

A Literature Review on the Synthesis of para-hydroxybenzoic Acid

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Abstract –In this paper, a review on the synthesis and characteristic of hydroxybenzoic acid, particularly para-hydroxybenzoic acid are discussed. An overview of the physical properties and chemical characteristics of para-hydroxybenzoic acid is provided. Different synthesis methods and mechanisms involved for the production of para-hydroxybenzoic acid and their analysis are presented. Para-hydroxybenzoic acid is used as the starting material for the preparation of various parabens.

Keywords— Synthesis, para-hydroxybenzoic acid, physical properties, chemical properties.

Introduction

Para-hydroxybenzoic acid and their derivatives have found a wide applications as food preservatives and stabilizers (antioxidants), as well as for synthesis of liquid crystalline polyethers [1-3]. Para-hydroxybenzoic acid is a phenolic derivative of benzoic acid. It is a white crystalline solid that is slightly soluble in water and chloroform but more soluble in polar organic solvents such as alcohols and acetone. Para-hydroxybenzoic acid is isomeric with 2-hydroxybenzoic acid, known as salicylic acid, a precursor to aspirin. Para-hydroxybenzoic acid can be synthesized by both chemical and biological method. Para-hydroxybenzoic acid is primarily known as the basis for the preparation of its esters, known as parabens, which are used as preservatives in cosmetics and some ophthalmic solutions. Parabens have been attracting great interest because of their importance in synthetic organic chemistry. Parabens have been widely used as antimicrobial preservative agents in foods, beverages, drugs and cosmetics for more than fifty years due to their broad antimicrobial spectrum, [4]. Paraben are very versatile in terms of food preservatives, differing from the other preservatives such as benzoates, propionates and sorbates because they are not weak acid compounds but have a wide pH range. The antimicrobial

activity of parabens is directly dependent on the chain length [5, 6]. In the plant world, 4-hydroxybenzoic acid and its derivatives are commonly found in various vegetable foods, such as barley, strawberries, black currants, peaches, carrots, onions, cocoabeans, vanilla; further in foods prepared from fruit plants such as grapes and fruit juices, yeast extract, wine vinegar and also in cheeses [7]. Methyl paraben found application in the synthesis of dimethyl 4, 4-(tetraphaioyldioxy) dibenzoates as a reactant for monomer preparation [8]. Methyl and propyl p-hydroxybenzoate are used in Rhannolipid based formulation for fire suppression and chemical and biological hazards [9]. Methyl and propyl p-hydroxy benzoates are used in collagen or gelatin based crumble as a preservatives [10]. Polyester is a manufactured fiber in which the fiber-forming substance is any long-chain, synthetic polymer composed of at least 85% of an ester of a substituted aromatic carboxylic acid [11].

Physical and Chemical properties

Para-hydroxybenzoic acid are organic compounds containing hydroxyl group and carboxylic acid group. The chemical formula of PHBA is C₇H₆O₃ with CAS Number of 99-96-7.

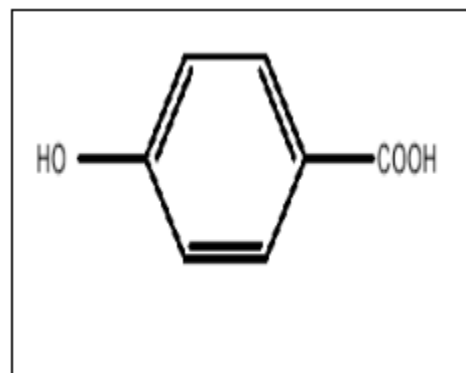


Fig 1: Structure of p-HBA

Physical State: solid, white crystalline powder

Odor : Odorless

Molecular Weight: 138.121 g/mol

Conversion factors: 1 ppm = 5.65 mg/m³; 1 mg/m³ = 0.18 ppm

Melting Point: 214-217 °C (338 °F).

Boiling Pt: 216.2 °C (421.2 °F)

Vapor Pressure: 2.9 x 10⁻⁶ mm Hg at 100 °C (212 °F), 1.9 x 10⁻⁷ mm Hg at 100 °C

Saturated Vapor Concentration: 3.8 x 10⁻³ mm Hg at 100 °C (212 °F)

Specific gravity: 1.46

Vapor Density (air = 1): 4.76

Solubility: 6.0 g/L @ 25°C in water; soluble in diethyl ether, acetone, very slightly soluble in cold water. It is freely soluble in alcohol, slightly soluble in chloroform, practically insoluble in carbon disulfide.

