Available online at www.sciencedirect.com
SCIENCE DIRECT®
Thermochimica Acta 410 (2004) 15–21
thermochimica acta
www.elsevier.com/locate/tca

A simultaneous TG–DTA study of the thermal decomposition of 2-hydroxybenzoic acid, 2-carboxyphenyl ester (salsalate)

Olga Shulga, Jeffrey Dunn*

Department of Chemistry, The University of Toledo, 2801 W. Bancroft St., Toledo, OH 43606, USA

Received 14 March 2003; received in revised form 26 June 2003; accepted 29 June 2003

Abstract

Simultaneous thermogravimetry–differential thermal analysis (TG–DTA) and gas and liquid chromatography with mass spectrometry detection have been used to study the kinetics and decomposition of 2-hydroxybenzoic acid, 2-carboxyphenyl ester, commercially known as salsalate. Samples of salsalate were heated in the TG–DTA apparatus in an inert atmosphere (100 ml min^{-1} nitrogen) in the temperature range 30–500 °C. The data indicated that the decomposition of salsalate is a two-stage process. The first decomposition stage (150–250 °C) had a best fit with second-order kinetics with E_a = 191–198 kJ/mol. The second decomposition stage (300–400 °C) is described as a zero-order process with E_a = 72–80 kJ/mol. The products of the decomposition were investigated in two ways:

(a) Salsalate was heated in a gas chromatograph at various isothermal temperatures in the range 150–280 °C, and the exit gas stream analyzed by mass spectrometry (GC–MS). This approach suggested that salsalate decomposes with the formation of salicylic acid, phenol, phenyl salicylate, and cyclic oligomers of salicylic acid di- and tri-salicylides.

(b) One gram samples of salsalate were heated in a vessel under nitrogen to 150 °C, and the residues were analyzed by liquid chromatography–mass spectrometry (LC–MS). The major compound detected was a linear tetrameric salicylate ester.

Keywords: TG–DTA; Thermal decomposition; Salsalate; Reaction scheme

1. Introduction

Salsalate (Fig. 1) is a dimer of salicylic acid. Like salicylic acid and its salts [1], salsalate is an anti-inflammatory and anti-rheumatic agent for oral admission. It is a white crystalline material with a melting point of 143–145 °C [2].

Salsalate is insoluble in acid gastric fluids, but readily soluble in the small intestine where it is partially hydrolyzed to two molecules of salicylic acid. The mode of anti-inflammatory action of salsalate and other nonsteroidal anti-inflammatory drugs in this class is not fully defined. Although salsalate is a weak inhibitor of prostaglandin synthesis in vitro, it appears to selectively inhibit prostaglandin synthesis in vivo, providing anti-inflammatory activity equivalent to aspirin [3–6]. Salsalate and the other anti-inflammatory drugs were subjected to clinical studies of its inhibitory effects on cyclooxygenase (COX) in blood.

Salsalate is known to have a conformational disorder in the crystal structure [7]. Recent X-ray crystallographic analysis has shown that within the crystal, 72% of the molecules have the hydroxy group in one of the two *ortho* positions (R-*ortho* position), and in the remaining 28% of the molecules have the hydroxy group in the alternate *ortho* position (R′-*ortho* position).

Some reports on the identity of the products of decomposition of salsalate have appeared in the literature. Reepmeyer [8] reported the isolation of linear oligomeric salicylate ester, and Mroso and coworkers [9] reported that salicylic acid was a major product. The present study provides a more detailed investigation of the decomposition process, and gives details of the temperature ranges in which specific intermediates were formed. The present study also focuses on the kinetic analysis of data obtained from thermogravimetric experiments. These data provide important information about the stability of the drug, and the calculated values of activation

* Corresponding author. Tel.: +1-419-530-7847; fax: +1-419-530-2141.
E-mail address: jeffrey.dunn@utoledo.edu (J. Dunn).

0040-6031/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0040-6031(03)00370-8

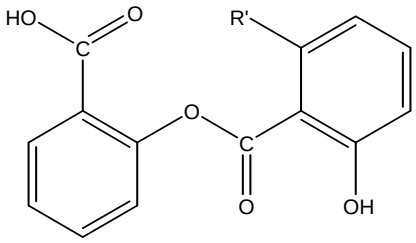


Fig. 1. Salsalate (R = R′ = OH).

energy and collision constant can be used as an alternative to accelerated stability testing [10,11] in predicting shelf life.

