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Preparation of α-hydroxyphenylacetic acid with cyclodextrins as an effective phase-transfer catalyst and its reaction mechanism

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Abstract: An effective procedure for the synthesis of α-hydroxyphenylacetic acid with cyclodextrin (CD) catalysts was developed. The phase-transfer catalyst types, catalyst loadings, reaction times, reaction temperatures, and substrate molar ratios were investigated to optimize the reaction conditions. In addition, the factors that affect the reaction were studied, and the relationship between benzaldehyde and β-cyclodextrin (β-CD) was analyzed through 2D-ROESY. The equilibrium constant when β-CD was used as the catalyst was calculated. The results indicated that β-CD is the optimal catalyst for the reported reaction (yield: 69.08%). Furthermore, the mechanism underlying the reported reaction was proposed.

Key words: Yclodextrin, benzaldehyde, α-hydroxyphenylacetic acid, equilibrium constant, reaction mechanism

1. Introduction

Numerous studies have been conducted on the supermolecule system since it was first proposed by Lehn.[1] Cyclodextrins (CDs), which are model host molecules in supramolecular chemistry, and their inclusion ability have received considerable attention from researchers. CDs are obtained through an enzymatic reaction and are cyclic structures that connect α-1,4-linked glucose units.[2,3] Three characterized forms of CDs exist: α-, β-, and γ-CD. The outer surface of the cavity of CDs is hydrophilic because of the presence of numerous hydroxyl groups, whereas the interior of the cavity of CD is hydrophobic. These characteristics allow CDs to accommodate various hydrophobic and hydrophilic compounds.[4,5] In particular, the cavity of β-cyclodextrin (β-CD) is shaped like a truncated cone. Various β-CD derivatives have different steric hindrances to improve some abilities. For instance, β-CD can improve the solubility of some hydrophobic molecules and intensify reactions in aqueous phase.[6–9]

Benzaldehyde is one of the simplest aromatic substitutes and is widely used in pharmaceutical intermediates and food spices.[10–12] A product of α-hydroxyphenylacetic acid has also been synthesized successfully. α-Hydroxyphenylacetic acid, also known as mandelic acid, is used to treat urinary tract infections.[13] As a result of its special structure, α-hydroxyphenylacetic acid has a broad range of pharmaceutical synthesis applications and has been applied in the synthesis of aspirin, cyclandelate, and some antibiotics.[14–17] However, the poor water solubility of benzaldehyde limits its applications.[18]

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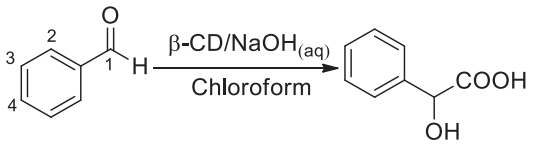
Three methods are widely used for the synthesis of α-hydroxyphenylacetic acid. The first is the cyanobenzaldehyde cyanide method. Although this method enables the facile synthesis of α-hydroxyphenylacetic acid, it presents some disadvantages that limit its industrial application.[19] For example, its yield is lower than that of other methods, and it requires the use of highly toxic substances such as sodium cyanide. Moreover, the final product obtained through this method is difficult to purify. The second method requires noxious starting materials, such as α,α-dibromo-acetophenone (or α,α-dichloroacetophenone), and involves a multistep reaction that is difficult to control.[20] The most general method used to synthesize α-hydroxyphenylacetic acid in the laboratory involves the use of a phase-transfer catalyst.[21−23] The addition of the phase-transfer catalyst increases yields to levels higher than those achieved by other methods.[24] However, some phase-transfer catalysts, such as the quaternary ammonium salt catalyst, are expensive. Vilar's group identified the constants of CD inclusion complexes with aromatic carbonyl compounds through spectrophotometric and electrochemical methods.[25] They used the simple and cheap phase-transfer catalyst β-CD and its derivatives in their study. They also identified the optimal reaction conditions by varying different reaction parameters. In the present work, the equilibrium constant of the reaction was investigated on the basis of nuclear magnetic resonance (NMR) data. The relationship between benzaldehyde and β-CD was also studied through 2D-ROESY. In addition, the mechanism underlying the reaction was proposed.

