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ORIGINAL RESEARCH

# Transforming aspirin into novel molecular salts of salicylic acid

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**Abstract** Aspirin is one of the most widely used analgesic, antipyretic, and anti-inflammatory drugs. Herein we disclose a way to transform aspirin into novel multicomponent crystal forms of salicylic acid, also a long-known analgesic with anti-inflammatory properties, among others, covering a broad spectrum of applications, including skin care products. A salicylic acid:salicylate ammonium salt and a salicylate:2-methyl-4-oxopentan-2-aminium molecular salt are concomitantly formed in acetone/ammonia solutions, resulting from aspirin decomposition. Furthermore the 2-methyl-4-oxopentan-2-aminium cation results from a sequence of in situ reactions: (i) imine formation, in which acetone is known to undergo under basic pH conditions; (ii) nucleophilic attack of α-carbon of the deprotonated acetone to the imine yielding 4-amino-4-methylpentan-2-one; and (iii) protonation of 4-amino-4-methylpentan-2-one. In the structures obtained for the novel multicomponent crystal forms, the strong charge-assisted $N^+$–H···$O/O^-$ hydrogen bonds between the drug molecule and the co-former play a key function in the supramolecular arrangement. The typical $\mathbf{R_2^2(8)}$ carboxylic···carboxylic homosynthon observed in salicylic acid was inhibited by the salt formation. These results are in agreement with the results of a careful survey on the Cambridge Structural Database.

**Keywords** Aspirin · Salicylic acid · Molecular salts · Acetone reactions · Supramolecular anion

## Introduction

Salicylic acid, also known as ortho-hydroxybenzoic acid or 2-hydroxybenzoic acid (Fig. 1), was used as early as 400 b.c. as an analgesic and is naturally prevalent in willow leaves, as well as in poplar and birch trees [1]. Salicylic acid has antiseptic, preservative, analgesic, and anti-inflammatory properties, covering a broad spectrum of applications, including skin care products [2, 3].

On the other hand, aspirin, acetylsalicylic acid, or, under IUPAC designation, 2-acetoxybenzoic acid was first synthesized in 1853 and by the turn of the nineteenth century became the world's best selling drug [4, 5]. It is a salicylate drug, often used as an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever, and as an anti-inflammatory medication. Aspirin also has an antiplatelet and is used long-term, at low doses, to help prevent heart attacks, strokes, and blood clot formation in people at high risk for developing this condition [6–22].

Aspirin is known to exist in two polymorphic forms: form I (Fig. 2a) [23] and form II [24] (Fig. 2b), and their supramolecular arrangements are related to each other by a relative shift of adjacent layers along the crystallographic *c* axis in space group $P2_1/c$ [8, 25].

Salicylic acid has some similarities to aspirin, not only on its analgesic action but also in its chemical structure, molecular and crystal packing arrangements [24–28]. The formation of the centrosymmetric homosynthon $\mathbf{R_2^2(8)}$ forming carboxylic acid dimers also occurs in salicylic acid as observed in both aspirin polymorphs [29]. Salicylic acid

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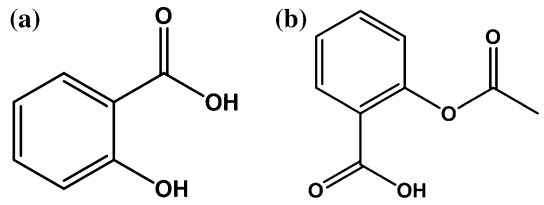



**Fig. 1** **a** Salicylic acid and **b** aspirin

supramolecular arrangement is further characterized by an intramolecular hydrogen bond between the hydroxyl and carboxylic groups forming a *S*(6) synthon [30–32] (Fig. 2c). All these features lead to a less flexible molecule with reduced intermolecular hydrogen-bonding capacity, which likely explains the low tendency for polymorphism, as opposed to its isomers, *p*- and *m*-hydroxybenzoic acids [3, 33].

