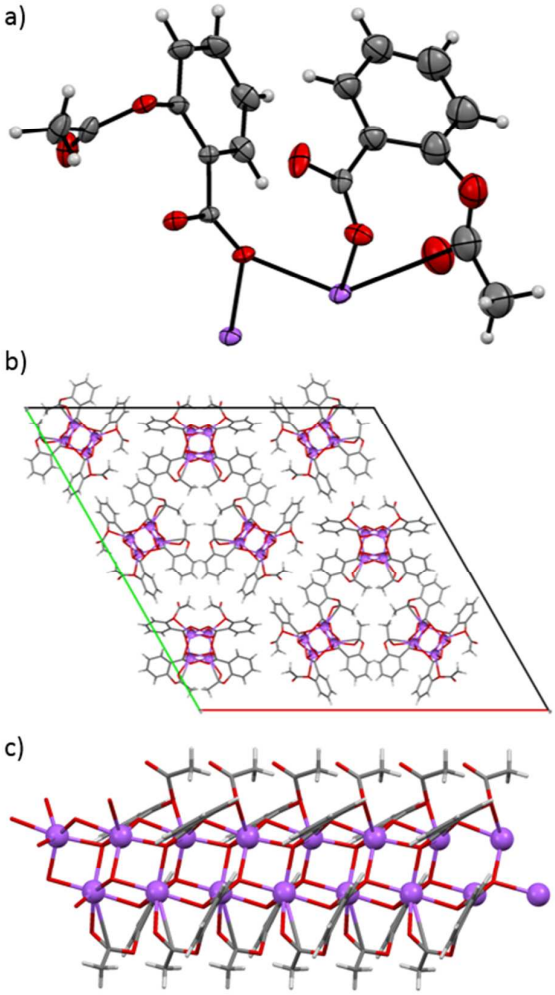


Figure 1. The crystal structure of sodium acetylsalicylate anhydrate; a) the asymmetric unit, b) the unit cell, c) a detailed view of the sodium channel surrounded with acetylsalicylate ions. Sodium cations displayed in magenta.

The purity of the prepared bulk material was confirmed by XRPD. When the experimental diffractogram is compared to the theoretical one, they correspond very well (Figure 2).

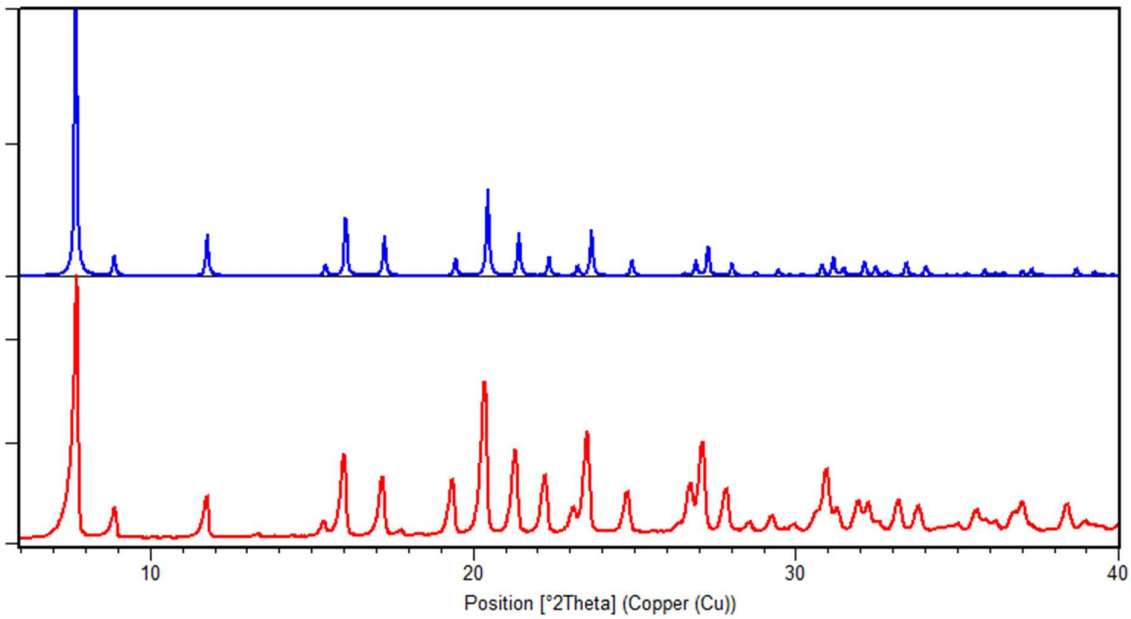


Figure 2. Comparison of the experimental (red) and calculated (blue) XRPD of ASNa anhydrate

