DFT Study On Reaction Mechanism of Di-tert-butyl Phenol to Di-tert-butyl Hydroxybenzoic Acid

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Research Article

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Abstract

Experimental studies on the Kolbe-Schmitt reaction and its side reactions have made great progresses, however the relative theoretical studies fall behind. In order to study the mechanism of Kolbe-Schmitt reaction with 2,6-di-tert-butylphenol and 2,4-di-tert-butylphenol as reactants, we carried out theoretical calculation studies at M06-2X/Def2-SVP/SMD level of theory using Gaussian 09 D.01 software package. For the reactant 2,6-di-tert-butylphenol, the main product and side product can convert to each other due to the dynamic equilibrium. However for 2,4-di-tert-butylphenol, the main product is thermodynamically favorable due to its lower Gibbs free energy, while the side product is kinetically favorable due to the lower activation energy barrier. We hope the study can shed light on Kolbe-Schmitt reaction.

1. Introduction

Aspirin the most widely used drug, can be synthesized by acetylation reaction of salicylic acid\[1\]. In 1859, Kolbe and his assistant Schmitt developed the synthesis method of salicylic acid by means of sodium phenoxide and CO\(_2\) at 125 °C and 100 atm, named as Kolbe-Schmitt reaction\[1–5\]. The possible mechanism is as follows: (1) Sodium phenoxide captured CO\(_2\), then carboxylation reaction occurred to form C(sp\(^2\))-C(sp\(^3\)) bond between CO\(_2\) and C atom in phenyl ring, (2) Proton transferred from C(sp\(^3\)) atom to phenoxide O atom, leading to sodium 4-hydroxybenzoate, which can be easily acidified to salicylic acid.

To date, experimental studies on Kolbe-Schmitt reactions have made great progress, the reaction substrates and catalysts were fully extended, and the reaction conditions were also studied and optimized\[6, 7\]. Besides ordinary high-pressure CO\(_2\) gas\[8–10\], the super critical CO\(_2\) was also applied as substrates\[11\]. Compared to catalyst-free reaction\[8, 9\], various catalytic system can promote reaction rate to a great extent, such as K\(_2\)CO\(_3\)\[11\], multiphase catalyst\[10\], enzymes\[12–18\], ultrasonics\[19\], UV light\[20\], etc. Thermodynamics and kinetics of Kolbe-Schmitt reaction were also investigated\[14, 21\].

Theoretical studies on Kolbe-Schmitt reactions are relatively less reported. Zoran Markovic and co-workers systematically investigated Kolbe-Schmitt reaction, including the effect of different MOPh (M=alkali, Li, K, Rb, Cs) salts on carboxylation reactions\[22\], the structure of KOPh-CO\(_2\) complex\[23\], and the possible mechanisms of intramolecular proton transfer step\[23\]. Yan and co-workers studied the reaction mechanism, reaction energy barriers and some key intermediates of Kolbe-Schmitt reaction between 2,5-dichloro phenoxide and CO\(_2\)\[24\]. Stanescu and co-workers investigated the solvent effects on Kolbe–Schmitt reaction kinetics, they found that solvents with high dielectric constant will lead to reversible reaction and lower yields of products\[25\]. Sheng and co-workers studied decarboxylases catalyzed Kolbe-Schmitt reactions by DFT-calculations\[16\].

Kolbe-Schmitt reaction is usually accompanied with side reaction, that is, alkali hydroxybenzoate (HOC\(_6\)H\(_4\)COOM, M=alkali) reacted with alkali phenoxide (MOPh), leading to phenol (HOPh) and dialkali
salicylate (HOC₆H₄COOM), as depicted in Figure 1. Side reaction will limit the yield less than 50%, resulting to great waste of substrates[26,27], however less attention was paid. Choosing sodium 2,5-dichlorophenoxide as substrate, Yan and co-workers studied the side reaction both experimentally and theoretically, they proposed that: (1) Side product is originated from main product, (2) Side reaction is responsible for the low yield of main product, (3) The side reaction is exothermic, the formation of side product is more thermodynamic favorable than that of main product.

