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Synthesis, Crystal Structure of Molecular Salts of 1-Phenylethanamine

Chenyu Ruan, Panyue Cao, Ziyi Zhang, Chengjun Jiang

School of Biological and Chemical Engineering, Zhejiang University of Science and Technology, Hangzhou, China
Email: jcj312@zust.edu.cn

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Abstract

Molecular salts, specifically 1-phenylethan-1-aminium 4-hydroxy-3-methoxybenzoate (1), 1-phenylethan-1-aminium 4-hydroxy-3,5-dimethoxybenzoate (2), and 1-phenylethan-1-aminium 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate (3), were successfully synthesized. The structures of $[C_8NH_{12}]^+[C_8H_7O_4]^-$(1), $[C_8NH_{12}]^+[C_9H_9O_5]^-$(2), and $[C_8NH_{12}]^+[C_{10}H_9O_4]^-$(3) were confirmed through single crystal X-ray diffraction, revealing that they belong to the tetragonal and monoclinic crystal systems. This synthesis methodology underscores the effectiveness of salt formation as a strategy in crystal engineering to modulate physicochemical properties, which may enhance separation efficiency and broaden applicability in pharmaceutical or industrial contexts.

Subject Areas

Chemical Engineering & Technology

Keywords

Synthesis, Crystal Structure, Molecular Salts

1. Introduction

Phenolic acids are polyphenols that occur naturally in plants, which are found in a variety of plant-based foods. There are many different phenolic acids found in nature, such as 4-hydroxy-3-methoxybenzoate, 4-hydroxy-3, 5-dimethoxybenzoate, 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate, which has antibacterial activities, sedative activities and local anesthetic effects [1]. Among the various types of phenolic acid, benzoic acid derivatives have attracted the most research interest. The chemical structures of these substances are all positional isomers of phenolic hydroxyl or methoxy groups, and various structures are usually found in the same plant.

Therefore, different phenolic acids should be separated and purified as pharmaceutical intermediates, pharmaceuticals, and personal care products. The main methods currently used to separate phenolic acids are solid-phase extraction, liquid-liquid extraction, chromatographic method, and other methods, such as capillary electrophoresis and ionic liquid-modified silica gel [2]. These methods are effective for separation, but they have limitations such as being excessively time-consuming, needing high solvent consumption, complicated to control, and producing environmentally damaging wastes. Salt formation is a crystal engineering technique that exploits the non-covalent interactions between the neutral or ionic components with a defined stoichiometry in a solid-state structure [3]. This has been proved to be a promising method that improves separation efficiency. The synthesis of the molecular salts by combining the donor and acceptor properties of molecules allows one to obtain new physical and chemical properties of the materials that are different from their individual constituent molecules. The salts are basically associated with various interactions such as non-covalent, van der Waals, non-classical hydrogen bonding, C-H…π, halogen and ionic interactions. The salt of 1-phenylethanamine has been reported a lot, For example, (R)-1-phenylethanaminium oxalate, (R)-1-phenylethanaminium 2-carboxy-4,6-dinitrophenolate and (R)-1-phenylethanaminium 4-methylbenzenesulfonate [4]. Non-steroidal Anti-Inflammatory Drugs-1-Phenylethylamine diastereomeric salts [5]. (RS)-1-phenylethan-1-aminium isonicotinate, (RS)-1-phenylethan-1-aminium flurbiprofenate, (RS)-1-phenylethan-1-aminium 2-chloro-4-nitro-benzoate, *et al.*, [6] 1-phenylethanaminium malate [7]. In this article, the synthesis, structural characterization and investigations of the structural properties of molecular salts, **(1)**, **(2)** and **(3)** of 1-phenylethanamine with different carboxylate ions derived from 4-hydroxy-3,5-dimethoxybenzoate, 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate and 4-hydroxy-3-methoxybenzoate (See **Figure 1**) reported. 1-Phenylethylamine is an interesting compound because it is a cost-effective and most common resolving agent, its amino group form stable salts with carboxylic acids and the carboxylate salts of 1-phenylethyl amine with phenolic acids found to exhibit change in physicochemical properties.