Two ammonium salts [34, 35] and five new aspirin multicomponent crystal forms have been reported: with 5-methoxysulfadiazine (1:1) [27], sulfadimidine (1:1) [28], carbamazepine [24, 36], DABCO [37], and D-theanine [38]. In all of them aspirin synthons were disrupted due to the formation of O–H···O, N–H···O, and/or N–H···N interactions with the co-formers.

Also several multicomponent crystal forms of salicylic acid have been reported [37, 39–53] with several co-formers such as meloxicam [42], temozolomide [43], carbamazepine [45, 46], theophylline [47], caffeine [48, 49], creatinine [50], as well as some $\beta$-cyclodextrine clathrates [54]. In most of these forms, the formation of ring synthons is common, except in the salt examples where the deprotonation of the carboxylic group makes it much more unlikely.

Taking this into consideration, we decided to further search for new multicomponent forms of aspirin using mono-, di-, and tricarboxylic acids and aminoacids as co-formers. In these studies, besides the intended supramolecular rearrangements, we have also induced traditional covalent reactions, yielding new multicomponent crystal forms of salicylic acid.

## Results and discussion

Polymorphic and multicomponent crystal form screenings of both aspirin and salicylic acid have been extensively reported previously. To expand these studies we decided to attempt the co-crystallization of aspirin with mono-, di-, and tricarboxylic acids and aminoacids, but these efforts were unsuccessful. Instead, we induced aspirin's in situ decomposition into salicylic acid when doing a salt screening in basic pH media. Two concomitant new multicomponent forms were obtained: an ammonium salt[1] with a supramolecular anion[2] formed by salicylic acid and salicylate (**1**) and a molecular salt (see footnote 1) between salicylate and 2-methyl-4-oxopentan-2-aminium (**2**). These crystal forms were structurally characterized, but as they were always concomitantly obtained (Fig. 3), we were unable to further characterize their separate thermal behavior and stability. Graph-set notation will be used to characterize the description of these novel crystal forms [58].

### Salicylic acid:salicylate ammonium salt, 1

The asymmetric unit of the ammonium salt consists on one neutral molecule of salicylic acid, one salicylate anion, and one ammonium cation (Fig. 4). The anionic nature of the salicylate was determined by the C–O distances [59] [1.272(2) and 1.267(2) Å] and confirmed by the location of all four hydrogen atoms from electron density map around the nitrogen. This crystal form of global formula $[NH4]^{+}\cdot[(SA)(HSA)]^{-}$ is a salt in which the anion is actually a supramolecular anion (see footnote 2) formed between neutral and deprotonated salicylic acid, having direct intermolecular hydrogen-bonding between them.

Both salicylic acid and salicylate display intramolecular *S*(6) interactions via $O–H_{OH}\cdots O_{COOH}$ [2.641(4) Å] and $O–H_{OH}\cdots O_{COO}–$ [2.513(4) Å], respectively. In the crystal packing we find no direct contacts between symmetry equivalent fragments. Salicylic acid interacts with the salicylate by both the hydroxyl and carboxyl groups [$O–H_{OH}\cdots O_{COO}–$ 2.974(5) Å and $O–H_{COOH}\cdots O_{COO}–$ 2.597(4) Å] and connects with the ammonium cations through $N–H\cdots O_{COOH}$ interactions [$N–H\cdots O_{COOH}$ 3.141(6) Å]. The salicylate is further hydrogen-bonded to the cations by two $N–H\cdots O_{COO}–$ [3.226(6), 2.732(5), and 2.859(6) Å] and one $N–H\cdots O_{OH}$ [2.934(6) and 2.964(6) Å]. Thus each ammonium cation connects to four salicylates and one salicylic acid molecule. A layer is formed in the *ab* plane, where tapes of alternated salicylic acid and salicylate are assisted by the ammonium cations that lie in the space between them (Fig. 5). Details on the hydrogen bonds present **1** are given in Table 1.

