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PAPER

Influence of impurities on the crystallisation of 5-X-aspirin and 5-X-aspirin anhydride polymorphs (X = Cl, Br, Me)†

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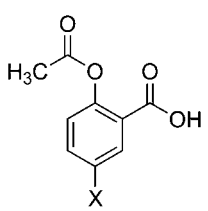
Crystallisation of 5-X-aspirin (X = Cl, Br) by ambient evaporation from organic solvents commonly yields a mixture of polymorphs I and II for X = Cl, but only polymorph I for X = Br. Addition of 5-X-aspirin anhydride (5–20 mol %) leads to sole production of polymorph II for X = Cl, and new production of polymorph II for X = Br. Slurry experiments show that polymorph I transforms to polymorph II for X = Cl, while polymorph II transforms to polymorph I for Br. Thus, addition of the anhydride during crystallisation apparently accelerates the I → II transformation for X = Cl, and inhibits the II → I transformation for X = Br. 5-X-Aspirin anhydride can be produced as a by-product during heating of 5-X-aspirin in organic solvents, or during synthesis from 5-X-salicylic acid, and the duration of the heating step in such a synthesis can therefore change the polymorphic form of the synthesised product. The 5-X-aspirin anhydrides (X = Cl, Br, Me) are also polymorphic. Crystallisation of the pure compound from organic solvents yields only polymorph I, while polymorph II can be obtained by heating in ethanol or acetone. For X = Cl or Br, the heating step produces significant quantities of 5-X-aspirin *in situ*, while for X = Me, it is necessary also to add 5-X-aspirin (5–20 mol %) to obtain polymorph II.

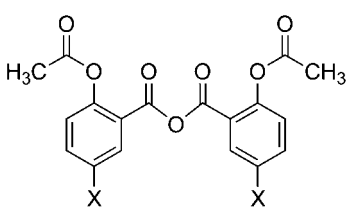
Introduction

Polymorphism is an intensely studied phenomenon that is relevant to any application area of crystalline molecular materials,[1] including notably the pharmaceutical industry.[2] To establish control over polymorphism in a general sense, the mechanisms of nucleation and crystal growth must be better understood at a molecular level, including specifically the way in which polymorphism emerges during these processes. A guiding principle is Ostwald's rule of stages,[3,4] which states that a system leaving one state and transforming to another seeks out the next least stable state rather than the thermodynamically most stable state. Although exceptions are known,[4] this guideline has provided a basis to control polymorphism during solution crystallisation of some compounds. For example, the metastable α polymorph of L-glutamic acid can be stabilised in a saturated glutamic acid solution for weeks in the presence of trimesic acid. The α form crystallises first from solution, then the additive decreases the rate of transformation to the more stable β form by binding selectively to β crystals, thereby slowing their growth.[5] Compounds that interact specifically with growing crystals in this way are referred to as "tailor-made additives/auxiliaries".[6,7]

We have studied in detail the polymorphism of aspirin.[8–11] The compound is quite unusual in that it can crystallise as an "intergrown" form containing domains with two distinct polymorphic structures, and we have reported that domains of the second aspirin polymorph can be introduced by crystallisation of aspirin in the presence of aspirin anhydride.[10] The anhydride apparently acts to inhibit solution-mediated transformation of the metastable form II to the more stable form I. An important chemical aspect of this observation is that aspirin anhydride is a common by-product of aspirin synthesis, and it can also be formed in significant quantities when aspirin is heated in various organic solvents.[12–14] The possibility to create the polymorph-inducing anhydride during synthesis or under common crystallisation conditions can lead to erratic crystallisation behaviour, which possibly accounts to some extent for the long-term uncertainty that was associated with aspirin polymorphism.[13,15–20]



5-X-A



5-X-AA

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† Electronic supplementary information (ESI) available: Details of PXRD and ^{13}C analyses. CCDC reference numbers 823448, 823449, 823451–823454, 823456 and 823457. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ce06065a