2. Results and discussion

α-Hydroxyphenylacetic acid was synthesized from benzaldehyde through phase-transfer catalysis (Scheme). To optimize the reaction conditions, α-hydroxyphenylacetic acid was synthesized with a broad range of phase-transfer catalysts, catalyst loadings, reaction times, reaction temperatures, and substrate molar ratios. The experiments were carried out three times, and the results are discussed in the following sections.



Scheme. Synthesis of α-hydroxyphenylacetic acid.

2.1. Selection of phase-transfer catalysts

The reaction was preliminarily assessed in the presence and absence of a phase-transfer catalyst. Different catalysts including β-CD, carboxymethyl-β-cyclodextrin (CM-β-CD), sulfobutylether-β-cyclodextrin (SBE-β-CD), and hydroxypropyl-β-cyclodextrin (HP-β-CD) (Figure 1) were used as the phase-transfer catalysts in an aqueous medium. The results are indicated in Figure 2.

The results displayed in Figure 2 show that the highest product yield (57.25%) was obtained when β-CD was used as the phase-transfer catalyst because β-CD lacks other substituents. Thus, benzaldehyde molecules can easily enter the cavity of β-CD. In addition, the structure of β-CD could protect benzaldehyde without the occurrence of the Cannizzaro side reaction. Therefore, β-CD was selected as the optimum catalyst on the basis of the experimental results.

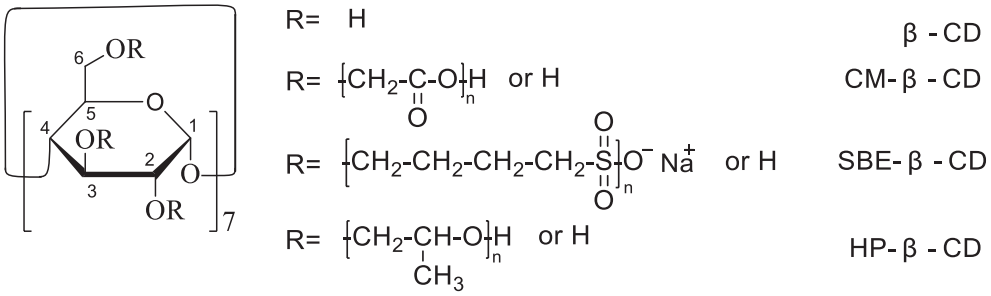


Figure 1. Molecular structures of the CD phase-transfer catalysts.

2.2. Effect of catalyst loading

Figure 3 shows that the yield of α-hydroxyphenylacetic acid gradually increased as β-CD loading increased. For example, the final product was obtained in 21.73% yield when the catalyst (β-CD) loading reached 3% of benzaldehyde. When β-CD loading reached 4% (with respect to the initial amount of aldehydes) of benzaldehyde, the yield of α-hydroxyphenylacetic acid reached 37.54%. However, as β-CD loading continued to increase (5%), product yield decreased due to existing competition with β-CD. Benzaldehyde molecules failed to completely enter the cavity of β-CD when β-CD was present in insufficient amounts (catalyst loading of 1%). Thus, when other benzaldehyde molecules remained in the organic phase, the reaction rate decelerated. In contrast, as the amount of β-CD increased in the presence of the same amount of benzaldehyde, the competition among β-CD molecules decreased the yield.