2. Experimental

2.1. Materials and Analytical Methods

4-hydroxy-3,5-dimethoxybenzoate(98%), 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate(98%), 4-hydroxy-3-methoxybenzoate (98%),1-phenylethanamine were purchased from Energy Chemical Co., Ltd. Analytical grade solvents were used for the crystallization experiments. All purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd.

***Single Crystal X-Ray diffraction* (*SXRD*)**

A single crystal of suitable size and good quality was measured by using an area detector on a Bruker APEX-II CCD diffractometer with graphite monochromatic Ga-Kα radiation (λ = 1.34138 Å). Absorption corrections were applied by using

multi-scan program. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation.

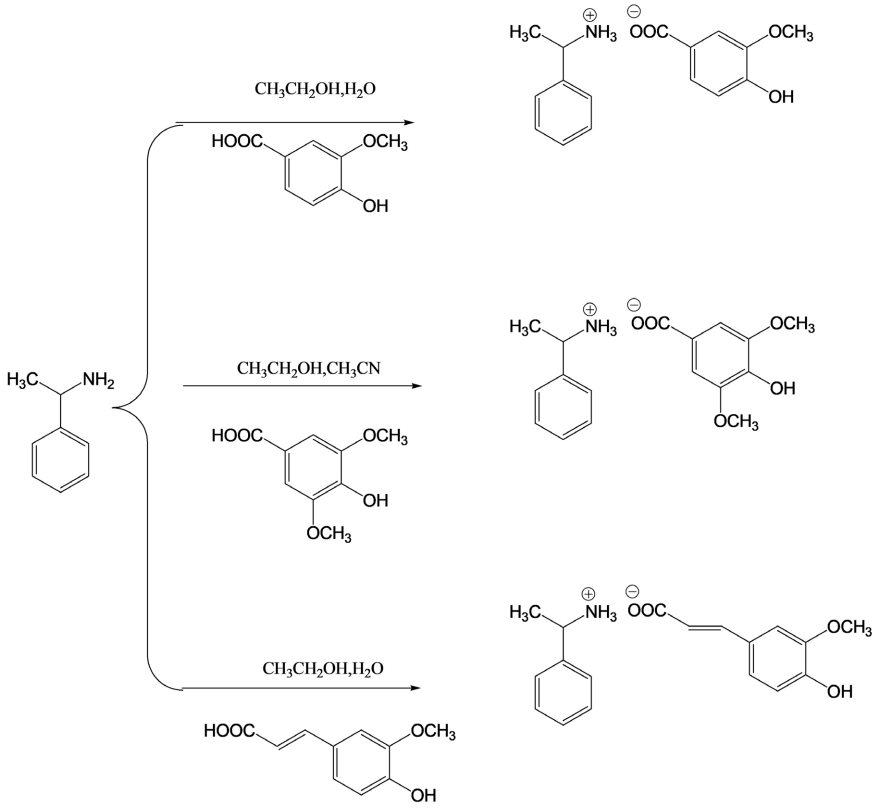

Figure 1. The synthesis, structural characterization and investigations of the structural properties of molecular salts.

2.2. Synthesis

Synthesis of 1-Phenylethan-1-aminium 4-Hydroxy-3-methoxybenzoate

A mixture of 4-hydroxy-3-methoxybenzoate (89 mg, 0.53 mmol) and 1-phenylethanamine (71 μL, 0.53 mmol) was dissolved in 3.4 mL of an 88% ethanol/water solution. The reaction mixture was stirred at 60˚C for 2 hours. After cooling to room temperature, the solution was allowed to stand for 36 hours, yielding crystals of the target compound.

Yield: 117 mg (70%) based on the formula $[C8H12N]^+[C8H7O4]^-$.

Synthesis of 1-Phenylethan-1-aminium 4-Hydroxy-3,5-dimethoxybenzoate

A mixture of 4-hydroxy-3,5-dimethoxybenzoate (121 mg, 0.6 mmol) and 1-phenylethanamine (80 μL, 0.6 mmol) was dissolved in 5 mL of an ethanol/acetonitrile mixture. The solution was heated and stirred at 60 ˚C for 2 hours. After cooling to room temperature, the mixture was left undisturbed for 24 hours, resulting in the formation of crystals of the target compound.

