



DFT computational study on decarboxylation mechanism of salicylic acid and its derivatives in the anionic state



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ARTICLE INFO

Article history:

Received 13 January 2016

Received in revised form

28 February 2016

Accepted 2 March 2016

Available online 5 March 2016

Keywords:

Density functional theory

Decarboxylation

Salicylic acid anion

ABSTRACT

The mechanisms of the decarboxylation of salicylic acid anion and its *ortho* substituted derivatives in gas phase and aqueous solution have been investigated by B3LYP method of DFT theory using the 6-31++G(d,p) basis set. The decarboxylation process includes hydrogen transfers from hydroxyl to carboxyl group and from carboxyl to the α -C of the aryl ring. The mechanism suggested is a pseudo-unimolecular decomposition of the salicylic acid anion and the hydrogen transfer from carboxyl to the α -C of the aryl ring is the rate determining step. Compared with the decarboxylation process in gas phase, the energy barriers in aqueous solution approximately declined by 25%–31% with the water mediation of the hydrogen transfer from carboxyl to the α -C of the aryl ring. The effects of substituents at the *ortho* position on the decarboxylation process were also investigated. Both the electron donating CH_3 and withdrawing group NO_2 at the *ortho* position of carboxyl group can further reduce the reaction energy barriers of the decarboxylation of salicylic acid anions.

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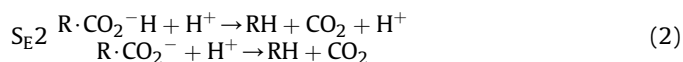
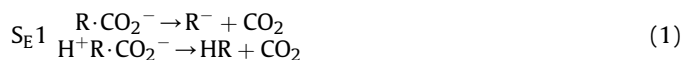
1. Introduction

Salicylic acid (SA, *ortho* hydroxy benzoic acid) is extensively used in agriculture, drugs, cosmetics and as intermediate in the synthesis of fine chemicals. In agriculture, it serves as a plant growth regulator [1] and an elicitor to create resistive materials against plant pathogens [2]. It has obvious effect on the fruit ripening, freshness of horticultural product and seed germination [3]. In the pharmaceutical field, salicylic acid is the main raw material for the synthesis of non-steroidal anti-inflammatory drug, aspirin [4]. It is also used in the removal of excessive keratin in hyperkeratotic skin disorders in cosmetics [5]. In addition, the salts of SA and SA derivatives are also extensively used in pharmaceutical field and industry, for example, bismuth subsalicylate can be used in the treatment of acute diarrhea in children [6] and indigestion [7]. Ca(II) and Zn(II) alkyl salicylates can be used as lubricant additives [8].

Therefore, the stability of SA, SA salts and its derivatives is very important for their application. On the other hand, each year, a large amount of these compounds are discharged into the

environment from its production, industrial sewage and pharmaceutical waste water, etc. [9]. Due to the toxicity of salicylic acid, its accumulation will cause severe environmental problem. The toxicity of salicylic acid is changed by substitutions on the carboxyl of its chemical structure [5]. Both from the stability of these compounds and environmental protection, the decarboxylation of SA are a subject worthy of our attention [10].

Decarboxylation is usually used in organic synthesis and it is also one of the main modes for the degradation of benzoic acids [11]. Brown and Phil et al. [12] discussed the thermal decarboxylation of various carboxylic acids and summarized that decarboxylation can occur either by a unimolecular (SE_1) or by a bimolecular mechanism (SE_2).



In order to intensify the decarboxylation process and make use of it in organic synthesis, some people investigated the catalysis of some metal ions on the decarboxylation of benzoic acids and coupling reactions. Cornella et al. [13] found that catalytic amounts of Ag(I) salts in DMSO can promote the protodecarboxylation of a

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wide variety of *ortho*-substituted benzoic acids under mild conditions and in excellent yields, highlighting a possible role for silver in decarboxylative cross-couplings. Lukas et al. [14] found the complex of Cu (I) with 1,10-phenanthroline can catalyzed decarboxylation of arenecarboxylates effectively with the assistance of microwave. Sun et al. [15] developed an Rh (I)-based catalyst system for various decarboxylative transformations of *ortho*-substituted arenecarboxylic acids. By exploiting ligand and reagent effects on reaction pathways, highly selective formation of hydro-decarboxylation and Heck–Mizoroki products could be achieved with low catalyst loadings and under mild conditions.

With the development of quantum chemistry and the computer performance, many reaction mechanisms can be obtained or verified by the computation. Compared with the experimental methods, the computation method can give details about the reaction paths and transition states. Li et al. [16] examined the effect of OH substitution on the rates and mechanisms of decarboxylation of benzoic acid in aqueous state using density functional theory (DFT). It was found from the water-catalyzed transition state that the one water incorporation of a six-member cyclic structure can dramatically reduce the activation energy of the decarboxylation by about 120–130 kJ/mol using B3LYP/6-31G//B3LYP/6-31G and by about 75 kJ/mol using B3LYP/6-31 + G(d,p)//B3LYP/6-31G(d). Water molecule acts as a bridge linked by two hydrogen bonds which enables concerted proton transfer and facilitates the bond cleavage of α -C and carboxyl to occur. Ruelle [17] investigated the mechanism of acrylic and benzoic acid decarboxylation both in aqueous solution and in the absence of water by ab initio methods using the STO-3G//STO-3G and 3-21G//STO-3G basis sets. This calculation showed a large decrease in the activation energy with the mediation of water. Chuchev et al. [18] investigated the mechanisms of decarboxylation of *ortho*-substituted benzoic acids using Gaussian 98 at B3LYP/6-311G(d,p). It was found that the *ortho* group participates in the development of the transition state and salicylic acid decarboxylated through a keto-like intermediate.