2.3. Effect of reaction temperature

Figure 4 demonstrates the effects of the reaction temperature. When the reaction temperature was lower than 60 °C, the α-hydroxyphenylacetic acid yield gradually increased as the reaction temperature increased. This

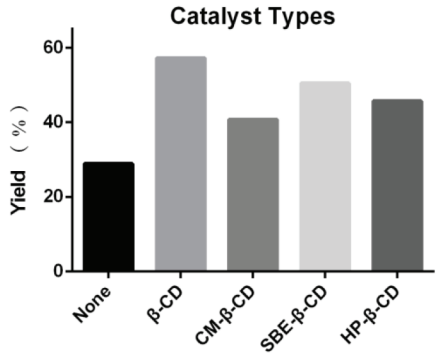


Figure 2. Effect of different phase-transfer catalysts on the yield. Conditions: molar ratio of benzaldehyde to chloroform 1:2; temperature 60 °C; reaction time 6 h; catalyst loading 1% (with respect to the initial amount of aldehydes). Yield: None, 28.89%; β-CD, 57.25%; CM-β-CD, 40.75%; SBE-β-CD, 50.47%; HP-β-CD, 45.67%.

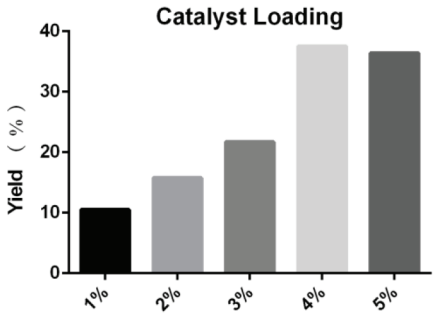


Figure 3. Effect of catalyst loading on yield. Conditions: molar ratio of benzaldehyde to chloroform 1:2; temperature 60 °C; reaction time 2 h; catalyst β-CD. Yield: catalyst loading of 1% (with respect to the initial amount of aldehydes), 10.51%; catalyst loading of 2% (with respect to the initial amount of aldehydes), 15.79%; catalyst loading of 3% (with respect to the initial amount of aldehydes), 21.73%; catalyst loading of 4% (with respect to the initial amount of aldehydes), 37.54%; catalyst loading of 5% (with respect to the initial amount of aldehydes), 36.42%.

result could be attributed to the following: in the presence of a certain amount of chloroform in the reaction, the number of activated molecules in chloroform (chloroform could become dichloro-carbene with the temperature rise) increased as temperature increased. However, chloroform cannot effectively reflux at temperatures below its boiling point. Therefore, the participation of chloroform in the reaction was hindered. Meanwhile, yield decreased when the temperature exceeded 60 °C, given the occurrence of the Cannizzaro side reaction, which requires high temperature and strong alkaline conditions. The volatilization of chloroform and decrease in effective reflux when the temperature exceeds 60 °C may be another potential reason for the reduction in yield. For example, the yield at 80 °C (29.64%) is more than that at 70 °C (19.72%). The reasons for this phenomenon are that the effective chloroform is increased when the temperature goes from 70 °C to 80 °C and the temperature of 80 °C may be restraining the side reaction.

2.4. Effect of reaction time

The results in Figure 5 indicate that the reaction yield first increased and then decreased as the reaction time increased. Yield increased with time when the reaction time was less than 4 h. At 4 h, the yield reached 69.08%. However, yield tended to decrease as the reaction time was prolonged because activated molecules may cause a side reaction that decreases the yield.

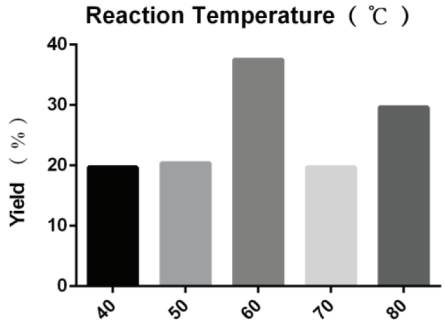


Figure 4. Effect of reaction temperature on yield. Conditions: molar ratio of benzaldehyde to chloroform 1:2; reaction time 2 h; catalyst β-CD; catalyst loading 4% (with respect to the initial amount of aldehydes). Yield: 40 °C, 19.71%; 50 °C, 20.43%; 60 °C, 37.54%; 70 °C, 19.72%; 80 °C, 29.64%.