The direct interactions between salicylic acid···salicylate were not seen in the salt reported by Downie and Speakman [34] where both entities interact directly with the ammonium cation and water molecules. The $N–H\cdots O_{COO}–$ and $N–H\cdots O_{OH}$ depicted in the salt reported herein are similar to the ones reported in the two ammonium salts previously reported [34, 35].

[1] We have used a long-used definition of salts (inorganic counterion) versus molecular salt (organic counterion) [55, 56].

[2] We have used the definition of supramolecular anion when referring to a supramolecular aggregate that as a whole has a negative charge, as used by Braga and co-workers [57].

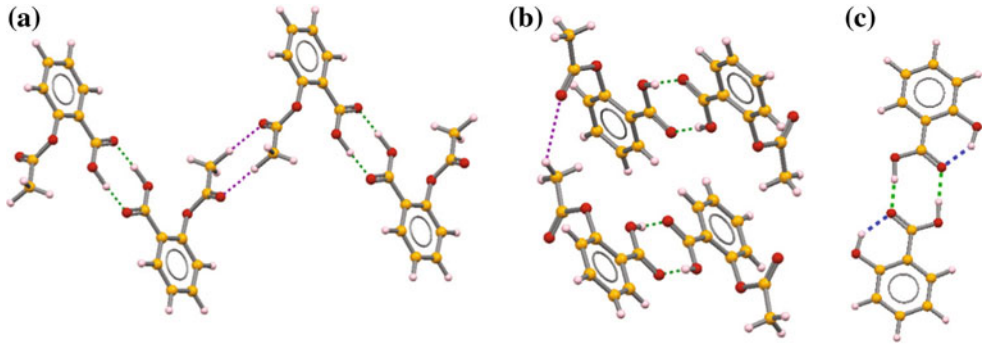



**Fig. 2** **a** Aspirin polymorph I: $\mathbf{R}_2^2$ synthon formed by the carboxylic groups (*green*) and $\mathbf{R}_2^2$ synthon formed by the C–H···O interactions (*purple*); **b** Aspirin polymorph II: $\mathbf{R}_2^2$ synthon formed by the carboxylic groups (*green*) and C–H···O interactions (*purple*) giving rise to catemeric chains; **c** salicylic acid $\mathbf{R}_2^2$ synthon formed by the carboxylic moiety (*green*) and the *S*(6) synthon (*blue*) (Color figure online)

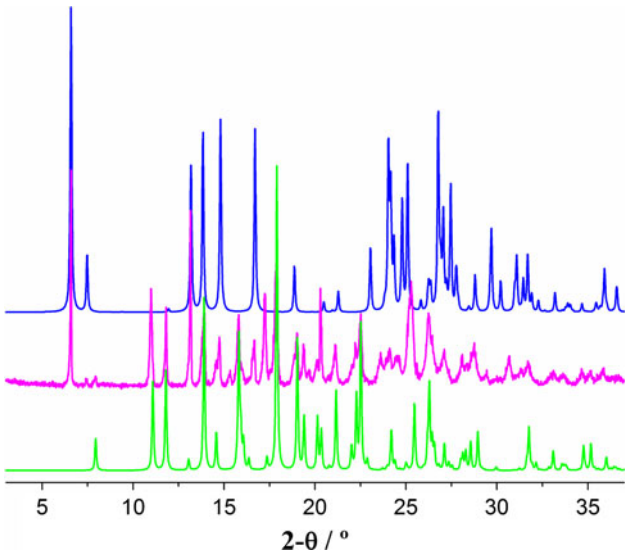



**Fig. 3** Experimental powder diffraction pattern obtained for the bulk sample at 293 K (*pink*) and calculated powder diffraction patterns for **1** (*blue*) and **2** (*green*) at 150 K, showing that the bulk obtained is a mixture of both forms (Color figure online)

## Salicylate:2-methyl-4-oxopentan-2-aminium molecular salt, 2

The asymmetric unit of this crystalline consists of one salicylate and one 2-methyl-4-oxopentan-2-aminium cation (Fig. 6). The assessment of the molecular salt nature was done both by the analysis of the C–O distances (1.260(3) and 1.252(3) Å) in the carboxylate moiety and the location of three hydrogen atoms on the nitrogen from the electron density map.

