Alkaline Hydrolysis of Cinnamaldehyde to Benzaldehyde in the Presence of β-Cyclodextrin

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A facile, novel, and cost-effective alkaline hydrolysis process of cinnamaldehyde to benzaldehyde under rather mild conditions has been investigated systematically in the presence of β-cyclodextrin (β-CD), with water as the only solvent. β-CD could form inclusion complex with cinnamaldehyde in water, with molar ratio of 1:1, so as to promote the reaction selectivity. The complex has been investigated experimentally and with computational methods. ^{1}H-NMR, ROESY, UV–Vis, and FTIR have been utilized to analyze the inclusion complex. It shows that the equilibrium constant for inclusion (Ka) is 363 M^{-1}, and the standard Gibbs function for the reaction, $\Delta_\gamma G_m^\Theta$ (298 K), is −14.6 kJ mol^{-1}. In addition, the structures of the proposed inclusion compounds were optimized with hybrid ONIOM theory. Benzaldehyde could be obtained at an yield of 42% under optimum conditions [50°C, 18 h, 2% NaOH (w/v), cinnamaldehyde:β-CD (molar ratio) = 1:1]. To explain the experimental data, NMR, FTIR, and elemental analysis results were used to determine the main reaction by-product 1-naphthalenemethanol. A feasible reaction mechanism including the retro-Aldol condensation of cinnamaldehyde and the Aldol condensation of acetaldehyde and cinnamaldehyde in basic aqueous β-CD solution has been proposed. The calculated activation energy for the reaction was 45.27 kJ mol^{-1} by initial concentrations method. © 2009 American Institute of Chemical Engineers *AIChE J,* 56: 466–476, 2010

Keywords: cinnamaldehyde, alkaline hydrolysis, benzaldehyde, β-cyclodextrin, inclusion complex, computational method, reaction mechanism, rate constants, activation energy

Introduction

Benzaldehyde production is an attractive industry, as benzaldehyde is the second largest perfume in the world, and it is also important for many pharmaceuticals.[1] With more care about food quality and natural essence from consumers, the demand for natural benzaldehyde is increasing quickly, and the synthesis of natural benzaldehyde is drawing much attention.[2] Conventionally, natural benzaldehyde is from alkaline hydrolysis of *Laetrile*, and hydrocyanic acid is obtained as a by-product. In this way, the natural benzaldehyde could be produced at high cost,

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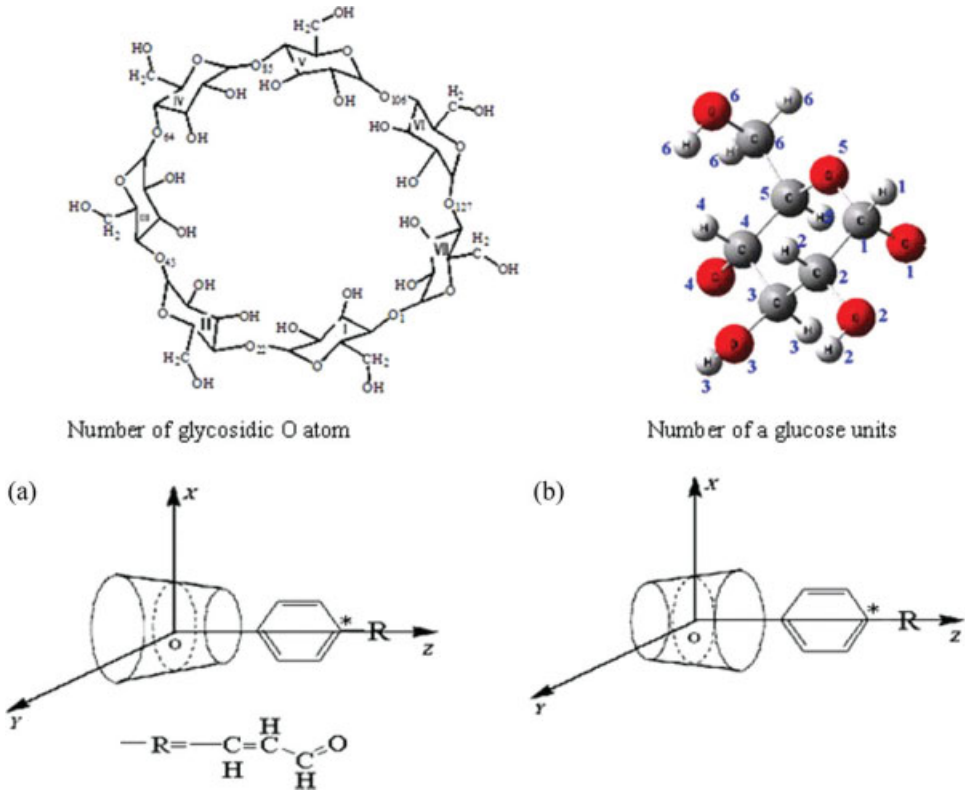


Figure 1. Atom number in β-CD, number of glycosidic O atom, number of a glucose units, and coordinate systems to describe the inclusion process of β-CD with guests: (a) head up and (b) head down.

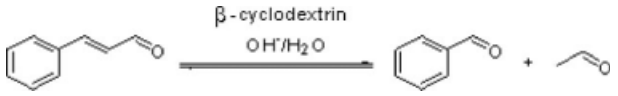
[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

because the toxic hydrocyanic acid should be removed thoroughly.

Another alternative for obtaining natural benzaldehyde is from natural cinnamon oil, which contains more than 80% of cinnamaldehyde. Benzaldehyde from hydrolysis of cinnamaldehyde does not contain hydrocyanic acid and chloride. Alkaline hydrolysis of cinnamaldehyde or natural cinnamon oil[3–5] is simple, but the yield for benzaldehyde is low because cinnamon oil and cinnamaldehyde are poorly soluble in water. Therefore, to promote the reaction, phase transfer catalysts or surfactants could be applied to enlarge the contact area between the two phases.[6–8] However, there are still some defects, e.g., many by-products and toxic phase transfer catalysts remained, making the process less benign. Gao and Lu[9] used near-critical water (the compressed liquid at 473–623 K) as the only solvent to facilitate the hydrolysis because the near-critical water can dissolve both organic and inorganic materials. Nevertheless, the method requires high temperature (553 K) and high pressure (15 MPa), which is unfavorable to preserve the natural essence of benzaldehyde. Therefore, it is significant to develop a new process with mild and clean reaction conditions to preserve natural essence of benzaldehyde, among which mild reaction temperature should be especially crucial.