2. Experimental

The salsalate sample was supplied by TCI America and used as-received. The bulk sample was split into 10 fractions with average particle size 82, 98, 115, 137, 165 and 196 μm by shaking on a Ro-tap Sieve Shaker, kindly provided by the Department of Pharmacy of the University of Toledo. Phenyl salicylate was purchased from Aldrich and used as-received.

Thermal analysis experiments were performed with a TA Instruments SDT 2960 simultaneous TG–DTA unit using platinum crucibles with a capacity of 110 μl and cross-sectional area of 0.305 cm^2. For salsalate, rising temperature experiments were conducted in the temperature range 30–500 °C at heating rates of 2, 4, 6, 8 and 10 °C min^{-1} in dry nitrogen flowing at 100 ml min^{-1}, with a sample mass in the 5–10 mg range. Phenyl salicylate was heated from ambient temperature to 400 °C at 10 °C min^{-1}, all other conditions being the same as those for salsalate.

A Hewlett Packard Gas chromatograph/Mass Spectrometer (GCD plus) with electron ionization detector was used to identify thermal decomposition products of salsalate. The temperature program consisted of three segments: first, the sample was held at a temperature of 60 °C for 3 min, second, a rising temperature segment with a heating rate of 20 °C/min up to the final temperature of 150, 170, 190, 210, 230, 260 and 280 °C, respectively, and third, an isothermal segment with the probe held at the final temperature for 10 min.

In order to verify the presence of the compounds found from GC–MS experiments, 1 g samples of salsalate were heated up to 150 °C in a vessel under nitrogen. The solid residues were dissolved in acetonitrile (HPLC grade) and analyzed by liquid chromatography–mass spectrometry (LC–MS) Esquire-LC (Hewlett Packard/Bruker).

3. Results and discussion

Fig. 2 represents the TG–DTA curves of the thermal decomposition of salsalate. Salsalate decomposes in two consecutive steps. The first mass loss occurs in the temperature range of 150–250 °C with the loss of 52% of material, the second mass loss takes place in the temperature range of