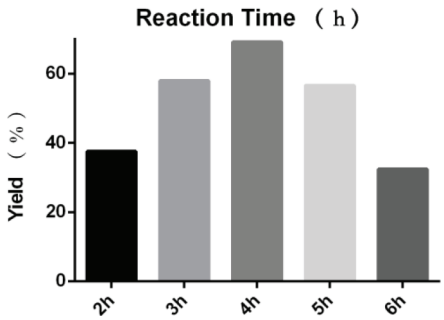


Figure 5. Effect of reaction time on yield. Conditions: molar ratio of benzaldehyde to chloroform 1:2; catalyst β-CD; catalyst loading 4% (with respect to the initial amount of aldehydes); temperature 60 °C. Yield: 2 h, 37.51%; 3 h, 57.89%; 4 h, 69.08%; 5 h, 56.58%; 6 h, 32.24%.

2.5. Effect of substrate molar ratio

The results in Figure 6 indicate that yield reached 69.08% when the n (benzaldehyde):n (chloroform) ratio was 1:2. The high yield may be attributed to the role of chloroform in this reaction: first, chloroform and sodium hydroxide produced dichlorocarbene to participate in the reaction. Second, a portion of chloroform acted as a reflux solvent.

2.6. CD recycling

In the study of the catalytic reaction process, it is not only necessary to find the optimal conditions of the reaction, but it is also important to reuse the catalyst. Through experiments we found that β-CD can be recycled 5 times under the best experimental conditions. At the experimental temperature, the structure of the β-CD can retain integrity. When the reaction is completed, the β-CD may be left in the aqueous phase after

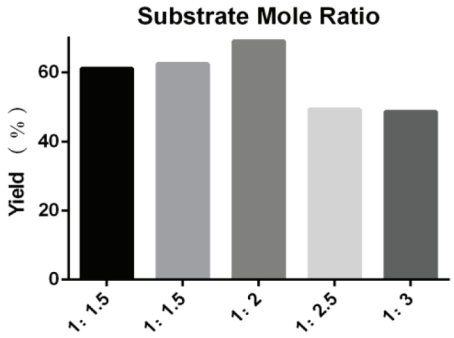


Figure 6. Effect of substrate molar ratio on yield. Conditions: catalyst β-CD; catalyst loading 4% (with respect to the initial amount of aldehydes); temperature 60 °C; reaction time 4 h. Yield: 1:1, 61.18%; 1:1.5, 62.53%; 1:2, 69.08%; 1:2.5, 49.34%; 1:3, 48.68%.

the posttreatment. Furthermore, the β-CD could be obtained by evaporating the aqueous phase. However, due to the leakage in the posttreatment, the β-CD is lost to varying degrees. Hence, the β-CD used in our experiment can be recycled 5 times.

2.7. NMR study

2.7.1. NMR titration

The H-3 and H-5 of glucose units are located in the inner cavity of β-CD.[26,27] Therefore, H-3 and H-5 can be applied as spectral probes to detect the presence of guest molecules. The inclusion of small molecules and β-CD occurs through the process of dynamic equilibrium. Binding and dissociation between the host and guest occur at each instant and correspond to the two states in which inclusion complexes are present. The inclusion ratio of the compound can be determined by plotting the ratio of the chemical shift on H-3 and H-5 on β-CD against the guest/host molar ratio. The identity of the inclusion compound can be inferred from the equilibrium constant provided by NMR data.