Organic reaction in aqueous media is a hotspot recently because water is the cheapest ''green'' solvent, and it has minimal impact on ecology. Thus, development of organic reactions in aqueous solution is one of the challenges for aqueous chemistry and chemical engineering.[10,11] As supramolecular host compounds, cyclodextrins (CDs) have attracted much attention and introduced many organic reactions in aqueous solution.[12–14] CDs are series of cyclic oligosaccarides most commonly formed by six, seven, and eight glucopyranose units, denominated as α-, β-, and γ-CD, respectively (as shown in Figure 1). They are water-soluble, nontoxic, and have a hollow truncated cone structure that is hydrophilic at the periphery and hydrophobic in the central cavity. CDs and their derivatives are well known for forming inclusion complexes with many organic compounds in aqueous solution under mild conditions.[15,16] β-CD is the cheapest among the CD family and is widely used in chemical separation, enzyme simulation, molecular recognition, and organic synthesis, etc.[17–20] The characteristics of β-CD, which could activate the substrate and promote its solubility, is the ability of catalyzing reactions and improving the reaction selectivity. In addition, β-CD could be easily recycled by addition of acetone.[21] On the basis of the green principle, a facile and novel alkaline hydrolysis of cinnamaldehyde to benzaldehyde promoted by β-CD has been developed, with water as the only solvent (Scheme 1) in this paper.

In recent years, it was reported that the solubility, physicochemical properties, and sustained release properties, etc. of the CDs inclusion complexes of cinnamaldehyde have been improved.[22–24] The aim of the present work is to investigate the role of β-CD on the alkaline hydrolysis of cinnamaldehyde to benzaldehyde. The characterization of the complexes, which are governed by noncovalent intermolecular interactions, e.g., Van der Waals force, hydrophobic-



Scheme 1. Alkaline hydrolysis of cinnamaldehyde to benzaldehyde promoted by β-CD.

lipophilic interaction, dipole-dipole interaction, dispersion interaction and hydrogen bond, etc, are important for understanding not only the geometry of the complex formed but also the reaction mechanism. In this sense, various methods, e.g., FTIR, ^{1}H-NMR, two dimensional (2D) NMR, UV–vis, and also computational techniques, have been used to investigate the inclusion complex in this work. As powerful complementary means of experimental studies, theoretical methods have been widely employed to describe geometries and calculate the stabilization energy of inclusion complexes.[25–27] Most of the theoretical calculations for CDs applied molecular mechanics methods due to the big size of these systems. With rapid development of theoretical research on supramolecular chemistry, hybrid ONIOM method[28] that applies multi-approaches (QM/QM or QM/MM) with varying accuracy and cost to treat different parts of a system, simultaneously, has captivated many researchers' interest, and it has been proved to be effective for investigating the β-CD/guests inclusion complexes.[29–31] In this paper, hybrid ONIOM method has been used to elucidate the structure of the β-CD inclusion complex of cinnamaldehyde so as to establish the most stable form of the complex based on quantum chemistry and give a theoretical evidence for the reaction mechanism.

In addition, the effects of various reaction parameters, e.g., molar ratio of β-CD to cinnamaldehyde, reaction temperature, reaction time, and the base concentration, were examined to optimize cinnamaldehyde conversion and selectivity for the target product benzaldehyde. The results let us to propose a mechanism for the hydrolysis of cinnamaldehyde in the presence of β-CD. Besides, the two reaction activation energies for the hydrolysis with and without β-CD have been compared for the first time to clarity why β-CD can promote the alkaline hydrolysis of cinnamaldehyde.

Experimental

Preparation of the β-CD inclusion complex of cinnamaldehyde

β-CD was purchased from Shanghai Boao Biotechnology, China. Cinnamaldehyde was obtained from Sinopharm Chemical Reagent, China. A measure of 1 mmol β-CD (1.1351 g) and 1 mmol cinnamaldehyde (0.1322 g) were dissolved in deionized water (25 mL) and the mixture was stirred at 323 K for 2 h. When the mixture was utterly clear, it was cooled at 277 K for 24 h and then centrifuged. The light yellow precipitate was washed with hot water and hot ethanol, successively, to completely remove the free β-CD and free cinnamaldehyde. Finally, the inclusion complex was dried in vacuo at 323 K for 24 h.

Characterization of the inclusion complex

FTIR spectroscopic measurements were carried out on a Bruker Equinox 55 FTIR spectrometer with pressing KBr troche. All spectra were recorded from 400 to 4000 cm$-^1$ at room temperature.

NMR spectra were recorded at room temperature on a Bruker DRX 400-AVANCE spectrometer (Bruker BioSpin, Rheinstetten, Germany) operating at 400 MHz, equipped with a 5 mm inverse probe and z-gradient coil. ^{1}H NMR spectrum was measured as: spectral width 8012 Hz, acquisition time 2.04 s, and a relaxation delay 2 s with 32 scans. Rotating-frame Overhauser Effect Spectroscopy (ROESY), which is one of the most important tools to confirm the formation of the host/guest systems, was acquired in the phase sensitive mode with the same spectrometer and Bruker standard parameters (pulse program roesyetgp). Spectra were obtained with a spin-lock mixing time of 200 ms, relaxation delay 2 s, and 32 scans were recorded.

UV–Vis spectra were measured on a HITACHI U-3010 UV–vis spectrometer to calculate the inclusion equilibrium constant and thermodynamic parameters. From the absorption curve of cinnamaldehyde, its concentration was determined by measuring the absorbance at 290 nm with β-CD (5×10^{-4} mol/L) as reference.

Besides, the inclusion complex was evaluated by theoretical calculations, and the theoretical results provide information of energy and structure of the β-CD/cinnamaldehyde. The initial structures of β-CD and guests were constructed using CS Chem 3D Ultra (Version 8.0), and they were fully optimized using PM3 method without any symmetry constraint. Then, the inclusion complexes were built from the PM3-optimized host and guests. The atom number in β-CD and the coordinate systems for describing the inclusion process of β-CD with guests were shown in Figure 1. Glycosidic oxygen atoms were placed onto the XY plane and their center was designated as the coordination origin, and the longer dimension of guests was placed onto the Z axis. The position of the guests in hydrophobic cavity was defined by Z_{C^*} and the docked angle (θ). Z_{C^*} is the Z coordinate of C* atom, whose unit is angstrom (Å). The docked angle (θ) is the angle between plane of benzene ring and YZ plane, whose unit is degree (°). The inclusion process was simulated by putting the substrate at one end of the β-CD and then letting it pass through the cavity of β-CD in steps. All the calculations were performed with Gaussian 03 D.01 program.[32]

Alkaline hydrolysis of cinnamaldehyde to benzaldehyde

All reactions were carried out in a glass reaction flask equipped with reflux condenser and magnetic stirrer. For a typical reaction run, NaOH (0.5 g) and β-CD (1 mmol, 1.1351 g) were dissolved in 25 mL deionized water at 323 K. Then, cinnamaldehyde (1 mmol, 0.1322 g) was added. The mixture was extracted by ethyl acetate and then centrifugated. The consumption of cinnamaldehyde and formation of products were monitored by GC-MS (Shimadzu GCMS-QP2010, Japan) with naphthalene as an internal standard. The reproducibility for all the data was within 5%.