The 2-methyl-4-oxopentan-2-aminium cation is formed in situ by a sequence of reactions: (i) imine formation that acetone is known to undergo under basic pH conditions; (ii) nucleophilic attack giving rise to 4-amino-4-methyl-pentan-2-one; and (iii) 4-amino-4-methylpentan-2-one protonation (Scheme I).

Both the salicylate and the 2-methyl-4-oxopentan-2-aminium cation display intramolecular interactions: $O-H_{OH}\cdots O^{-}_{COO}-\left[2.502(3)\text{Å}\right]$ in the first case and $N^{+}$–H···$O_{CO}$ [2.811(4) Å] for the cation (Fig. 7).

2-Methyl-4-oxopentan-2-aminium cations build pairs via $N^{+}$–H···$O_{CO}$ [2.905(4) Å] interactions that give rise to $\mathbf{R}_2^2(\mathbf{4})$ synthons. Furthermore, each cation connects with two different anions through different $N^{+}$–H···$O_{COO}$– [2.757(4) and 2.775(4) Å] hydrogen bonds forming tetramers based on $\mathbf{R}_4^2(\mathbf{8})$ motifs. There are no direct interactions between salicylates. These interactions give rise to chains that grow along the *a* axis (Fig. 7; Table 1).

## Experimental

### Synthesis

Reagents and solvents were acquired from Sigma-Aldrich.

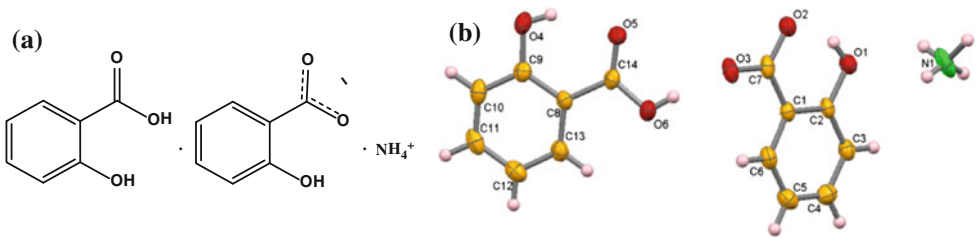



**Fig. 4** **a** $[NH4]^{+}.[(SA)(HSA)]^{-}$ salt, **1**; **b** molecular diagram of **1**. Ellipsoids are set at 50 % probability

