Salicylic Acid

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1. Introduction

Salicylic acid [69-72-7], also called 2-hydroxybenzoic acid or o-hydroxybenzoic acid, is widely distributed in the plant kingdom in the form of esters.

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1. Introduction

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Some 2400 years ago HIPPOCRATES prescribed decoctions of willow leaves as a treatment for fever and pain. The active principle in willow leaves is salicylic acid, whose biosynthesis is based on the deamination of phenylalanine to trans-cinnamic acid which, when hydrolyzed and oxidized at the β-carbon atom, gives salicylic acid.

Salicylate esters are found in several plant genera, the principal ones being Salix, Spiraea, and Gaultheria. For example, methyl salicylate is present in large quantity in the form of a glucoside in birch bark, various spiraeas (meadowsweet or Spiraea ulmaria), and wintergreen leaves.

Salicylic acid was first obtained in 1838 by R. Piria, an Italian chemist at the Institute of Pisa, by melting salicylaldehyde, obtained from meadowsweet, with caustic potash. In 1844 the French chemist CAHOURS obtained salicylic acid by hydrolysis of methyl salicylate. The final step, namely preparation from a natural source, was accomplished in 1874 by the German chemist H. KOLBE, who synthesized the acid by carboxylation of sodium phenoxide, a process still in use.

Salicylic acid and its derivatives are used mainly to synthesize pharmaceutical products and as intermediates in the production of dyes and agrochemical and perfumery products.

2. Physical and Chemical Properties

Physical Properties. Salicylic acid, C7H6O3, Mr 138.12, crystallizes in the form of colorless needles (water) or monoclinic prisms (ethanol), mp 159 ºC; salicylic acid begins to sublime at 76 ºC; flash point (closed cup) 157 ºC; heat of sublimation 81.8 kJ/mol; density $d_2^0$ 1.443; dissociation constants $K_1 1.05 \times 10^{-3}$, $K_2 4.0 \times 10^{-14}$ (19 ºC); vapor pressure 1.66 mbar (110 ºC) and 19.3 mbar (150 ºC); solubility (per 100 g of solution) in methanol 38.46 g (21 ºC), ethanol 34.87 g (21 ºC), chloroform 1.55 g (30 ºC), benzene 1.00 g (30 ºC); solubility (per 100 mL of solution) in diethyl ether 23.4 g (17 ºC), acetone 31.3 g (23 ºC); extremely soluble in ammonia, insoluble in liquid sulfur dioxide. Solubility in water:

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Salicylic acid is an aromatic \( o \)-hydroxy carboxylic acid, and in contrast to its \textit{meta} and \textit{para} isomers (\textit{\textsuperscript{\( \rightarrow \)}} Hydroxycarboxylic Acids, Aromatic, Chap. 4.1.) it is subject to intramolecular hydrogen bonding and steam volatility. It also sublimes more readily than its isomers (\textit{\textsuperscript{\( \rightarrow \)}} Sublimation, Chap. 4.2.1.), and is substantially more acidic: dissociation constants for the \textit{meta} and \textit{para} isomers are \( \approx 8.7 \times 10^{-5} \) and \( \approx 3.3 \times 10^{-5} \), respectively.

**Chemical Properties.** The difunctional salicylic acid molecule combines the properties of phenols with those of aromatic carboxylic acids. One equivalent of alkali hydroxide neutralizes only the carboxyl group. An excess of hydroxide is required to form the dialkali salt, from which the free OH group reforms in the presence of carbon dioxide. Chelation occurs with some metal ions such as Fe(III), leading to a violet coloration. Salicylic acid can be used as an indicator in EDTA determinations of Fe(III) [6].

