Benzoic Acid

1 Nonproprietary Names

BP: Benzoic acid
JP: Benzoic acid
PhEur: Acidum benzoicum
USP: Benzoic acid

2 Synonyms

Benzenecarboxylic acid; benzeneformic acid; carboxybenzene; dracylic acid; E210; phenylcarboxylic acid; phenylformic acid.

3 Chemical Name and CAS Registry Number

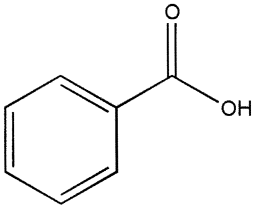
Benzoic acid [65-85-0]

4 Empirical Formula and Molecular Weight

$C_7H_6O_2$

122.12

5 Structural Formula



6 Functional Category

Antimicrobial preservative; therapeutic agent.

7 Applications in Pharmaceutical Formulation or Technology

Benzoic acid is widely used in cosmetics, foods, and pharmaceuticals (*see* Table I), as an antimicrobial preservative.[1–3] Greatest activity is seen at pH values between 2.5–4.5; *see* Section 10.

Benzoic acid also has a long history of use as an antifungal agent[4] in topical therapeutic preparations such as Whitfield's ointment (benzoic acid 6% and salicylic acid 3%).

Table I: Uses of benzoic acid.

Use	Concentration (%)
IM and IV injections	0.17
Oral solutions	0.01–0.1
Oral suspensions	0.1
Oral syrups	0.15
Topical preparations	0.1–0.2
Vaginal preparations	0.1–0.2

8 Description

Benzoic acid occurs as feathery, light, white or colorless crystals or powder. It is essentially tasteless and odorless or with a slight characteristic odor suggestive of benzoin.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for benzoic acid.

Test	JP 2001	PhEur 2002	USP 25
Identification	+	+	+
Characters	—	+	—
Congealing range	121–124°C	121–124°C	121–123°C
Water	≤0.5%	—	≤0.7%
Residue on ignition	≤0.05%	—	≤0.05%
Sulfated ash	—	≤0.1%	—
Readily carbonizable substances	+	+	+
Readily oxidizable substances	+	+	+
Heavy metals	≤20 ppm	≤10 ppm	≤0.001%
Halogenated compounds and halides	+	≤300 ppm	—
Appearance of solution	—	+	—
Assay	≥99.5%	99.0–100.5%	99.5–100.5%

10 Typical Properties

Acidity/alkalinity: pH = 2.8 (saturated aqueous solution at 25°C)

Antimicrobial activity: only the undissociated acid shows antimicrobial properties, the activity therefore depends on the pH of the medium. Optimum activity occurs at pH values below 4.5; at values above pH 5, benzoic acid is almost inactive.[5] It has been reported that antimicrobial activity is enhanced by the addition of protamine, a basic protein.[6]

Bacteria: moderate bacteriostatic activity against most species of Gram-positive bacteria. Typical MIC is 100 µg/mL. Activity is less, in general, against Gram-negative bacteria. MIC for Gram-negative bacteria may be up to 1600 µg/mL.

Molds: moderate activity. Typical MICs are 400–1000 µg/mL at pH 3; 1000–2000 µg/mL at pH 5.

Spores: inactive against spores.

Yeasts: moderate activity. Typical MIC is 1200 µg/mL. The addition of propylene glycol may enhance the fungistatic activity of benzoic acid.

Autoignition temperature: 570°C

Boiling point: 249.2°C

Density:

1.311 g/cm^3 for solid at 24°C
1.075 g/cm^3 for liquid at 130°C

Dissociation constant: the dissociation of benzoic acid in mixed solvents is dictated by specific solute–solvent interactions as well as by relative solvent basicity. Increasing the organic solvent fraction favors the free acid form.[7]
pK_a = 4.19 at 25°C
pK_a = 5.54 in methanol 60%
Flash point: 121–131°C
Melting point: 122°C (begins to sublime at 100°C).
Moisture content: 0.17–0.42% w/w
Partition coefficients:
Benzene : water = 0.0044[8]
Cyclohexane : water = 0.30[9]
Octanol : water = 1.87[10]
Refractive index:
n_D^{15} = 1.5397 for solid
n_D^{132} = 1.504 for liquid
Solubility: apparent aqueous solubility of benzoic acid may be enhanced by the addition of citric acid or sodium acetate to the solution; *see* Table III.