The thermal analysis of sodium acetylsalicylate anhydrate (Figure 3) revealed that it melts at 229 °C, which is significantly higher than acetylsalicylic acid (180 °C [31]). At 237 °C, the sample started to oxidatively decompose. Similarly to acetylsalicylic acid, ASNa anhydrate slowly decomposes throughout the whole thermal analysis. It experiences a continual elimination of the acetic anhydride, which is evidenced by the decreasing mass of the sample measured by TG.

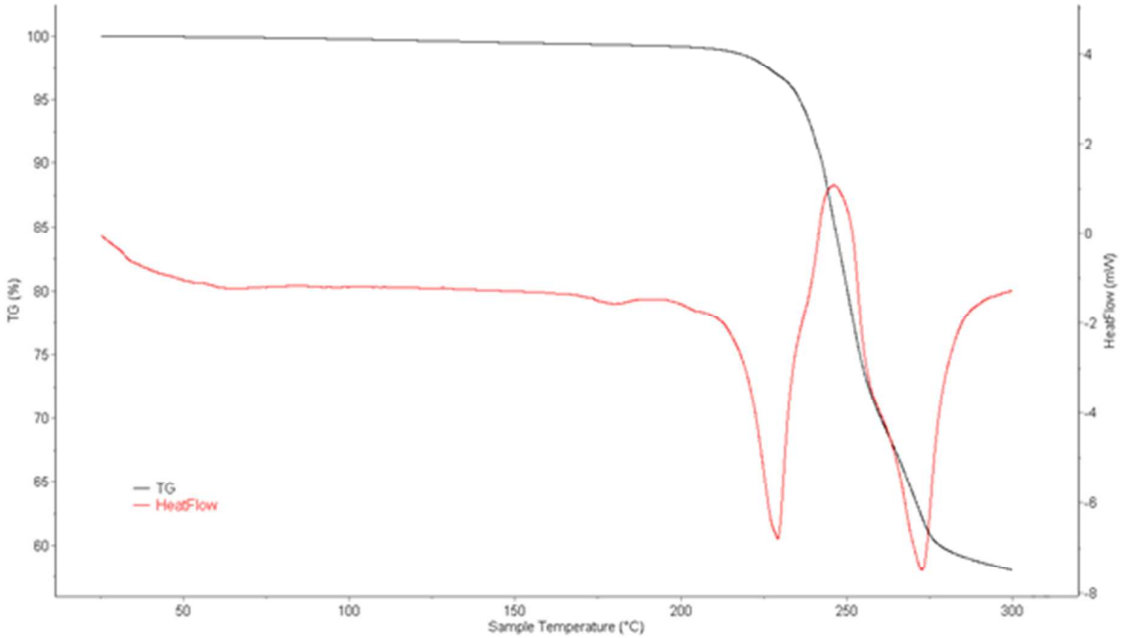


Figure 3. The thermal analysis (TG/DSC) of sodium acetylsalicylate anhydrate

Table 2. The thermal phenomena of sodium acetylsalicylate anhydrate

Temp. range	DSC	TG	Explanation
25-215°C	-	-3%	Slow deacetylation
215-237°C	endothermic peak at 229°C	-4%	Melting of anhydrate of ASNa; deacetylation
237-300°C	exothermic	-36%	Oxidative decomposition

