Physicochemical Properties of Salts of *p*-Aminosalicylic Acid. I. Correlation of Crystal Structure and Hydrate Stability

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Received April 22, 1991; accepted April 24, 1992

The potassium (K), sodium (NA), calcium (CA), and magnesium (MG) salts of *p*-aminosalicylic acid were obtained, and their thermal behavior was characterized by means of differential scanning calorimetry (DSC) and thermogravimetric analysis (TG). Their crystal and molecular structures were determined by single-crystal X-ray diffraction after powder patterns had shown them to be nonisomorphous. Different degrees of hydration were observed for the solid salts, and an assessment of hydrate stability to dehydration was made from thermogravimetric studies. The onset temperature of dehydration (T_t) of each salt varied within the series and exhibited correlation with *X*-ray determined structure. The observed onset of dehydration of MG and CA was higher than that of NA and is consistent with stronger ion–dipole interactions for the divalent salts. Crystallographic determination of the bond lengths between the metal ion and the water oxygens were 2.4 and 2.9 Å for NA, between 2.0 and 2.1 Å for MG, and 2.4 Å for CA. The open nature and presence of a channel feature in the structure of the sodium salt may have facilitated escape of water molecules from the crystal. Particle presentation (e.g., size, crystallinity) was also shown to affect dehydration behavior.

KEY WORDS: pharmaceutical salt selection; salts of *p*-aminosalicylic acid; hydrates; crystal structure; thermal stability.

INTRODUCTION

Salts are usually considered alternatives for drug delivery when the physicochemical characteristics of the parent drug molecule are unsuitable for an adequate formulation. Several preformulation salt-screening studies are reported (1–7) and a comprehensive review of the use of pharmaceutical salts exists in the literature (8).

Considerable variation in solubility, dissolution rate, and other pharmaceutically important properties can result from the use of different salt forming counterions. Further, because of a lack of predictive relationships between the physicochemical properties of counterions and those of the resultant salts (9), the selection of an appropriate salt form, with the desired combination of properties, can be a difficult semiempirical choice.

The tuberculostatic agent *p*-aminosalicylic acid (PAS) is one example of the many drugs which have been marketed as salts. A series of its salts was synthesized and their properties were evaluated in an attempt to provide predictive information.

In a preformulation selection program, if a salt has water associated with its crystal lattice, then characterization of this water is necessary. Further, the stability of salt hydrates is known to vary with change of the salt counterion and is important when selecting an appropriate salt form for formulation. For example, as part of a preformulation drug form selection program, Hirsch *et al.* used thermal analysis techniques to compare stabilities of the water of hydration in different salt forms of fenoprofen (1). The crystal structures of these salts were not determined and thus no attempt was made to explain the dehydration behavior of the salts with respect to their solid-state structures. This paper presents a systematic study of the effect of counterion change on both the crystal structure and the hydration/dehydration behavior of salts of another drug, namely, *p*-aminosalicylic acid. Resulting from the chemically trivial change of counterion, the substantial differences observed in the crystal structure and thermal behavior of the salts are discussed and a correlation between crystal structure and hydrate stability is examined.

MATERIALS AND METHODS

Materials

p-Aminosalicylic acid (PAS; 4-amino-2-hydroxybenzoic acid), the dihydrate of its sodium salt (NA), and its potassium salt (K) were obtained from Sigma Chemical Co. (Poole, UK) and were at least 99% pure on the manufacturer's certificate of analysis. NA was divided into two sieve fractions; NA1 possessed a particle size <250 μm, and NA2 >250 μm. Recrystallization of NA from ethanol/water gave NA3. All other materials were commercially available and were of at least reagent grade.

Confirmation of Synthesis of PAS Salts

Elemental analyses and water contents by the method of Karl Fischer were determined by the Analytical Chemistry Department, Pfizer Central Research (Sandwich, Kent, UK). The results were consistent with theoretical values.

Preparation of Magnesium Salt (Batch MG)

A solution of 96 g magnesium chloride hexahydrate in 100 ml water was slowly added with stirring to a solution of 200 g NA in 250 ml warm water. Stirring was continued for 3 hr, after which the crystals were filtered and washed with small quantities of water. The crystals were then dried at 40°C under reduced pressure. One hundred forty grams of MG was recovered, representing a yield of 74%.