With the realisation that the polymorphism of aspirin can be influenced by the presence of aspirin anhydride during crystallisation, we set out to test whether this might also be the case for other aspirin derivatives. Specifically, we consider here 5-X-aspirin (**5-X-A**), with X = Cl, Br or Me. Crystal structures have been reported for these compounds by Hursthouse and co-workers,[21] and we refer to the published structures as **5-X-A** form I. Compounds **5-Cl-A** and **5-Br-A** are isostructural, while the structure of **5-Me-A** is different. Hursthouse *et al.* have also observed polymorphism for **5-Cl-A**,[22] and we refer to this second polymorph as form II. Our interest here is to examine the possible influence of 5-X-aspirin anhydride (**5-X-AA**) on the crystallisation of **5-X-A**.

We consider principally two routes: (i) specific synthesis and isolation of **5-X-AA**, followed by its controlled addition to solution crystallisation of **5-X-A**; (ii) *in situ* production of **5-X-AA** during heating of **5-X-A** in organic solvents, especially in acetic anhydride during synthesis from 5-X-salicylic acid. The *in situ* methods are of particular interest because they represent circumstances where **5-X-AA** might be prepared inadvertently during common synthesis or crystallisation protocols.

Experimental

Synthesis of 5-X-aspirin

5-X-aspirin (X = Cl, Br, Me) was synthesized from 5-X-salicylic acid (purchased from Sigma Aldrich) and acetic anhydride in the presence of H_2SO_4. 5-X-salicylic acid (0.018 mol) was mixed with acetic anhydride (0.04 mol) and conc. H_2SO_4 (0.5 ml), and the mixture was heated at 60 °C for 20 mins. The solution was then cooled in an ice bath and H_2O (40 ml) was added. The resulting precipitate was isolated by filtration and recrystallised from acetone.

Synthesis of 5-X-aspirin anhydride

5-X-aspirin anhydride (X = Cl, Br, Me) was synthesized from 5-X-aspirin and *N,N′*-dicyclohexylcarbodiimide (DCC). 5-X-aspirin (0.04 mol) was dissolved in cold acetone (30 ml) and mixed with DCC (0.02 mol) dissolved in cold acetone (15 ml). The mixture was stirred for 1 hour in an ice bath, then kept overnight in a refrigerator at 4 °C. A white precipitate of dicyclohexylurea was filtered off and the solvent was evaporated under vacuum to give the crude anhydride product as an oil. A crystalline product could be obtained from hot ethanol or methanol.

Characterisation methods

Single-crystal X-ray diffraction data were collected on a Bruker-Nonius X8-APEXII CCD diffractometer using graphite-monochromated MoKα radiation (λ = 0.7107 Å). Powder X-ray diffraction data were recorded under ambient conditions on a Siemens D5000 instrument in Bragg-Brentano geometry using Ge(111)-monochromated CuKα radiation (λ = 1.5406 Å). ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature with a Bruker Avance III (100 MHz) instrument, using the solvent as an internal standard.

Results and discussion

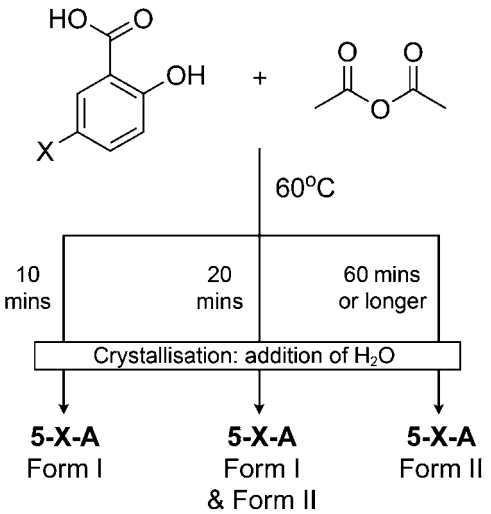
Crystallisation of 5-Cl-A

For **5-Cl-A**, polymorphism is evident for crystallisation of the pure compound by slow evaporation from various organic solvents under ambient conditions. Commonly, we obtained mixtures of forms I and II from a given crystallisation trial, except on crystallisation from 2-propanol and acetonitrile, for which only form II was obtained. Slurrying experiments establish that form I transforms to form II in contact with a saturated solution of **5-Cl-A** in various organic solvents, with the transformation typically taking place over a period of hours to days, and with the fastest transformations occurring in acetonitrile and 2-propanol (see PXRD data in ESI†). Thus, the frequent observation of mixtures of polymorphs (concomitant polymorphism) for **5-Cl-A** during crystallisation by slow evaporation corresponds to interrupted solvent-mediated transformation of I → II, and the isolation of form II alone from 2-propanol or acetonitrile is consistent with these solvents facilitating the most rapid transformation.