3.2 ASNa dihydrate

ASNa dihydrate crystallizes in the monoclinic system with the $P\ 2_1/c$ space group. In the asymmetric unit, it contains a molecule of acetylsalicylate, a sodium cation and two molecules of water (Figure 4a). The unit cell contains four ASNa and eight molecules of water (Figure 4b). The crystal packing consists of hydrophobic and hydrophilic layers (Figure 4c). The hydrophobic layers are stabilized by π-π interactions with the benzene rings in the herringbone packing[32,33]. In the hydrophobic layers, the sodium ion is bonded by the Van der Waals interactions to two water molecules and to three different molecules of acetylsalicylate. Each water molecule donates two H-bonds, one to the aspirin carboxylate and one to another water molecule. All Na-O bond distances shorter than 2.5 Å and the corresponding angles for ASNa dihydrate are shown in Table S2 in Supporting information. The ASNa dihydrate has the longest average distance of Na-O of all the ASNa forms. However, it exhibits the highest calculated density value. The distances of the carboxyl oxygen atoms and the water molecules to the Na1 cation are very similar.

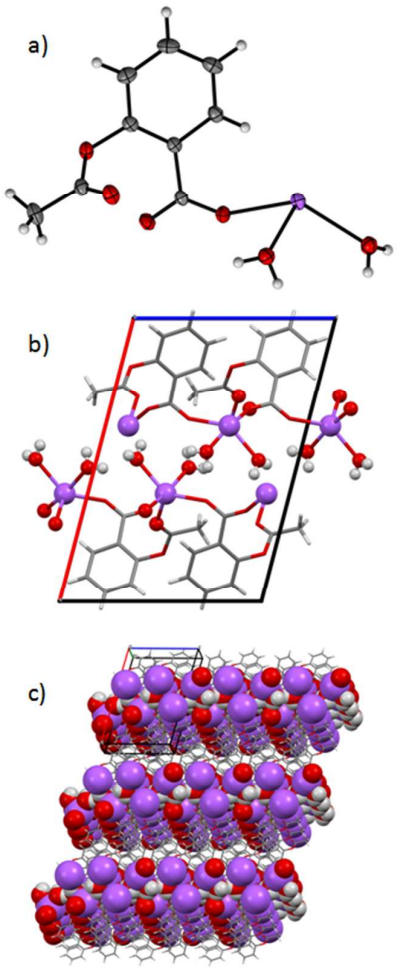


Figure 4. The crystal structure of sodium acetylsalicylate dihydrate; a) the asymmetric unit, b) the unit cell, c) the hydrophilic layers containing the sodium cations. Sodium cations displayed in magenta.

To complement the crystallographic investigation, the desolvation behaviour was studied by the thermal methods. For the TG/DSC analysis, the sample of ASNa dihydrate had to be measured wet, because it was too unstable on air. Even then, the measurement was accompanied by decomposition (deacetylation). The crystal water constitutes approximately 15 % of molecular weight of ASNa dihydrate. It leaves the structure in a range of 55 - 125 °C, see Figure 5. In this range, the sample recrystallizes to ASNa anhydrate and also partially decomposes to sodium salicylate. This was verified by XRPD of the sample after TG/DSC to 130 °C, see Figure 6. After that, the sample is still slowly decomposing and, at 228 °C, the formed ASNa anhydrate melts. The phenomena accompanying the thermal analysis are explained in detail in Table 3.