The above experimental results easily revealed that β-CD has good catalytic activity as a distinct phase-transfer catalyst. Therefore, we analyzed the mechanism underlying the formation of the inclusion complexes of benzaldehyde and β-CD. According to the chemical shift of H-3, the optimal inclusion ratio was calculated. Then equilibrium constants were calculated in accordance with physical calculations. The change in atomic magnetic displacement inferred from NMR data indicates that β-CD and benzaldehyde were enriched at the ratio of 1:1 (Figure 7).

The equilibrium constant K_a can be calculated from the data provided by ^{1}H NMR.[28] When the ratio of the subject and object is 1:1, the expression of the equilibrium constant K_a is

$$C + S \overset{K_a}{\longleftrightarrow} CS$$

$$K_a = \frac{[CS]}{[C]\ [S]}$$

After a series of mathematical transformations, we obtain an equation for the chemical shift change value and K_a:

$$S_0 = \frac{\frac{\Delta\delta}{K_a} - \frac{\Delta\delta^2 C_0}{Q} + C_0\Delta\delta}{Q - \Delta\delta},$$

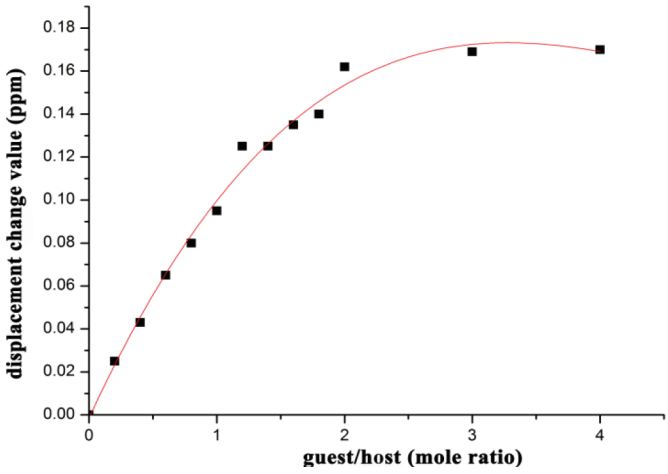


Figure 7. Displacement change in the value of H-3.

where S_0 is the total benzaldehyde concentration and C_0 is the total CD concentration. $\Delta\delta$ is the change in chemical shift given by $\Delta\delta = \delta_{CD} - \delta_{obs}$ for the H-3 of CD. Q is the H-3 chemical shift difference between CD and "pure" CD inclusion complexes given by $Q = \delta_{CD} - \delta_{CS}$, which was obtained through mathematical simulation by plotting $\Delta\delta$ against the guest-to-host molar ratio.[29,30] The values of the equilibrium constant (K_a) calculated using the above formula are indicated in the Table. In addition, high equilibrium constants are associated with the complete progression of the reaction.

Table. Equilibrium constant (K_a) of different catalysts (NMR titration of β-CD and benzaldehyde at 25 °C [400 MHz; D_2O:CD_3OD = 1:1]).

Serial number	Catalyst type	Equilibrium constant (Ka L/mol)
1	$\beta-$CD	27707
2	CM-β-CD	155.6
3	SBE-β-CD	1412
4	HP-β-CD	4000

2.7.2. 2D-ROESY spectra of NMR

In this reaction, β-CD acts primarily as a catalyst and is not directly related to chemical bond linkage. Therefore, the 2D-ROESY spectra are used to pinpoint when benzaldehyde enters the β-CD cavity.[31−34] Spatial conformation is determined by the interaction between the carbonyl group on benzaldehyde with the hydroxyl groups on β-CD.

The 2D-ROESY experiment (Figures 8 and 9) also corroborates the hypothesis derived from the ^{1}H NMR titration experiments. As inferred from the 2D-ROESY map of β-CD/benzaldehyde inclusion complexes (Figure 8), a spatial interaction between the benzene ring on benzaldehyde and the H-3 and H-5 of β-CD exists. In contrast, this correlation is difficult to infer from the 2D-ROESY spectrum of CM-β-CD/benzaldehyde inclusion complexes.

