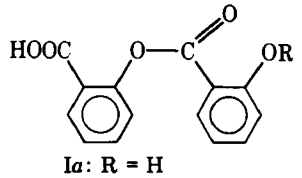
Thermal Decomposition of Aspirin: Formation of Linear Oligomeric Salicylate Esters

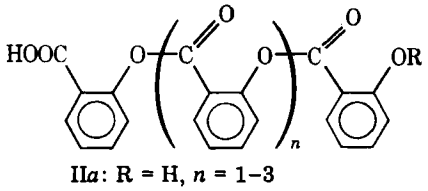
Keyphrases □ Decomposition, thermal—aspirin, formation of linear oligomeric salicylate esters □ Aspirin—thermal decomposition, formation of linear oligomeric salicylate esters □ Salicylate esters—thermal decomposition of aspirin, formation of linear oligomeric salicylate esters

To the Editor:

Although there are numerous reports on aspirin stability or degradation described in terms of decreasing amounts of aspirin or increasing amounts of salicylic acid, few recognize the existence of decomposition products other than salicylic acid. Pyrolysis of aspirin with simultaneous distillation of products at 300–350° (15 mm) produces cyclic polymers of salicylic acid, referred to as salicylides; the *cis*-disalicylide and the trisalicylide have been isolated[1] (1–4). Salicylsalicylic acid (I*a*) (5) and acetylsalicylsalicylic acid (I*b*) (6, 7) have also been recognized as decomposition products of aspirin. Aspirin anhydride (8), salicylsalicylic acid (I*a*) (9), and acetylsalicylsalicylic acid (I*b*) (10) have been detected as impurities in aspirin tablets. Presented here is the discovery that thermal decomposition of aspirin, in the solid state or in organic solution, produces not only



I*a*: R = H
I*b*: R = —$COCH_3$



II*a*: R = H, n = 1–3
II*b*: R = —$COCH_3$, n = 1–4

I*a* and *b*, but higher linear oligomeric salicylate esters (II*a*) and their acetate derivatives (II*b*).

When a mixture of aspirin and magnesium carbonate[2] (2:1) was heated in the solid state at 85° for 2 hr, a complex mixture was obtained[3]. The reverse-phase C-18 high-performance liquid chromatogram of this mixture showed components corresponding in retention time to salicylic acid, I*a*, I*b*, and several components with longer retention times (Fig. 1). Chromatographic separation and crystallization provided several pure compounds, three of which were shown to be salicylic acid, I*a*, and I*b* by comparison with authentic compounds. Compounds with longer retention times had UV spectra characteristic of salicylates.

