COMMUNICATION

Hard to swallow dry: formation of linear and cyclic oligomers in the anhydrous thermal decomposition of acetylsalicylic acid

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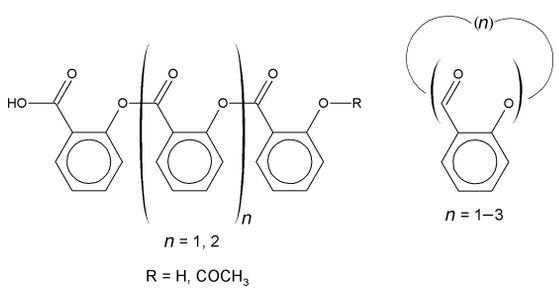
The combination of thermal analysis and mass spectrometry reveals that thermal decomposition of acetylsalicylic acid under anhydrous conditions occurs by formation of its linear oligomers, which are subsequently converted to cyclic oligomers.

Both moist and anhydrous conditions promote the thermal decomposition of the starting material, acetylsalicylic acid **1**, the active ingredient in aspirin formulations and a widespread analgesic, anti-inflammatory and antipyretic agent. With water present, the hydrolysis of **1** leads to the formation of salicylic acid **2** and acetic acid **3**.[1–3] For anhydrous conditions, there have been reports that **1** decomposes by polymerization to form only linear oligomers[4] of **1** and **2** or only cyclic oligomers[5,6] of **1** and **2** (Scheme 1).



Scheme 1

Thermogravimetric analysis (TGA) using a nonisothermal heating program has shown that the thermal decomposition of **1** occurs by a two-step mass loss (Fig. 1).[7–9] Here, the point of inflection between the two steps occurs at ~60% mass loss at a temperature of ~290 °C for a heating rate of $\beta = 40$ °C min^{-1}. Running an isothermal TGA experiment at 125 °C for 400 minutes results in rapid initial mass loss that later plateaus at a value of ~60% mass loss (not shown). An analogous isothermal experiment has been carried out in a differential scanning calorimeter (DSC). Immediately after completion of the isothermal segment the residue was heated at $\beta = 10$ °C min^{-1} up to 600 °C. This DSC scan has not shown the endotherm at 135 °C[10] characteristic of the melting of **1** that suggests that little, if any, **1** is present in the residue after the 125 °C isothermal segment.

The remaining residue from the isothermal TGA experiment (henceforth, referred to as "the residue") was analyzed by electron impact mass spectrometry (EI-MS). The electron impact probe followed a three-segment temperature program starting at a temperature of 0 °C and consisting of a 30 second segment at a linear heating rate of $\beta = 2.0$ °C min^{-1}, a nine minute nonisothermal segment at $\beta = 40$ °C min^{-1}, and a ten minute isothermal segment at 360 °C. The spectra were taken as a series of successive scans with a period of ~5 s. Fig. 2 shows a mass spectrum obtained for the residue at ~267 °C that contains major peaks at *m*/*z* 120, 121, 163 and 240. This spectrum is distinctly different from the respective mass spectra of **1** and/or **2**. A mass spectrum of **1** typically exhibits three major peaks

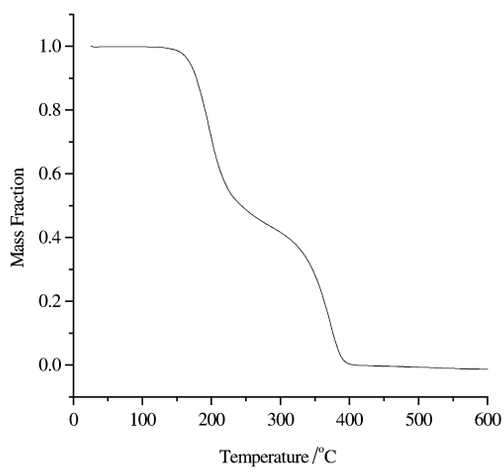


Fig. 1 Open pan nonisothermal TGA trace of an acetylsalicylic acid sample collected in a flowing N_2 atmosphere (70 ml min^{-1}) at a constant heating rate of $\beta = 40.0$ °C min^{-1}.