Large-scale alkaline hydrolysis of cinnamaldehyde was carried out under the optimum reaction conditions as: NaOH (7.5 g) and β-CD (15 mmol, 17.0265 g) were dissolved in 375 mL deionized water at 323 K and then cinnamaldehyde (15 mmol, 1.9830 g) was added while stirring. The process

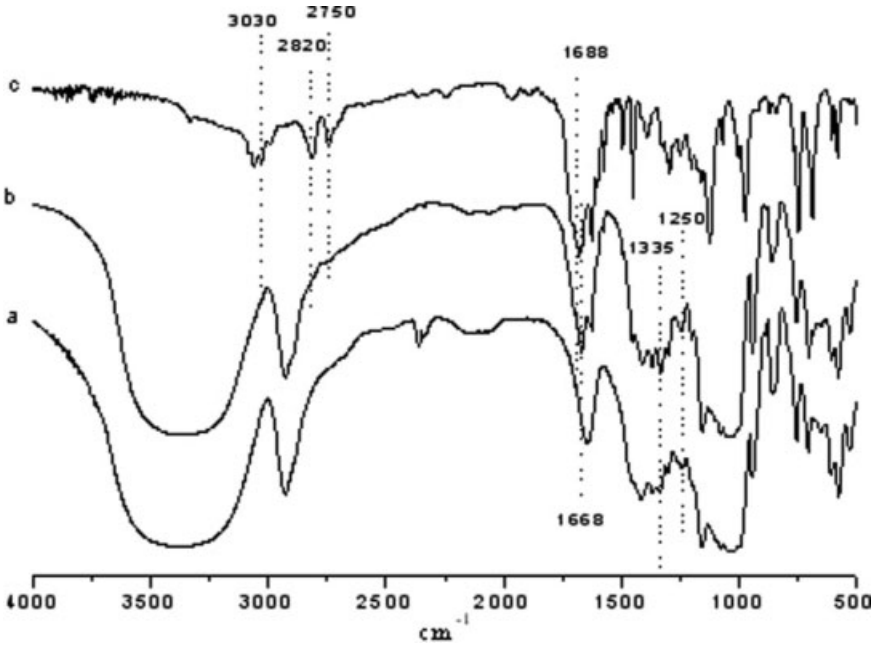


Figure 2. FTIR spectra of β-CD (a), the inclusion complex between β-CD and cinnamaldehyde (b), and cinnamaldehyde (c).

was monitored by GC-MS with naphthalene as the internal standard. When the reaction was complete, the mixture was extracted by ethyl acetate and then centrifuged. The products were purified on a silica gel column (200–300 mesh ASTM) with the mixture of ethyl acetate and petroleum ether (1:30, volume ratio) as eluent.

The main by-product obtained from the large-scale experiment was characterized by elemental analysis, NMR, FTIR, and GC-MS. Elemental analysis was carried out on a Vario EL III elemental analyzer (Elemental, Germany). GC-MS: *m/z* 158, 141, 129, 115, 102, etc. FTIR: 3381, 3047, 2883, 1595, 1509, 1434, 1076, 1002, 797, 773, and 711 cm^{-1}. ^1H NMR (DMSO, 400 HZ): δ 8.13 (1H, m, H-8), 7.88 (1H, m, H-5), 7.86 (1H, m, H-4), 7.64–7.53 (4H, m, H-2, H-3, H-6 and H-7), 5.41 (1H, s, OH), and 5.05 (2H, s, CH_2) ppm. ^{13}C NMR (DMSO, 100 HZ): δ 138.09 (C, C-1), 133.42 (C, C-10), 130.97 (C, C-9), 128.58 (CH, C-5), 127.50 (CH, C-4), 126.84 (CH, C-7), 125.86 (CH, C-6), 125.66 (CH, C-3), 124.49 (CH, C-2), 123.98 (CH, C-8), and 61.46 (CH_2, C-1′) ppm.

Kinetic experiments

Kinetic experiments were performed under pseudo first order conditions [(H_2O) (dmt) (cinnamaldehyde)]. The initial concentration method was taken without considering the reverse reaction and side reactions. Generally, the kinetic characteristic was measured as: 0.5 g NaOH and 1 mmol β-CD were dissolved in 25 mL of deionized water at 323 K (or at 313, 333, and 343 K) in a 250-mL 3-necked round-bottomed flask. Then 0.001 mol (or 2.5×10^{-4}, 5.0×10^{-4}, and 7.5×10^{-4} mol) cinnamaldehyde was added while stirring. The reaction mixture was sampled with a syringe at regular time intervals from 1 to 10 min. The sample was extracted by ethyl acetate and analyzed by GC-MS with naphthalene as an internal standard. Kinetic experiments without β-CD were carried out in the same way. The reproducibility for the rate constants measured was all within 5%.

Results and Discussion

Characterization of inclusion complex

FTIR Results. FTIR was used to investigate the peak changes on host/guest interaction between β-CD and cinnamaldehyde. Figure 2 shows the FTIR spectra of cinnamaldehyde, β-CD, and the inclusion complex. The IR spectrum of inclusion complex (curve b) is similar to that of β-CD (curve a), indicating that the frame of β-CD in complex is not changed. When curve b is compared with pure cinnamaldehyde (curve c), disappearance in the stretching absorption of C—H in benzene ring at 3030 cm^{-1} and reduction in the absorption peak intensity of C—H in aldehyde group (—CHO) at 2820 and 2750 cm^{-1} are also observed. These changes could be attributed to the fact that cinnamaldehyde enters into the cavity of β-CD. For cinnamaldehyde, the C=O stretching absorption at 1688 cm^{-1} is shifted to 1668 cm^{-1} in inclusion complex. Furthermore, the absorption of C—O—H in inclusion complex at 1335 and 1250 cm^{-1} was significantly intensified when compared with β-CD.[33] These changes are obvious evidences for interaction between cinnamaldehyde and β-CD in inclusion complex. Such interaction is mainly regarded as hydrogen bond. Because of the formation of hydrogen bond, the single bond property of C=O increases, its bond length extends and the corresponding force constant decreases, which results in blue shift of the absorption frequency of C=O and increase of the absorption intensity of C—O—H.