Salicylic acid is esterified by alcohols in the presence of strong acids without significant etherification. Combined ether–esters can be prepared from dialkali salicylate in the presence of alkyl halide; these are converted by alkaline hydrolysis into the corresponding alkoxybenzoic acids. The phenolic OH group is etherified by an alkaline aqueous solution of dialkyl sulfate, and esterified by the action of acyl halides or acid anhydrides. Reduction with sodium and amyl alcohol affords tetrahydrosalicylic acid, whose oxidation product is pimelic acid [7]. Catalytic hydrogenation of salicylic acid esters over Raney nickel produces esters of cis-trans-2-hydroxycyclohexane carboxylic acid [8].

Since electrophilic reactants attack the less sterically hindered 5-position in preference to the 3-position, it is possible to obtain either 5-substituted or 3,5-disubstituted derivatives directly. For example, the monosubstituted products obtained on nitration, sulfonation, halogenation, alkylation, acylation, or coupling with diazonium salts are generally salicylic acids substituted at the 5-position. Derivatives substituted exclusively at the 3-position are obtained by indirect means, such as substitution of sulfosalicylic acid at the 5-position, followed by elimination of the sulfonic group. More severe conditions may lead to decarboxylation as well. Thus, 2,4,6-trinitrophenol (picric acid) is obtained upon treatment of salicylic acid with fuming nitric acid, and tribromophenol results from treatment with bromine in the presence of water.

When heated at or above its melting point salicylic acid decomposes into phenol and carbon dioxide. Under a carbon dioxide atmosphere at \( 230^\circ \text{C} \) the main product is phenyl salicylate. At \( 250^\circ \text{C} \), xanthone is formed in parallel with phenol. For the behavior of salicylic acid as a function of temperature see [9].

\[ \text{Xanthone} \]

**Analysis.** Quantitative determination of salicylic acid is generally accomplished by titration in an alkaline medium. Kolthoff’s method permits salicylic acid also to be determined with a bromide solution, which converts it to tribromophenol [10]. For trace analysis it is convenient to use colorimetric methods with the reagent iron(III) chloride [11]. Thin-layer chromatography (TLC) provides a convenient test of purity, since each of the isomeric acids can be detected by alkaline coupling (caustic soda) with diazotized \( p \)-nitroaniline, spraying with Fe(III) chloride, or fluorescence under UV light. The TLC approach is often replaced today by reversed-phase high-performance liquid chromatography (HPLC).

3. **Production**

**Kolbe–Schmitt Synthesis.** Salicylic acid is prepared on an industrial scale by the Kolbe–Schmitt synthesis from dry sodium phenoxide in a stream of carbon dioxide at \( 150–160^\circ \text{C} \) and a pressure of 5 bar.

\[ \text{ONa} + \text{CO}_2 \rightleftharpoons \text{COONa} + \text{OH} \]

The use of pressure (SCHMITT, 1884) results in a yield of about 90 %, whereas without pressure (KOLBE, 1874) the yield does not exceed
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50% because disodium salicylate and phenol are formed in equivalent amounts.

\[
\text{CO}_3 \text{Na} + \text{ONa} \rightarrow \text{CO}_3 \text{Na} + \text{OH} \text{-Na}
\]

2 \[
\text{CO}_3 \text{Na} \rightarrow \text{ONa} + \text{OH} + \text{CO}_2
\]

Alternative reaction mechanisms for the carboxylation of phenoxy salts have been described in the literature [12]. 4-Hydroxyisophthalic acid, which yields salicylate by direct release of CO\(_2\) (or by carboxylation of phenolate), has been discussed as a possible intermediate in the reaction process [13]. An electrophilic substitution mechanism via a complex formed between phenol, one molecule of CO\(_2\), and an alkali metal, has also been suggested [14]. Temperature, the nature of the alkali metal, and the CO\(_2\) pressure are all of decisive importance with respect to the reactivity and selectivity of the phenoxy [12, 15].