Deliberate addition of **5-Cl-AA** to the crystallisations did not alter the outcome, except that it appeared to accelerate the I → II transformation. In the absence of **5-Cl-AA**, the first-appearing crystals are always form I, and these crystals transform to form II within *ca* 3 days in the solvent under ambient conditions. In the presence of **5-Cl-AA**, however, the first crystals that can be isolated are always form II. Thus, crystallisation conditions that frequently produced bulk mixtures of forms I and II in the absence of **5-Cl-AA** produced only form II when **5-Cl-AA** was present. Similarly, during synthesis of **5-Cl-A** by acetylation of 5-Cl-salicylic acid in acetic anhydride (Scheme 1), the polymorph formed on direct precipitation of the synthesis mixture was found to be dependent on the duration of the synthesis heating step: heating for 10 mins produced only form I, heating for 20 mins produced a mixture of forms I and II, and heating for 60 minutes or longer produced only form II. This reflects an increasing production of **5-Cl-AA** during heating, evident from ^{13}C NMR (see ESI†). The outcome is also crucially dependent on the quantity of acid that may be added. Smaller quantities of acid provide form II, while greater quantities provide form I. This arises because aspirin anhydride is hydrolysed rapidly under acidic conditions.

Crystallisation of 5-Br-A

Crystallisation of **5-Br-AA** by evaporation from numerous organic solvents under ambient conditions always produced only form I. However, form II could be obtained by addition of **5-Br-AA** (in the range 5–20 mol %) to the crystallisations under ambient conditions, as confirmed by measured unit-cell parameters for single crystals, and PXRD of the bulk (see ESI†). Form II could also be obtained by heating **5-Br-A** in acetic anhydride to prepare **5-Br-AA** *in situ*. For this system, slurrying experiments establish that form II undergoes solvent-mediated transformation to form I, opposite to the situation in **5-Cl-A**. Comparative experiments establish also that the transformation rate for **5-Br-A** in a given solvent is faster than for **5-Cl-A**. The isolation of only form I during evaporation crystallisation of pure **5-Br-A**, rather than the concomitant polymorphism



Scheme 1 Summary of synthesis conditions and polymorphs produced for acetylation of 5-X-salicylic acid. Addition of acid to the synthesis can also influence the polymorphic outcome (see text).

frequently observed for **5-Cl-A**, is consistent with this more rapid solvent-mediated II → I transformation. The presence of **5-Br-AA** during crystallisation apparently acts to inhibit the II → I transformation, thereby allowing form II to be isolated.

Structures of the 5-X-A polymorphs (X = Cl, Br)

Crystallographic information for the **5-X-A** polymorphs is summarised in Table 1. Except for **5-Br-A** form II, the structures have been reported previously by Hursthouse and co-workers.[21] Form II of **5-Br-A** is isostructural with form II of **5-Cl-A**, so that the **5-X-A** polymorphs comprise two isostructural sets. The structures contain comparable 2-D layers of hydrogen-bonded dimers (horizontal in Fig. 1). The distinction between them is that the orientation of the neighbouring layer in form II is reflected with respect to that in form I, the mirror plane being perpendicular to the *c* axis of form II (vertical in Fig. 1).