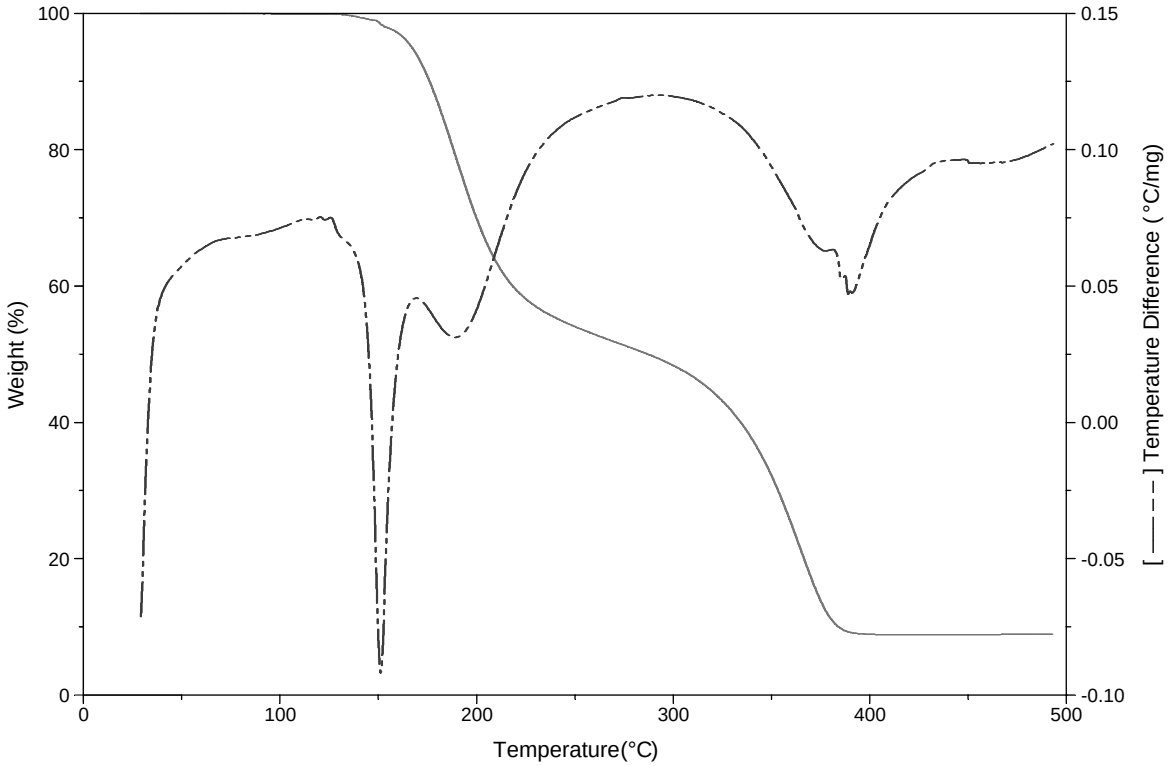


Fig. 2. TG–DTA plot of the decomposition of salsalate, heating rate 10 °C min^{-1}, nitrogen flow rate 100 ml min^{-1}.

Table 1
Retention times and relative peak intensity for peaks in the gas chromatogram of salsalate

Retention time (min)	Relative peak intensity
4.69	<200000
7.56	2000000
10.03	<200000
11.23	640000
19.67	<200000

260–400 °C with 48% loss. The DTA plot shows three distinct endothermic peaks, one of which at 153 °C corresponds to the melting of salsalate, the other two peaks correspond to the two mass losses. Partial overlap of first and second endothermic peaks occur, indicating that decomposition commences directly after melting.

3.1. Identification of decomposition products

Attempts to determine the gases evolved during decomposition by coupled TG–MS failed, as significant condensation of one of the evolved gases blocked the transfer line connecting the TG to the MS. Unfortunately, the transfer line temperature was not sufficient to keep this product in the gaseous state. To overcome this problem, solutions of salsalate were injected into a GC–MS system with the column temperature set at various values in the decomposition range of salsalate.

3.1.1. GC–MS study

Solutions of salsalate in methylene chloride (3.4 mg/ml) were injected into a GC column initially at 60 °C and heated to 260 °C at 20 °C min^{-1} in a helium atmosphere. It was assumed that the mechanism of decomposition in the GC column is similar to that in the TG apparatus. Heating salsalate in the GC column resulted in the identification of five products (Table 1). The major peak appears at 7.56 min and corresponds to salicylic acid. Identification was performed by analysis of mass spectra and verified by comparison with the MS database. Other compounds identified were phenol (4.69 min), phenyl salicylate (10.03 min), *cis*-disalicylide (11.23 min) and tri-salicylide (19.67 min). None of the mass spectra had a molecular ion peak at $m/z = 258$, which corresponds to the molecular weight of salsalate, which means that salsalate had completely decomposed by 260 °C.

During our TG experiments the formation of white crystals was noticed. Crystals were collected and analyzed by ^{1}H and ^{13}C NMR and identified as salicylic acid. The formation of salicylic acid from the decomposition of salsalate was also noted by Mroso and coworkers [9].

In order to trace the formation of each product, a series of GC–MS experiments were performed where the final temperature of the column was varied. Variations of the relative abundance of each compound with column temperature are presented in Table 2. Table 2(A) shows variation of the relative abundance of salicylic acid with temperature. It is seen that salicylic acid is formed in a large quantity. When the column temperature rises from 150 to 170 °C the relative abundance of salicylic acid decreases, but as the column temperature continues to increase the relative abundance increases again and reaches the highest level at 260 °C. This suggests that salicylic acid is the product from at least two different reactions.