Table III: Solubility of benzoic acid.

Solvent	Solubility at 25°C unless otherwise stated
Acetone	1 in 2.3
Benzene	1 in 9.4
Carbon disulfide	1 in 30
Carbon tetrachloride	1 in 15.2
Chloroform	1 in 4.5
Cyclohexane	1 in 14.6[9]
Ethanol	1 in 2.7 at 15°C 1 in 2.2
Ethanol (76%)	1 in 3.72[11]
Ethanol (54%)	1 in 6.27[11]
Ethanol (25%)	1 in 68[11]
Ether	1 in 3
Fixed oils	Freely soluble
Methanol	1 in 1.8
Toluene	1 in 11
Water	1 in 300

11 Stability and Storage Conditions

Aqueous solutions of benzoic acid may be sterilized by autoclaving or by filtration.

A 0.1% w/v aqueous solution of benzoic acid has been reported to be stable for at least 8 weeks when stored in polyvinyl chloride bottles, at room temperature.[12]

When added to a suspension, benzoic acid dissociates, with the benzoate anion adsorbing onto the suspended drug particles. This adsorption alters the charge at the surface of the particles, which may in turn affect the physical stability of the suspension.[13]

The bulk material should be stored in a well-closed container in a cool, dry place.

12 Incompatibilities

Undergoes typical reactions of an organic acid, e.g. with alkalis or heavy metals. Preservative activity may be reduced by interaction with kaolin.[14]

13 Method of Manufacture

Although benzoic acid occurs naturally, it is produced commercially by several synthetic methods. One process involves the continuous liquid-phase oxidation of toluene in the presence of a cobalt catalyst at 150–200°C and 0.5–5.0 MPa (5.0–50.0 atm) pressure to give a yield of approximately 90% benzoic acid.

Benzoic acid can also be produced commercially from benzotrichloride or phthalic anhydride. Benzotrichloride, produced by chlorination of toluene, is reacted with 1 mole of benzoic acid to yield 2 moles of benzoyl chloride. The benzoyl chloride is then converted to 2 moles of benzoic acid by hydrolysis. Yield is 75–80%.

In another commercial process, phthalic anhydride is converted to benzoic acid, in about an 85% yield, by hydrolysis in the presence of heat and chromium and disodium phthalates.

Crude benzoic acid is purified by sublimation or recrystallization.

14 Safety

Ingested benzoic acid is conjugated with glycine in the liver to yield hippuric acid, which is then excreted in the urine;[15] care should be taken when administering benzoic acid to patients with chronic liver disease.[16] Benzoic acid is a gastric irritant, and a mild irritant to the skin.[17–19] It is also a mild irritant to the eyes and mucous membranes.[20] Allergic reactions to benzoic acid have been reported, although a controlled study indicated that the incidence of urticaria in patients given benzoic acid is no greater than in those given a lactose placebo.[21]

The WHO acceptable daily intake of benzoic acid and other benzoates, calculated as benzoic acid, has been set at up to 5 mg/kg body-weight.[22,23] The minimum lethal human oral dose of benzoic acid is 500 mg/kg body-weight.[24]

LD_{50} (cat, oral): 2 g/kg[24]
LD_{50} (dog, oral): 2 g/kg
LD_{50} (mouse, IP): 1.46 g/kg
LD_{50} (mouse, oral): 1.94 g/kg
LD_{50} (rat, oral): 1.7 g/kg
See also Sodium benzoate.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Benzoic acid may be harmful by inhalation, ingestion, or skin absorption and may be irritant to the eyes, skin, and mucous membranes. Benzoic acid should be handled in a well-ventilated environment; eye protection, gloves, and a dust mask or respirator are recommended. Benzoic acid is flammable.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (IM and IV injections, irrigation solutions, oral solutions, suspensions, syrups and tablets, rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Sodium benzoate.

18 Comments

Benzoic acid is known to dimerize in many nonpolar solvents. This property, coupled with pH-dependent dissociation in aqueous media, comprises a classic textbook example of the effects of dissociation and molecular association on apparent partitioning behavior. The principles involved may be practically applied in determination of the total concentration of benzoate necessary to provide a bacteriostatic level of benzoic acid in the aqueous phase of an oil-in-water emulsion.

The EINECS number for benzoic acid is 200-618-2.

19 Specific References

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22 Date of Revision

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