NMR results

The ^1H NMR experiments were performed to evaluate the chemical shift difference ($\Delta\delta = \delta_{\text{Inclusion}} - \delta_{\beta\text{-CD}}$) between

Table 1. ^{1}H-NMR Chemical Shifts of β-CD and the Inclusion Complex of β-CD and Cinnamaldehyde in D_2O

	1H	2H	3H	4H	5H	6H
$\delta_{\beta\text{-CD}}$ (ppm)	4.948	3.540	3.841	3.458	3.733	3.754
$\delta_{\text{Inclusion}}$ (ppm)	4.932	3.518	3.774	3.453	3.645	3.742
$\Delta\delta$ (ppm)	−0.016	−0.022	−0.067	−0.005	−0.088	−0.012

pure β-CD and the inclusion complex using D_2O as solvent. The chemical shifts for the pure β-CD and the inclusion complex in molar ratio of 1:1 are showed in Table 1. It is obvious that the chemical shifts of the internal protons H3 and H5 of β-CD has increased, which is a strong evidence for the inclusion of cinnamaldehyde into the β-CD cavity. All the changes on the internal hydrogen atoms of β-CD could be attributed to the change of electronic density caused by interaction with the cinnamaldehyde molecule.[34]

Two-dimensional (2D) NMR is a powerful tool for investigating inter- and intra-molecular interaction so as to understand the geometry of supramolecular complex.[35] To gain more conformational information especially for the aldehyde group in complex, ROESY experiment was employed to study the inclusion complex. The contour map expansion for 1:1 molar ratio of β-CD/cinnamaldehyde is presented in Figure 3a and 3b. As shown in Figure 3a, cross peak correlation between aromatic hydrogen atoms of cinnamaldehyde (region from δ 7.36 to δ 7.74) and the internal (H3 and H5, region at δ 3.65 and δ 3.34) protons of the β-CD molecule was observed. These observations are in agreement with the ^{1}H NMR results, where larger changes for these protons are observed, which should be caused by the inclusion of the aromatic ring in the cavity of the β-CD. As shown in Figure 3b, cross-peak correlation between hydrogen in aldehyde group (region at δ 10.20) and the hydrogen atoms of —OH (2) and —OH (3) (region from δ 5.60 to δ 5.70) of β-CD was also observed.[33] It is noteworthy that no cross-peak correlation was observed between aldehyde group and —OH (6) (region at δ 4.44) of β-CD. These observations indicate the aldehyde group of cinnamaldehyde is near the secondary face of β-CD, and may form hydrogen bond with the —OH group of β-CD, which are in accordance with the FTIR results.

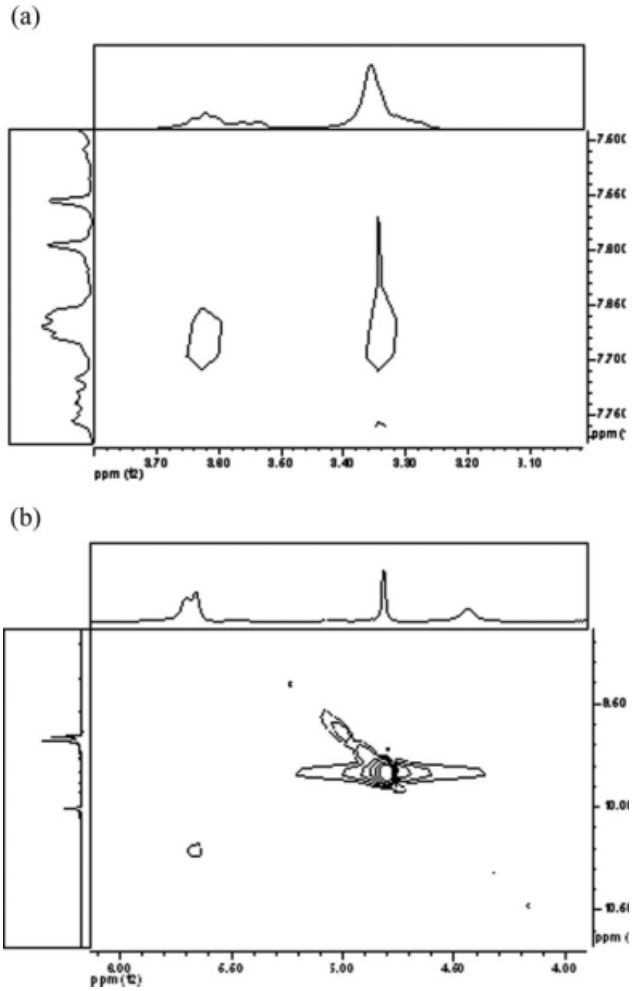


Figure 3. Expansion of the 2D ROESY contour plot (400 MHz, mixing time of 200 ms) of the inclusion complex of cinnamaldehyde with β-CD.

UV–vis results

For the β-CD, guest complex is formed with stoichiometry of 1:1 (molar ratio), the equilibrium is expressed as Eq. 1.

$$M + N \overset{K_a}{\rightleftharpoons} MN \tag{1}$$

According to Hildebrand-Benesi relation, the following equation could be obtained:

$$[M]_0/\Delta A = 1/K_a\Delta\varepsilon[N]_0 + 1/\Delta\varepsilon \tag{2}$$

where K_a is the inclusion equilibrium constant for the guest and β-CD, $[N]_0$ is the initial concentration of guest, $[M]_0$ is the initial concentration of β-CD, ΔA is the absorption changes of the inclusion complex, and $\Delta\varepsilon$ is the extinction coefficient difference of β-CD before and after inclusion. When the concentration of β-CD was given, the absorbance changes with different concentration of guests in aqueous β-CD solution were recorded. Figure 4 depicts a plot of $[M]_0/\Delta A$ as a function of $1/[N]_0$ for cinnamaldehyde, and good linear correlations were observed, confirming the formation of a 1:1 inclusion complex. From the intercept and slope of this plot, K_a is

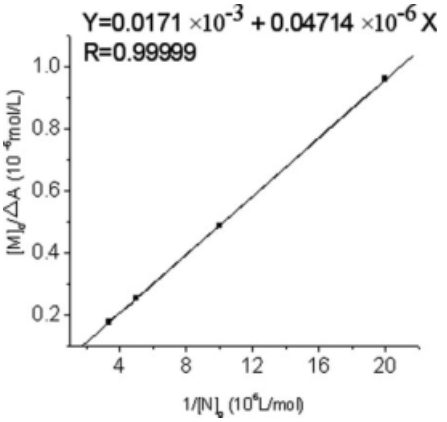


Figure 4. Benesi-Hildebrand plot of $[M]_0/\Delta A$ vs. $1/[N]_0$ for cinnamaldehyde.