Clear signals are observed for all of the H-3/Ar-H-2, H-3/Ar-H-3, H-5/Ar-H-2, and H-5/Ar-H-3 crossing points. The absence of the signal for the H-3/Ar-H-4 and H-5/Ar-H-4 protons is suggestive of a complexation geometry wherein the guest is partially included in the host cavity. The possible inclusion geometry can be

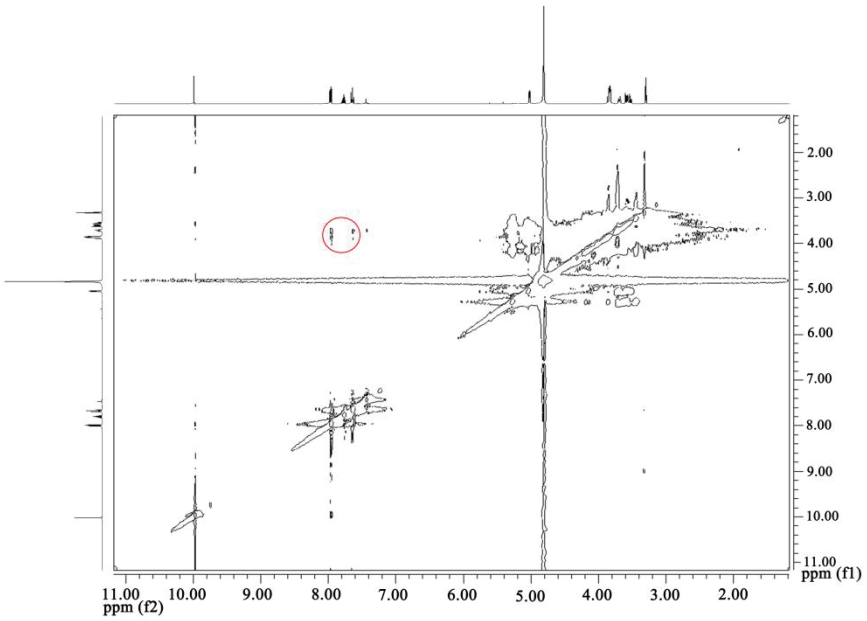


Figure 8. 2D-ROESY map of β-CD/benzaldehyde inclusion complexes.

