THERMAL STUDIES ON THE SODIUM SALTS OF AMINOSALICYLIC ACIDS

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Abstract

The effect on the stability of the isomers of aminosalicylic acid of formation of their sodium salts has been studied by use of differential scanning calorimetry and thermogravimetry, coupled with evolved gas analysis by Fourier transform infrared spectroscopy. X-ray powder diffraction and infrared spectroscopy provided complementary information.

The DSC curves for the sodium salts of all of the isomers showed complex dehydration/decomposition endotherms. From the initial mass losses of the TG curves, the amounts of water per mole of salt were estimated as 0.5, 2.4 and 1.4 moles for the sodium salts of 3-aminosalicylic acid, 4-aminosalicylic acid and 5-aminosalicylic acid, respectively. TG-FTIR results for the sodium salt of 3-aminosalicylic acid showed the evolution of carbon dioxide in three stages: below 150°C, between 200 and 300°C and continuous formation up to 500°C. This behaviour differs from that of 3-aminosalicylic acid itself, which forms CO_2 between 225 and 290°C. For the sodium salt of 4-aminosalicylic acid, the formation of carbon dioxide starts from 250ºC and is still being formed at about 650ºC. 4-aminosalicylic acid decarboxylates above 150ºC. 5-aminosalicylic acid and its sodium salt showed no evolution of carbon dioxide below 600ºC.

Keywords: aminosalicylic acids, DSC, sodium salts, TG-FTIR

Introduction

4-aminosalicylic acid (4-ASA) and its calcium, potassium and sodium salts have been used in various combinations (with drugs like streptomycin, dehydrostreptomycin and isoniazid [1]) for the treatment of tuberculosis. The sodium salt of 4-ASA is reported to be [2] a dihydrate, $C_6H_3(OH)(NH_2)COONa·2H_2O$, and occurs as a yellowish-white, odourless powder. The salt is soluble in ethanol and very soluble in water. The pH for its maximum stability is 7.0–7.5. Freshly prepared solutions are nearly colourless, but they develop an amber and, eventually, a dark brown to black colour on standing, due to decarboxylation. The potassium and calcium salts behave similarly. Formation of these salts increases the stability of the acids and is useful for drug storage. The solution for patient administration is recommended to be prepared only a few hours before use.

Decarboxylation of 4-ASA in the solid state has been found to be topochemical and autocatalytic with an induction period followed by a rapid accelatory period [1, 3]. The

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reaction has been reported to be accelerated by water and to be independent of the carbon dioxide pressure. Sunlight can also induce decarboxylation. The formation of an arenium ion has been used to explain the decarboxylation of 4-ASA in solution. The rate of reaction is independent of the 4-ASA concentration. The first step is the dissociation of the carboxylic acid proton, followed by the electrophilic protonation of the aromatic ring, and loss of carbon dioxide. This therefore suggests that the proton for electrophilic protonation, comes from the dissociation of ArCOOH or ArOH. Decomposition in the solid-state is thought to occur by the same mechanism and to propagate through the crystal by addition of carboxylate from either ArCOOH or ArCOO$^-$ [4].

The sodium salt of 4-ASA, which has similar applications to pure 4-ASA, has been reported to be stable at temperatures below 100°C, but to decompose at higher temperatures [4]. The decomposition of the salt rules out the proposal that the carboxylic proton is responsible for the decomposition of 4-ASA.

5-ASA has been used for along time in commercial formulations for the treatment of chronic bowel inflammation. The compound decarboxylates to form 4-aminophenol (4-AP) and also tends to undergo auto-oxidation. These reactions lead to stability problems in pharmaceutical formulations. Cendroskwa and co-workers [5] suggested that the degradation of 5-ASA could be observed by colour changes. 4-AP is known to autoxidise rapidly in aqueous media to give strongly coloured derivatives. Jensen and co-workers reported [6] HPLC studies done to determine the major degradation products of 5-ASA itself and of pharmaceutical formulations containing 5-ASA as the active ingredient.

The work done by Gujrathi and Jose [7] on 3-ASA, 4-ASA and 5-ASA revealed marked differences in the molecular structures of 3-ASA and 5-ASA compared to that of 4-ASA. The results show that 3-ASA and 5-ASA contain dipolar species (COO$^-$ and NH$_3^+$), while 4-ASA contains neutral species (COOH and NH$_2$).