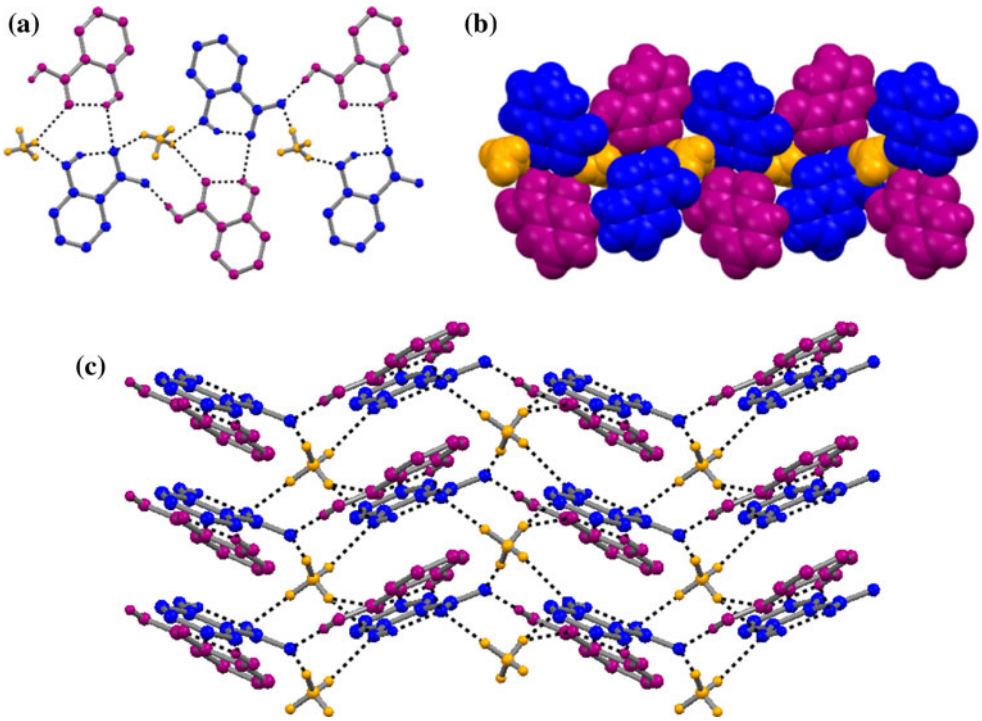



**Fig. 5** Crystal packing of **1** depicting **a** tapes formed by salicylic acid (*purple*) and salicylate (*blue*) assisted by the ammonium cations (*yellow*) in a view along *a*; **b** space filling representation of the tapes; **c** the tapes assisted by the ammonium cations in a view along *c*. Hydrogen atoms not involved in hydrogen-bonding are not displayed for clarity (Color figure online)

**Table 1** Hydrogen bond details for **1** and **2**

| Structure | Sym. op. | D–H···A | d(D–H) (Å) | d(H···A) (Å) | d(D···A) (Å) | (DĤA) (°) |
|---|---|---|---|---|---|---|
| **1** | $x, y, z$ | $O-H_{OH}\cdots O^{-}_{COO}-$ | 0.82 | 1.78 | 2.513(4) | 148 |
| | $-1+x, y, z$ | $N^{+}-H\cdots O_{OH}$ | 0.78(4) | 2.22(4) | 2.934(6) | 153(4) |
| | $1-x, -1/2+y, 1/2-z$ | $N^{+}-H\cdots O^{-}_{COO}-$ | 1.06(4) | 2.58(4) | 3.226(6) | 119(3) |
| | $1-x, -1/2+y, 1/2-z$ | $N^{+}-H\cdots O^{-}_{COO}-$ | 1.06(4) | 1.68(4) | 2.732(5) | 173(3) |
| | $2-x, -1/2+y, 1/2-z$ | $N^{+}-H\cdots O^{-}_{COO}-$ | 0.98(5) | 2.01(4) | 2.859(6) | 144(4) |
| | $x, y, z$ | $O-H_{COOH}\cdots O_{COOH}$ | 0.82 | 1.93 | 2.641(4) | 145 |
| | $1-x, -1/2+y, 1/2-z$ | $O-H_{OH}\cdots O^{-}_{COO}-$ | 0.82 | 2.44 | 2.974(5) | 124 |
| | $x, y, z$ | $N^{+}-H\cdots O_{OH}$ | 0.86(5) | 2.30(4) | 2.964(6) | 134(3) |
| | $1-x, 1/2+y, 1/2-z$ | $N^{+}-H\cdots O_{COOH}$ | 0.86(5) | 2.49(4) | 3.141(6) | 133(4) |
| | $-1+x, -1+y, z$ | $O-H_{COOH}\cdots O^{-}_{COO}-$ | 0.82 | 1.78 | 2.597(4) | 176 |
| **2** | $1-x, 1-y, 1-z$ | $N^{+}-H\cdots O^{-}_{COO}-$ | 0.99(3) | 1.84(3) | 2.775(4) | 158(3) |
| | $x, y, z$ | $O-H_{OH}\cdots O^{-}_{COO}-O-H_{OH}\cdots O^{-}_{COO}-$ | 0.82 | 1.77 | 2.502(3) | 148 |
| | $x, y, z$ | $N^{+}-H\cdots O^{-}_{COO}-$ | 0.98(3) | 1.79(3) | 2.757(4) | 173(3) |
| | $x, y, z$ | $N^{+}-H\cdots O_{CO}$ | 0.94(3) | 2.16(3) | 2.811(4) | 125.6(8) |
| | $-x, 1-y, 1-z$ | $N^{+}-H\cdots O_{CO}$ | 0.94(3) | 2.21(3) | 2.905(4) | 130(2) |