Yield: 113 mg (59%) based on the formula $[C8H12N]^+[C9H9O5]^-$.

Synthesis of 1-Phenylethan-1-aminium 3-(4-Hydroxy-3-methoxyphenyl)

prop-2-enoate

A mixture of 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate (116 mg, 0.6 mmol) and 1-phenylethanamine (80 μL, 0.6 mmol) was dissolved in 5 mL of a 64% ethanol/water solution. The reaction mixture was heated and stirred at 60˚C for 2 hours. Upon cooling to room temperature, the solution was left to crystallize for 12 hours, yielding crystals of the target compound.

Yield: 101 mg (58%) based on the formula $[C8H12N]^{+}[C9H9O5]^{-}$.

2.3. Single-Crystal X-Ray Diffraction

Single-crystal X-ray diffraction data of 1, 2 and 3were collected on a Bruker APEX-II CCD diffractometer using Cu–Kα radiation. All measurements were performed at 170 K. Diffraction data were collected with the Bruker APEX2 program and reduced with the Bruker SAINT one. Structures were solved using the SIR-2004 package and refined by full-matrix least-squares against F2 using all data (SHELX2018/3. In all structures, the non hydrogen atoms were anisotropically refined. All hydrogen atoms were found in the Fourier difference map. Their co-ordinates were freely refined, while their thermal parameters were set in accordance with the atoms to which they are bonded. Table 1 reports crystal data and refinement parameters for all structures.

Table 1. Crystal data and refinement parameters of (1), (2) and (3).

	(1)	(2)	(3)
CCDC	2417541	2404816	2412522
Empirical formula	$C_{16}H_{19}NO_4$	$C_{17}H_{21}NO_5$	$C_{18}H_{21}NO_4$
Formula weight	289.32	319.35	315.36
Temperature/K	170.00	170.00	170.00
Crystal system	tetragonal	monoclinic	monoclinic
Space group	I-4(82)	$P2_1$	$P2_1/n(14)$
a/Å	22.162(9)	6.0322(2)	6.3524(2)
b/Å	22.162	16.0271(6)	12.3528(4)
c/Å	6.301(3)	9.0421(3)	20.7256(7)
α/˚	90	90	90
β/˚	90	105.568(2)	96.3100(10)
γ/˚	90	90	90
Volume/Å^3	3095(3)	842.11(5)	1616.48(9)
Z	8	2	4
ρ_{calc}g/cm^3	1.242	1.259	1.296
μ/mm^{-1}	0.468	0.490	0.476
F (000)	1232.0	340.0	672.0
Crystal size/mm^3	0.3 × 0.06 × 0.05	0.18 × 0.05 × 0.03	0.25 × 0.1 × 0.07
Radiation	GaKα (λ = 1.34139)	GaKα (λ = 1.34139)	GaKα (λ = 1.34139)

Continued

2Θ range for data collection/°	4.906 to 121.086	8.832 to 121.468	7.26 to 121.596
Index ranges	−22 ≤ h ≤ 28, −22 ≤ k ≤ 28, −8 ≤ l ≤ 8	−7 ≤ h ≤ 7, −20 ≤ k ≤ 20, −11 ≤ l ≤ 11	−8 ≤ h ≤ 7, −16 ≤ k ≤ 16, −26 ≤ l ≤ 26
Reflections collected	13,768	34,479	64,784
Independent reflections	3411 [R_{int} = 0.0711, R_{sigma} = 0.0725]	3792 [R_{int} = 0.0512, R_{sigma} = 0.0366]	3658 [R_{int} = 0.0458, R_{sigma} = 0.0332]
Data/restraints/parameters	3411/0/194	3792/1/213	3658/0/212
Goodness-of-fit on F^2	1.088	1.058	1.088
Final R indexes [I ≥ 2σ(I)]	R_1 = 0.0502, wR_2 = 0.1159	R_1 = 0.0384, wR_2 = 0.1001	R_1 = 0.0373, wR_2 = 0.0963
Final R indexes [all data]	R_1 = 0.0604, wR_2 = 0.1213	R_1 = 0.0395, wR_2 = 0.1008	R_1 = 0.0389, wR_2 = 0.0975
Largest diff. peak/hole / e $Å^{-3}$	0.21/−0.21	0.43/−0.21	0.27/−0.21
Flack parameter	0.2(2)	0.03(6)	

3. Results and Discussion

Single crystal X-Ray diffraction

The crystal data and structural refinement parameters for **(1)**, **(2)** and **(3)** are given in Table 1.