Experimental

Materials

The aminosalicylic acid isomers, 3-ASA, 4-ASA and 5-ASA, were obtained from Aldrich Chemical Co. Ltd (UK) and were used without further treatment.

Preparation of sodium salts

The sodium salts of 3-ASA, 4-ASA and 5-ASA were prepared by reacting equivalent amounts of the acids and sodium hydroxide solution. The solutions were left to stand overnight to evaporate slowly. The salts of 3-ASA and 5-ASA were black in colour while that of 4-ASA was brown.

Instruments

Thermal analyses were carried out on a Perkin Elmer Series 7 TG and DSC. The TG could be linked to a Perkin Elmer 2000 FTIR via a heated interface and a gas cell (both supplied by Perkin Elmer) and was calibrated using magnetic standards. Unless other-

wise stated, sample masses were between 2 and 5 mg, in an open platinum pan, and the atmosphere was flowing nitrogen. The heating rate used was usually 10°C min^{-1}. DSC experiments were carried out in standard aluminium pans with lids, but uncrimped. Calibration was done using the melting point and enthalpy of melting of indium.

X-ray powder diffraction patterns were recorded for the sodium salts of the acids, for sodium carbonate, and for the residues after decomposition of the salts. Copper K$_\alpha$ radiation (0.15418 nm), a voltage of 40 kV, and a current of 20 mA were used. The readings were recorded for 2θ values from 5 to 60 degrees.

Results and discussion

Thermal behaviour of the aminosalicylic acids

The differences in the thermal behaviour of the isomers of aminosalicylic acid have been reported [8, 9]. The FTIR stacked plot (Fig. 1) shows onset of the evolution of carbon dioxide gas from a sample of 3-ASA after 17.5 min of heating at 10°C min^{-1} from an initial temperature of 50°C, giving an onset temperature of about 225°C. The
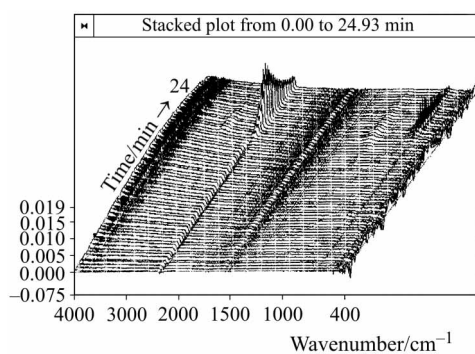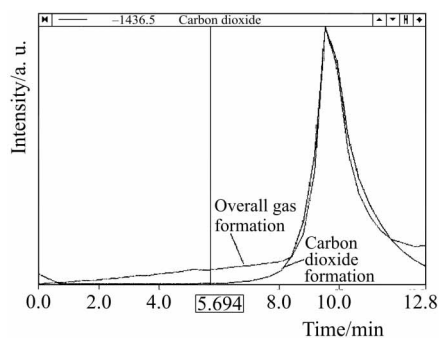

Fig. 1 A stacked plot of FTIR spectra recorded during a TG run on 3-ASA, heated at 10 K min^{-1} in flowing nitrogen
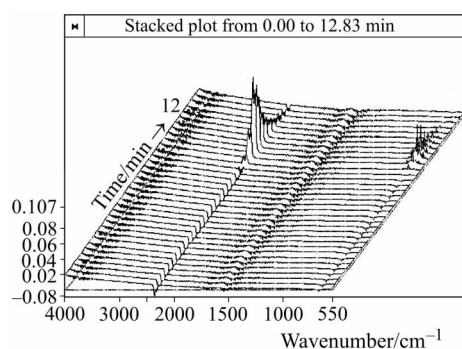
Fig. 2 A stacked plot of FTIR spectra recorded during a TG run on 4-ASA, heated at 10 K min^{-1} in flowing nitrogen

evolution of carbon dioxide continued with a maximum at about 260°C and evolution was still being observed at 290°C. At this temperature, the TG curve shows almost complete mass loss (95%). The decarboxylation process thus occurs near the temperature of the endotherm (230 to 250°C) observed on the DSC curve.