On the mode of action of 5-X-AA

The preceding experimental observations are consistent with a structure-based mechanism for the action of **5-X-AA**. Given that forms I and II of **5-X-A** (X = Cl, Br) comprise two isostructural sets, it is reasonable to assume that any preferential interaction of **5-X-AA** with growing crystals of one of the two polymorphs should be comparable in both systems. The experimental observations are consistent with **5-X-AA** inhibiting the growth of form I. For X = Br, form I appears after solvent-mediated transformation of form II, and the impurity thereby facilitates isolation of form II in the manner typical of a tailor-made additive. Since the rate of the II → I transformation in these systems is relatively fast compared to the rate of solvent evaporation, the impurity serves to provide a polymorph that is not otherwise seen during evaporation crystallisation under ambient conditions. For X = Cl, the order of appearance of the polymorphs from solution is reversed so that **5-X-AA** inhibits growth of the crystals that would otherwise appear first. The result is that form II is isolated alone from crystallisations that otherwise yield the concomitant presence of forms I and II.

Crystallisation of 5-Me-AA

To date, we have not observed polymorphism for **5-Me-A**. However, whilst attempting to prepare the anticipated **5-Me-A** form II by heating in acetic anhydride, we identified two polymorphs for the anhydride **5-Me-AA** (Table 2). Initially, we isolated single crystals of a monoclinic form (denoted **5-Me-AA** form II). When the reaction mixture was left to stand for several days, crystals of a triclinic form (denoted form I) appeared. Forms I and II were readily distinguished by their habits, being needles and blocks, respectively. The bulk sample after

Table 1 Crystallographic data for the polymorphs of **5-X-A** (X = Cl, Br, Me)

	Cl (Form I)[a]	Br (Form I)[a]	Me [b]	Cl (Form II)	Br (Form II)
CCDC	NUWTOP	NUWTIJ	NUWVEH	823448	823449
Formula	$C_9H_7ClO_4$	$C_9H_7BrO_4$	$C_{10}H_{10}O_4$	$C_9H_7ClO_4$	$C_9H_7BrO_4$
Formula weight	214.60	259.06	194.18	214.60	259.06
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/n$	$P2_1/c$	$P2_1/c$
T/K	120	120	120	150	150
a/Å	10.1217(4)	10.3912(4)	10.1301(3)	5.0838(4)	5.0940(2)
b/Å	4.7359(1)	4.7265(1)	4.8831(1)	17.9622(15)	17.8642(7)
c/Å	19.4447(7)	19.5116(9)	18.9682(7)	10.4409(7)	10.6736(4)
α/°	90	90	90	90	90
β/°	96.219(2)	96.383(2)	100.696(2)	98.445(3)	98.935(2)
γ/°	90	90	90	90	90
Volume/Å^3	926.60(5)	952.35(6)	921.98(5)	943.09(13)	959.51(6)
Z	4	4	4	4	4
Reflns collected				12316	7302
Unique reflns				1659	1666
R_{int}				0.030	0.023
Obs refln ($I>2\sigma(I)$)				1425	1505
*R*1 ($I>2\sigma(I)$)				0.031	0.020
*wR*2 (all data)				0.086	0.052
GOF on F^2				1.05	1.03

[a] Data taken from ref. 21. [b] Polymorphism has not been observed to date for X = Me.

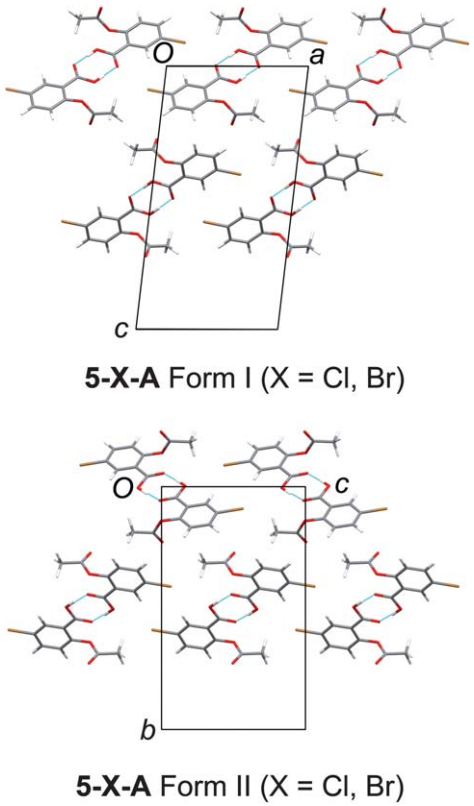


Fig. 1 Crystal structures of **5-X-A** (X = Cl, Br) forms I and II. The structures contain comparable layers of hydrogen-bonded dimers (horizontal).