However, sodium 2,5-dichlorophenoxide has an electron-deficient aromatic ring, are these conclusions still valid for electron-rich phenoxide? Besides originating from main product, is there any other possible reaction pathway to form side product? In order to solve these questions, we choose the two reactions depicted in Figure 1 to carry out theoretical calculation studies. We hope our study can bring new insights to side reaction of Kolbe-Schmitt reaction.

2. Computational Methods

Kolbe-Schmitt reaction generally adopts conditions of 140-160°C, 6-8 MPa and dimethylbenzene used as the solvent[24,26], therefore in the theoretical calculations, permittivity (\(\text{eps}\)) and dynamic permittivity (\(\text{epsinf}\)) of the solvent model are set as 2.4 and 1.9, respectively. The geometries of all the structures were optimized within the Gaussian 09 D.01 program[28] using the M06-2X[29]-D3[30] method with Def2-SVP basis set. The vibrational frequency was also calculated at the same level to ensure that the optimized structures are at the minimum or saddle point of the potential energy surface. The solvent effect was considered by employing the Solvation Model Based on Density (SMD)[31]. IRC calculations[32,33] are also performed at the same level to ensure that each transition state is connected to the corresponding reactant and product. Shermo software[34] was used to calculate Gibbs free energy of all optimized structures at 160°C and 8 MPa. And the optimized structures were displayed in CYLview[35] software.

3. Results And Discussion

Reactions that generate \(P(A)\) and \(P(B)\) are defined as the main reactions, and those generate \(\text{side-P(A)}\) and \(\text{side-P(B)}\) as side reactions. The following is the mechanisms of these reactions and the changes of Gibbs free energies.

3.1 Reactions of potassium 2,6-di-tert-butylphenol (A) as the reactant

The reaction mechanism of potassium 2,6-di-tert-butylphenol (A) and \(CO_2\) is shown in Figure 2. At first, A binds with \(CO_2\) through a O-K coordination bond to form the complex \(A-CO_2\) with the Gibbs free energy increase of 1.7 kcal/mol. Then \(CO_2\) is electrophilically added to C4 of benzene ring through the transition state \(TS1-A\) to obtain the electrophilic addition product \(IM1-A\). From \(A-CO_2\) to \(TS1-A\), the Gibbs free energy barrier need to overcome is only 11.3 kcal/mol. Then the reaction may go through two different
pathways, one is the rotation of the carboxyl in CO$_2$, which makes two O atoms in CO$_2$ coordinate with the K atom, and the reaction goes through the transition state TS2-A with the free energy increase of 6.6 kcal/mol to form the intermediate IM2-A, the other one is the occurrence of intramolecular proton transfer reaction through TS2-A'. Since the transition state TS2-A' has a four-membered ring structure, which has larger ring tension, its free energy is much higher than that of TS2-A. Therefore, the subsequent reaction of TS2-A' will not be investigated. After the formation of IM2-A, the O-K coordination bond breaks and the intermediate IM3-A is formed through TS3-A which needs to cross the Gibbs free energy barrier of 1.5 kcal/mol from IM2-A. In IM3-A, the K atom is connected with CO$_2$ moiety and the original phenol completely changes to benzoquinone structure. Next, IM3-A combines with a molecular of A to obtain the intermediate IM4-A with the energy increase of 0.3 kcal/mol. In IM4-A, the O atom of the benzoquinone structure in IM3-A forms a new coordination bond with the K atom of A, and the O atom in A forms a weak hydrogen bond with the H atom on C4 in IM3-A. Afterwards, the intermediate IM5-A can be obtained through intermolecular H$^+\text{-}K^+$ exchange reaction in TS4-A. IM5-A can remove a molecular of A-phenol (2,6-diterbutylphenol) to obtain side-P(A) directly, or undergo a O-H hydrogen bond formation through IM6-A and a intramolecular H$^+\text{-}K^+$ exchange reaction again through TS5-A to generate IM7-A. Finally, the decomposition of IM7-A gives the main product P(A) and a molecular of A. It can be seen from the potential energy diagram that there is a dynamic equilibrium between the side product side-P(A) and the main product P(A), which can rapidly transform into each other at 160 $^\circ$C by crossing the Gibbs free energy barrier of 14.1 kcal/mol. Moreover, the relative Gibbs free energy of side-P(A) and P(A) is close, both of them may be observed in the experimental system. The optimized structure of Kolbe-Schmitt reaction in which A (potassium 2,6-di-tert-butylphenol) participates is shown in Figure 3.