Up to now, most of the computations focused on the decarboxylation process of SAs in neutral or acidic condition. There are less computation on the decarboxylation process of them in anion state. Salicylate exist in salicylic acid anions form, in view of the importance of the salts of SAs, the decarboxylation processes of unsubstituted, *ortho* methyl and *ortho* nitro salicylic acid anions were investigated using DFT quantum chemistry calculation with Gaussian09 package in this paper.

2. Computational methods

All quantum calculations and structure optimization were performed by density functional theory [19] calculations using the Gaussian 09 software at the level of B3LYP/6-31++G (d,p). After full optimization of the reactant and product structures, the QST2 module, which allowed simultaneous optimizations of reactant, product and transition state, was employed to find the transition state, and then IRC (Intrinsic reaction coordinate) calculations were run starting from transition state geometries in both forward and reverse directions, which verified if the transition state linked the proper reactant and product. Harmonic frequencies were calculated for all stationary points to determine whether a given structure is a minimum or a transition state. All included initial states, stable intermediates and final products have only real harmonic frequencies and each transition state exists only a single imaginary frequency. These entropy terms have not been included in the reported barriers. All reactions occur along the ground state, singlet potential energy surface. The effect of the added water molecule was confirmed by single point calculations along the potential surface using the PCM model at the same B3LYP/6-31++G (d,p)

level. The reaction energy barrier was the energy difference between the transition state and reactant with the zero-point correction.

3. Results and discussion

3.1. Decarboxylation process of salicylic acid anion in gas phase

The nature of the SA anion plays a key role in its decarboxylation, thus our computations focus on the decarboxylation process of the mono-anions of salicylic acids.

First, the decarboxylation of SA anion in gas phase was calculated. In order to give a consistent starting state for the computation, the single point energies of four typical conformers in Fig. 1 were obtained at B3LYP/6-31++G (d,p) after the structure optimization. The results are listed in Table 1. It was found that the lowest energy conformer was R2, which all atoms are in the same plane with the hydrogen of the hydroxyl group is located on the side of the carboxyl group.

In the gas phase, as the first step of the decarboxylation, the hydrogen H (15) of the hydroxyl group approaches to the carboxyl group to form the transition state 1 (TS1). The bond length of H (15) to the O (10) atom in hydroxyl is 1.180 Å, and the distance of H (15) to the O (8) atom of carboxyl is 1.240 Å. The angle for O (10)–H (15)–O (8) is 161.1°. With H(15) further approaching to the O(8) atom of carboxyl, an intermediate structure was formed (IM1) with 1.450 Å of the bond length for H(15) and O(10) in hydroxyl, and 1.052 Å of bond length for H(15) and the O(8) atom of carboxyl. The closer distance of H (15) to O (8) in carboxyl group indicated that H (15) had been transferred to the carboxyl group. The second step started from the rotation of carboxyl group along the C (1)–C (7) bond. When carboxyl group rotated by 90°, the H(15) atom start to drift away from the carbonyl group toward α -C(1) forming the transition state 2 (TS2) with the only imaginary frequency of -1494.24 cm^{-1} . The bond length of H (15) and α -C (1) is 1.315 Å, and the length of H (15)–O (8) bond is 1.409 Å. The distance of C (1)–C (7) bond stretched to 1.551 Å. The energy barrier of this step is 56.8 kcal/mol. Finally, with the further approach of H(15) atom to the α -C(1) of benzene ring, the distance between α -C(1)–C(7) bond lengthened and CO₂ departed from the benzene, forming the final product (P1). Fig. 2 shows the reaction pathway for decarboxylation of SA anion in gas phase and Fig. 3 lists the structures of transition states in the reaction pathway.

In comparison with the decarboxylation of neutral salicylic acid in gas phase previously reported [18], the reaction pathway of salicylic acid anion in gas phase in this paper is similar to that of neutral salicylic acid with anti-conformer. But the process of hydrogen transfer from o-hydroxyl group to the carbonyl was only included in anionic state in our study.

3.2. Decarboxylation process of salicylic acid anion in aqueous solution

Because most reactions can conduct in aqueous condition and the water molecule is often participate in some reactions, the solvent effect was considered by using self-consistent reaction field (SCRF) polarizable continuum model (PCM) and one water molecule mediated decarboxylation process of SA anion was calculated. The energy minimized structure of the starting state (6) in the water mediated salicylic acid anion decarboxylation process was shown in Fig. 4. The first transition state (TS3) was similar to TS1 in gas phase. H (15) transferred from hydroxyl through the transition state TS3 to carboxyl group to form the intermediate (IM2), in which the water molecule was not involved. The structure of TS3 can be seen in Fig. 5. This is an easy conducted process because the

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