Table 2(B) shows that phenyl salicylate has begun to form at 190 °C and the amount doubled by the time the column temperature reached 210 °C. At 260 °C almost all the phenyl salicylate has been decomposed. The TG–DTA curve of pure phenyl salicylate is presented in Fig. 3. It decomposes in a one-stage process, which starts at 125 °C and ends at 230 °C. There is a further small mass loss of 3% between 230 and 270 °C, which may be due to some impurity or the decomposition of some byproduct of the phenyl salicylate decomposition. The DTA curve shows two endothermic peaks, the first corresponding to the melting of phenyl salicylate (44 °C), and the second corresponding to the decomposition of phenyl salicylate. Since salsalate decomposes above the decomposition temperature of phenyl salicylate, as soon as phenyl salicylate forms in the TG–DTA apparatus, it must decompose immediately. Phenyl salicylate is reported to decompose to form salicylic acid and phenol [12], and so this reaction contributes to the salicylic acid formed in the first mass loss. However, the very low concentration of phenol detected suggests that the formation of phenyl salsalate is a minor reaction.

Table 2(C) shows that *cis*-disalicylide begins to form at 190 °C, and the relative abundance continues to increase up to the maximum column temperature of 260 °C. The

Table 2
Variation of the relative abundance of the decomposition products of salsalate with temperature as determined by GC–MS

(A) Salicylic acid		(B) Phenyl salicylate		(C) *Cis*-disalicylide		(D) Tri-salicylide	
Final temperature (°C)	Relative abundance	Final temperature (°C)	Relative abundance	Final temperature (°C)	Relative abundance	Final temperature (°C)	Relative abundance
150	1800000	150	–	150	–	150	–
170	1200000	170	–	170	–	170	–
190	1500000	190	<10000	190	20000	190	–
210	1500000	210	20000	210	30000	210	–
230	1800000	230	15000	230	40000	230	–
260	2000000	260	<5000	260	50000	260	<10000

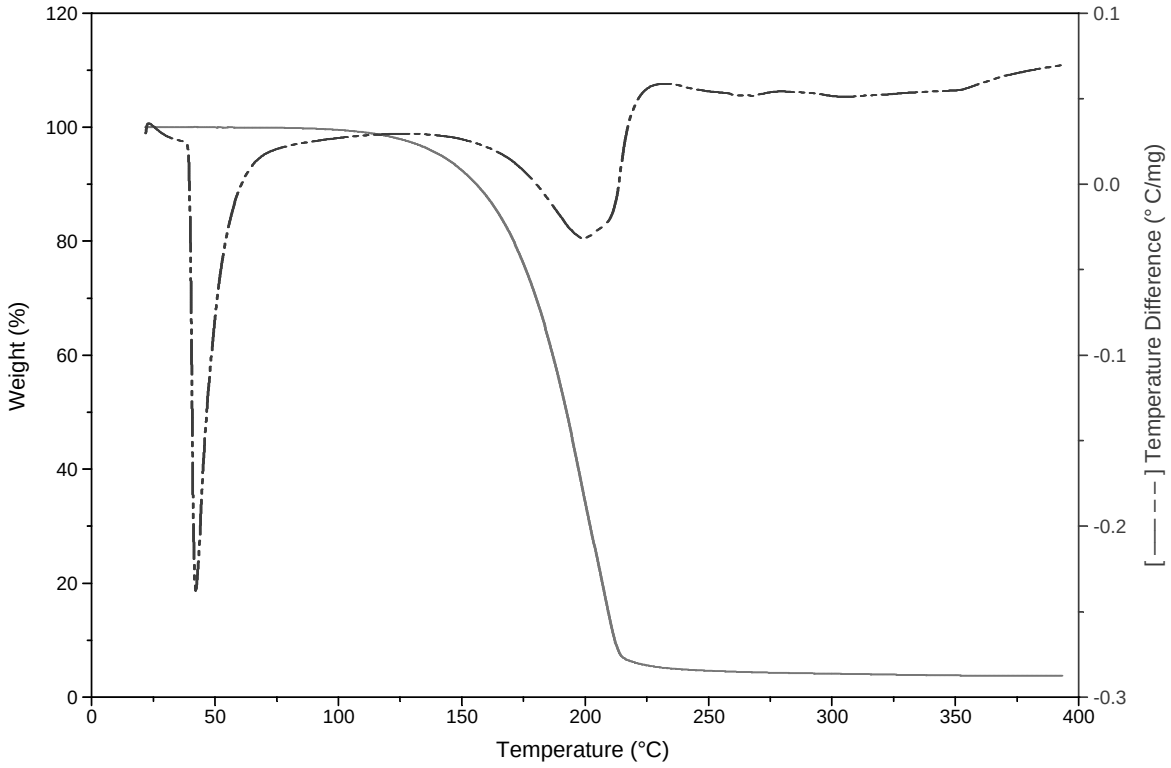


Fig. 3. TG–DTA plot of phenyl salicylate heated at 10 °C min^{-1}, nitrogen flow 100 ml min^{-1}.