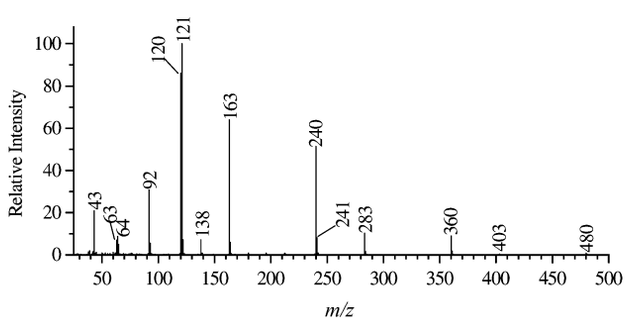


Fig. 2 A mass spectrum for *m*/*z* = 20–400 of scan No. 80 that corresponds to a temperature of ~267 °C.

having *m*/*z* 120 (100%), 138 (60%), and 43 (60%),[11] which are consistent with the formation of **2** and **3**. Further, mass spectra of **1** and **2** typically show a constituent at *m*/*z* 121 (a fragment of **2**) which is about three times smaller than the one at *m*/*z* 138.[11] However the mass spectrum of the residue (Fig. 2) exhibits the biggest peak at *m*/*z* 121 which is about five times greater than the peak at *m*/*z* 138.

The fragmentation pattern of the residue supports the formation of linear oligomers of **1**. The major peaks at *m*/*z* 121 and 163 in the spectrum of the residue appear to be associated with the fragment to the right of the parentheses of the linear oligomer for R = H and $COCH_3$, respectively (see Scheme 1). The fragment in parentheses can give rise to the major peaks at *m*/*z* 120 and 240. These fragments also show up (Fig. 2) in combination with aforementioned fragments to give smaller peaks at *m*/*z* 283 (163 + 120), 241 (121 + 120), 361 (121 + 240), and 403 (163 + 240). The fragment to the left of the parentheses ($M = 137$) likely undergoes further fragmentation by splitting off the OH group and giving rise to a peak at *m*/*z* 120.

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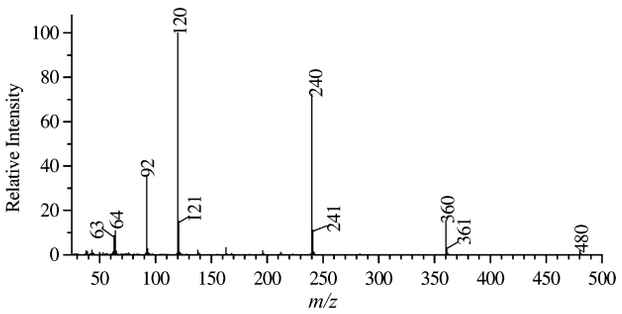


Fig. 3 A mass spectrum for $m/z = 20$–400 of scan No. 101 that corresponds to a temperature of ~337 °C.