Stability and Reactivity: Stable in water at pH, 7 and 9. Incompatible with oxidizing agents, reducing agents

Partition coefficient (Log Pow): 1.37 pK₁= 4.582, pK₂= 9.23

Synthesis method of p-HBA

Para-hydroxybenzoic acid can be synthesized by both physical and chemical method

□ Chemical method

According to Liu Guoping, Tong Guomin, money Jianhua studied the method of synthesis of p-HBA by reacting phenol with potassium hydroxide. A 50% solution of KOH, phenol and kerosene and isooctanol certain ingredients, with the mass ratio of 1:1:2, put into the reactor, at about 120°C and atmospheric pressure All above were transferred to the carboxylation reactor, while carboxylation with CO₂ was done until the temperature of the reactor was 200°C, and the pressure was 0.4 MPa, the reaction was completed after about 4 h. After carboxylation reaction, demineralized water was added to the material, to obtain an aqueous solution of potassium benzoic acid. Potassium, unreacted phenol and the solvent is recycled to the reactor into a salt, separating by phase separation process to achieve phase column. p-hydroxybenzoic acid containing solid material to the centrifuge separation and is washed with water to obtain a solid p-hydroxybenzoic acid, p-hydroxybenzoic acid and the product was obtained by drying & the drying temperature 160°C. According to Toshinobu Suzuki, Makiko Ijiri, Hitoshi

Saima, Tadahiro Wakui invented an improved process for preparing para-hydroxybenzoic acid comprises of reacting potassium phenol with carbon dioxide in an inert reaction medium or without using a reaction medium in the presence of at least one compound selected from the group consisting of the compounds represented by general formula I or II wherein compounds I and II are sources of potassium and are substantially free from carboxylation during said process at a reaction temperature of 230-450°C and at a carbondioxide pressure ranging from atmospheric pressure to 6 kg/cm². A pressure vessel was charged with 6.62 g of potassium phenolate and 25 ml of NeoSK-1400 (a dibenzyltoluene mixture medium produced by Soken Chemical K.K. With stirring at 1,000 r.p.m., reaction was carried out at a carbon dioxide pressure of 8 kg/cm² (G) and 230° C. for one hour. An analysis of the reaction product after conversion to acid form showed a para-hydroxybenzoic acid yield of 46.4% on the basis of the potassium phenolate, with 1.7% salicylic acid forming as a by-product. According to Irwin Pearl studied a reaction between p-hydroxybenzaldehyde and sodium hydroxide in the presence of water. The whole mixture was stirred properly .to this mixture silver nitrate was added. An immediate reaction took place and the temperature rose considerably. The mixture was stirred for 30 minutes without heating and filtered. The precipitated spongy silver was washed with water and was stored under water. The combined filtrate and washings were acidified with sulfur dioxide to give p-hydroxybenzoic acid melting at 212-213°C The aqueous filtrate, upon saturating with sodium chloride and extracting with ether, yielded an additional of p-hydroxybenzoic acid melting at 207-209 °C which, upon crystallization from water, melted at 212-21 °C. A. Suerbaev, G. B. Akhmetova, and K. M. Shalmagambetov found a method for para carboxylation of phenol with potassium ethyl carbonate. Previously Jones [5] reported the synthesis in 50% yield of salicylic acid by heating to 175°C of a mixture of sodium ethyl carbonate with phenol; with potassium ethyl carbonate, a mixture of salicylic acid and p-hydroxybenzoic acid was obtained (yield 30%). However, by performing the reaction in the conditions in [5] we failed to obtain the target products (o- and p-hydroxybenzoic acids) because of the oxidative

condensation and compaction that resulted in tarring and charring of the reaction mixture. Previously they studied in detail carboxylation of arenes with metal alkyl carbonates [6]. They found that alkaline metal alkyl carbonates can be used to success in carboxylation of phenols and naphthols. The reactions were shown to be strongly affected by the nature of the metal in the salt, nature of the gas medium (air, argon, carbon dioxide), temperature, and pressure. Blanka Vrchtová, Martina Macková, Tomáš Macek and Kateřina Demnerová studied the synthesis of p-hydroxybenzoic acid from p-chlorobenzoic acid. The reaction pathway is as follows:

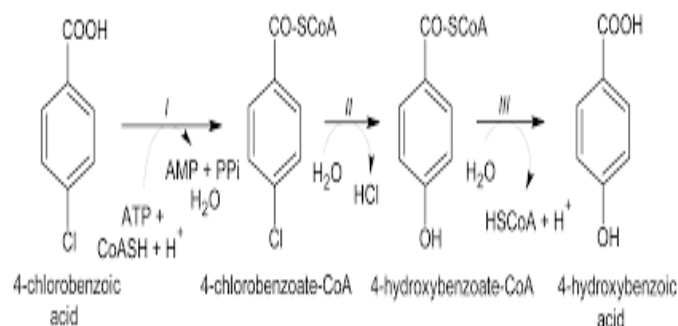


Fig. 2: p-HBA from p-chlorobenzoic acid

This pathway begins with the conversion of 4-CBA to 4-chlorobenzoate-CoA catalyzed by 4-chlorobenzoate: CoA ligase with the consumption of 1 molecule of ATP. This reaction is followed by replacement of chlorine atom with hydroxyl group- derived from water catalyzed by 4-chlorobenzoate:CoA dehalogenase. The last step of 4-CBA dehalogenation is the hydrolysis of 4-hydroxybenzoate-CoA thioester by the enzyme 4-hydroxybenzoate:CoA thioesterase with formation of 4-hydroxybenzoate.