melting point of *cis*-disalicylide is 230–235 °C [13], so that *cis*-disalicylide is in its molten form when it starts to decompose in the TG apparatus above 260 °C during the second mass loss. The melting endotherm peak is not apparent as a separate event, as it overlaps with the endothermic first stage decomposition. A small amount of tri-salicylide was noticed when the final column temperature was 260 °C (Table 2(D)).

The structure of phenyl salicylate is presented in Fig. 4. The mass spectrum of phenyl salicylate shows a peak at a *m*/*z* ratio of 214, which corresponds to the parent ion. The most intense peak is at $m/z = 121$, and corresponds to the loss of 93 a.u., which is the loss of a $C_6H_5O^-$ fragment (A in Fig. 4) to form fragment B. A low intensity peak at $m/z = 93$ corresponds to the $C_6H_5O^-$ fragment. This ion is not stable and is fragmented further to give a peak with *m*/*z* ratio of 77, corresponding to the loss of oxygen.

The formation of di- and tri-salicylides was noticed first during the decomposition of aspirin by Barker et al. [13] and recently confirmed by Long et al. [14]. The latter also suggested that a linear oligomer of acetylsalicylic acid was first formed, followed by cyclization, yielding salicylic acid, *cis*-disalicylide and tri-salicylide. According to our study, *cis*-disalicylide and tri-salicylide were also detected by GC/MS. The structure of disalicylide is presented in Fig. 5. The mass spectrum fragmentation pattern shows the parent ion peak at $m/z = 240$. A peak at $m/z = 120$ corresponds to the splitting of the molecular ion into two equal parts, i.e. two $C_6H_4COO^-$ fragments. Further fragmentation produces the $C_6H_4O^-$ ion with a peak at $m/z = 92$.

Fig. 6 shows the structure of tri-salicylide. The mass spectrum fragmentation pattern shows the parent ion at $m/z = 360$. This then fragments into a dimer with $m/z = 240$, and a strong peak at $m/z = 120$ indicates the presence of the monomeric $C_6H_4COO^-$ fragment.

3.1.2. LC–MS study

In additional experiments, 1 g samples of salsalate were heated in a vessel under nitrogen to 150 °C, cooled, and the product analyzed by LC–MS. This avoided additional heating and hence decomposition that would occur if the

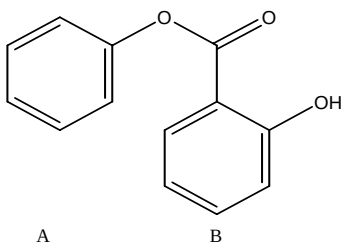


Fig. 4. Structure of phenyl salicylate.

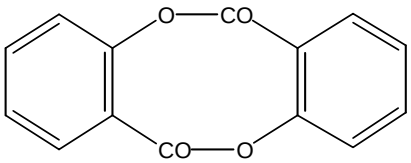


Fig. 5. Structure of *cis*-disalicylide.