evaporation to dryness was shown by PXRD to contain a significant quantity of **5-Me-A** (see ESI†). For pure samples of **5-Me-AA** prepared by independent synthesis (using the method described in the Experimental section), crystallisation from various organic solvents yielded only form I, therefore suggesting that form II might be prepared only in the presence of **5-Me-A**. Systematic addition of **5-Me-A** did not in fact have any influence on the crystallisation of **5-Me-AA** under ambient conditions, but form II could be obtained reproducibly by refluxing **5-Me-AA** in ethanol or acetone with the concurrent addition of 10 mol % of **5-Me-A**. Reflux without addition of **5-Me-A** yielded only form I (*i.e.* the varying crystallisation outcome is not solely attributable to temperature), while addition of larger amounts of **5-Me-A** yielded form II together with crystalline **5-Me-A** after evaporation to dryness. Slurrying experiments confirmed that form II of **5-Me-AA** transforms rapidly to form I in organic solvents, so that the presence of **5-Me-A** during reflux in ethanol or acetone serves apparently to stabilise the first-appearing **5-Me-AA** polymorph II.

Crystallisation of 5-X-AA (X = Cl, Br)

Extension of these results to **5-X-AA** with X = Cl and Br also yielded two polymorphs for these compounds (Table 2).‡ The orthorhombic forms (which are isostructural, denoted form I) were obtained on crystallisation from organic solvents under ambient conditions, while the monoclinic forms (which are not isostructural, denoted form II) could be obtained by reflux in acetic anhydride or ethanol, in this case without any requirement to add **5-X-A**. The fact that **5-X-A** is generated *in situ* during heating is apparent from PXRD of the bulk products, which clearly contain crystalline **5-X-A** (see ESI†). In this case, an explicit link between the observed polymorphism and the presence of **5-X-A** is less clear, however, since heating cannot be decoupled from the generation of **5-X-A**, *i.e.* it is not possible to heat **5-X-AA** without introducing significant amounts of **5-X-A**. It is also quite difficult to obtain pure samples of **5-X-AA** (X = Cl, Br), since some decomposition to **5-X-A** is invariably observed. For **5-Me-AA**, the situation is different because it is the most stable of the anhydrides in solution, so that the amount of **5-Me-A** generated on heating is much less than the amounts of **5-Cl-A** or **5-Br-A** generated from **5-Cl-AA** or **5-Br-AA** under the same conditions.

Structures of the 5-X-AA polymorphs (X = Cl, Br, Me)

In form I of **5-Me-AA** (Fig. 2), the molecules adopt a conformation where the planes of the aromatic rings are essentially perpendicular. Face-to-face intermolecular interactions between rings link the molecules into columns along the *c* axis. Between columns, centrosymmetric C–H···O motifs exist between acetyl groups, comparable to those in aspirin form I.[23] In **5-Me-AA** form II, the molecules adopt a flatter conformation, in which the angle between the planes of the aromatic rings is *ca* 70°. The rings form edge-to-face contacts between molecules, and layers can be envisaged in the *bc* plane (horizontal in Fig. 2). There are two distinct interlayer regions (central in Fig. 2, and between the upper and lower boundaries of the unit cell). Both contain C–H···O contacts formed from the aromatic rings to the acetyl groups, while one of them (central in Fig. 2) also contains catemeric C–H···O motifs between acetyl groups, comparable to those in aspirin form II.[9]