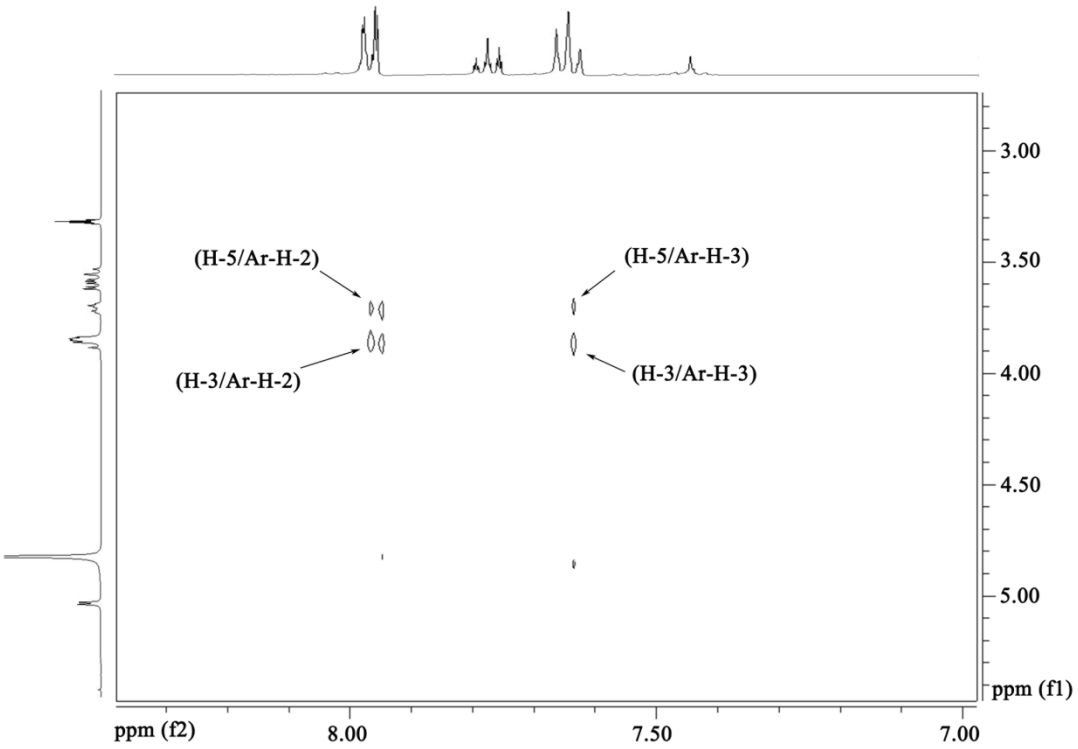


Figure 9. Partial NMR spectrum corresponding to the 2D-ROESY experiments performed on β-CD/benzaldehyde complexes.

deduced from inspection of the molecular models, i.e. one CD encapsulating one guest. In addition, Figure 8 shows that the H-3 signal is stronger than the H-5 signal. Therefore, in this orientation, Ar-H-2 and Ar-H-3 are

closer to H-3 than to H-5. Therefore, we proposed the structures of β-CD/benzaldehyde inclusion complexes (Figure 10).

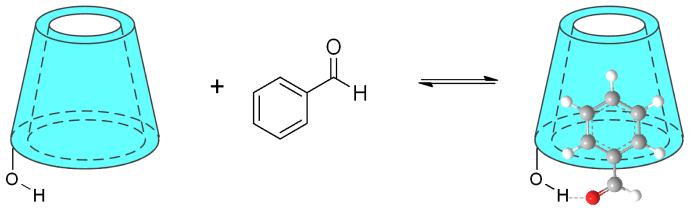


Figure 10. Proposed structure of β-CD/benzaldehyde complexes.

2.8. Possible mechanism of the reaction

In order to explore the possible mechanism of this reaction, we used 2D-ROESY to explain the relationship between β-CD and benzaldehyde. In the NMR spectra, we found that small molecules form inclusion complexes with β-CD. In this reaction, the CD acted as phase transfer because the reactants are in two phases. First, the β-CD encapsulated benzaldehyde to form an inclusion complex by a stable hydrogen bond. Then chloroform converted to dichlorocarbene in a strong sodium oxide solution to further attack the carbonyl group on the benzaldehyde. Finally, mandelic acid was obtained. The corresponding reaction mechanism (Figure 11) was proposed on the basis of the type, conditions, and NMR data of the reaction.