➤ Biological Method:

V. Kumar, N. Thakur, T. Bhalla studied the biological method for the synthesis of p-HBA.

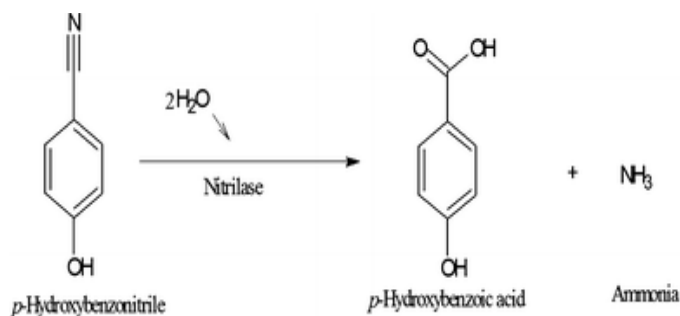


Fig. 3: p-HBA from p-hydroxybenzoinitrile

Mutants of *Gordonia terrae* were generated using chemical mutagens for better activity, stability and higher

substrate/product tolerance of its nitrilase enzyme. Mutant E9 showed two-time increase in activity and tolerated p-hydroxybenzoinitrile (p-HBN) up to 50 mM. Response surface methodology and inducer mediation approach further enhanced the production of enzyme to 2.5-fold. The bench scale production of p-hydroxybenzoic acid (p-HBA) was carried out in a fed-batch reaction (500-mL scale) using whole-cell nitrilase of mutant E9 in 0.1 M potassium phosphate buffer (pH 8.0) at 40 °C. Total six feedings each at an interval of 45 min resulted in accumulation of 360 mM (21.6 g) of p-HBA with a purity of 99 %. The catalytic and volumetric productivity of bioprocess using mutant *G. terrae* was improved to 1.8 g h⁻¹ gDCW⁻¹ and 43.2 g L⁻¹, respectively, from 0.78 g h⁻¹ gDCW⁻¹ and 28.8 g L⁻¹ using resting cells of wild strain. *K_m* and *V_{max}* of purified nitrilase from mutant E9 were 55 U mg⁻¹ and 1.8 mM for p-HBN with a higher turnover number of 36 s⁻¹ × 10⁻³. Jessica L Barker and J W Frost et al.: studied a series of recombinant *Escherichia coli* strains have been constructed and evaluated for their ability to synthesize p-hydroxybenzoic acid from glucose under fed-batch fermentor conditions. The maximum concentration of p-hydroxybenzoic acid synthesized was 12 g/L and corresponded to a yield of 13% (mol/mol). Synthesis of p-hydroxybenzoic acid began with direction of increased carbon flow into common pathway of aromatic amino acid biosynthesis. This was accomplished in all constructs with overexpression of a feedback-in-sensitive isozyme of 3-deoxy-D-arabino-heptulosonic acid 7-phosphate synthase. Expression levels of enzymes in the common pathway of aromatic amino acid biosynthesis were also increased in all constructs to deliver increased carbon flow from the beginning to the end of common pathway. Chorismic acid, the last metabolite of the common pathway, was converted into p-hydroxybenzoic acid by *ubiC*-encoded chorismatylase constructs differed in the strategy used for overexpression of chorismatylase and also differed as to whether mutations were present in the host *E. coli* to inactivate other chorismate-utilizing enzymes.