1-phenylethan-1-aminium 4-hydroxy-3-methoxybenzoate, CCDC4417541, **a** = 22.162(9)Å, **b** = 22.162Å, **c** = 6.301(3)Å, **a** = 90˚, **b** = 90˚, **g** = 90˚, The asymmetric unit of (1) contains one cation, $[C_8NH_{12}]^+$and [C8H7O4]$^-$ ion, 2-fold rotation axis with direction[0, 0, 1]at 0, 0, z.4-fold rotoinversion axis with direction [0, 0, 1]at 0, 0, z with inversion at [0, 0, 0], centring vector [1/2, 1/2, 1/2], 2-fold screw axis with direction [0, 0, 1]at 1/4, 1/4, z with screw component[0, 0, 1/2] and 4-fold rotoinversion axis with direction [0, 0, 1] at 1/2, 0, z+1/4 with inversion at [1/2, 0, 1/4]. 1-phenylethan-1-aminium 4-hydroxy-3,5 -dimethoxybenzoate, CCDC2404816, **a** = 6.0322(2)Å, **b** = 16.0271(6)Å, **c** = 9.0421(3)Å, **a** = 90˚, **b** = 105.568(2)˚, **g** = 90˚. The asymmetric unit of (1) contains one cation, $[C_8NH_{12}]^+$ and $[C_9H_9O_5]^-$ ion, 2-fold screw axis with direction [0, 1, 0] at 0, y, 0 with screw component [0, 1/2, 0]. 1-phenylethan-1-aminium 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate, CCDC2412522, **a** = 6.3524(2)Å, **b** = 12.3528(4)Å, **c** = 20.7256(7)Å, **a** = 90˚, **b** = 96.3100(10)˚, **g** = 90˚,The asymmetric unit of (1) contains one cation, $[C_8NH_{12}]^+$ and $[C_{10}H_9O_4]^-$ion, 2-fold screw axis with direction [0,1, 0] at 1/4, y, 1/4 with screw component[1, 1/2, 0], inversion at [0, 0, 0], glide plane perpendicular to [0, 1, 0] with glide component [1/2, 0, 1/2]. The carboxylic acid in both the anions adopts anti-conformation with the O-H bond directing opposite to the C = O bond.

4. Conclusion

In this study, three novel molecular salts of 1-phenylethanamine with phenolic acid derivatives—4-hydroxy-3-methoxybenzoate (1), 4-hydroxy-3,5-dimethoxybenzoate (2), and 3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate (3) were successfully synthesized via a straightforward crystallization approach. Single-crystal

X-ray diffraction confirmed their distinct crystal systems: compound **1** crystallized in the tetragonal system (space group I-4), while **2** and **3** adopted monoclinic systems (space groups $P2_1$ and $P2_1/n$, respectively). Structural analysis revealed intricate non-covalent interactions, including hydrogen bonding and van der Waals forces, which stabilized the crystal lattices. The asymmetric units of all salts comprised a 1-phenylethan-1-aminium cation paired with carboxylate anions, with variations in symmetry elements such as screw axes and glide planes dictating their packing arrangements. The synthesis methodology highlights the efficacy of salt formation as a crystal engineering strategy to modulate physicochemical properties, potentially enhancing separation efficiency and applicability in pharmaceutical or industrial contexts. This work contributes to the growing repertoire of 1-phenylethanamine-based molecular salts, offering insights into structure-property relationships and paving the way for future exploration of their functional applications.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary Data

CCDC No, 2417541, 2404816, 2412522 contain the supplementary crystallographic data for the structural analysis. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/CIF.