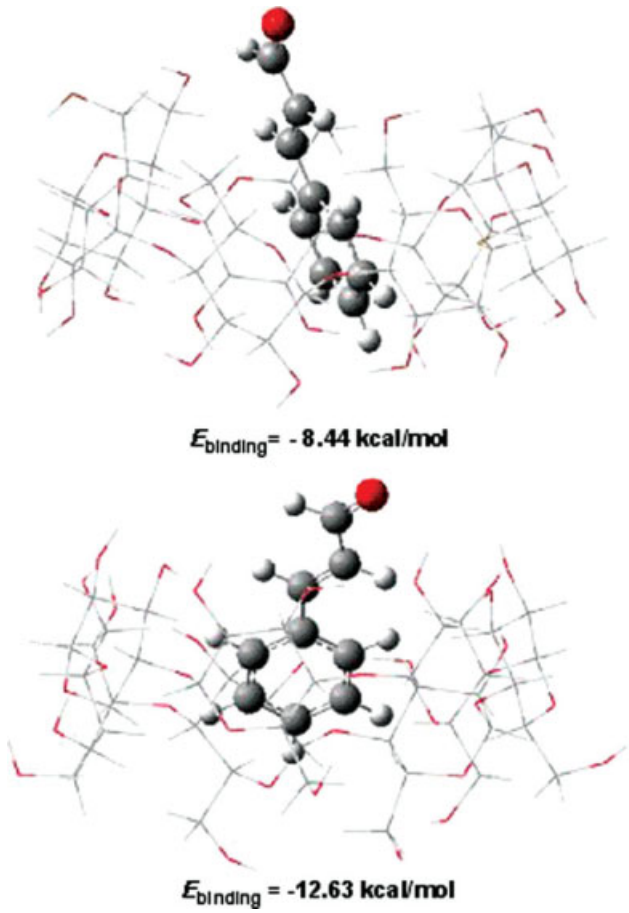


Figure 5. Optimized structure of inclusion complexes obtained by ONIOM (B3LYP/6-31G (d):PM3) method, and the 'head up' and 'head down' of cinnamaldehyde/β-CD complexes were displayed on the left and right, respectively.

[Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

363 M^{-1} at 298 K, $\Delta_\gamma G_m^\Theta$ (298 K), is −14.6 kJ mol^{-1}. The negative value for the change of standard Gibbs free energy (ΔG) indicates the spontaneous formation of host–guest inclusion complexes in aqueous solution at 298 K.

Theoretical Results

Z coordinate of C* atom (Z_{C*}) and docked angle (θ) were selected to define the initial position of guests in hydrophobic cavity of β-CD. Geometries of the inclusion complexes optimized by ONIOM (B3LYP/6-31G(d):PM3) were displayed in Figure 5. The distance between O atom of carbonyl in cinnamaldehyde and H2, and H3 atoms of secondary hydroxyls in β-CD, and that between H atom of carbonyl and O atoms of secondary hydroxyl in β-CD were listed in Table 2.

The negative binding energy demonstrated that β-CD interacted with cinnamaldehyde to form stable inclusion complexes spontaneously. The cinnamaldehyde/β-CD head up was less favorable than the other one, and the binding energies were −8.44 and −12.63 kcal mol^{-1}, respectively. As shown in Figure 5, the global minima were found to be at approximately $Z = 1$ Å and $\theta = 75°$ for the head up, or at $Z = 2$ Å and $\theta = 120°$ for the head down.

The results in Table 2 indicated that it was easier for cinnamaldehyde molecule to penetrate the cavity of β-CD from secondary side than from primary side. For the head up inclusion complex, the distances between O/H atoms of carbonyl in cinnamaldehyde and 2-OH/3-OH in β-CD ranged from 8.071 to 11.791 Å, and such great interval made against the host–guest inclusion. However, it has been found in the head down inclusion complex that the O atom of carbonyl in cinnamaldehyde was close to H_2 atom of 2-hydroxyl of VI/VII glucosic units and H3 atom of 3-hydroxyl of V/VI glucosic units in β-CD; on the other hand, the H atom of aldehyde in cinnamaldehyde was close to O_2 atom of V/VI glucosic units and O_3 atom IV/V glucosic units in β-CD. If the cut-off criteria of the H···O distance was designed to be less than 4.5 Å, the distances for effective interactions were in the order of O-VI-H2 (3.092 Å), H-V-O3 (3.432 Å), O-VI-H3 (3.726 Å), H-IV-O3 (3.868 Å), O-V-H3 (3.874 Å), H-VI-O2 (4.033 Å), H-V-O2 (4.180 Å),

Table 2. The Distances Between O Atom of Carbonyl in Cinnamaldehyde and H_2/H_3 Atoms of Hydroxyl in β-CD and the Distances Between H Atom of Aldehyde and O_2/O_3 Atoms of Hydroxyl in β-CD Obtained by ONIOM(B3LYP/6-31G(d):PM3) Atoms Method

	I-O2	II-O2	III-O2	IV-O2	V-O2	VI-O2	VII-O2
Head up	8.788	8.071	8.863	10.206	10.072	10.931	11.369
Head down	10.182	10.907	9.344	5.845	4.180	4.033	5.826
	I-O3	II-O3	III-O3	IV-O3	V-O3	VI-O3	VII-O3
Head up	8.148	8.242	9.411	9.850	10.476	11.174	10.692
Head down	10.551	10.210	7.702	3.868	3.432	5.077	7.365
	I-H2	II-H2	III-H2	IV-H2	V-H2	VI-H2	VII-H2
Head up	9.837	10.269	11.265	11.791	11.185	11.240	11.548
Head down	9.884	11.117	10.131	6.976	5.583	3.092	4.456
	I-H3	II-H3	III-H3	IV-H3	V-H3	VI-H3	VII-H3
Head up	9.136	10.103	10.935	10.446	10.319	10.727	10.729
Head down	10.443	10.568	8.528	5.658	3.874	3.726	7.045

The atomic number is shown in Figure 1, and the distance is in Å.

Table 3. Influence of Different Amount of β-CD on the Hydrolysis of Cinnamaldehyde

β-CD: Cinnamaldehyde (mmol: mmol)	Conversation of Cinnamaldehyde (%)	Yield of Benzaldehyde (%)	Yield of 1-Naphthalene-methanol (%)
0:1	29	16	12
1:1	>99	34	31
1:2	90	33	30
1:3	78	28	27
1:4	59	22	21
2:1	60	20	16

Reaction condition: H_2O (25 mL), NaOH (0.75 g), 18 h, and 323 K.

and O-VII-H2 (4.456 Å). According to the modeled results, the interaction between the O atom of carbonyl in cinnamaldehyde and H2 of VI glucosic unit in β-CD is the strongest among all effective interactions. The result was in agreement with the foregoing experimental and characterized results.