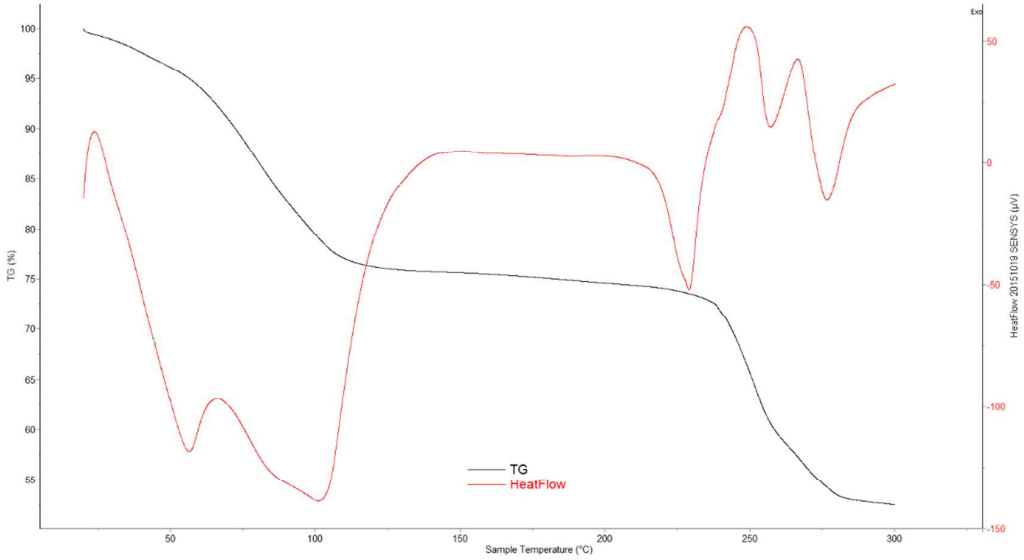


Figure 5. The thermal analysis (TG/DSC) of sodium acetylsalicylate dihydrate

Table 3. The thermal phenomena of sodium acetylsalicylate dihydrate

Temp. range	DSC	TG	Explanation
25-55°C	endothermic	-5%	Evaporation of the free and adsorbed water and the beginning of deacetylation
55-125°C	endothermic	-18%	Dehydration of crystal water; deacetylation; recrystallization
125-220°C	-	-2%	Slow deacetylation
220-235°C	endothermic peak at 228°C	-2%	Melting of the anhydrate of ASNa; decomposition
235-300°C	exothermic	-20%	Oxidative decomposition

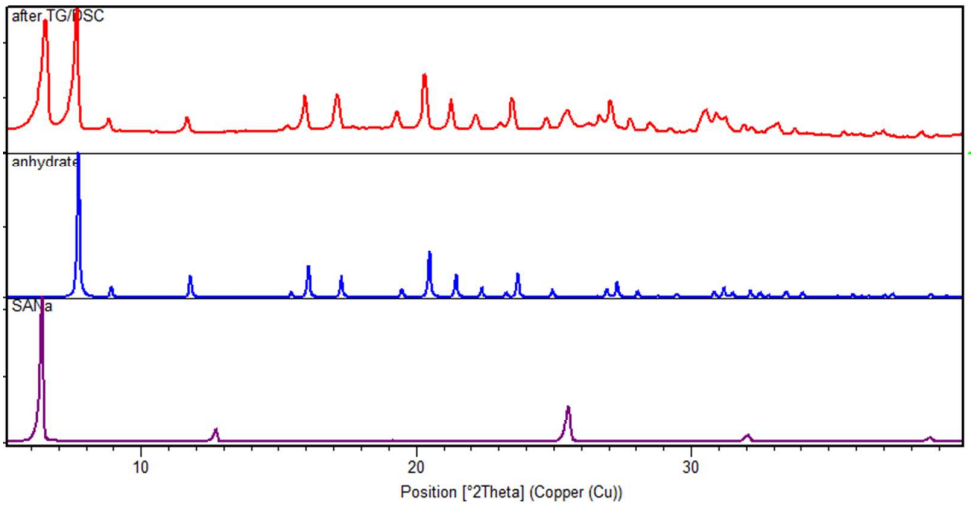


Figure 6. XRPD of ASNa dihydrate sample after dehydration during TG/DSC up to 130 °C (top); ASNa anhydrate (middle); sodium salicylate (bottom).

The inclusion of the water molecules in the crystalline structure is probably the cause of the high instability of this solid form, because it can readily catalyse the hydrolysis leading to the deacetylation (Scheme 1). This instability is the reason that other analyses routinely used to study pharmaceutical hydrates, such as DVS, critical water activity determination or variable humidity XRPD, could not be performed.

3.3 ASNa 2:1 hemihydrate

AsNa 2:1 hemihydrate crystallizes in the monoclinic system with the *C* 2/*c* space group. In the asymmetric unit, it contains a molecule of acetylsalicylate, a half of a sodium cation and a half of a water molecule (Figure 7a). Sodium ions and water oxygen atoms lie on twofold rotation axis and the carboxyl hydrogens are placed midway between two acetylsalicylate molecules on the centre of symmetry (Figure 7b). This means that each of the acetylsalicylate anions has a formal charge of -½ and that the unit cell contains eight molecules of AS, four sodium cations and four molecules of water (Figure 7c).