Fig. 3 The Gram–Schmidt reconstruction curves for the overall gas formation and for the evolution of CO_2, recorded during a TG run (heating rate 10 K min^{-1} in flowing nitrogen)

The stacked plot of FTIR spectra (Fig. 2) recorded during a TG run on 4-ASA (starting temperature 50°C and heating rate 10 K min^{-1}) showed that CO_2 evolution occurred between 130 and 170°C with maximum production at 150°C. The Gram–Schmidt reconstructions (Fig. 3) for the overall gas formation and the evolution of carbon dioxide confirm the formation of carbon dioxide only. The temperature of melting of 4-ASA is about 130°C [8].

Thermal behaviour of the sodium salts of 3-ASA, 4-ASA and 5-ASA
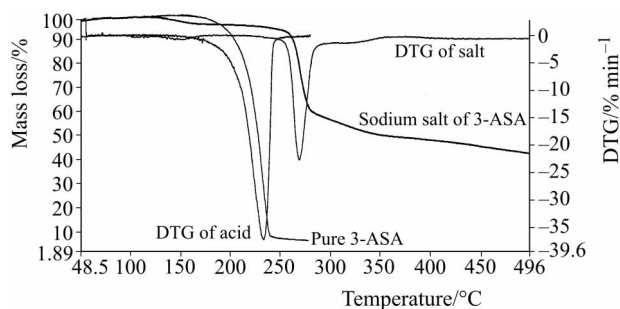
The sodium salt of 3-ASA

The DSC curve for the sodium salt of 3-ASA (Fig. 4) shows two endotherms. The first is broad with onset at 91°C (ΔH=91 kJ mol^{-1}). The second is a complex endotherm with an initial sharp peak at an onset temperature of 254°C, followed by a broader peak with a slow return to the baseline.
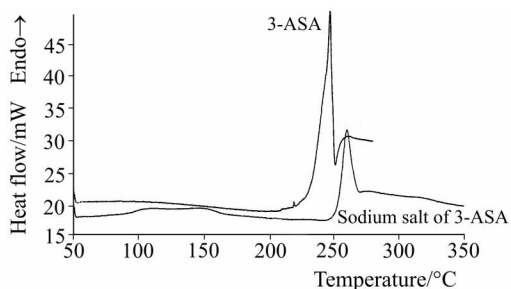

Fig. 4 DSC curves for a – 3-ASA and b – the sodium salt of 3-ASA (heated in flowing nitrogen in uncrimped aluminium pans at 10 K min^{-1})

The TG and DTG curves (Fig. 5) show a mass loss from 100 to 170ºC (about 5%) and a mass loss from 240 to 340ºC of 45%, with a discontinuity after 35% mass loss at about 280ºC, which was followed by a slow mass loss that was not complete at 500ºC. The calculated mass loss for decarboxylation is 23.8% of anhydrous salt. The initial mass loss of 5%, if assumed to be water, corresponds approximately to a hemi-hydrate $(3-NH_2-C_6H_3(OH)COONa\cdot0.5H_2O)$. Many sodium salts of organic acids decompose to form sodium carbonate (Fig. 7). The calculated mass loss for the anhydrous sodium salt to form Na_2CO_3 is 39.0%.


Fig. 5 TG and DTG curves for 3-ASA and the sodium salt of 3-ASA (heated in flowing nitrogen in an open platinum pan at 10 K min^{-1})

Evolved gas analysis (EGA) by TG-FTIR, corresponding to the TG curves shown in Fig. 5, showed formation of both water and carbon dioxide (Fig. 6). Carbon dioxide is produced at three different stages: the first below 150ºC, the second between 200 and 300ºC and the third stage is continuous formation up to 500ºC. The thermal behaviour of this salt is quite different from that of the sodium salts of 4-ASA and of 5-ASA.
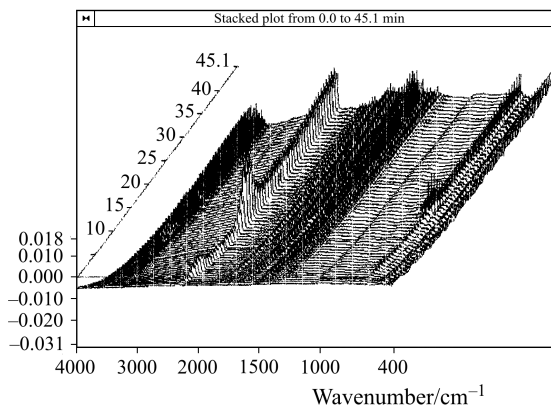
Fig. 6 A stacked plot of FTIR spectra recorded during a TG run (Fig. 5) on the sodium salt of 3-ASA in nitrogen (heating rate of 10 K min^{-1})