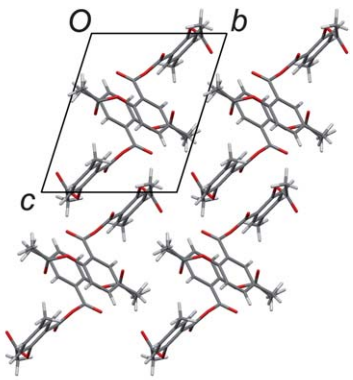
For **5-Cl-AA** and **5-Br-AA**, form I is isostructural. The molecular conformation is comparable to that in **5-Me-AA** form I, except that one of the acetyl groups points in the opposite direction with respect to the remainder of the molecule. The structure contains face-to-face contacts between aromatic rings of neighbouring molecules along the *b* axis, but these are distorted to accomodate other interactions, particularly that between the acetyl group and the central O atom of a neighbouring molecule. The columns along the *b* axis can be envisaged to form 2-D sections in the *ab* planes, with neighbouring molecules forming C–H···O contacts between the aromatic rings and the carbonyl groups of the anhydride unit, and with one C–Cl bond directed towards the centroid of a neighbouring aromatic ring. This description of layers in the *ab* planes highlights similarity with **5-Cl-AA** form II (Fig. 4), which contains closely comparable 2-D sections. In both **5-Cl-AA** polymorphs, the principal contacts between layers are C–H···O contacts between the aromatic rings and the acetyl groups. The distinction between the polymorphs is that the orientation of the neighbouring layer in form II is reflected with respect to that in form I, the mirror plane being perpendicular to the *a* axis. The structures therefore look essentially identical in projection along *a* (Figs. 3 and 4).

‡ Crystallisation from acetonitrile produced needle crystals of a solvate **5-X-AA**·CH_3CN, for X = Cl and Br. The crystals lose solvent rapidly and to date we have obtained only poor quality X-ray crystal structures.

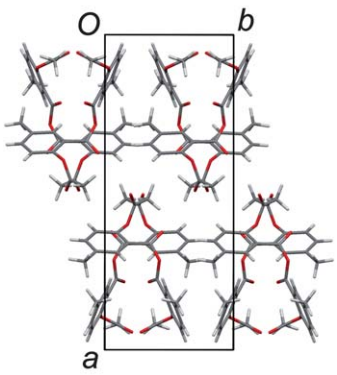
Table 2 Crystallographic data for the polymorphs of **5-X-AA** (X = Cl, Br, Me)

	Cl (Form I)	Br (Form I)	Me (Form I)	Cl (Form II)	Br (Form II)	Me (Form II) [a]
CCDC	823451	823453	823456	823452	823454	823457
Formula	$C_{18}H_{12}Cl_2O_7$	$C_{18}H_{12}Br_2O_7$	$C_{20}H_{18}O_7$	$C_{18}H_{12}Cl_2O_7$	$C_{18}H_{12}Br_2O_7$	$C_{20}H_{18}O_7$
Formula weight	411.18	500.10	370.34	411.18	500.10	370.34
Crystal system	orthorhombic	orthorhombic	triclinic	monoclinic	monoclinic	Monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P2_1/c$
T/K	150	150	150	150	150	150
a/Å	10.5412(7)	10.5579(5)	9.9176(9)	10.7838(3)	16.9944(7)	20.749(2)
b/Å	12.4530(8)	12.5176(7)	9.9757(10)	14.2206(4)	7.9432(4)	8.3818(8)
c/Å	13.5129(10)	13.7487(8)	11.5419(17)	12.3774(4)	14.0330(7)	10.6736(10)
α/°	90	90	95.485(7)	90	90	90
β/°	90	90	109.352(7)	107.635(3)	105.825(2)	97.440(5)
γ/°	90	90	117.882(4)	90	90	90
Volume/Å^3	1773.8(2)	1817.02(17)	908.32(18)	1808.90(9)	1822.52(15)	1840.7(3)
Z	4	4	2	4	4	4
Reflns collected	18370	17330	10529	7319	24574	47624 [a]
Unique reflns	3363	3427	3189	3766	3205	5172
R_{int}	0.040	0.030	0.042	0.021	0.039	0.065 [a]
Obs refln (I>2σ(I))	2943	3211	1997	2966	2629	3242
R1 (I>2σ(I))	0.030	0.018	0.045	0.040	0.023	0.040
wR2 (all data)	0.065	0.039	0.113	0.102	0.050	0.086
GOF on F^2	1.01	0.99	1.00	1.03	1.01	0.90
Flack parameter	−0.01(5)	0.005(5)				

[a] The crystal was integrated as a non-merohedral twin with two components related by 180° rotation around a*. The total number of reflections and R_{int} value correspond to all single-component and overlapped reflections. Refinement performed using SHELXL HKLF-5 format: refined BASF = 0.476(1).