Anal. Calc. $Mg(C_7H_6NO_3)_2 \cdot 4H_2O$: C, 41.97; H, 5.03; N, 6.99; H_2O, 18.0. Found: C, 42.14; H, 5.07; N, 6.97; H_2O, 18.6.

Preparation of Calcium Salt (Batches CA and CA2)

A solution of 38 g calcium chloride dihydrate dissolved

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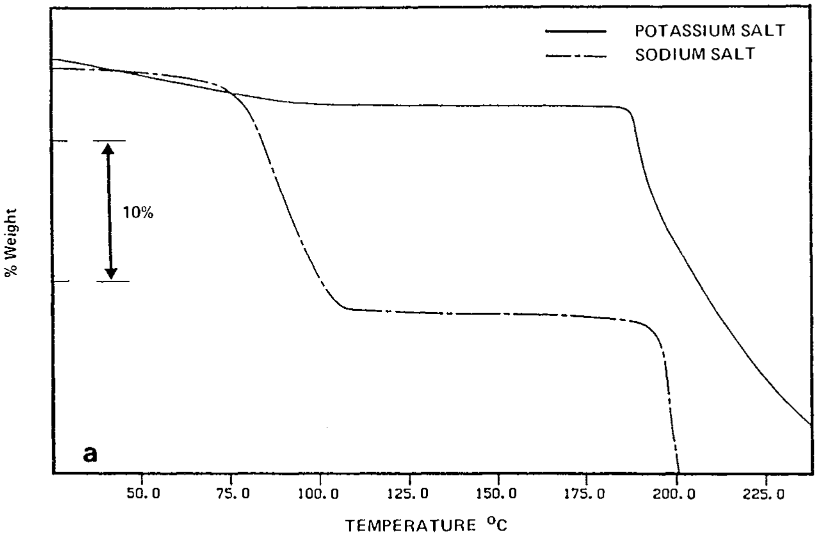

Fig. 1a. Thermogravimetric scans of the potassium and sodium salts of *p*-aminosalicylic acid. Program rate, 20°C/min.

in 50 ml water was slowly added with stirring to a solution of 100 g NA in 140 ml warm water. Stirring was continued for 1 hr, with the mixture being placed in a water bath maintained at 20°C. The precipitated first crop, after washing with water and methanol, gave 45 g (yield 50%) and was less pure than the second crop (batch CA) obtained from the mother liquor after storage at 4°C for 5 days. The latter was washed with water and dried under reduced pressure at room temperature.

Anal. CA Calc. $Ca(C_7H_6NO_3)_2 \cdot 3H_2O$: C, 42.21; H, 4.55; N, 7.03; Ca, 10.06; H_2O, 13.6. Found: C, 42.47; H, 4.47; N, 6.90; Ca, 10.1; H_2O, 12.8.

Differential Scanning Calorimetry (DSC)

Scans of samples were recorded on a Perkin–Elmer DSC7 differential scanning calorimeter connected to a Perkin–Elmer 7700 computer via the TAC7 microprocessor controller. The system, using Perkin–Elmer TAS7 software, was able to calculate extrapolated onset temperature, peak temperature, and enthalpy values for each thermal event. The temperature axis was calibrated with pure indium, with a melting point of 156.60°C and was checked using a zinc standard, with a melting point of 419.47°C. The environment of samples was varied by heating in (a) uncovered aluminium pans, (b) a crimped aluminium pan with a pinhole in the lid, (c) and a crimped volatile sample pan. An empty pan, sealed in the same way as the sample, was used as reference. Sample mass (1–10 mg) and heating rate (5–40°C/min) were varied according to the purpose of the experiment.