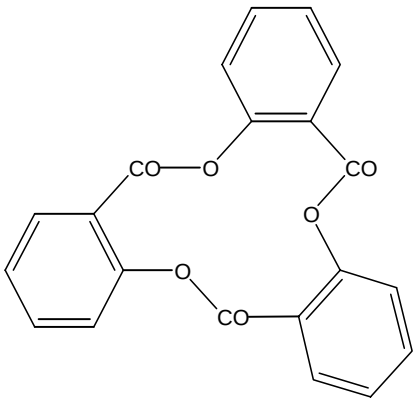
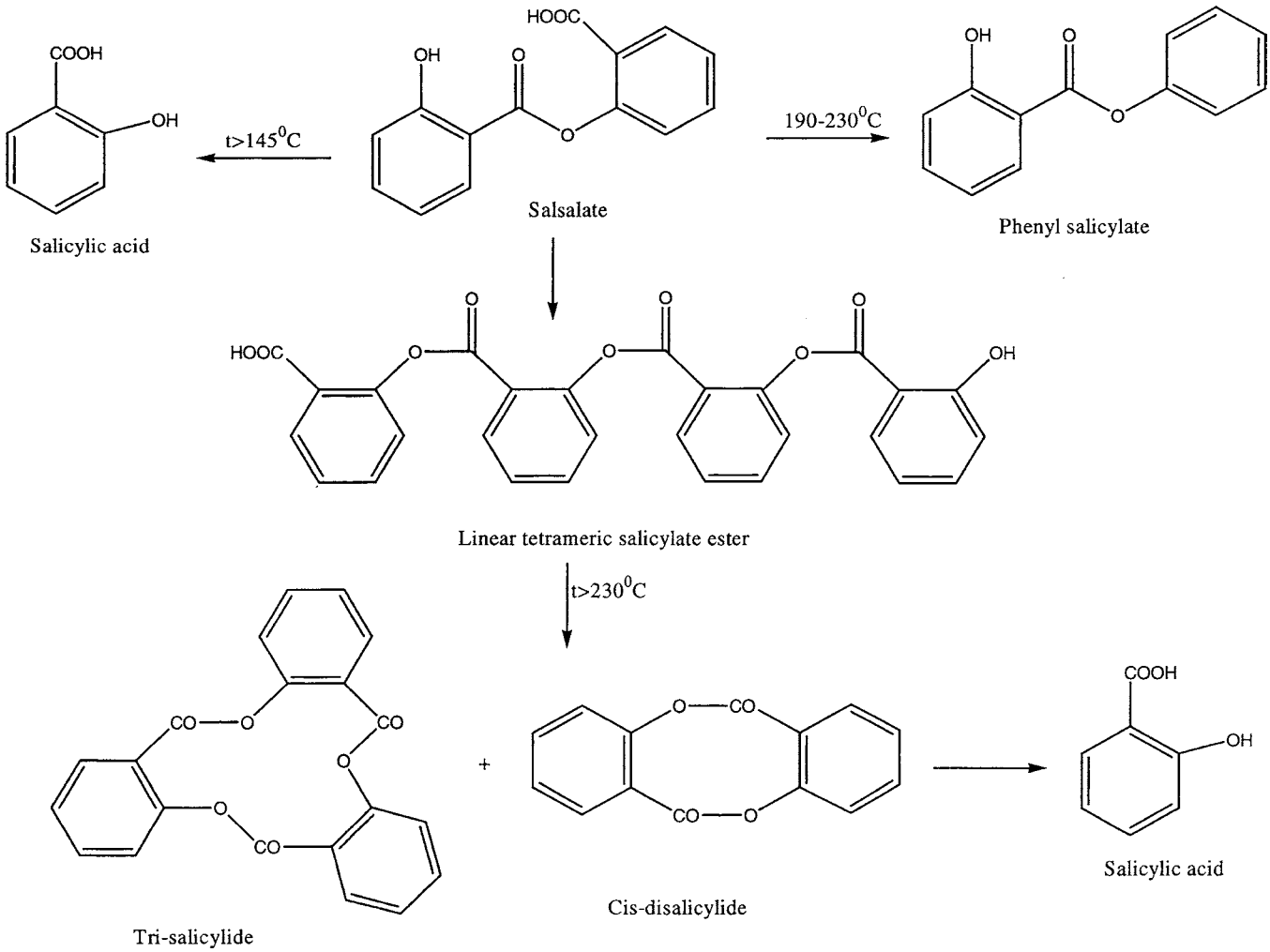


Fig. 6. Structure of tri-salicylide.

substance was analyzed by GC–MS analysis. The mass spectrum of the substance obtained from electrospray ionization (EIS) for negatively charged ions was determined. A molecular ion peak appears at $m/z = 498$, which corresponds to a linear tetramer of salicylic acid (Scheme 1). Further fragmentation produces peaks at $m/z = 376$, 257, and 137. Each of these peaks correspond to the loss of a unit with $m/z = 120$, which corresponds to the molecular weight of a fragment of the tetramer $C_7H_4O_2$ (see Scheme 1), and results from scission of the C–O link. A peak at $m/z = 137$ has the highest intensity and corresponds to the anion of salicylic acid formed from fragmentation of the linear tetramer.