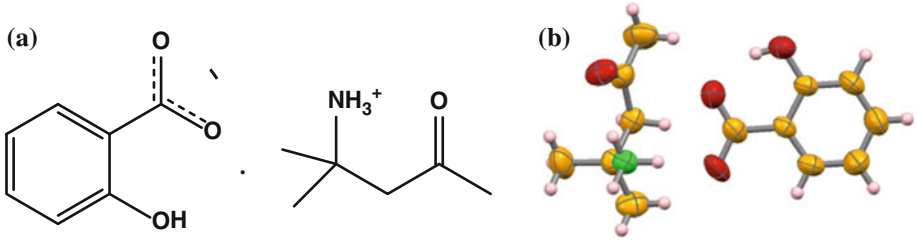
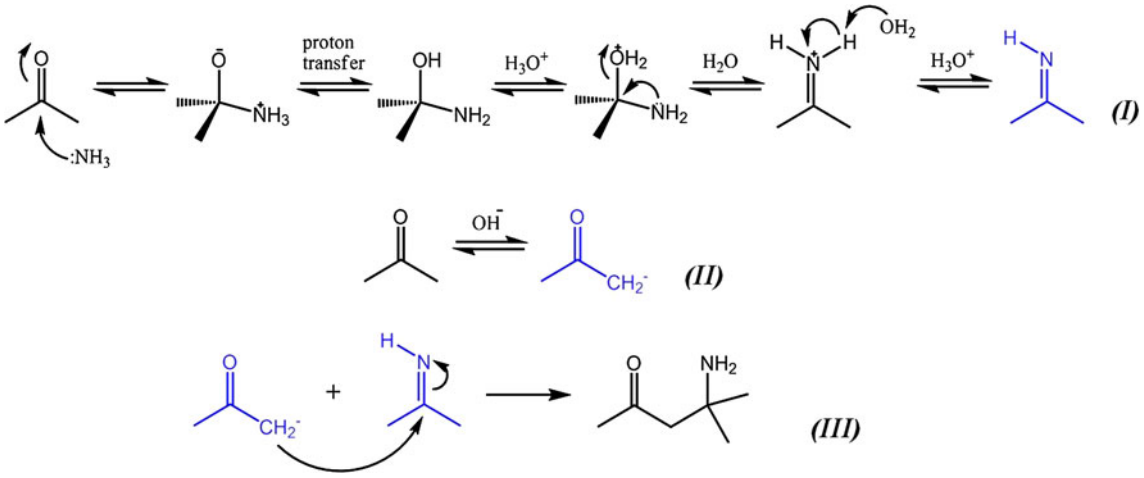



**Fig. 6** **a** Salicylate:2-methyl-4-oxopentan-2-aminium molecular salt, **2**; **b** molecular diagram of **2**. Ellipsoids are set at 50 % probability




**Scheme 1** General mechanisms for (I) imine formation; (II) deprotonation of acetone α-carbon; and (III) nucleophilic attack to the imine giving rise to 4-amino-4-methylpentan-2-one