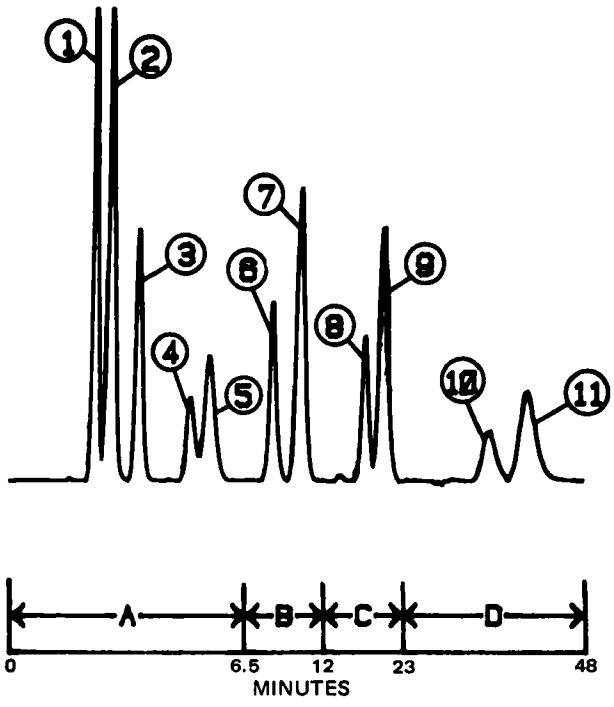


Figure 1—*Reversed-phase C-18 high-performance liquid chromatogram of decomposed aspirin. Mobile phase: water–acetic acid–methanol (420:10:570); flow rate: 2.0 ml/min; detection: UV absorbance at 254 nm. Recorder settings (att = attenuator (2↑), cs = chart speed, cm/min): (A) att 9, cs 0.5; (B) att 6, cs 0.2; (C) att 4, cs 0.1; (D) att 3, cs 0.1. Key (each compound is followed by its retention time in minutes): (1) aspirin, 2.19; (2) salicylic acid, 2.62; (3) Ib, 3.40; (4) Ia, 4.88; (5) IIb (n = 1), 5.40; (6) IIa (n = 1), 8.26; (7) IIb (n = 2), 10.18; (8) IIa (n = 2), 17.23; (9) IIb (n = 3), 19.63; (10) IIa (n = 3), 33.93; (11) IIb (n = 4), 39.13.*

Acetyl compounds (I*b* and II*b*) could be readily differentiated from free phenolic compounds (I*a* and II*a*) by a significant difference in their absorbance maxima (near 278 nm for acetyl compounds and 309 nm for free phenols) in acidic or neutral aqueous alcohol and very rapid cleavage of the acetate esters in 0.01 *N* aqueous ethanolic sodium hydroxide, a reaction completed in 2 min at room temperature, to form the corresponding free phenolic compounds, whose absorbance maxima were near 340 nm in basic solution.

Hydrolysis of the salicylate esters in 0.01 *N* aqueous ethanolic sodium hydroxide occurred over several hours, much slower than acetate ester hydrolysis, and eventually each oligomer (I*a*, I*b*, II*a*, II*b*) was completely converted to salicylic acid (λ_{max} 297 nm). This afforded a means to measure the equivalent weight of each compound in terms of the number of salicyl moieties in the molecule. This technique was suitable for the lower oligomers; however, the higher the oligomer, the closer its equivalent weight approaches those of its neighboring homologues, making it more difficult to differentiate among them.

Like aspirin, I*a* also undergoes thermal decomposition[4]. Being free of acetyl compounds, decomposed I*a* was a

[1] Tetra- and hexasalicylides were also isolated when salicylic acid was treated with phosphorus oxychloride or when salicyloyl chloride was heated (1, 2).

[2] Although aspirin itself decomposes when heated, the rate is greatly accelerated by weak bases such as magnesium carbonate.

[3] A similar mixture was obtained when aspirin was heated in benzene or toluene with or without magnesium carbonate in suspension.

[4] The rate of decomposition of I*a* is slower than that of aspirin. This is attributed to the lower reactivity of the salicylate ester relative to the acetate ester. As with aspirin decomposition, I*a* decomposition is catalyzed by magnesium carbonate.

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much less complex mixture than decomposed aspirin, and its components were more easily separated. The linear trimer (II*a*, $n = 1$) was isolated from decomposed I*a* as a white crystalline solid, mp 150–152°; UV: λ_{max} (ethanol) 228 (ϵ 27,200), 281 (4350), and 310 (4900) nm; IR (chloroform): ν_{max} 1746 (strong, unassociated ester C=O stretching) and 1696 (strong, intramolecular hydrogen-bonded ester C=O stretching[5] and intermolecular hydrogen-bonded acid C=O stretching) cm^{-1}; NMR (deuterochloroform): δ 10.07 (s, 2H, COOH and OH, exchanged with deuterium), 8.43–7.87 (m, 3H, aromatic protons *ortho* to C=O), and 7.87–6.57 (m, 9H, remaining aromatic protons) ppm.

Anal.—Calc. for $C_{21}H_{14}O_7$: C, 66.67; H, 3.73. Found: C, 66.88; H, 3.92.

Compound II*a* ($n = 1$) was acetylated to provide a compound identical to II*b* ($n = 1$) isolated from decomposed aspirin. Compound II*b* ($n = 1$) was obtained as a white crystalline solid, mp 161.5–163°; UV: λ_{max} (ethanol) 227 (ϵ 29,900) and 277 (4500) nm; IR (chloroform): ν_{max} 1750 (strong, C=O stretching of three ester groups) and 1703 (weak, intermolecular hydrogen-bonded acid C=O stretching) cm^{-1}; NMR (deuterochloroform): δ 8.43–7.80 (m, 4H, COOH proton, which exchanged with deuterium, and three aromatic protons *ortho* to C=O), 7.80–6.90 (m, 9H, remaining aromatic protons), and 2.23 (s, 3H, $—CH_3$) ppm.