The various stages in the industrial synthesis of salicylic acid [16] are outlined in Figure 1. Carboxylation may be carried out if in autoclaves heated with steam or heat-exchange fluids and equipped with counterblades, or in powerful mill autoclaves. The process is still conducted mainly in a batchwise manner. To ensure that reaction proceeds satisfactorily, the reaction mass must not only be in a finely ground state during the carboxylation stage, but water must also be rigorously excluded. The presence of water reduces the yield by protonating the phenoxy and releasing alkali-metal hydroxide, which then converts CO\(_2\) into carbonate with the regeneration of water. Water may also be formed in situ via a secondary etherification reaction [15]. Sodium phenoxy is prepared with a 1–2% molar excess of caustic soda; larger amounts of alkali lead to the formation of water, as described above. Anhydrous sodium phenoxy may be prepared either in the autoclave mixer itself by evaporation of an aqueous solution of phenoxy, starting at normal pressure and then gradually introducing vacuum, or in special drying equipment. In order to prevent discoloration and tar formation it is important that the carbon dioxide contains as little oxygen as possible (<0.1%).

The carboxylation step is exothermic: \(\Delta H = -90.1 \text{ kJ/mol}\). Using a 6\(\text{m}^3\) reactor, about 3 t of sodium phenoxy is converted into salicylic acid in 25 h. Phenol derived from the formation of disodium salicylate is recovered by distillation. The crude sodium salicylate is dissolved in a mixture of water and a decolorizing agent (e.g., activated charcoal, aluminum, or zinc powder [17]). Salicylic acid is then precipitated with sulfuric acid. This synthesis can be accomplished in a continuous manner by working with a solution of the anhydrous phenoxy in a suitable medium. Recommended solvents are phenol itself [18], higher alcohols [19], dialkyl ketones [20], nitrobenzene [21] and, as a dispersant [22], gasoline.

Other Processes. Consideration has been given to producing salicylic acid by air oxidation of \(\alpha\)-cresolate at 230°C in the presence of a copper-based catalyst [23] or copper benzoate (175–215°C) [24]. Alkaline copper benzoate can also be converted by heat treatment into salicylate directly [25]. Benzoylsalicylic acid is an intermediate in the synthesis of phenol from toluene by the Dow process (\(\rightarrow\) Phenol, Chap. 4.2.).

Salicylic acid can also be obtained by fermentation of such polycyclic aromatic compounds as naphthalene with the aid of microorganisms [26] (\(\rightarrow\) Biotechnology).

4. Quality Specifications, Storage and Transportation, and Environmental Protection

Quality Control. Technical-grade salicylic acid obtained from the Kolbe–Schmitt process is already extremely pure: salicylic acid content 99.5%; phenol, \(p\)-hydroxybenzoic acid, or 4-hydroxisophthalic acid 0.05–0.1% (as impurity); ash < 0.1%; water 0.2%.

An even higher quality acid (pharmaceutical grade) can be obtained by crystallizing the sodium salicylate from water at a temperature not exceeding 20°C [27], or by sublimation of the acid at 20 mbar and a temperature of 154°C.
Salicylic Acid

Figure 1. Simplified representation of salicylic acid production by the Kolbe–Schmitt method

[28] or with the aid of a carrier gas. A more modern process achieves sublimation directly by utilizing the heat of neutralization from the reaction of sodium salicylate with hydrogen chloride [29].

The quality specifications of the European Pharmacopoeia are limited to the following items: identity check; color (ethanolic solution); melting point (158–161 °C); assay (99.0–100.5 %); if sulfated ash (< 0.1 %); heavy metals (< 20 ppm); chloride (< 100 ppm); if sulfates (< 200 ppm); and loss on drying < 0.5 %.

Storage and Handling. Salicylic acid dust is combustible in air. The low combustion energy for the process indicates a high level of combustion sensitivity, so appropriate measures must be adopted to avoid sources of ignition and to protect against potentially severe explosive effects. Explosive conditions can be avoided by maintaining the oxygen level at < 8 %.

The explosive characteristics of salicylic acid dust (particle size < 100 µm) are as follows: minimum combustion temperature, 490 °C; minimum combustion concentration, 30 g/m³; minimum combustion energy, < 5 mJ; maximum pressure produced, 7.2 bar; maximum rate of pressure increase, 216 bar/s [unpublished work carried out by Rhône-Poulenc in accordance with ISO 6184/1].