### 3.2 Reactions of potassium 2,4-di-tert-butylphenol (B) as the reactant

The reaction mechanism of potassium 2,4-di-tert-butylphenol (B) and CO$_2$ as reactants is shown in Figure 4. B binds with CO$_2$ through a O-K coordination bond to form the complex B-CO$_2$ with the Gibbs free energy increase of 2.6 kcal/mol firstly. Afterwards, CO$_2$ is electrophilically added to C6 of benzene ring through the transition state TS1-B to obtain the electrophilic addition product IM1-B. From B-CO$_2$ to TS1-B, the Gibbs free energy barrier need to overcome is only 11.2 kcal/mol. The hydrogen atom at C6 position in IM1-B transfers to the carboxyl O atom in CO$_2$ moiety to realize intramolecular proton transfer with the energy barrier of 25.2 kcal/mol, and this step of the reaction goes through the transition state TS2-B to generate the intermediate IM2-B. In IM2-B, the O atom in B part and that in CO$_2$ part are connected to each other through a O-H...O hydrogen bond and a O-K coordination bond. Subsequently, the K atom and the H atom exchange between two O atoms, the O-K coordination bond breaks and intramolecular proton transfer occurs at the same time, the main product P(B) is generated through TS3-B with the energy barrier of only 0.5 kcal/mol. Starting with B as the reactant to obtain P(B), the Gibbs free energy drops by 15.8 kcal/mol. For IM1-B, intramolecular proton transfer can also occur directly to transfer the H atom to the phenolic hydroxyl O atom without subsequent re-transfer process. But this
process of generating the intermediate IM2-B through TS2-B' has a theoretically high Gibbs free energy barrier and is difficult to achieve.

The reaction pathways for side products are as follows. Firstly, the O-K coordination bond between the benzoquinone O atom and K atom in IM1-B breaks, the rotation of carboxyl occurs and a new O-K coordination bond is formed in CO₂ moiety. After the above process, the intermediate IM2-B' is obtained through the transition state TS2-B' with the Gibbs free energy barrier of 3.5 kcal/mol. Then IM2-B' captures a molecular of B to form the intermediate IM3-B' through two O-K coordination bonds and a O-H...O hydrogen bond. Afterwards, the intermolecular proton transfer occurs through the transition state TS3-B' to form the complex IM4-B'. From IM3-B' to TS3-B', the Gibbs free energy barrier need to overcome is only 1.3 kcal/mol. Finally, the K atom transfer in IM4-B' happens with the generation of the side product side-P(B) and B-phenol. From B as the reactant to the side product side-P(B), the Gibbs free energy drops by 12.5 kcal/mol. Although the Gibbs free energy decrease of the main product P(B) is more than side-P(B), which indicates that it is favorable in thermodynamics, the activation energy required of side-P(B) is lower, which is dynamically advantageous, so the main product P(B) and the side product side-P(B) compete with each other. Starting from IM2-B', the reaction may also form the main product P(B) through TS3-B', but this process can not actually occur due to the high free energy of TS3-B'. The optimized structures of Kolbe-Schmitt reaction in which B (potassium 2,4-di-tert-butylphenol) participates is shown in Figure 5.

4. Conclusions

In summary, we have theoretically studied the Kolbe-Schmitt reactions and corresponding side reactions of potanssium 2,6-di-tert-butylphenoxide (A) and potanssium 2,4-di-tert-butylphenoxide (B). For the reactions starting from A, the main product P(A) and side product side-P(A) can convert to each other due to the dynamic equilibrium between them, However for the reactions starting from B, the main product P(B) is thermodynamically favorable due to its lower relatively Gibbs free energy, while the side product side-P(B) is kinetically favorable due to the lower activation energy barrier of reaction pathway. We hope the study can shed light on Kolbe-Schmitt reaction.