The crystal packing consists of infinite chains of alternating sodium ions and AS anions that run along the c-axis (Figure 8a). Each sodium ion is bonded to four molecules of acetylsalicylate and one molecule of water. Water molecules form three-centred H-bonds that crosslink the individual chains (Figure 8b). All Na-O bond distances shorter than 2.5 Å and the corresponding angles for ASNa 2:1 hemihydrate are shown in Table S3 in Supporting information. As could be expected, the highly unstable structure of ASNa – hemihydrate exhibits the lowest density. There is one remarkably short bond (2.210(5) Å) between Na1 and water O6, which occupies a 2-fold axis. The special position arrangement is reflected by the symmetry of the rest Na-O bonds, which cluster in pairs sharing equal distances and angles.

The preparation of this form in larger quantity necessary for further analysis was not successful.

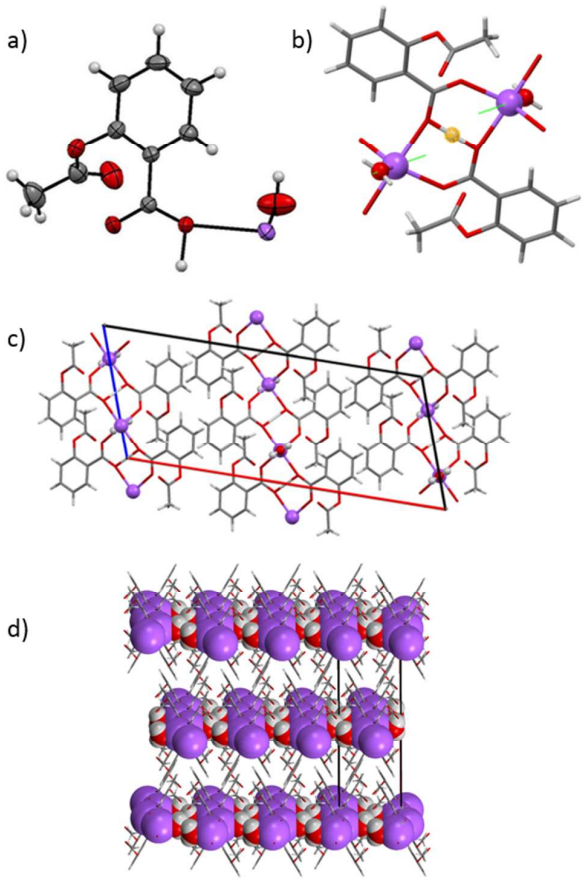


Figure 7. The crystal structure of ASNa 2:1 hemihydrate; a) the asymmetric unit, b) the special positions c) the unit cell, d) the hydrophilic layers containing the sodium cations. Sodium cations displayed in magenta.

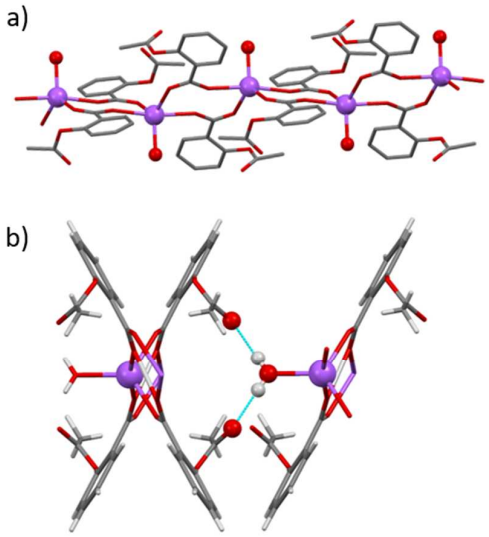


Figure 8. a) the chains of alternating sodium and acetylsalicylate ions in ASNa 2:1 hemihydrate; b) water molecule connecting the parallel chains by H-bonding. Sodium cations displayed in magenta.

3.4 Structural Comparison

The three novel sodium salts were compared to all 27 up-to-date published structures of acetylsalicylate salts. Both the conformation of the AS anion and their molecular packing were studied using CrystalCMP[34] software.