This is the first report of the linear tetramer. Reepmeyer [8] reported the formation of a crystalline compound when salsalate was heated to 150–160 °C, which was identified as a linear oligomeric salicylate ester with a MW of 378 g/mol, an empirical formula $C_{21}H_{14}O_7$, and a melting point of 150 °C. This compound was not found during our GC–MS experiments. Long et al. [14] were able to detect a mixture of a linear trimeric salicylate ester and its acetate derivative during the decomposition of aspirin.

The presence of phenyl salicylate was also confirmed by heating 1 g samples of salsalate to 170 °C and performing LC–MS experiments. The mass spectra from GC–MS and LC–MS experiments were identical with the database mass spectrum for phenyl salicylate.



Scheme 1. Decomposition of salsalate.

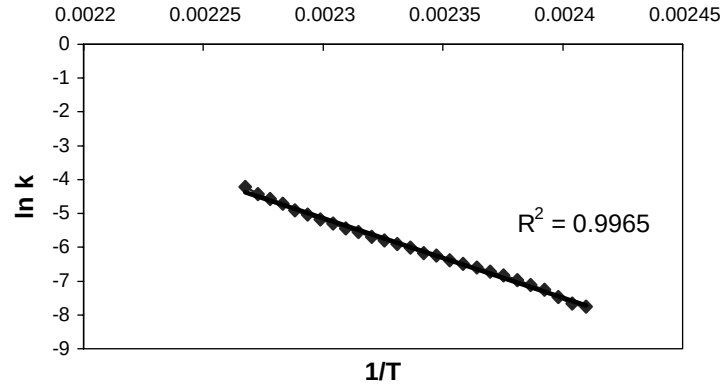


Fig. 7. Typical Arrhenius plot calculated from the first stage mass loss of salsalate using a second-order (F2) kinetic model. Heating rate 2 °C min^{-1}, nitrogen flow 100 ml min^{-1}, particle size 115–137 μm.

3.2. Kinetic analysis

Although the first stage decomposition of salsalate consisted of more than one reaction, the data collected from the mechanistic studies suggested that there was one major reaction, with the formation of salicylic acid and the linear tetramer, and one minor reaction with the formation of phenyl salicylate and phenol. This view is supported by the relative intensities of the peaks in the GC–MS record (Table 1), where the peaks for phenol (derived from the decomposition of phenyl salicylate) (4.69 min) and phenyl salicylate (10.03 min) are extremely small compared to the peak for salicylic acid (7.56 min). Theoretical calculations based on the major reaction indicates an expected mass loss of 52%, which compares well with the observed 52% mass loss. Therefore, it can be concluded that the first mass loss of the decomposition of salsalate is primarily due to the formation of salicylic acid (see Scheme 1). It was decided to attempt kinetic analysis to see if the major reaction was sufficiently dominant to make a reasonable assignment of a kinetic model possible. Similarly, the second decomposition reaction seemed to be dependent on the decomposition of the tetramer with the formation of the cyclic compounds which in turn decompose to salicylic acid. The kinetic analysis of each decomposition step was carried out in the usual manner, by calculation of α, the fraction decomposed, at small rising temperature increments, and then plotting $\ln k$ versus $1/T$. The slope of the line gives $-E/R$, and the intercept gives $\ln A$.

Of the several models evaluated, the second-order (F2) mechanism gave the best straight line fit for plots of $\ln k$ versus $1/T$ (Fig. 7) for the first mass loss. Table 3 presents the E values calculated at various particle sizes, and shows relatively stable E values in the range 191–198 kJ/mol.

Kinetic analysis of the second mass loss showed that a zero-order mechanism was the best fit (Fig. 8). The calculated E values were in the range 72–80 kJ/mol.