X-ray powder diffraction patterns for the sodium salt of 3-ASA, its residue after heating to 500°C, and that of pure sodium carbonate powder are given in Fig. 7. The
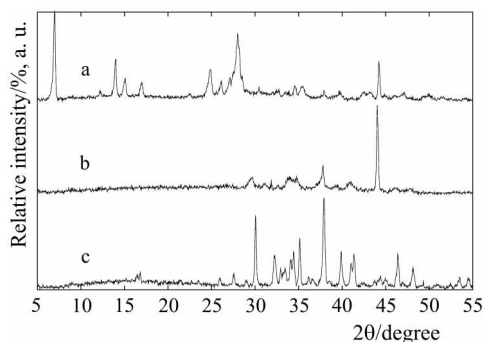
Fig. 7 The XRD patterns for a – the sodium salt of 3-ASA; b – the residue after heating the sodium salt of 3-ASA to 500°C, and c – pure sodium carbonate

XRD pattern of the residue after heating the salt is quite different from that of the original salt and is similar to that of pure Na_2CO_3. This indicates the formation of some Na_2CO_3 on heating the salt. The original black colour of the salt did not change as was observed for the sodium salt of 4-ASA.

The sodium salt of 4-ASA

The DSC curve for the sodium salt of 4-ASA showed two endotherms occurring far below the melting point of 4-ASA (Fig. 8). The first endotherm is broad and appears between 50 and 100°C, where a sharper endotherm begins (100 to 110°C). The endotherm between 50 and 100°C is accompanied by a two-stage mass loss in the TG curve (Fig. 9). There was an initial mass loss between 40 and 50°C of about 2%, followed by another mass loss of about 20% from 50 to 100°C, and then a two-stage mass loss from 230 to 330°C (total mass loss of 9.0%). Calculations done, using the mass loss between 50 and 100°C of 20%, gave the number of moles of water in the salt to be about 2.4. Wesolowski [2] has reported the formation of a dihydrate ($4-NH_2-C_6H_3(OH)COONa\cdot2H_2O$). The expected mass loss for dehydration of the dihydrate is 17.1%. By about 650°C, the total mass loss is about 38.0%. The calcu-
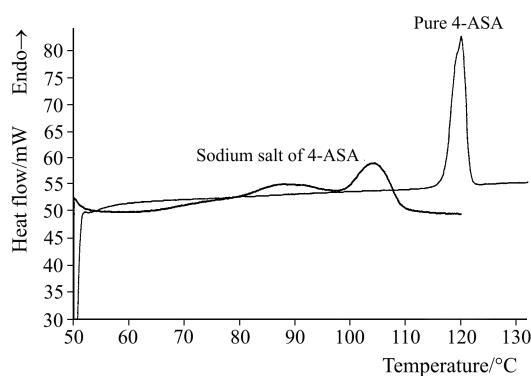

Fig. 8 DSC curves for 4-ASA and the sodium salt of 4-ASA (heated in flowing nitrogen in uncrimped aluminium pans at 10 K min^{-1})
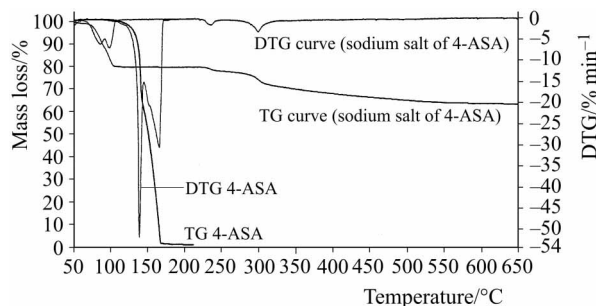
Fig. 9 TG and DTG curves for 4-ASA and the sodium salt of 4-ASA (heated in flowing nitrogen in an open platinum pan at 10 K min^{-1})

lated mass loss for decarboxylation of the dehydrated salt is 25.0% and the calculated mass loss for decarboxylation of the hydrated salt is 21%. Therefore, the residue of about 62.0% could be sodium carbonate (Fig. 13). Comparison with the TG curve for pure 4-ASA shows that the anhydrous salt is thermally more stable than the acid.