Reaction Studies

Effect of β-CD amount

The data in Table 3 demonstrated the effects of β-CD amount on the reaction of cinnamaldehyde. It is well known that β-CD and substrate can form host–guest inclusion complex. The complexation depends on the size, shape, and hydrophobicity of the guest molecule. β-CD obviously promoted the hydrolysis of cinnamaldehyde compared with the blank experimental result. It is because the inclusion complex can enhance the solubility of cinnamaldehyde in water. Besides, β-CD could activate the substrates by interaction similar to the deprotection of 2-heptyl-1,3-dioxolane[36] or oxidation of 1-octanol[37] in water. More β-CD strongly promotes the conversion of cinnamaldehyde accompanied with slight increase of the yield of benzaldehyde. However, excessive β-CD would hamper the reaction. The optimal molar ratio of β-CD/cinnamaldehyde is 1.

The effect of reaction temperature

Table 4 shows the effects of temperature on the alkaline hydrolysis. It seemed that the conversion rate and the selectivity for benzaldehyde were closely related to the reaction temperature. The conversion rate increased rapidly with rising temperature. The yield of benzaldehyde also increased from 26 to 42% when the temperature increased from 313 to 323 K. However, elevated temperature can promote the polymerization and disproportionative condensation of benzaldehyde, the yield of benzaldehyde would decrease with the temperature rising from 323 to 343 K. Compared with the hydrolysis of cinnamaldehyde in the absence of β-CD,[3,6,9] the yield of benzaldehyde was almost unchanged, but the optimal reaction temperature decreased a lot (the reaction temperature of general alkaline hydrolysis is about 373 K and that of near-critical water method is 553 K), which is especially advantageous for retaining the natural essence of benzaldehyde.

The effect of alkaline variety

In fact, the hydrolysis reaction is a retro-Aldol condensation catalyzed by alkaline catalyst either homogeneously or heterogeneously. While using the same amounts of β-CD and cinnamaldehyde, the effect of different bases on the hydrolysis reaction is illustrated in Table 5.

Table 4. Influence of Different Reaction Temperature on the Hydrolysis of Cinnamaldehyde

Temperature (K)	Reaction Time (h)	Conversation of Cinnamal-dehyde (%)	Yield of Benzalde-hyde (%)	Yield of 1-Naphthalene-methanol (%)
313	22	>99	26	22
323	18	>99	42	38
333	12	>99	34	32
343	9	>99	31	29

Reaction condition: β-CD (1 mmol, 1.1351 g), cinnamaldehyde (1 mmol, 0.1322 g), NaOH (0.5 g), and H_2O (25 mL).

These data indicated that alkaline is important for the conversion rate and yields of benzaldehyde. The conversion rate and the yield of benzaldehyde were considerably increased as the alkalescence raised (entries 1 and 4, entries 2 and 3). These effects can be explained by the stronger basicity that is necessary for catalyzing the retro-Aldol condensation type reactions. Generally, the yield of benzaldehyde with inorganic alkaline catalysts is higher than that with organic bases (entries 1–7), owing to their basicity and solubilization. The optimal base is NaOH under the identical reaction condition.

Effect of the amount of NaOH

NaOH can promote the reversible Aldol reaction. The corresponding results for the amount of NaOH on the reaction are shown in Figure 6.

From Figure 6, plot of the yield of benzaldehyde vs. the amount of NaOH has a turning point while the concentration of NaOH is 2% (w/v), i.e., 0.5 g NaOH in 25 mL water. It is contrary to the common knowledge that stronger alkalescence is beneficial for more target product. This is because strong base can promote the hydrolysis of cinnamaldehyde, but it also can promote the polymerization and other disproportionative condensation of benzaldehyde and the Aldol condensation between acetaldehyde and cinnamaldehyde at the same time. Moreover, the alkaline hydrolysis of cinnamaldehyde is related with the deprotonation ability of β-CD at different pH. Deprotonation of β-CD in alkaline medium was previously investigated.[38–40] In aqueous alkaline solutions, β-CD does not deprotonate at pH less than 12.0. Further increase of pH results in the deprotonation of OH-

Table 5. Influence of Different Bases on the Hydrolysis of Cinnamaldehyde

Entry	Base	pH of Solution	Reaction Time (h)	Conv. (%)	Yield (%)
1	KOH	13.5	18	>99	30
2	NaOH	13.2	18	>99	42
3	Na_2CO_3	11.9	40	80	19
4	K_2CO_3	12.1	40	70	21
5	$H_2NCH_2CH_2OH$	11.6	18	95	Trace
6	$N(CH_2CH_2OH)_3$	11.1	18	10	10
7	$N(CH_2CH_3)_3$	12.0	18	67	31
8	KOH + $N(CH_2CH_3)_3$	12.8	18	96	29

Reaction condition: β-CD (1 mmol, 1.1351 g), cinnamylaldehyde (1 mmol, 0.1322 g), base (0.5 g), H_2O (25 mL), and 323 K.

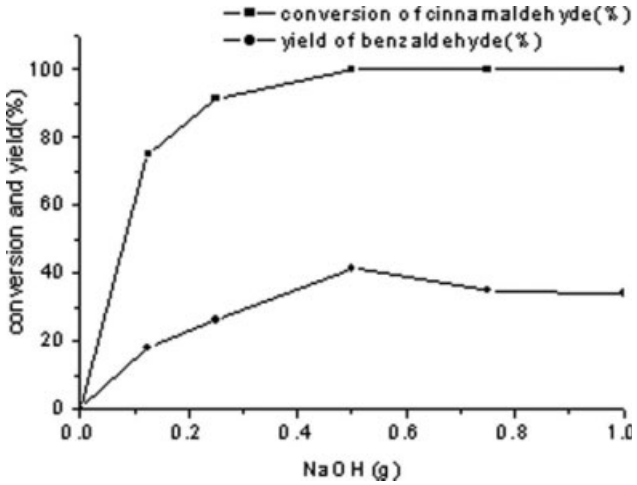


Figure 6. Influence of the amount of NaOH on the retro-Aldol condensation of cinnamaldehyde.

groups adjacent to C-2 and C-3 carbon atoms of β-CD glucopyranose units, whereas the deprotonation of OH-groups adjacent to C-6 carbon atoms is expressed less markedly.[40] As a result, the reaction mechanisms are different for solutions with different pH.