Thermogravimetric Analysis (TGA)

Analyses were performed on a Perkin–Elmer TGA7

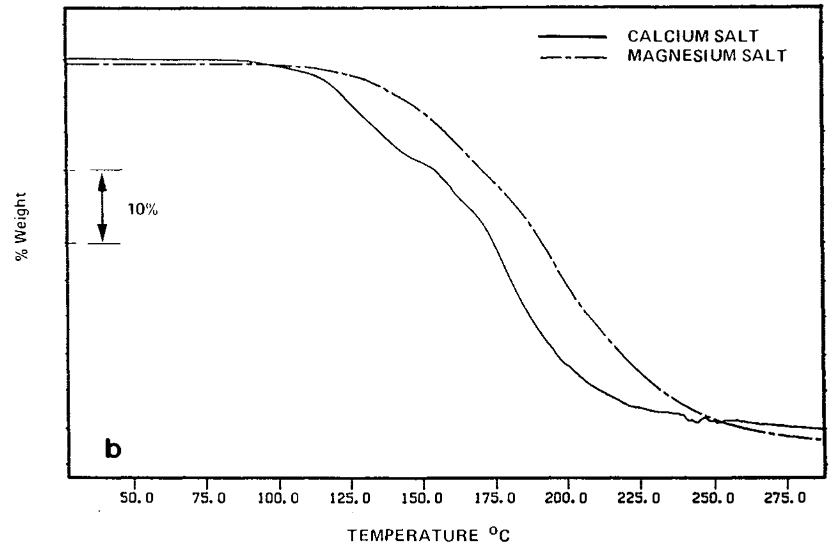

Fig. 1b. Thermogravimetric scans of the calcium and magnesium salts of *p*-aminosalicylic acid. Program rate, 20°C/min.

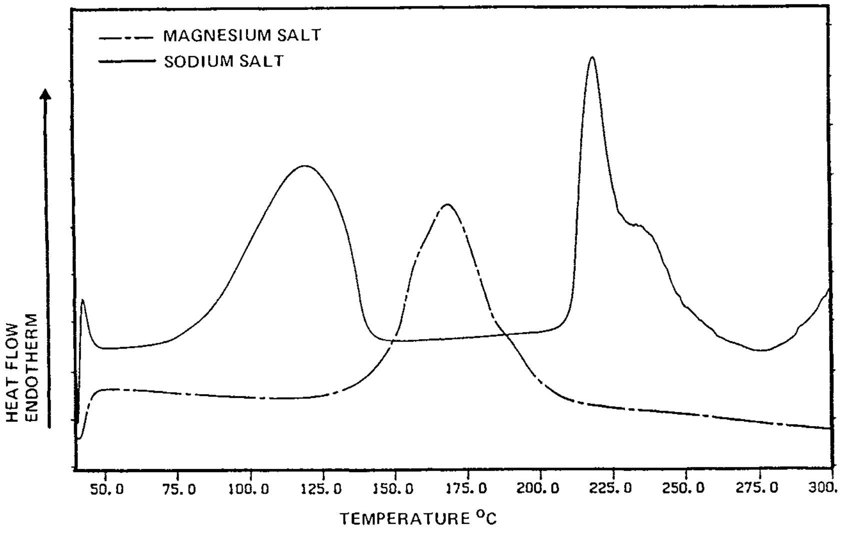

Fig. 2. Differential scanning calorimetry traces of the sodium and magnesium salts of *p*-aminosalicylic acid. Program rate, 20°C/min.

thermogravimetric system connected to a PE Model 7700 computer via a a PE Model TAC7 microprocessor controller. The temperature axis was calibrated using the ferromagnetic materials provided by Perkin–Elmer. A quantitative assessment of hydrate stability was made by determining the temperature at which 2% by weight of the water content of each salt was lost (10). This was called the threshold temperature of dehydration T_t and was obtained from TG studies using sample masses of between 4 and 10 mg and a heating rate of 5°C/min and under nitrogen purge.

Powder X-Ray Diffraction Patterns (PXRD)

The powder X-ray diffraction patterns of the samples were obtained using a Siemens Model D500 diffractometer fitted with a scintillation counter and a CuKα radiation source (wavelength = 0.15418 nm).

X-Ray Single-Crystal Structure Determination (SCXRD)

Unit cell dimensions and atomic coordinates were determined using a Stoe Stadi-4 single-crystal x-ray diffractometer with CuKα radiation of wavelength 0.15418 nm. Suitably sized crystals ca 0.5 × 0.5 × 0.5 mm were chosen to minimize differential absorption effects and were mounted on the goniometer. Cell constants and orientation matrix for data collection were obtained from the least-squares refinement of the setting angles of at least 20 reflections. Data were then collected at room temperature by using the ω-2θ scan technique out to a 2θ of 115.0°. Constancy of representative reflections acting as standards throughout data collection indicated crystal stability. The intensities were corrected for Lorentz and polarization factors but not for absorption or extinction effects. Nonhydrogen atomic positions were located using direct methods from an electron density map (E-map) calculated from the set of phases with lowest figure of merit. Structure refinement was carried out using the SHELX-76 program utilizing full-matrix least-squares techniques. Refinements were first performed with isotropic and then anisotropic temperature factors. Final models had all nonhydrogen atoms thermally anisotropic. The PLUTO plotting program was used to draw molecular representations.