Transportation. Salicylic acid is not subject to any transport restrictions. The acid is transported in bags (25 kg), drums (50 kg), big bags (500–1000 kg), or bulk containers (15–20 t).

Environmental Protection. Effluent and gaseous emission problems are comparable to those posed by phenol.

Freshwater ecotoxicity of salicylic acid on Daphnia magna: (ED₅₀, 24 h; immobilization): 180 mg/L (AFNOR T 90 301 Standard, French). Salicylic acid is readily biodegradable and very slightly bioaccumulable.

5. Uses and Economic Aspects

Salicylic acid is used mainly in the synthesis of acetylsalicylic acid, the most commonly dispensed pharmaceutical product. In the form of esters, amides, and salicylic acid salts it serves as a starting material for other pharmaceutical products. Technical-grade salicylic acid is used primarily as an intermediate in the production of agrochemical products, dyes, and colorants, as well as in the rubber industry and in the manufacture of phenolic resins.

Salicylic acid itself offers therapeutic benefits in the treatment of rheumatic disorders, for which purpose it is usually administered in the form of the readily soluble sodium salt. On account of its keratolytic action the acid is also widely used for cleaning the skin and removing scales.

By virtue of its bacteriostatic properties it is used as a disinfectant or preservative; however, its presence is not permitted in foods.
Economic Importance. The distribution of salicylic acid in terms of application can be estimated as follows: acetylsalicylic acid 55%, esters and salts 18%, resins 10%, dyes and colorants 10%. The development and introduction of new analgesics that compete aggressively with acetylsalicylic acid has had a direct effect on market evolution, and a steady decline in the consumption of acetylsalicylic acid has been observed. It is expected that the discovery of new uses will stabilize the situation.

6. Salicylic Acid Derivatives

Salts. The carboxyl group in salicylic acid is easily converted into salts by the action of metal carbonates. In order to prevent discoloration, aqueous salt solutions should be kept slightly acidic. Salts are obtained in solid form by concentrating their aqueous solutions.

Sodium salicylate \([54-21-7]\), \(C_7H_5NaO_3\), \(M_t\) 160.11, forms white, odorless, shiny crystalline flakes; solubility (in a solution of 100 mL): water 125 g (25°C), ethanol 17 g (15°C). The technical-grade product (99.5%) is obtained by evaporating a solution of sodium salicylate; pharmaceutical-quality material [30] is prepared by two successive crystallizations of sodium salicylate hexahydrate from a 45% aqueous solution at 10°C. Sodium salicylate is used as an analgesic, antipyretic, and antineuralgic.

Other Salts. Besides sodium salicylate, a number of other common salts are known (e.g., ammonium, magnesium, calcium, aluminum), as is morpholine salicylate. Several of the salts are marketed under various trade names.

Esters. Several important salicylate esters are described below (→ Flavors and Fragrances, Chap. 2.6.5.). These are formed by reaction with the appropriate alcohols. All are soluble in both ether and alcohol, but only sparingly soluble in water.

Methyl salicylate [119-36-8], oil of wintergreen, \(C_9H_8O_3\), \(M_t\) 152.15, is a colorless, oily liquid with a characteristic odor, \(mp - 9°C\), \(bp 222°C\), \(d^20°\) 1.184. Methyl salicylate is synthesized by heating a mixture of salicylic acid and methyl alcohol in the presence of sulfuric acid. It is used to treat neuralgia and rheumatism, as well as to stimulate capillary blood circulation. It is also used as an insecticide, sunscreen, fragrance, and synthetic intermediate.

Benzyl salicylate [118-58-1], \(C_{14}H_{12}O_3\), \(M_t\) = 228.25, is a clear liquid or colorless to opaque crystalline mass with a characteristic odor, \(mp 24°C\), \(bp 318°C\), \(d^15°\) 1.180. It is obtained from a mixture of sodium salicylate and benzyl chloride, or by transesterification of methyl salicylate in the presence of benzyl alcohol. It is present in ylang-ylang and carnation oils, and is widely employed as an additive in soaps, in detergents, and in perfumery products (→ Benzyl Alcohol, Chap. 8.4.).