Anal.—Calc. for $C_{23}H_{16}O_8$: C, 65.72; H, 3.84. Found: C, 65.53; H, 4.03. Compound II*b* ($n = 1$) was also found in several samples of buffered aspirin tablets; it was isolated from one of them and identified.

The tetramer (II*a*, $n = 2$) was isolated from decomposed I*a* as white crystals, mp 177–183° (dec); IR (chloroform): ν_{max} 1744 (strong, stretching of two unassociated ester carbonyl groups) and 1693 (strong, intramolecular hydrogen-bonded ester carbonyl stretching[5] and intermolecular hydrogen-bonded acid carbonyl stretching) cm^{-1}.

Anal.—Calc. for $C_{28}H_{18}O_9$: C, 67.47; H, 3.64. Found: C, 67.63; H, 3.77.

In the aromatic region the NMR spectrum (deuterochloroform) had two multiplets that were not fully resolved until the solution was shaken with deuterium oxide, which indicated that the exchangeable phenolic and carboxylic acid protons were obscured by aromatic proton absorption.

The methyl esters of I*a*, I*b*, trimer (II*a*, $n = 1$), tetramer (II*a*, $n = 2$), and acetyl-trimer (II*b*, $n = 1$) were synthesized by treatment of the acids with methyl iodide; solid–liquid phase transfer catalysis (11) was used to avoid acetate or salicylate ester hydrolysis during methylation. IR spectra for each of the five methyl esters in carbon tetrachloride supported their structures; the following assignments were made for carbonyl stretching frequencies: ν_{max} 1735–1731 (methyl esters), 1758–1754 (unassociated carbonyl of ester groups between aromatic rings), 1700–1695 (intramolecular hydrogen-bonded ester[5]), 1780–1779 (acetate ester) cm^{-1}. The NMR spectrum (deuterochloroform) of each compound had a singlet near δ 3.7 (methyl ester protons) and two multiplets, one downfield from δ 7.8 (aromatic protons *ortho* to C=O) and the other upfield from δ 7.8 (remaining aromatic protons). In addition to these peaks, the spectra of the three phenolic compounds showed a sharp singlet near δ 10.25 (hydroxide proton, which was exchangeable with deuterium), and the spectra of the two acetyl derivatives showed a singlet at δ 2.25 ($CH_3CO_2—$). The integrals of each compound's spectrum gave the proper ratio of protons for the assigned structures.

Additional proof that these compounds were oligomers was provided by their relative retention on a reverse-phase C-18 high-performance liquid chromatogram. Plots of logarithms of capacity factors (k') for a homologous series have been shown to be linear in a number of cases (12). A plot of log k' *versus* number of salicyl moieties for each of the components in decomposed I*a* was found to be linear[6]. Two linear plots were obtained for decomposed aspirin: one for the free phenols[6], components corresponding in retention time to components in decomposed I*a*, and one for the acetyl compounds[7], the remaining components in the chromatogram. The linear oligomers, produced from aspirin at low temperatures as reported here, are undoubtedly precursors to the previously reported cyclic salicylate oligomers (1–4) produced at much higher temperatures.

Sample analyses showed that the levels of linear salicylate oligomers were generally higher in buffered than in plain aspirin tablets. Subsequent experiments revealed that the thermal decomposition reaction was catalyzed by weakly basic substances, such as magnesium hydroxide or magnesium carbonate, compounds often used in buffered aspirin formulations.

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[5] A strong intramolecular hydrogen bond exists between the ester carbonyl on the terminal aromatic ring and the phenolic group *ortho* to it.

[6] Log k' *versus* salicyl moieties was plotted for four compounds corresponding to dimer (I*a*) through pentamer (II*a*, $n = 3$); the correlation coefficient was 0.9994.

[7] Log k' *versus* salicyl moieties was plotted for five compounds corresponding to dimer (I*b*) through hexamer (II*b*, $n = 4$); the correlation coefficient was 0.9998. Each acetyl compound eluted from the C-18 column prior to its corresponding free phenol.