The similarities and differences in the molecular packing were analyzed employing a packing similarity tree diagram. The tree diagram is used for a clear analysis of similarity in the crystal packing of a group of structures. It can compare the crystal packing of chosen molecules or fragments of the structure. Therefore, it can be easily used to analyze a family of polymorphs, hydrates, solvates, salts and co-crystals. During the calculation, the clusters of 10 molecules are generated for each form and all clusters are compared to each other. The similarity is calculated on the bases of the distance and rotation of the respective molecules. Figure S1 in SI shows the diagram for all of the 30 AS salts, while Figure 9 shows only those published here and those forming isostructural families.

From the packing similarity dendrogram, we can identify three distinct 'isostructural' families. Out of the 30 crystal structures included in the calculation, 19 do not belong to any 'isostructural' family (meaning that the crystal packing of their AS ions is unique).

The largest isostructural family contains seven structures, while the other two only contain two structures each. The smaller families are both formed from Cu salts. The larger family contains ASNa dihydrate and ASNa 2:1 hemihydrate. It also contains the first ever described structure of an aspirin salt with benzamidine.[35] It was found that ASNa 2:1 is highly similar to the 2:1 salt with potassium (Figure 10). ASNa anhydrate is one of the structures that do not belong to any isostructural family.

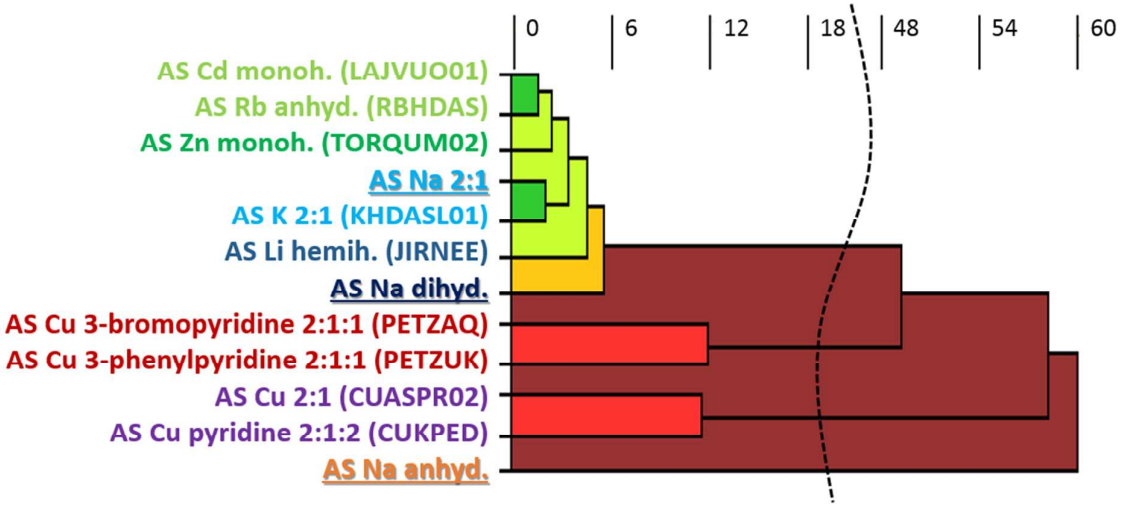


Figure 9. Packing similarity tree diagram of different AS salts. AS Na salts highlighted. Only AS molecules considered. A part of the figure between 18 and 48 has been deleted, to make the figure shorter and more readable - this deletion is indicated by the curved line. Only the structures belonging to isostructural families shown - please see the SI for the figure with all known AS salts. Calculated by CrystalCMP[34].