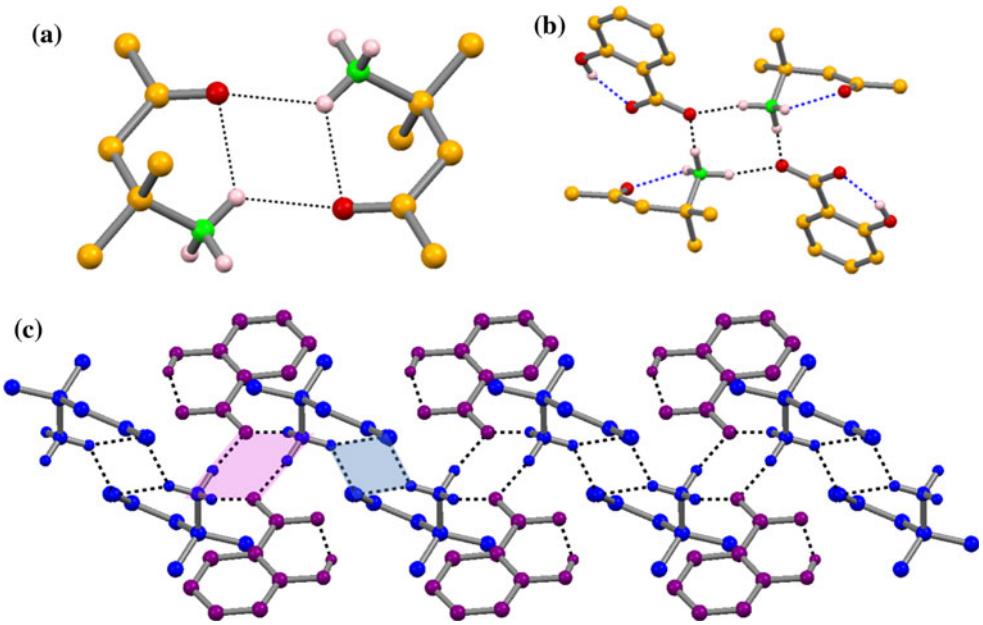



**Fig. 7** Crystal packing of **2** depicting **a** the $\mathbf{R}_2^2(\mathbf{4})$ synthons formed by pairs of 2-methyl-4-oxopentan-2-aminium cations; **b** the tetramers formed by $\mathbf{R}_2^2(\mathbf{8})$ synthons between two cation–anion pairs and the intramolecular interactions shown in *blue*; **c** chain of cations and anions based on the previously mentioned $\mathbf{R}_2^2(\mathbf{4})$ (*blue*) and $\mathbf{R}_2^2(\mathbf{8})$ (*purple*) synthons growing along *a*. Hydrogen atoms not involved in hydrogen-bonding were omitted for clarity (Color figure online)

50 mg of aspirin was dissolved in a 1:1 blend of ammonia and acetone. The solution was left to crystallize at room temperature and after 3 days colorless crystals of **1** (needle) and **2** (plate) were concomitantly formed in similar proportion.

## Characterization

### *Single-crystal X-ray diffraction*

X-ray data were collected at 150 K on a Bruker AXS-KAPPA APEX II diffractometer. Bruker AXS-KAPPA APEX II diffractometer with graphite-monochromated radiation (Mo Kα, $\lambda = 0.71069$ Å). The X-ray generator was operated at 50 kV and 30 mA and the X-ray data collection was monitored by the APEX2 program. All data were corrected for Lorentzian, polarization and absorption effects using SAINT [60] and SADABS [61] programs. Crystals suitable for X-ray diffraction study were mounted on a loop with Fomblin© protective oil.

SIR97 [62] and SHELXS-97 [63] were used for structure solution and SHELXL-97 [63] was used for full-matrix least-squares refinement on $F^2$. These three programs are included in the package of programs WINGX-Version 1.80.05 [64].