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REFERENCES

- [1] Lemeshek-Khodorovskaya, K., Khimicheskieservantydyapishchevykhproduktov (Chemical Preservatives for Foodstuffs), Moscow: Pishchevaya Promyshlennost, 1969, p. 29.
- [2] EU Patent 373 619, Izobret.Stran Mira, 1991, no. 7, p. 18.
- [3] EU Patent 186 629, Izobret.Stran Mira, 1987, no. 6, p. 30.
- [4] Soni M. G., Burdock G. A., Taylor S. L.; Greenberg N. A., Food Chem.Toxicol, 2001,39,513.
- [5] Robach M. C., Food Technol. 1980, 34, 81.
- [6] Dziezak J. D., Food Technol, 1986, 40,104.
- [7] Anthony C.Dweek Natural Parabens, (site visited) on September 2010
- [8] Luigi Abis, Riccardo Po, GiulianaSchimperna, Edoardo Merlo. Micromol. Chem. Phys, 1994, 195,181-193.
- [9] KeithDeSantowww.faqs.org/patents/app/20090126948, 2008. (Site visited on September 14, 2010)
- [10] Richard M. Herreid, Austin, Minn., U.S.Patent, 090, 915, 2000.
- [11] Market data compiled by the Fibers Economics Bureau, www.fibersource.com. (site visited on September 14, 2010)
- [12] Thuku RN, Brady D, Benedik MJ, Sewell BT (2009) Microbial nitrilases: versatile, spiral forming, industrial enzymes. J ApplMicrobiol 106:703–727
- [13] Martinkova L, Kren V (2010) Biotransformations with nitrilases. CurrOpinChemBiol 14:130–137
- [14] Gong JS, Lu ZM, Li H, Shi JS, Zhou ZM, Xu ZH (2012) Nitrilases in nitrile biocatalysis: recent progress and forthcoming research. Microb Cell Fact 11:142–148
- [15] Bhatia SK, Mehta PK, Bhatia RK, Bhalla TC (2012) Anisobutyronitrile-induced bienzymatic system of Alcaligenes sp. MTCC 10674 and its application in the synthesis of α -hydroxyisobutyric acid. Bioprocess BiosystEng 36:613–625
- [16] Bhatia SK, Mehta PK, Bhatia RK, Bhalla TC (2013) Optimization of arylacetone nitrilase production from Alcaligenes sp. MTCC 10675 and its application in mandelic acid synthesis. ApplMicrobiolBiotechnol 98:83–94
- [17] Liu ZQ, Zhang XH, Xue YP, Xu M, Zheng YG (2014) Improvement of Alcaligenesfaecalis nitrilase by gene site saturation mutagenesis and its application in stereospecific biosynthesis of (R)-(-)-mandelic acid. J Agric Food Chem 62:4685–4694
- [18] Lindsey, A.S., Chem. Rev., 1957, vol. 57, p. 583.
- [19] Jones, J.I., Chem. Ind., 1958, no. 8, p. 228.
- [20] Suerbaev, X.A., Shalmagambetov, K.M., Abyzbekova, G.M., Mikhnenko, O.E., Akhmetova, G.B., and Zhubanov, K.A., Vestn. Kaz.Nats. Univ., Ser. Khim., no. 4, p. 287.
- [21] Spravochnikkhimika (Chemist's Handbook), Nikol'skii, B.P., Ed., Moscow: Khimiya, 1964, p. 938.
- [22] Zhuang, Z. H, Gartemann, K. H, &Eichenlaub, R. Dunaway-Mariano D Characterization of the 4-hydroxybenzoyl-coenzyme A thioesterase from Arthrobacter sp. Strain SU. Applied and Environmental Microbiology. (2003). , 69(5), 2707-2711.
- [23] Kobayashi, K, & Katayama-hirayama, K. Tobita S Metabolic pathway of benzoic acid in an Acinetobacter sp. that mineralizes 4-chlorobenzoic acid. Japanese Journal of Toxicological and Environmental Health. (1998). , 44(1), 25-33.
- [24] Hoskeri, R. S, Mulla, S. I, &Shouche, Y. S. Ninnekar HZ Biodegradation of 4-chlorobenzoic acid by Pseudo monasaeruginosa PA01 NC. Biodegradation. (2011).22(3), 509-516.
- [25] Chang, K. H. Dunaway-Mariano D Determination of thechemical pathway for 4-chlorobenzoate:coenzyme A ligase catalysis. Biochemistry. (1996). , 35(41), 13478-13484.
- [26] Gulick, A. M, & Lu, X. Dunaway-Mariano D Crystal structure of 4-chlorobenzoate:nCoA ligase/synthetase in the unliganded and aryl substrate-bound states. Biochemistry. (2004). , 43(27), 8670-8679.
- [27]Niedan, V. Schöler HF Natural formation of chlorobenzoic acids (CBA) and distinction between PCB-degraded CBA. Chemosphere. (1997). , 35(6), 1233-1241.
- [28] PEARLJ ., Org. Chem., 12,79 (1947).
- [29] GEISSMANC, hapter 3 in Adams "Organic Reactions," John Wiley and Sons, New York, N. Y., 1944, Vol. 11, pages 104-107.
- [30] Amaratunga M, Lobos JH, Johnson Bf, Williams D. 2000. Genetically engineered microorganisms and method for producing 4-hydroxybenzoic acid. US patent 6030819
- [31] BartolomeB, Jubete Y, Martinez E, de la Cruz F. 1991.

Construction and properties of a family of pACYC184-derived cloning vectors compatible with pBR322 and its derivatives.

Gene 102:75-78

[32] Chaudhari S, Duncan K, Coggins JR. 1987. 3-Dehydroquinate dehydratase from Escherichia coli. Methods Enzymol 142:320-324.