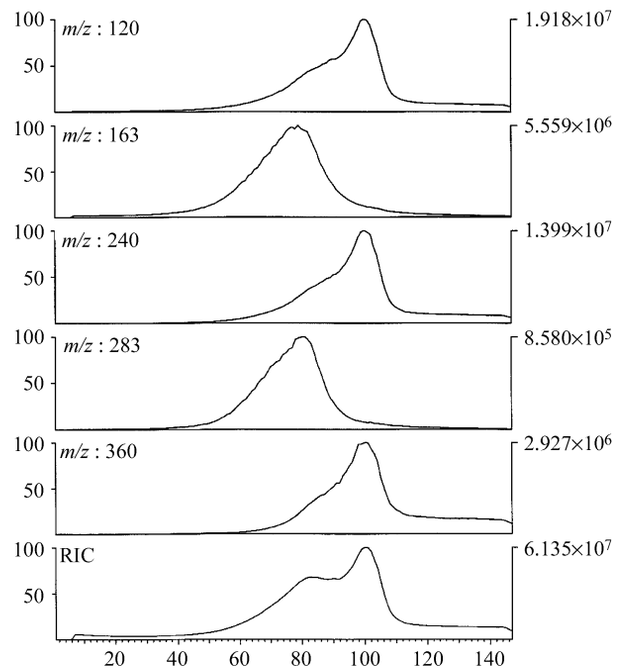
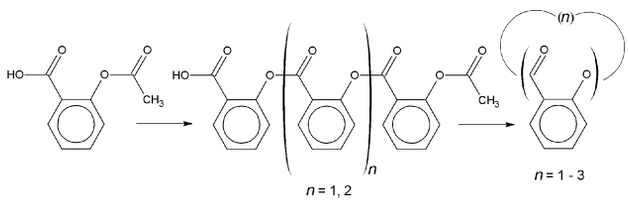


Fig. 4 Integrated mass spectra for $m/z = 120$, 163, 240, 283, and 360 and for the relative ion count as a function of scan number. Elapsed time in seconds is ~5 times the scan number. For scans 1–110, temperature (°C) is ~3.3 times the scan number.

The peaks at *m/z* 120, 240, and 360 (Fig. 2) may also result from fragmentation of cyclic oligomers of **1**. However, based on the fact that the intensities of these peaks are comparable with the intensities of the peaks at *m/z* 121 and 163 resulting from the linear oligomer, the cyclic oligomer is unlikely to be the major source of the fragments having *m/z* 120, 240 and 360. We, therefore, assert that the major process that occurs in the condensed phase during the initial stage of decomposition (*i.e.*, 60% mass loss) of **1** is its conversion into the linear oligomers.

The situation changes dramatically when the residue is heated above 300 °C (the second stage of mass loss in Fig. 1). A representative mass spectrum for this stage is shown in Fig. 3. The three major peaks are now observed at *m/z* 120, 240, and 360 (as well as a very small peak at *m/z* 480), whereas the constituents characteristic of the linear oligomers (*m/z* 121, 163, 241, and 283) are now presented as minor peaks. This pattern suggests that as the formation of linear oligomers decreases, the formation of cyclic oligomers increases. This is illustrated in Fig. 4 which presents the evolution of several constituents during decomposition of the residue. It is remarkable that the evolution of the constituents of *m/z* 120, 240, and 360 shows a shoulder that corresponds to the maximum rate of evolution of the constituents (*m/z* 163 and 283) characteristic of the fragmentation of the linear oligomers. This fact suggests that during the second stage of decomposition, the formation of the constituents of *m/z* 120, 240, and 360 is primarily associated with fragmentation of the cyclic oligmers.

Therefore, the decomposition of **1** is associated with a sequence of condensed phase reactions, initially forming linear oligomers and later forming cyclic oligomers, which can be presented as shown in Scheme 2.



Scheme 2

To our knowledge, this is the first report of the formation of cyclic oligomers of **1** from the linear ones. Previous studies have detected the formation of only linear oligomers[4] or only cyclic oligomers.[5,6] In the latter case, the cyclic oligomers have been proposed to form directly from **1**. Note that the proposed scheme does not rule out the possibility of the formation of a dimeric structure related to an acetylsalicylic acid anhydride ($M = 342$). We do not observe a spectral peak at the parent *m/z* ratio of 342. However, if cleaved at the C–O ester bond (as observed in the linear and cyclic oligomers), this anhydride should give rise to peaks at *m/z* values of 43 and 120 that have been detected.

Our current efforts are focused on further elucidating the reaction mechanism and obtaining reliable kinetic characteristics of the process that can be used to predict the thermal stability of **1**. All these results will soon be reported in a full paper.

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