A TG-FTIR run (Fig. 10) for the sodium salt of 4-ASA (corresponding to the TG curve in Fig. 9) showed the evolution of CO_2, and hence the occurrence of decarboxylation at temperatures higher than 250°C. The evolution of carbon dioxide continued and showed no maximum by 650°C. The mass loss starting at 250°C is thus related to the formation of carbon dioxide. The GSR plot (Fig. 11) for the formation of carbon dioxide shows slow release at lower temperatures and more rapid release after 50 min (550°C). A similar plot (Fig. 12) for the evolution of H_2O shows that this occurs between 90 and 130°C, at a heating rate of 10 K min^{-1}.
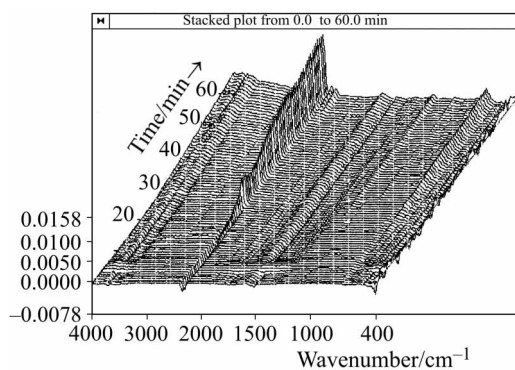

Fig. 10 A stacked plot of FTIR spectra recorded during a TG run (Fig. 9) on the sodium salt of 4-ASA, heated in an open platinum pan in nitrogen at 10 K min^{-1}

X-ray powder diffraction patterns of the sodium salt of 4-ASA, the residue after heating to 650°C, and pure Na_2CO_3 are shown in Fig. 13. The XRD patterns for the residue (changed from brownish to white colour) and that of pure Na_2CO_3 are very similar. The results showed that the salt decomposed to form sodium carbonate after heating up to 650°C.
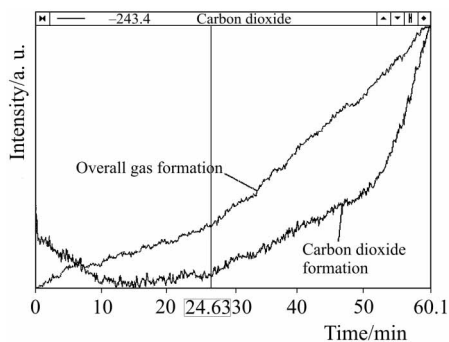
Fig. 11 The Gram–Schmidt reconstruction (GSR) curves for the overall release of gases as well as the evolution of CO_2 from the sodium salt of 4-ASA, heated in flowing nitrogen at 10 K min^{-1}
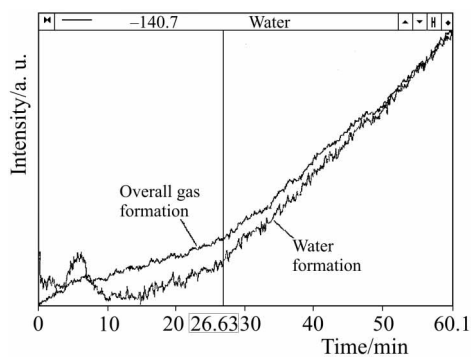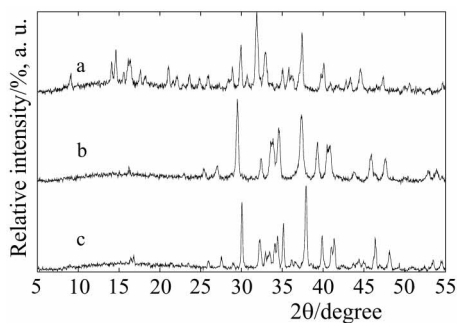

Fig. 12 The Gram–Schmidt reconstruction (GSR) curve for the overall release of gases as well as the evolution of H_2O from the sodium salt of 4-ASA, heated in flowing nitrogen at 10 K min^{-1}