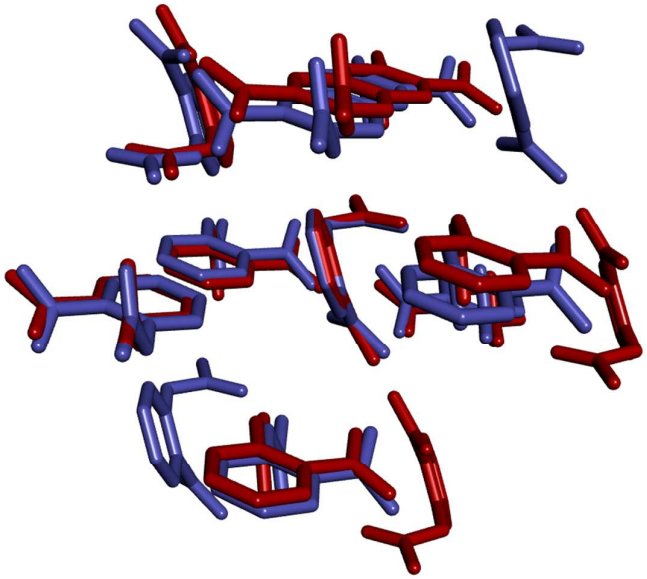


Figure 10. Similar molecular packing of the acetylsalicylate anions in 2:1 sodium and potassium salts; ASNa 2:1 hemihydrate (red) and KHDASL01 (violet). Calculated by CrystalCMP[34].

Another calculation in CrystalCMP[34] was performed to sort the structures based on their AS conformation. To do this, the number of neighbouring molecules was set to 0 and the inversion test was enabled. From Figure S2 in SI, we can identify that AS salts crystallize with seven distinct conformations of the AS anion. The overlay of these conformations is shown in Figure 11. Variability was observed in both of the flexible regions of the AS molecule (the rotation of the carboxylate and the torsion of the ester side chain).

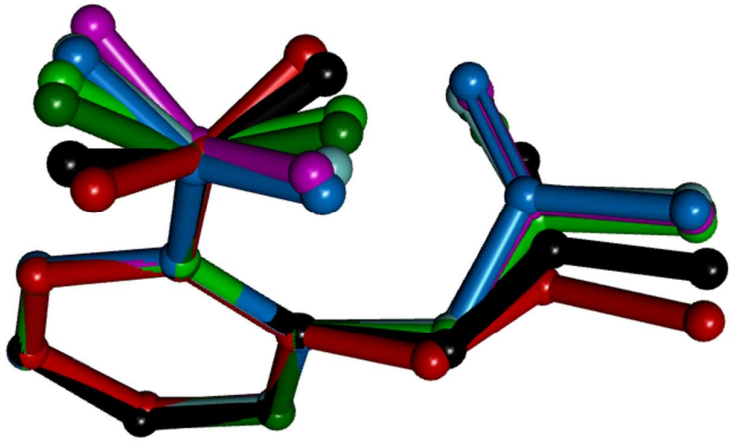


Figure 11. Conformational variability of acetylsalicylate in the various crystal structures. Only representative structures are shown for each group identified by CrystalCMP[34]: *ASNa anhydrate* dark green; *ASNa dihydrate* pink; *ASNa 2:1 hemihydrate* sea-foam; *AMALEG* light green; *SEYHOV* blue*; IVUYEE* red; *FEHGAB* black.

4 Conclusions

After long 87 years since the first drug product containing this compound was introduced to the market we report the crystallization and structural characterization of the sodium salts of acetylsalicylic acid (sodium aspirin). Although several products are available with sodium aspirin as their active ingredient, its crystal structure remained unknown until today. Anhydrate and dihydrate forms of the 1:1 sodium aspirin salt were prepared. Together with the crystal structure solution, the forms were characterized by thermal analysis and a complex decomposition pathway of the dihydrate was discovered. Additionally, the crystal structure of the novel 2:1 sodium salt was solved as a hemihydrate. The crystal structures were compared to all up-to-date published crystal structures of aspirin salts with regard to the conformation of the acetylsalicylate anion and its molecular packing. It was observed, that, only three isostructural families exist among the 30 structures, while two thirds of the salts crystallize with a unique packing of the acetylsalicylate anions.

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ASSOCIATED CONTENT
*S Supporting Information. Calculation results from CrystalCMP. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
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Sodium Aspirin Salts: Crystallization and Characterisation

Miroslava Búdová, Eliška Skořepová, Jan Čejka

Table of Contents Graphics

Synopsis

Currently, several drug products are available with sodium aspirin as their active ingredient, but, until now, its crystal structure remained unknown. We have investigated the multicomponent system of sodium acetylsalicylate with the following results: an anhydrate and a dihydrate of a 1:1 salt were identified together with a hemihydrate of a 2:1 salt. Both of the hydrated sodium salts belong to the same isostructural family, while the anhydrate crystallizes with a unique packing of the acetylsalicylate anions.