RESULTS AND DISCUSSION

Physicochemical Properties

The thermal behavior of the PAS salts could be classified into two groups. For the monovalent ion salts K and

Table I. Extent of Hydration of PAS Salts

Salt of PAS	Moles of H_2O	Calc. H_2O (%, w/w)	Detm. H_2O (% w/w)	
			KF	TG
K	—	—	3.0	2.8
NA	2	17.1	17.2	17.6
CA	3	13.6	12.8	Decomposed
MG	4	18.0	18.6	Decomposed

Table II. Dehydration Threshold Temperatures (T_t) of PAS Salts, with the Standard Deviation of Three Determinations in Parentheses

Salt of PAS	Description	T_t (°C)
K	<250 μm	36 (0.3)
NA1	<250 μm	46 (2.5)
NA2	>250 μm	53 (4.2)
NA3	Recrystallized unsized	57 (5.6)
MG	<250 μm	107 (2.1)
CA	Unsized	110 (4.7)

Table III. Crystal Characteristics of PAS Salts

Parameter	MG	NA	CA
Chemical formula	Mg $C_{14}H_{12}N_2O_6 \cdot 4H_2O$	Na $C_7H_6NO_3 \cdot 2H_2O$	Ca $C_{14}H_{12}N_2O_6 \cdot 3H_2O$
Molecular weight	400.6	211.1	398.4
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/C$	$P2_1/A$	$P2_1/C$
Cell constant			
a (Å)	6.772 (2)	7.004 (6)	6.939 (1)
b (Å)	13.284 (2)	14.734 (15)	11.123 (1)
c (Å)	9.599 (1)	8.861 (7)	20.955 (3)
β (deg)	97.16 (2)	97.89 (6)	98.75 (1)
V (Å^3)	857	906	1613
Z	2	4	4
F (000)	420	440	824
μ (cm^{-1})	13.37	14.07	39.47
Density (calc.) (g/cm^3)	1.55	1.56	1.64
No. obsd. data	2495	2722	3918
No. unique data	1180	845	1949
No. variables	137	137	264
Unweighted agreement factor, *R*	0.0728	0.0751	0.0594

NA, the TG scans recorded at 20°C/min show a two-stage weight loss (Fig. 1a). First, at temperatures below 100°C a weight loss due to dehydration occurred; and second, a weight loss due to melting/decomposition was observed at temperatures of about 200°C. Similarly recorded TG scans for the divalent ion salts MG and CA revealed that this two-stage process of weight loss was not apparent since a merging of the dehydration and melting/decomposition events occurred (Fig. 1b). This differentiation between the monovalent and the divalent salts was confirmed by DSC data. The DSC scan for NA recorded at 20°C/min shows two endotherms, and that recorded for MG shows a single broad endotherm, possibly resulting from a combination of thermal events (Fig. 2).

Water was associated with all the salts of PAS in the solid state (Table I) but its nature and behavior varied. The amounts of water determined by Karl Fischer titration (KF) were such that CA and MG corresponded to stoichiometric tri- and tetrahydrates, respectively. The TG-determined initial weight loss of 17.5% for NA confirmed it to be a dihydrate and that it lost both moles of water before melting. The 3% (w/w) water associated with K was loosely bound and corresponded to only 0.3 mol of water (w/w). It was not considered to be stoichiometric water of crystallization. Within this series, a general trend was observed that the propensity to form hydrates increased as the ionic potential of the cations increased. This was evident from the increase in the number of moles water associated with the salts as the