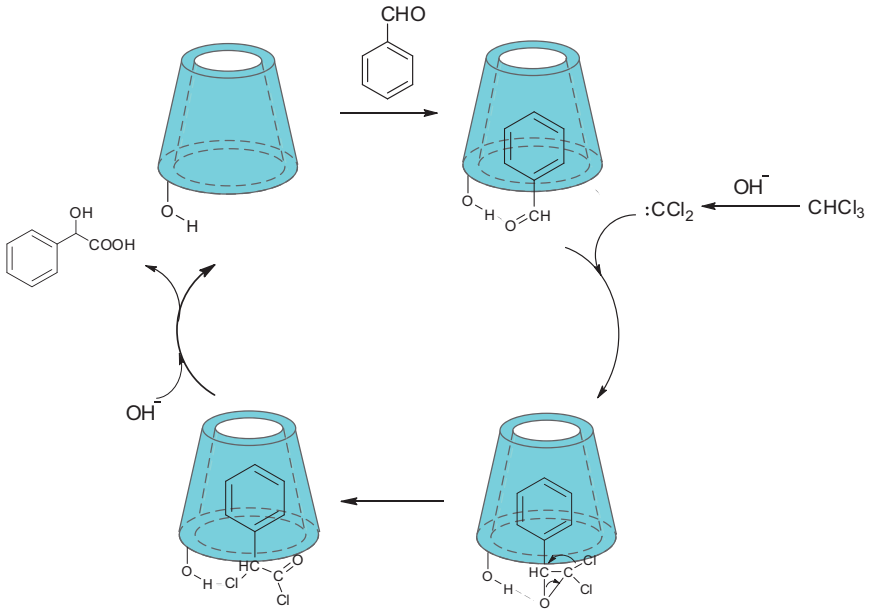


Figure 11. Proposed mechanism underlying the oxidation of benzaldehyde to α-hydroxyphenylacetic acid.

2.9. Product structure and identification

The synthesized product was characterized through NMR spectroscopy, ^{1}H NMR (400 MHz, D_2O (TSM)) δ: 7.57, 7.44, 7.42, 7.40, 7.35, 5.19,[35] and the IR spectrum, ν_{max} (cm^{-1}, KBr): 3397 (OH), 1717 (C=O), 1299 (C-O). The results were consistent with those reported in the literature and confirmed using melting point data for the temperature range of 133–134 °C.[36,37]

2.10. Conclusions

An efficient method for the synthesis of α-hydroxyphenylacetic acid was successfully developed. The experimental results demonstrate that β-CD is the optimal catalyst for this reaction given its excellent catalytic activity and ecofriendliness. The effects of reaction parameters, including catalyst type, catalyst loading, reaction time, reaction temperature, and raw material molar ratios, were investigated. As shown by the one-dimensional atomic spectrum, the change in the chemical shift of hydrogen atoms outside of β-CD is supported by the action of β-CD and accounts for the yield of α-hydroxyphenylacetic acid. The interaction between benzaldehyde and β-CD cavity has been induced indirectly. The inclusion ratio of β-CD with benzaldehyde was identified using one-dimensional spectral data. The host-to-guest ratio is 1:1. The results were compared with 2D ROESY NMR data. A spatial interaction between hydrogen in β-CD and benzaldehyde exists. This research provides the basis for the sustainable, integrated exploitation of α-hydroxyphenylacetic acid as a cheap and easily available source of high-value chemical materials for industrial and pharmaceutical applications.

3. Experimental

3.1. Materials

Ethyl acetate was provided by Tianjin Beichen Chemical Co., Ltd. β-CD, CM-β-CD, SBE-β-CD, and HP-β-CD were supplied by Shanghai BuBei Chemical Co., Ltd. In some experiments, β-CD and its derivatives were dried at 80 °C under vacuum for 5 h immediately before utilization. Sodium hydroxide, dilute hydrochloric acid, and chloroform were supplied by Yantai Both Chemical Co., Ltd. All reagents were of analytical grade.

3.2. Method

First, 1 mL (0.01 mol) of freshly distilled benzaldehyde, 2 mL (0.025 mol) of chloroform, and a certain amount of phase-transfer catalyst were added to the reaction flask with a stirring magnet. Next, 4 mL of 50% sodium hydroxide solution was added dropwise when the reactor temperature reached 55 °C. The reaction was allowed to proceed for several hours. After the reaction was finished, an appropriate amount of water was added to dissolve the solid product. Unreacted chloroform was removed with ethyl acetate. The aqueous layer was acidified to pH 1 with dilute hydrochloric acid, extracted three times with ethyl acetate, and dried with anhydrous magnesium sulfate. The dried solution was spin-removed in a rotary evaporator to remove ethyl acetate. Finally, 1 to 10 times the amount of distilled water was added to the crude product, and the pure product of α-hydroxyphenylacetic acid was recrystallized. The structure of the product was characterized using the melting point and NMR data.

Acknowledgments

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