Isoamyl salicylate [87-20-7], \(C_{13}H_{16}O_3\), \(M_t\) 208.26, is a colorless liquid with the fragrance of orchids, \(bp 270°C\), \(d^20°\) 1.050. Isoamyl salicylate is used as a fragrance and stabilizer in perfumery and as an antirheumatic agent (topical application).

Phenyl salicylate [118-55-8], salol, \(C_{12}H_{10}O_3\), \(M_t\) 241.22, is a colorless, crystalline powder, \(mp 43°C\), \(bp 172°C\) at 16 mbar. It is obtained from a mixture of salicylic acid and phenol in the presence of sulfuric acid, or by transesterification of methyl salicylate in the presence of sodium phenoxide. Phenyl salicylate is used as an antiseptic, preservative, as a sunscreen and a general photoprotective agent for synthetic products, and as an emollient.

Acetylsalicylic Acid (→ Analgesics and Antipyretics, Chap. 2.1.; → Anti-inflammatory – Antirheumatic Drugs, Chap. 3.1.; → Cardiovascular Drugs, Chap. 5.3.1.1.). Acetylsalicylic acid [50-78-2], \(C_9H_8O_4\), \(M_t\) 180.15, is isolated as monoclinic colorless needles or crystalline powder (from water), or as flat platelets (from isoamyl alcohol), \(mp 143 – 144°C\) depending on the heating rate and crystalline form; dissociation constant \(K = 2.8 × 10^{-4}\) (25°C); solubility (in 100 mL of solvent): water 0.25 g (15°C), ethanol 20 g (25°C), ether 5 g (18°C). The compound hydrolyzes to some extent during recrystallization from water.

Acetylsalicylic acid is prepared by reacting acetic anhydride with salicylic acid at a temperature of < 90°C either in a solvent (e.g., acetic acid or aromatic, acyclic, or chlorinated hydrocarbons) or by the addition of catalysts such as
acids or tertiary amines [31]; for quality specifications see [30]. Acetylsalicylic acid is used as an antipyretic, analgesic, and anti-inflammatory agent, and it has an antirheumatic effect. Acetylsalicylic acid also has antithrombosis and anticoagulant properties. It is marketed by Bayer as a consumer product under the trade name Aspirin and as a bulk product by Rhône-Poulenc (Rhone).

Other Derivatives.

**Salicylamide** [65-45-2], C\(_7\)H\(_7\)NO\(_2\), \(M_r\) 137.13, is a white crystalline powder, mp 140 °C, sparingly soluble in water and soluble in alcohol. It is obtained by the ammonolysis of methyl salicylate [32]. Salicylamide is used as an analgesic, antipyretic, antirheumatic, sedative, and fungicide.

**Salicylanilide** [87-17-2], C\(_{13}\)H\(_{11}\)NO\(_2\), \(M_r\) 213.33, forms colorless and odorless crystals, mp 136–137 °C. It is sparingly soluble in water and soluble in alcohol and chloroform. The substance is prepared from a mixture of salicylic acid and aniline in the presence of PCl\(_3\) [33]. Salicylanilide and particularly its derivatives are powerful fungicides, and are used in the synthesis of dyes, colorants, lacquers, and textiles, and also as a disinfectant. It is distributed commercially under the trade name Shirlan (ICI).

**3-Chlorosalicylic acid** [1829-32-9], 3-chloro-2-hydroxybenzoic acid, C\(_7\)H\(_5\)ClO\(_3\), \(M_r\) 172.57, mp 180 °C, is obtained either by the carboxylation of sodium 2-chlorophenoxide (Kolbe–Schmitt synthesis) or by chlorination of 5-sulfosalicylic acid, followed by displacement of the sulfonic group by means of superheated steam [34] (ICl). It is used as an intermediate in the synthesis of agrochemical products and disinfectants. The ethanolamine salt of 5-chlorosalicylic acid 4-nitro-2-chloroanilide (Bayluscid, Bayer) is used as an antiparasitic agent to combat schistosomiasis (→ Molluscicides).