5. Calculated Original Data

Calculated original datum are listed in Table 1 and Table 2. Table 1 is the calculated original data of A-involved Kolbe-Schmitt reaction. Table 2 is the calculated original data of B-involved Kolbe-Schmitt reaction. All Energies are in a.u.. Imaginary frequencies (ν, s) of transition states are in cm⁻¹.
Table 1
The calculated original data of A-involved Kolbe-Schmitt reaction. All energies are in a.u.. Imaginary frequencies (νs) of transition states are in cm⁻¹.

| Name      | Gibbs free energy       | νi  | Name      | Gibbs free energy       | νi  |
|-----------|-------------------------|-----|-----------|-------------------------|-----|
| CO₂       | -188.386685             |     | TS4-A     | -2628.932712            |  -603.7 |
| A         | -1220.282117            |     | IM5-A     | -2628.960559            |     |
| A·CO₂     | -1408.666059            |     | A-phenol  | -620.971928             |     |
| TS1-A     | -1408.648085            | -259.6 | side-P(A) | -2007.987379            |     |
| IM1-A     | -1408.649208            |     | IM6-A     | -2628.952674            |     |
| TS2-A     | -1408.638678            | -66.4 | TS5-A     | -2628.938071            | -653.6 |
| IM2-A     | -1408.641031            |     | IM7-A     | -2628.952865            |     |
| TS3-A     | -1408.638746            | -48.9 | P(A)      | -1408.676711            |     |
| IM3-A     | -1408.651696            |     | TS2-A'    | -2007.987379            | -1729.1 |
| IM4-A     | -2628.933332            |     |           |                         |     |

Table 2
The calculated original data of B-involved Kolbe-Schmitt reaction. All energies are in a.u.. Imaginary frequencies (νs) of transition states are in cm⁻¹.

| Name      | Gibbs free energy       | νi  | Name      | Gibbs free energy       | νi  |
|-----------|-------------------------|-----|-----------|-------------------------|-----|
| B         | -1220.285658            |     | IM2-B'    | -1408.648781            |     |
| B·CO₂     | -1408.668156            |     | IM3-B'    | -2628.952763            |     |
| TS1-B     | -1408.650348            | -206.1 | TS3-B'    | -2628.950741            | -285.7 |
| IM1-B     | -1408.651070            |     | IM4-B'    | -2628.974972            |     |
| TS2-B     | -1408.610935            | -1576.4 | B-phenol  | -620.9769991            |     |
| IM2-B     | -1408.679091            |     | side-P(B) | -2008.000950            |     |
| TS3-B     | -1408.678167            | -34.9 | TS2-B'    | -1408.575844            | -1887.9 |
| P(B)      | -1408.697598            |     | TS3-B*    | -1408.575294            | -2010.4 |
| TS2-B'    | -1408.645643            | -32.0 |           |                         |     |

Declarations

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**Conflict of Interest**

The authors declare no conflict of interest.

**Availability of data and material**

All data about cartesian coordinates is available which is in supporting information.

**Authors' contributions**

Neng-Zhi Jin, Qi-Bin Zhang: Data analysis, Writing-review & editing. Rong Liu: Data analysis and discussion. Pan-Pan Zhou: Calculations and Data collection.

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Figures
Figure 1

Intermediates (A and B), products (A-phenol and B-phenol) and side products (side-P(A) and side-P(B)) of Kolbe-Schmitt reaction with 2,6-di-tert-butylphenol (A-phenol) and 2,4-di-tert-butylphenol (B-phenol) as reactants.
Figure 2

The mechanism of Kolbe-Schmitt reaction in which A (potassium 2,6-di-tert-butylphenol) participates. The Gibbs free energies of [A+CO2] were set to 0.0 kcal/mol as a reference.

Figure 3

The optimized structures of A-involved Kolbe-Schmitt reaction. Distances are in Å, some hydrogen atoms and intermolecular interactions were omitted for clarity.
Figure 4

The mechanism of Kolbe-Schmitt reaction in which B (potassium 2,4-di-tert-butylphenol) participates. The Gibbs free energies of [B+CO2] were set to 0.0 kcal/mol as a reference.
Figure 5

The optimized structures of B-involved Kolbe-Schmitt reaction. Distances are in Å, some hydrogen atoms and intermolecular interactions were omitted for clarity.

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