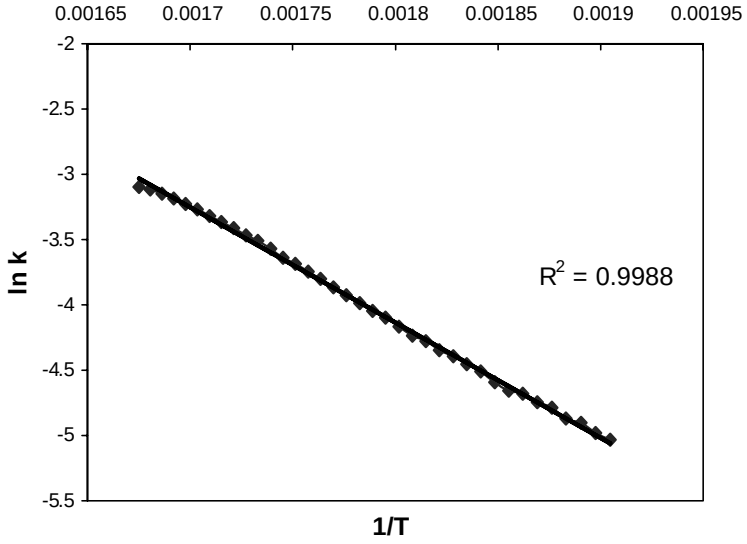


Fig. 8. Typical Arrhenius plot calculated from the second stage mass loss of salsalate using a zero-order kinetic model. Experimental conditions are the same as for Fig. 7.

Table 3
Variation of the activation energy E_a (kJ/mol) and A with particle size calculated by the application of a second-order (F2) kinetic model[a]

Particle size (μm)	E_a (kJ/mol)	ln A
<82	198	51.7
82–98	186	48.4
98–115	197	51.5
115–137	195	50.9
137–165	199	49.7
165–196	191	

[a] Heating rate 2 °C min^{-1}, nitrogen flow 100 ml min^{-1}.

4. Conclusions

The decomposition of salsalate was studied by thermal analysis. It was found that it undergoes a two-stage decomposition process with multiple product formation, with salicylic acid the major product. The residue remaining at 230 °C is the tetrameric salicylate ester, which on further heating undergoes cyclization to yield *cis*-disalicylide and tri-salicylide. The second mass loss is due to the decomposition of *cis*-disalicylide and tri-salicylide to yield more salicylic acid. Kinetic analysis found that the first decomposition stage best fitted to a second-order kinetic model (F2), with calculated energy of activation values of 191–198 kJ/mol. The second decomposition stage is best fitted to a zero-order process with activation energy values of 72–80 kJ/mol.

The GC–MS and LC–MS techniques were found to be useful in identifying the decomposition products from the thermal degradation of salsalate. Clearly, there were differences in the temperature ranges in which reactions took place in the TG–DTA and GC–MS, and some caution must be exercised in extrapolating the GC–MS data to the TG–DTA experiments. However, in this case the results did provide information which seemed to fit the observations and the previously published literature.

References

[1] A. Radecki, M. Wesolowski, Pharm. Acta Helv. 55 (2) (1980) 54–60.
[2] S. Budavari (Ed.), The Merck Index, 8th ed., Merck & Co., Inc., Rahway, NJ, 1989, pp. 930–931.
[3] P.A. April, Arthrit. Rheum. 19 (4) (1990) 20–28.
[4] E.K. Estes, A. Kaplan, Arthrit. Rheum. 23 (1980) 1303–1307.
[5] J. Pulgarin, L. Bermejo, Talanta 51 (2000) 89–98.
[6] B. Cryer, M. Feldman, Am. J. Med. 104 (1998) 413–421.
[7] P. Cox, G. Gilmour, S. McManus, Int. J. Pharm. 204 (2000) 133–136.
[8] J. Reepmeyer, J. Pharm. Sci. 72 (3) (1983) 322–323.
[9] A. Po, P. Mroso, W. Irwing, Int. J. Pharm. 16 (1983) 115–123.
[10] S. Lerdkanchanaporn, D. Dollimore, Thermochim. Acta 324 (1998) 15–23.
[11] P. Argawal, D. Dollimore, Thermochim. Acta 324 (1998) 1–8.
[12] H. Wolfman, M. Patrunky, M. Zimmerman, Zentralblatt fuer Pharmazie, Pharmakotherapie und Laboratoriumdiagnostik 121 (4) (1982) 203–210.
[13] W. Barker, W.D. Ollis, T.S. Zealley, J. Chem. Soc. (1951) 201.
[14] G. Long, S. Vyazovkin, N. Gamble, C. Wight, J. Pharm. Sci. 91 (3) (2002) 800–809.