**5-(2,4-Difluorophenyl)salicylic acid** [22494-42-4] (Diflunisal, Merck), C\(_{13}\)H\(_8\)F\(_2\)O\(_3\), \(M_r\) 250.20, mp 212–213 °C.

This compound can be prepared by acetylation of 2,4-difluorobiphenyl, followed by oxidation to 4-acetyloxy-2,4′-difluorobiphenyl which, when heated under pressure in the presence of potassium carbonate and carbon dioxide, undergoes hydrolysis and carboxylation [37]. Diflunisal is a newly marketed analgesic [38] (→ Analgesics and Antipyretics, Chap. 2.1.; → Antiinflammatory–Antirheumatic Drugs, Chap. 3.1.).

7. Toxicology

Salicylic acid and its derivatives are resorbed by the skin and mucous membranes. Salicylic acid esters dissociate hydrolytically under the influence of esterases. Depending on the pH of the urine, salicylic acid is either oxidized to gentisic acid, or it is eliminated by the kidneys in the form of salicyluretic acid or glucuronide salicylate. Since the elimination rate of salicylic acid is lower than the rate of resorption, in certain cases there is a danger that it may accumulate in the body.

Salicylic acid has keratolytic activity and is a tissue irritant. In the stomach this irritant action affects mainly the mucous-producing cells and striated cells. Long-term treatment with
Salicylates slows the rate of blood coagulation by reducing platelet aggregation. Prostaglandin biosynthesis is also inhibited by salicylic acid and its derivatives, which partly explains their anti-inflammatory action. The acid and its derivatives display antipyretic and analgesic effects, and are fungicides and bacteriostatic agents [39].

Symptoms of cutaneous and pulmonary hypersensitivity to salicylates are well known, but it appears that these reactions are not always the result of true allergy. A decrease in the synthesis of prostaglandins and, consequently, other biologically active mediators is evidently involved here as well. Cross-sensitization has been established, for example, between methyl salicylate and acetylsalicylic acid [40–42].

One-time doses in excess of 10 g may prove fatal. The main cause of such acute intoxication is the disturbance of the acid–base equilibrium. Severe cases of intoxication may produce delirium, tremor, respiratory insufficiency, sweating, exsiccosis, hyperthermia, or coma. Symptoms of less severe intoxication include hyperventilation, tinnitus, nausea, vomiting, impaired vision and hearing, vertigo, and nervous disorders.

In the case of chronic intoxication, symptoms include digestive disorders and gastric and intestinal pain, sometimes with serious hemorrhaging, which nevertheless often remains hidden. Salicylate-induced anaemia, which may be observed in cases of chronic administration, is an iron deficiency due to hidden bleeding. In the elderly the symptoms of chronic intoxication are often of a neuropsychiatric nature, including confusion and agitation. Despite the very harmful effects of salicylates on tissues, no hepatic or renal problems have been reported to date following chronic administration of pure forms of the compound [34,43–45].

Experiments with various species of animals have shown that administration of relatively large doses of salicylic acid and its derivatives may have a teratogenic effect. The causative agent is probably salicylic acid. These findings have never been confirmed in humans, however, and there are no grounds for concern assuming the maintenance of appropriate hygiene and proper working conditions [46–49]. In addition to possible local symptoms of irritation due to salicylic acid and its derivatives, the major safety consideration is a risk of allergy. All renewed contact with these products should be avoided by those with a previous history of hyperallergic reactions.

8. References

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Salpeter $\rightarrow$ Nitrates and Nitrites
Saluretics $\rightarrow$ Diuretics
Samarium $\rightarrow$ Rare Earth Elements