Fig. 13 XRD patterns for a – the sodium salt of 4-ASA; b – the residue after heating the sodium salt of 4-ASA to 650°C and c – pure sodium carbonate
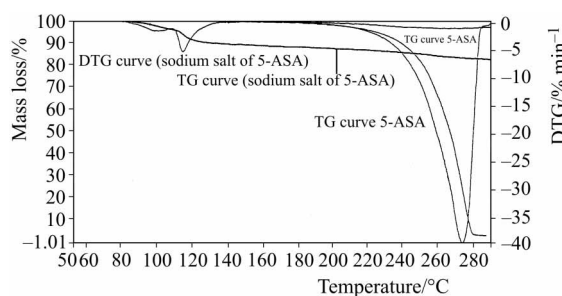
The sodium salt of 5-ASA

A DSC curve (Fig. 14) for the sodium salt of 5-ASA showed a broad endotherm between 110 and 150°C. The TG curve (Fig. 15) showed a two-stage process from 80 to 140°C with total mass loss of 12%. This was followed by a slow mass loss between 140 and 500°C. The total mass loss by 500 is about 25%.
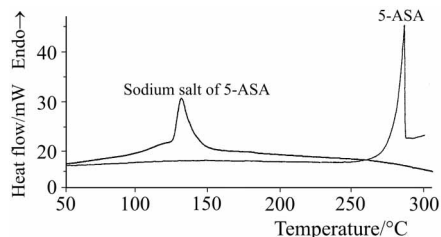

Fig. 14 DSC curves for 5-ASA and the sodium salt of 5-ASA, heated in flowing nitrogen in uncrimped aluminium pans at 10 K min^{-1}

Fig. 15 TG and DTG curves for 5-ASA and the sodium salt of 5-ASA, heated in flowing nitrogen in an open platinum pan at 10 K min^{-1}

TG-FTIR analysis of the gases evolved from the salt did not show any decarboxylation process. Calculations from the 12% mass loss in the TG curve for the salt, if assumed to be water, gave 1.4 moles of water (5-NH$_2$-C$_6$H$_3$(OH)COONa·1.4H$_2$O). The calculated mass loss for decarboxylation of the dehydrated salt is 25.1% and for the formation of sodium carbonate is 39.0%.
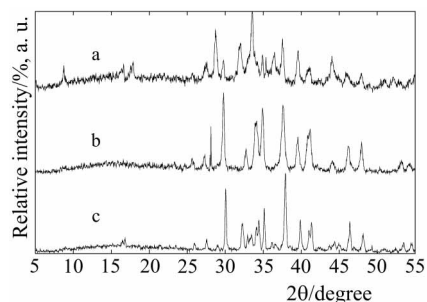
Fig. 16 XRD patterns for a – the sodium salt of 5-ASA; b – the residue after heating the sodium salt of 5-ASA to 650°C and c – pure sodium carbonate

Table 1 Thermal behaviour of the sodium salts of aminosalicylic acids

Sodium salt of	Number of moles H_2O	TG/°C	CO_2 evoluton	DTG max/°C	DSC (op) endotherm onset/°C	ΔH/kJ mol^{-1}
3-ASA	0.5	100–170	100–500	150 and 275	91 and 254	91 complex
		240–340				
4-ASA	2.4	50–100		80 and 100 (doublet)	50 and 100	complex
		230–330	250–650	240		
				300		
5-ASA	1.4	80–140	none detected	90 and 110 (doublet)	110	complex

    X-ray powder diffraction patterns of the sodium salt of 5-ASA, the residue after heating to 650°C, and of pure Na_2CO_3 are shown in Fig. 16. The XRD pattern of the residue of the salt after heating to 650°C resembled that of sodium carbonate although the residue was still darkly coloured.

Conclusions

Results for the sodium salts of 3-ASA, 4-ASA and 5-ASA are summarised in Table 1. Most of the DSC endotherms were complex. Different hydrates were found for the three salts and hence their dehydrations were different. Dehydration is a two-stage process for the 4-ASA and 5-ASA salts. The process of decarboxylation for the salts of 3-ASA and 4-ASA occurred over a wide range of temperatures. Decarboxylation of the 5-ASA salt could not be detected. Once they had been dehydrated, the anhydrous sodium salts were generally more stable towards thermal decomposition than the acids themselves.

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