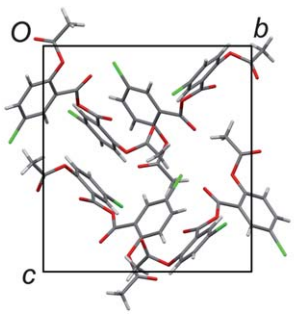


5-Me-AA Form I



5-Me-AA Form II

Fig. 2 Crystal structures of the **5-Me-AA** polymorphs.



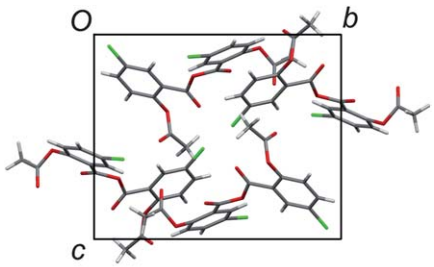
5-X-AA Form I (X = Cl, Br)

Fig. 3 Crystal structure of **5-X-AA** form I (X = Cl, Br).

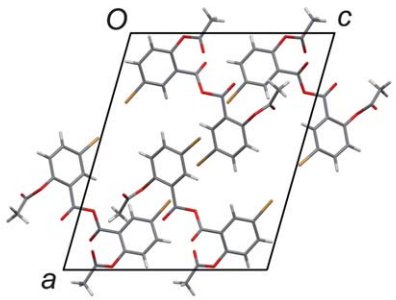
The structure of **5-Br-AA** form II is distinct. It resembles **5-Me-AA** form I, in that it contains face-to-face contacts between the aromatic rings, but the molecule has a flatter conformation (*ca* 45° between ring planes), and there are also clear Br···Br contacts (3.5352(3) Å).

Conclusions

We have shown that the outcome of solution crystallisations for the polymorphic 5-X-aspirin (X = Cl, Br) can be influenced by the presence of 5-X-aspirin anhydride, in a manner similar to that shown for aspirin itself.[10] For X = Cl, the effect is subtle because the impurity inhibits growth of form I, which in any case transforms to form II on standing in the crystallisation solvent. The presence of the anhydride can influence whether or not concomitant polymorphism is observed under given



5-Cl-AA Form II



5-Br-AA Form II

Fig. 4 Crystal structures of **5-X-AA** form II (X = Cl, Br). For **5-Cl-AA**, similarity with the structure of **5-X-AA**-form I (Fig. 3) is seen more clearly by shifting the molecules *ca* $^1/_4$ unit along the *b* axis.

crystallisation conditions. For X = Br, the influence of the anhydride is more clear because it serves to yield a polymorph that is not otherwise seen under comparable crystallisation conditions.

We have also found that the 5-X-aspirin anhydrides (X = Cl, Br, Me) are polymorphic and that the crystallisation outcome for these compounds appears also to be influenced by the presence of 5-X-aspirin. The link in this case is less clear, because it is difficult to prepare pure samples of the anhydride for X = Cl and Br, and heating seems to be required together with the additive for polymorphism to be observed.

The fact that impurities can influence crystallisation outcomes is of course well known. The principal significance of this work probably lies in an illustration of polymorph control induced by specific impurities that can be generated as by-products during synthesis or a common crystallisation procedure such as heating in an organic solvent. In several of the cases described here, for example, the polymorphic outcome can depend critically on the duration of heating during synthesis of the compound. For **5-Cl-A** in particular, a difference of only a few minutes during the heating step in Scheme 1 is sufficient to change the crystallisation outcome completely. Such circumstances can lead to erratic and apparently irreproducible crystallisation results, especially if the impurities remain undetected.

Acknowledgements

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