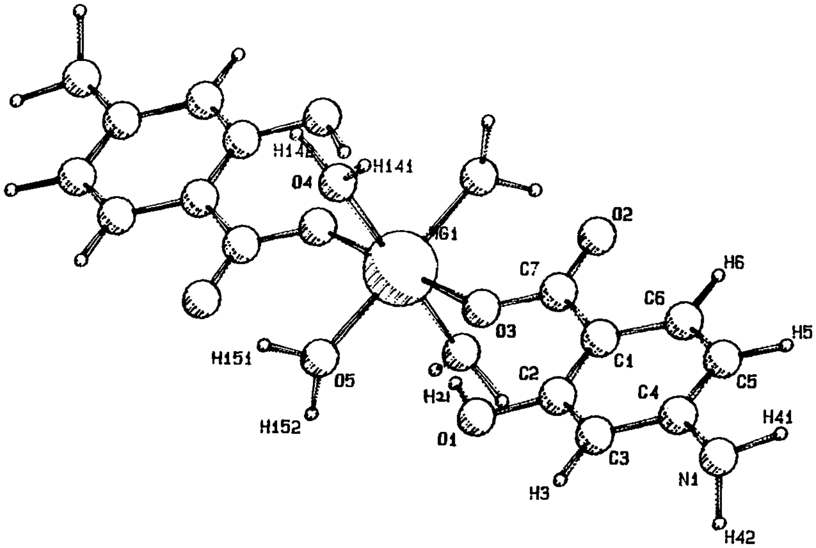

Fig. 3. Molecular conformation of MG showing atom numbering scheme.

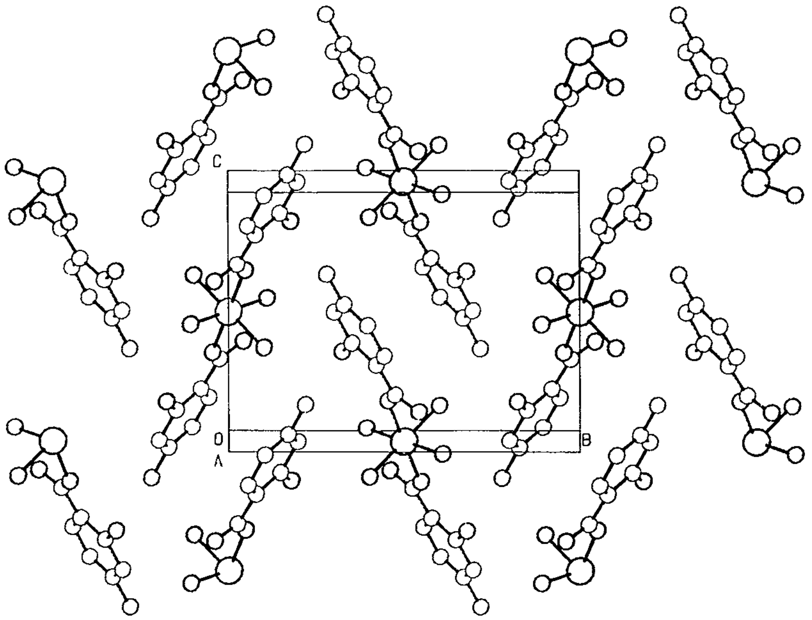

Fig. 4. Molecular packing diagram of MG with hydrogen atoms omitted for clarity.

ionic radius decreased and charge on the cation increased. A similar generalization is reported for ionic solids (11). However, the practical usefulness of such a generalization to predict the behavior of another salt series is limited, since salts may form several stoichiometric hydrates with different amounts of water dependent on the crystallization conditions.

The stability of the water to partial dehydration also varied for the salts; the temperature at which 2% of the total water content of the salts was lost (T_t) was used as a measure of the stability of the solvated and adsorbed water to dehydration. This approach was used by Byrn and co-workers (10) to study the desolvation of thymine hydrate, caffeine hydrate, theophylline hydrate, cytosine hydrate, and deoxyadenosine hydrate and is based on the observation that the hydrates that are unstable at room temperature show a gradual loss of solvent from approximately 40°C to higher temperatures. Taking into account this behavior and reproducibility considerations, preliminary experiments confirmed a T_t value after 2% water loss to be less subjective than using the standard software to determine a thermal event onset temperature.