**Table 2** Crystallographic details for **1** and **2**

| | **1** | **2** |
|---|---|---|
| Chemical formula | $C_7H_6O_3{\cdot}C_7H_5O_3{\cdot}NH_4$ | $C_7H_5O_3{\cdot}C_6H_{14}NO$ |
| $M_r$ | 293.27 | 253.29 |
| Temperature (K) | 150(2) | 150(2) |
| Wavelength (Å) | 0.71069 | 0.71069 |
| Morphology, color | Needle, colorless | Plate, colorless |
| Crystal size (mm) | 0.2 × 0.04 × 0.02 | 0.2 × 0.1 × 0.04 |
| Crystal system | Monoclinic | Monoclinic |
| Space group | $P2_1/c$ | $P2_1/c$ |
| $a$ (Å) | 3.857(7) | 7.504(6) |
| $b$ (Å) | 13.171(6) | 8.545(4) |
| $c$ (Å) | 26.849(3) | 22.273(4) |
| $a$ (°) | 90 | 90 |
| $b$ (°) | 91.393(3) | 92.897(2) |
| $g$ (°) | 90 | 90 |
| $V$ (Å$^3$) | 1364(3) | 1426.4(13) |
| $Z$ | 4 | 4 |
| Calculated density (Mg m$^{-3}$) | 1.429 | 1.180 |
| Absorption coefficient (mm$^{-1}$) | 0.113 | 0.087 |
| Reflections collected/ unique | 13048/2756 | 11036/2694 |
| $R_{int}$ | 0.1 | 0.0653 |
| GoF | 0.895 | 0.932 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1 = 0.0505$, $wR_2 = 0.0991$ | $R_1 = 0.0517$, $wR_2 = 0.1156$ |

MERCURY 3.0 [65] was used for packing diagrams. PLATON [66] was used for hydrogen bond interactions. Crystallographic details for **1** and **2** are given in Table 2.

Non-hydrogen atoms were refined anisotropically using a full-matrix least-squares refinement. All the hydrogen atoms were inserted in idealized positions and allowed to refine riding in the parent carbon atom, except for those bonded to the N atoms, which were located in a difference map.

*X-ray powder diffraction*

Data were collected in a D8 Advance Bruker AXS $\theta - 2\theta$ diffractometer, with a copper radiation source (Cu K$\alpha$, $\lambda = 1.5406$ Å) and a secondary monochromator, operated at 40 kV and 30 mA.

The program Mercury 3.0 [65] was used for calculation of X-ray powder patterns on the basis of the single-crystal structure determinations. The identity of single crystals and the bulk material obtained from solution and grinding/kneading experiments was always verified by comparison of the calculated and observed X-ray powder diffraction patterns.

## Conclusions

In this study we demonstrated that aspirin tends to decompose into salicylic acid in high pH (basic) environments. Furthermore, multicomponent crystal forms with salicylic acid were easily formed.

As mentioned in the introduction, several multicomponent crystal structures with aspirin have been reported [67] as well as several salicylic acid co-crystals [37, 39–46, 48–54, 68]. From a Cambridge Structural Database [69] survey including multicomponent forms of salicylates and organic cations containing amines presented in supplementary information (Tables S1, S2), we observed that the typical $\mathbf{R_2^2(8)}$ homosynthon is commonly disrupted by direct anion–cation interactions of the type $N^+$–H···O/$O^-$, considering from primary to aromatic amines. This is also observed in both forms discussed herein, where the $N^+$–H···O/$O^-$ interactions play a main role, forming different ring synthons. Also due to the presence of charges in **1** and **2**, most of the hydrogen-bond interactions are charge-assisted which reinforces the supramolecular arrangements, like those found in the survey. The intramolecular $S(6)$ synthon is never disrupted, indicating that it is a very strong intramolecular hydrogen bond, which may be one of the causes for the lack polymorphs of salicylic acid. This synthon is also present in most of the structures analyzed in the survey reinforcing its strength.

## Supporting information

The crystal structures reported in the manuscript entitled "Transforming aspirin into novel molecular salts of salicylic acid," authored by Vânia André, Inês Martins, Sílvia Quaresma, Marta Martins and M. Teresa Duarte, have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers: CCDC 914535 and CCDC 914536.

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