Large-scale experiment

Large-scale experiment for the alkaline hydrolysis of cinnamaldehyde to benzaldehyde in the presence of β-CD was carried out under the optimum reaction conditions, as shown in Scheme 2. The yield of purified benzaldehyde was 40%. Comparing with other hydrolysis of cinnamaldehyde without β-CD,[3,6,9] this process provided similar yield for benzaldehyde under much milder conditions which is very important to preserve natural essence of benzaldehyde during the reaction process.

Recovery of β-CD

After the hydrolysis reaction was completed, the inclusion complexes were re-dissolved in organic solvent and the guests were re-released from the inclusion complexes. Then the lower white precipitation (β-CD) could be easily recycled by addition of acetone and centrifugation. When the volume ratio of acetone to water reached 2:1, 95% β-CD could be recovered. The recycled β-CD could be reused for three times without loss of reaction activity and selectivity.

Reaction mechanism studies

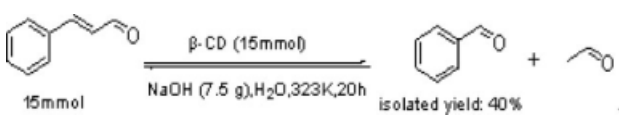
By-product Analysis. To explore the reaction mechanism, the main by-product from the large-scale experiment was collected by column chromatography and its yield was about 37%, similar to the yield of benzaldehyde. The main by-product was analyzed by NMR, FTIR, GC-MS, and elemental analysis.

The GC-MS result for the main by-product suggested a molecular weight of 158 and ion peaks at 141, 129, 115, 102, etc. C:H (weight ratio) was 79:6 through elemental analysis, which suggested a molecular formula of $C_{11}H_{10}O$. Unsaturated degree of the by-product was 7, which indicated it belong to aromatic compound. The characteristic peaks of 3381 cm^{-1} (ν_{OH}), 1002 cm^{-1} (ν_{CO}), 2883 cm^{-1} (ν_{CH_2}), 1434 cm^{-1} (δ_{CH_2}), 3047 cm^{-1} (ν_{CH} of benzene ring), 1595 cm^{-1}, and 1509 cm^{-1} ($\nu_{C=C}$), 773 and 711 cm^{-1} were found in the FTIR spectra, which suggested that the by-product belonged to mono-substituted aromatic compound with —OH and $-CH_2$ groups. The ^{1}H NMR spectrum revealed the presence of seven protons in the aromatic region (δ 7.53–8.13 ppm), a pair of doublets integrating to two protons (δ 5.05 ppm), and an alcohol proton (δ 5.41 ppm). This was supported by the presence of 11 signals in the ^{13}C NMR spectrum consisting of 10 carbons in the aromatic region (δ 123.98–138.09 ppm) and a carbon (δ 61.46 ppm). Therefore, the structure of the main reaction by-product was elucidated as 1-naphthalenemethanol on all characterization information, which should be formed from the Aldol condensation between acetaldehyde and cinnamaldehyde. Acetaldehyde could be well soluble in water. When the concentration of acetaldehyde in water reached a certain value, acetaldehyde was able to react with cinnamaldehyde. This was verified by GC-MS while monitoring the hydrolysis process.

Proposed reaction mechanism

Usually the mechanism of alkaline hydrolysis of cinnamaldehyde to benzaldehyde was considered as retro-Aldol condensation and base acted as nucleophile. However, the crossed Aldol condensation reaction of cinnamaldehyde with the hydrolysis products, acetaldehyde and benzaldehyde, also took place. This is because both acetaldehyde and cinnamaldehyde owned protons at α- position of the carbonyl group. In addition, benzaldehyde was prone to its own disproportionation and polymerization reactions. So the hydrolysis was a complicated process with several side reactions.

It was reported that the mechanism of β-CD-mediated hydrolysis of esters is related with the formation of an inclusion complex between the guest and the β-CD.[41] The reactions accelerated by β-CD is enthalpy controlled. One of the OH groups at the secondary rim of cyclodextrin reacts with the carbonyl carbon of the ester by displacing the leaving group and giving the acylated cyclodextrin as intermediate. But under our optimum reaction conditions (pH = 13), only few cyclodextrin is in its ionized form,[40] the inclusion complex should mainly be formed with the unionized cyclodextrin. That means, owing to intermolecular hydrogen bonds among the inclusion complex of cinnamaldehyde with β-CD, the hydrolysis mechanism in the present paper is different from that for aryl esters. As shown in Figure 7, a possible reaction mechanism has been proposed for the alkaline hydrolysis of cinnamaldehyde in the presence of β-CD based on the earlier experimental and computational results, which could explain the role of β-CD and the by-product formed.



Scheme 2. Large-scale alkaline hydrolysis of cinnamaldehyde to benzaldehyde promoted by β-CD.

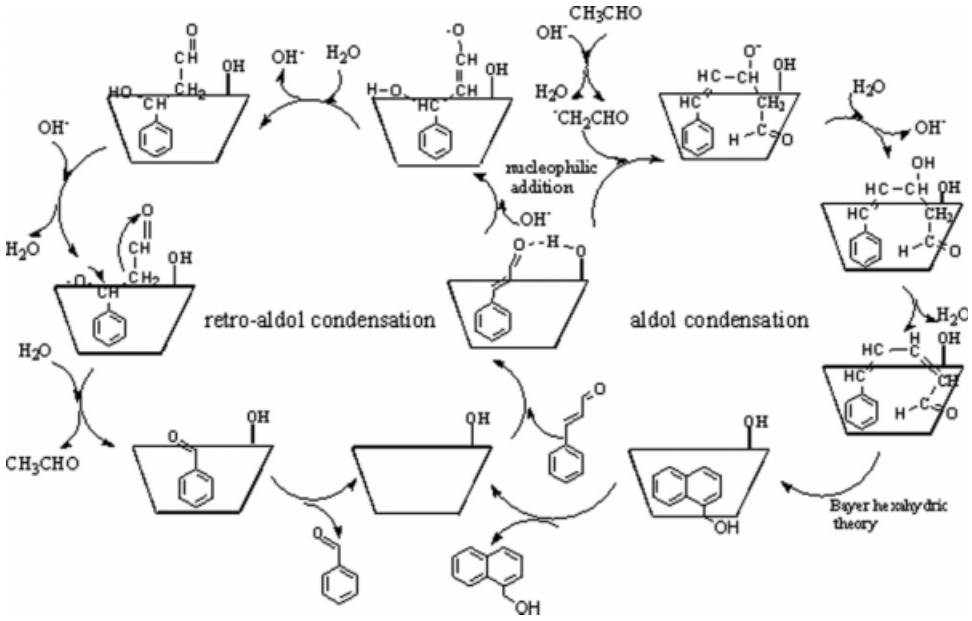


Figure 7. The mechanism of the alkaline hydrolysis of cinnamaldehyde and the by-product formed.