Byrn and co-workers identify crystal packing, the influence of nuclei and defects, and hydrogen bonding as factors that could influence solid-state desolvation reactions. The crystal packing and hydrogen bonding of PAS salts are discussed later but an examination of Table II shows that both intrasalt and intersalt variation had an affect on T_t. The monovalent ion salts K and NA gave much lower T_t values than the divalent ion salts CA and MG. This was in accordance with the previously discussed thermal analysis data. The salts of fenoprofen (1) behave similarly with TG data, indicating the calcium dihydrate salt to be more stable than the sodium dihydrate salt. Particle size was seen to have an effect on T_t, since its value was lower for particles of NA less than 250 μm than for those greater than 250 μm. Such a difference may be explained in terms of heat transfer and surface area differences. The transfer of heat between large particles is less than that between smaller particles, which have a relatively larger total surface area and a greater number of interparticular contacts. Furthermore, another intrasalt variation, the number of nuclei and defects in the various batches of NA, was also indicated to affect T_t. A higher T_t value was recorded for NA3 (a recrystallization of NA) than for NA2 and NA1. Solid-state reactions and, particularly, desolvation reactions are known to begin at thermodynamically favorable nuclei and defects. NA3, being a slow recrystallization, was thought to have fewer defects and therefore offer the greatest resistance to the onset of dehydration; its higher T_t value supports this proposition. Once again the salts of fenoprofen (1) show similar behavior. The calcium salt of fenoprofen is crystalline as a dihydrate but is amorphous both as a monohydrate and as the anhydrate. From a simplistic thermodynamic consideration, an amorphous form will have infinitely more defects and nuclei than a crystalline form and this would explain why the amorphous calcium fenoprofen was less stable to dehydration than the crystalline sodium and calcium dihydrates. However, in the case of the hydrate behavior of PAS salts, the data suggested that intrasalt effects were less significant than those produced by a change of counterion and that crystal structure may be more predominant in controlling behavior.

Crystal Structures

Since the X-ray powder patterns of the four salts were not translationally related, it was concluded that their structures were nonisomorphous. In order to understand their physicochemical properties better, it was considered important to analyze the crystal structures of the salts and to compare their molecular packing arrangements. Unfortunately,

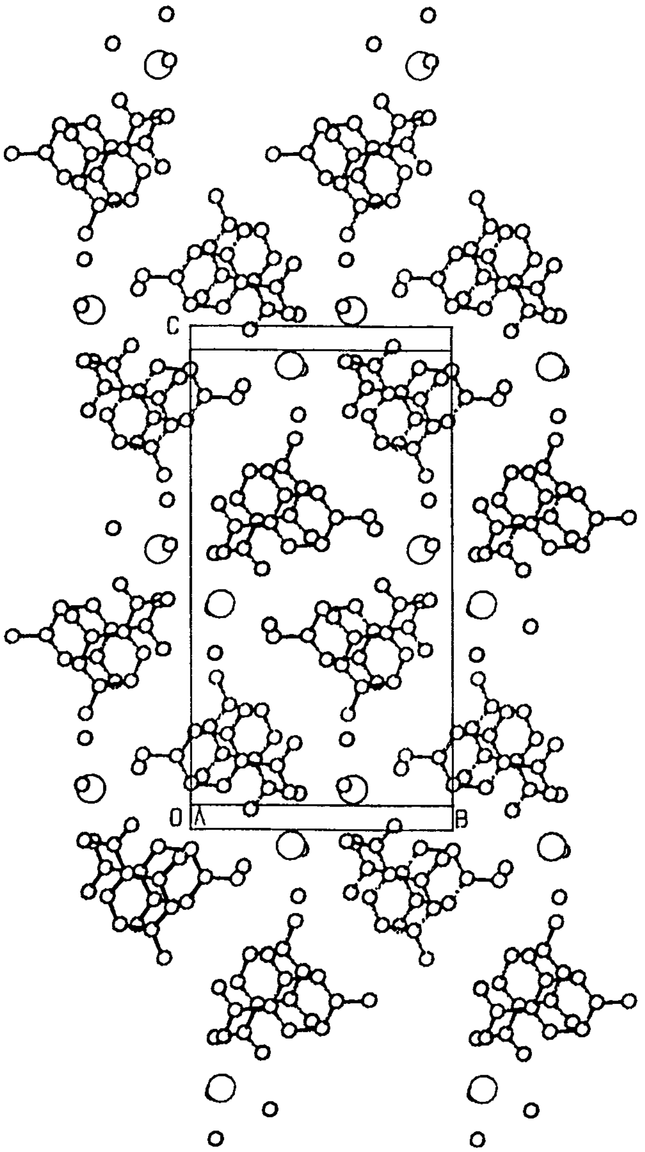

Fig. 5. Molecular packing diagram of CA with hydrogen atoms omitted for clarity.

crystals of K could not be grown sufficiently large to collect X-ray diffraction data. However, needles of CA and NA and tabular crystals of MG were of a suitable size for X-ray diffraction studies. Table III lists the crystal data and relevant collection parameters for NA, MG, and CA salts. Fractional atomic coordinates and anisotropic temperature factors can be obtained from the authors upon request.

All three structures were monoclinic but different unit cell dimensions and angles were obtained for each salt. The bond angles and bond lengths obtained for the PAS ring in all three salts were consistent with those of PAS (12) and its hydrochloride salt (13).

The magnesium salt had the simplest structure of the hydrates. One magnesium ion was coordinated to two PAS molecules and four water oxygens to make up its six coordination (Fig. 3). The water oxygen-to-metal ion distances are between 2 and 2.1 Å. This is the shortest distance in the hydrated salts and indicated that the water was firmly bound. The unit cell of the magnesium salt contained two magnesium ions, the packing structure being such that there were no channels for water escape (Fig. 4).

The calcium salt structure differed in that two calcium ions shared six water molecules and four PAS molecules, the sixfold coordination of the calcium ion being maintained by PAS molecules bridging the calcium ions (Fig. 5). Two different PAS molecules were observed in the asymmetric unit of the CA structure (Fig. 6). One molecule maintained an intramolecular hydrogen bond; the other did not. The reason for this is that for the calcium to be six coordinated, both oxygens from the carboxylate group were coordinated in one molecule, yet only one oxygen was coordinated in the other. Water to metal ion distances were 2.4 Å. Four calcium ions were contained in each unit cell, and once again, no channels for water escape were observed.

In the sodium salt, each sodium ion is coordinated to one water molecule at a distance of 2.9 Å and one at 2.4 Å. These were the largest such bond distances observed within the salts and possibly explained the lower affinity of the water to dehydration when compared to the divalent salts. The structure of the sodium salt viewed above the plane of a PAS molecule (Fig. 7) revealed a very open structure with an observable channel of water oxygens. It is suggested that this channel was a significant contributing factor to the relative ease with which the sodium salt lost its water of crystallization.

Examination of their crystal structures suggests that the thermal stability of the hydrates could be accounted for by the strength of metal ion-to-water dipole bonding. The divalent salts had stronger ion–dipole interactions because of short bond distances and thus gave higher threshold temperatures of water loss (Table IV). In comparison, the sodium salt, with weaker ion–dipole interactions because of larger bond lengths and also because of its more open structure, gave a lower threshold temperature of water loss.

In summary, both the degree of hydration and the dehydration stability of PAS salts varied with salt counterion. The X-ray-determined crystal structures of the sodium, calcium, and magnesium salts of PAS were nonisomorphous. Hydrate stability is of pharmaceutical consequence since processing operations involving thermal energy such as drying or compaction could partially remove water of crystallization or cause a mixture of hydrated and dehydrated forms to exist within formulations. The selection of an appropriate salt form remains important for the optimization of formulation properties; these results enable us to account for the relative stability of PAS salts to dehydration in terms of ion–dipole interactions resulting from their widely different crystal packing features.

ACKNOWLEDGMENTS

The authors would like to thank SERC and Pfizer (UK) (Dr. R. Davidson) for a CASE award for R. Forbes and Mr. R. Nettleton for PXRD and SCXRD data collection.