Only two principal pathways (formation of benzaldehyde and 1-naphthalenemethanol) are considered because the two products are dominant. The pathway involves the reaction of hydroxide ion (OH^-) with coordinated substrate because Gadosy and Barra had reported that external nucleophiles could react with coordinated substrates and even with higher rate in some cases. In Figure 7, β-CD and cinnamaldehyde can form the inclusion complex with the intermolecular hydrogen bond O—H···O at the second rim of β-CD. The strong electron withdrawing ability of the oxygen atom in hydrogen bond facilitates formation of the oxygen anion (O^-) and the nucleophilic attack of external hydroxide ion on the substrate. Through the retro-Aldol condensation of cinnamadehyde in the β-CD-mediated alkaline solution, benzaldehyde and acetaldehyde have been produced. When the concentration of acetaldehyde increased to a certain value, acetaldehyde may react with external hydroxide ion to form carbanion (C^-), which nucleophilically attacks cinnamaldehyde to give an oxygen anion. Through the Aldol condensation, an aldehyde compound containing conjugated large π bond was generated. According to its spatial structure characteristics and Bayer hexahydric theory, 1-naphthalenemethanol was formed.

Kinetic studies

To explore the promotion nature of β-CD over the alkaline hydrolysis cinnamaldehyde, only the retro-Aldol condensation was taken into account for kinetics studied in terms of the initial concentration method. The hydrolysis rate was monitored before the reaction had proceeded significantly as the following approximation holds:

$$-\mathrm{d}C_\mathrm{A}/\mathrm{d}t = kC_\mathrm{A}^n \tag{3}$$

Here C_A is the concentration of the β-CD inclusion complex of cinnamaldehyde or cinnamaldehyde in the absence of β-CD. In this case, the initial rate for benzaldehyde produced was measured as a function of the initial concentration of reactant. Logarithms were taken for both sides of Eq. 3:

$$\lg(-\mathrm{d}C_\mathrm{A}/\mathrm{d}t) = \lg k + \mathrm{nlg}\ C_\mathrm{A} \tag{4}$$

These kinetic experiments were carried out at different temperatures ranging from 313 to 343 K and different initial concentrations for reactant ranging from 0.01 to 0.04 M. From the intercept and slope values of these plots of lg ($-\mathrm{d}C_\mathrm{A}/\mathrm{d}t$) vs. lg C_A, the obtained rate orders and rate constants were listed in Table 6.

Similar kinetic measurements in the absence of β-CD were also made for the reaction system. The corresponding rate orders and rate constants were given in Table 7.

The rate orders were nearly equal to 1 for all the cases, which indicated first-order behavior for the hydrolysis for cinnamaldehyde or its complex with β-CD. The slopes of

Table 6. The Rate Orders and Rate Constants at Different Reaction Temperature in the Presence of β-CD

T (K)	n	k (min^{-1})	Correlation Coefficient (R)
313	0.94	0.0457	0.9991
323	1.09	0.0806	0.9984
333	1.09	0.128	0.9995
343	1.04	0.213	0.9995

Table 7. The Rate Orders and Rate Constants at Different Reaction Temperature in the Absence of β-CD

T (K)	n	k (min^{-1})	Correlation Coefficient (R)
313	0.87	0.0178	0.9986
323	1.06	0.0428	0.9982
333	0.97	0.0722	0.9975
343	1.02	0.126	0.9996

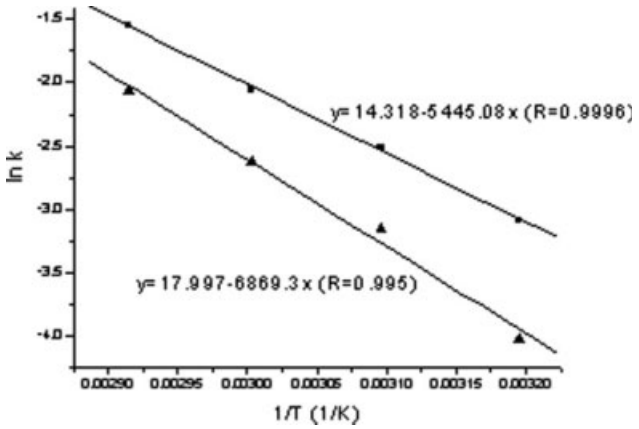


Figure 8. Arrhenius plots of the rate constants for the alkaline hydrolysis cinnamaldehyde (squares: in the presence of β-CD; triangles: in the absence of β-CD).

these plots gave the reaction rate constants at each temperature. The rate constants were apparently increased with raising temperature. However, it is clearly concluded that the rate constant in the presence of β-CD is higher than in the absence of β-CD at the same temperature, suggested that β-CD is able to accelerate the alkaline hydrolysis of cinnamaldehyde. The rate constants in Tables 6 and 7 were used to draw the Arrhenius plot of ln k vs. $1/T$, as presented in Figure 8. The plots were linear and the calculated activation energies E_a from the slopes were 45.27 kJ/mol for the inclusion complex and 57.11 kJ/mol in the absence of β-CD. It is evident that β-CD is a good catalyst for the alkaline hydrolysis of cinnamaldehyde.

Conclusions

CDs have particular inclusion properties and kinetics due to their structure characteristics. Host-guest interaction between cinnamaldehyde and β-CD was analyzed by FTIR, ^{1}H NMR, ROESY, UV–vis, and computational method. These characteristics demonstrated the formation of 1:1 complexes between them. The inclusion equilibrium constant K_a was 363 M^{-1} at 298 K and $\Delta\gamma G_m^{\Theta}$ (298K) is −14.6 kJ·mol^{-1}, which indicated that the inclusion process is spontaneous at 298 K. The benzene ring of cinnamaldehyde was included into the cavity of β-CD, and the aldehyde group forms hydrogen bond with the secondary alcohol of β-CD. It is the hydrogen bond that facilitates formation of the oxygen anion (O^-) and the nucleophilic addition of external hydroxide ion with cinnamaldehyde, which results into the acceleration of β-CD over alkaline hydrolysis of cinnamaldehyde. However, both acetaldehyde and cinnamaldehyde own α-proton to the carbonyl group, making the hydrolysis much complicated and the yield of the target product benzaldehyde was decreased. Formation of the by-product is interpreted based on the spatial structure characteristics and Bayer hexahydric theory. Comparing with other reports on hydrolysis of cinnamaldehyde in the absence of β-CD, the present system provided the similar yield for benzaldehyde under much milder conditions, which is very important to preserve natural essence of benzaldehyde. In addition, the kinetics studied with the initial rates method showed the participation of β-CD decreased the activation energy (E_a) of the hydrolysis, which was a first order reaction.

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