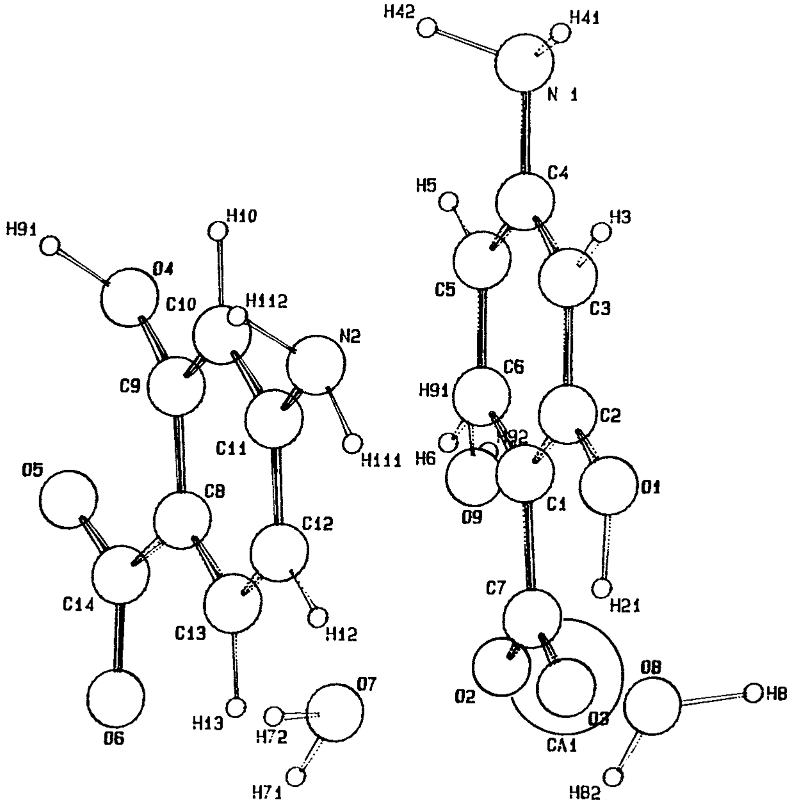

Fig. 6. Molecular conformation of CA showing atom numbering scheme.

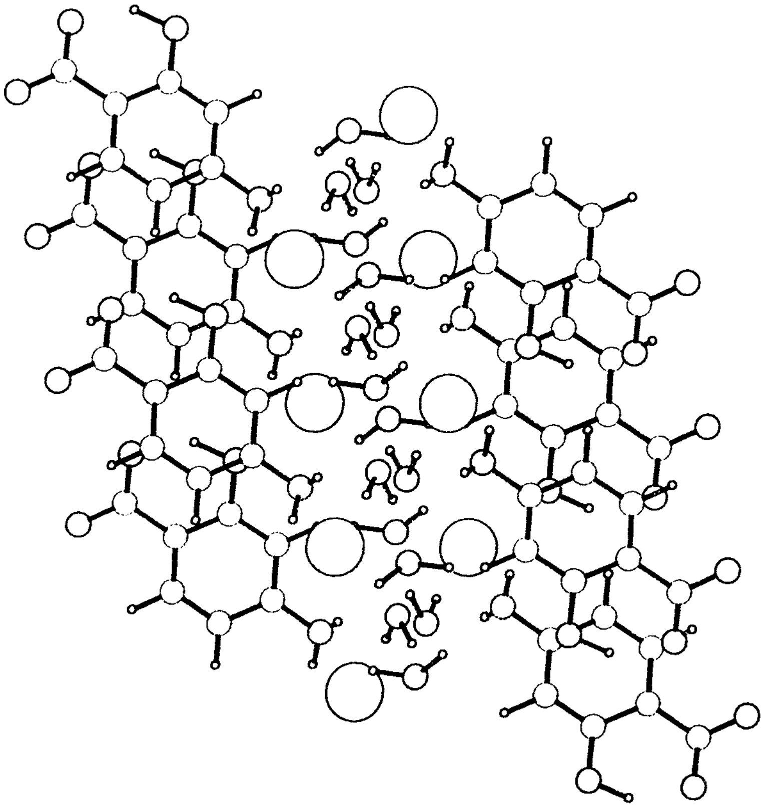

Fig. 7. Molecular packing diagram of NA.

Table IV. Water Oxygen-to-Metal Ion Bond Distances and Threshold Temperature of Dehydration, T_t, for PAS Salts

Salt cation	T_t (°C)	Water-to-metal bond distance (Å)
Na^+	46 (2.5)[a]	2.4–2.9
Mg^{2+}	107 (2.1)	2.0–2.1
Ca^{2+}	110 (4.7)	2.4

[a] Standard deviation in parentheses; $n = 3$.

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