Asymmetric aldol condensation of acetyl ferrocene with aromatic aldehydes via the formation of the β-cyclodextrin inclusion complexes

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Abstract

By the formation of β-cyclodextrin (β-CD) inclusion complex, the aldol condensation of the acetyl ferrocene ($FcCOCH_3$) with aromatic aldehyde was investigated. The study reveals that the definite asymmetry-inducing ability of β-CD gives optical yields of the products in the range 6.0–30.4%. Also, alkali metal halides at a lower reaction temperature, can also give different results on the stereoselectivity of the reaction system. When the experiment was carried out in the solid state condition, an enhanced optical yield was obtained.

Keywords: Aryl aldehyde; Acyl ferrocene; Chirality; Enzyme template

1. Introduction

It is well known that cyclodextrin (CD), a cyclic oliogomer molecule of six to eight units of glucose, tends to form inclusion complexes with many suitable guest molecules by the interaction of hydrophobic or generalized lyophobic force and acts as an enzymatic model [1]. In recent years, different asymmetric syntheses catalyzed by CD has attracted extensive attention [2].

Importantly in asymmetric synthesis, aldol condensation can form a chiral product when a guest reagent is included. However, its application is greatly restricted by a series of side reactions, such as dehydration and polymerization.

Here we describe the asymmetric aldol condensation of acetyl ferrocene with aromatic aldehydes using β-CD as an inducing agent. Optically active products were obtained. The enantiomeric excess of some of the compounds synthesized were determined by analyzing the ratio of diastereomers formed with a known optically active compound. A mechanism of the chiral induction by β-CD has been proposed and the influences of the different MCl (M = K or Na) and reaction temperature on the asymmetric induction were also studied, the reaction in the solid state condition was also investigated.

Scheme 1 depicts the asymmetric aldol reaction of acetyl ferrocene with aromatic aldehydes. Table 1 gives the melting points and elemental analysis results of the compounds synthesized, and table 2 contains the spectral data thereof.

2. Results and discussion

It is our purpose here to investigate the asymmetry-inducing ability of β-CD. Firstly, we dissolved β-CD in warm water in the presence of alkali metal halides, and to this solution a solution of acetyl ferrocene in ether was added; an orange-yellowish suspension was obtained after evaporation of the ether. According to the

literature, the inclusion complex was then formed. The reaction of the inclusion complex with aromatic carbonyl compounds was carried out after the aromatic

aldehyde was added to the suspension and the aldol condensation product with one chiral center was then formed:
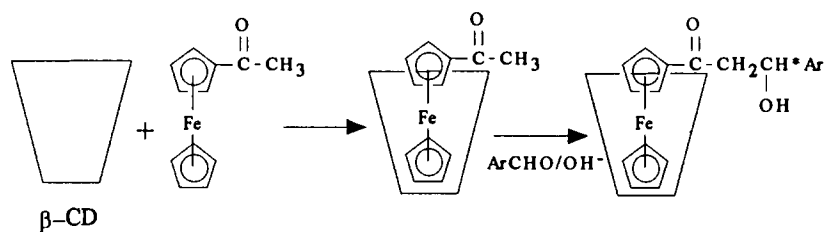
The enantioselectivity of this reaction induced by the β-CD is shown in Table 3. Harada and Takahashi [3] previously reported that the ferrocene and its derivatives can form 1 : 1 stoichiometric inclusion complexes with β-CD, which are thermally stable. This asymmetric induction can be attributed to the steric requirement in the inclusion complex formation. The ferrocenyl framework penetrates the cavity of β-CD tightly and entirely by the axial inclusion mode. The side chain locates away from the wall to permit an interaction between the acetyl group and the nucleophilic 2-hydroxyl group of β-CD.

Moreover, the rotation of the acyl group might be inhibited. The factors presented here become the chief cause for this asymmetric induction by β-CD. Since the dissociation constant of the complex is 10^{-2}–10^{-3} [4], the formation of the β-CD inclusion complexes with the aryl ring likewise cause asymmetric induction.

Yoshiki and Noboru [5] presented a view that the sense of the enantioselectivity can be interpreted by assuming reasonable binding modes. During the reaction progress of this aldol condensation, the nucleophilic reagent tends to attack from the opposite direction of the host molecule. In other words, it prefers to choose the Si prochiral face of the carbonyl group and form the S configuration.

Under alkali conditions, the proton of the C_2–OH of the glucose moiety was removed from β-CD, thus causing C_2–O^- tilt of 5–10° inwardly relative to its original position. This can partly change the asymmetric

cavity structure of β-CD and favor its asymmetry-inducing activity.

3. Effect of the alkali-metal halides on enantioselectivity

The reaction of Fc-COCH$_3$ and o-chlorobenzaldehyde induced by β-CD, for example, the specific rotation of the product was found to increase with the presence of alkali metal halides (Table 4).

The cooperative effect of alkali metal halides may be attributed to the formation of a ternary complex from β-CD, FeCOR and chloride ion in the reaction system [6].

4. Effect of reaction temperature on enantioselectivity

It is known that temperature has a definite influence upon the optical purity of the product. The lower the temperature, the higher the enantio excess percentage in general. It seems that the favorable orientation of the nucleophilic attack on the carbonyl center is governed by its stable configuration, which is sensitive to the temperature imposed on the system. On the contrary, a workable condition for the reaction to take place is not the lowest temperature. Most of the reactions were carried out at room temperature. A higher specific
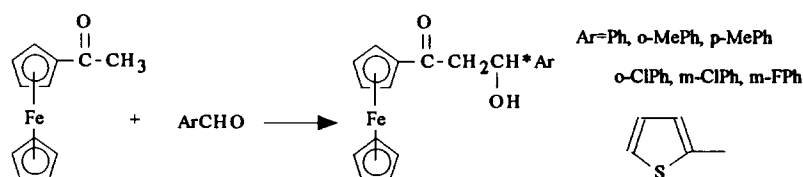
Table 1
The physical constants of the compounds synthesized

Entry	Formula	Melting point (°C)	C (calculated) (%)	H (calculated) (%)
1	FcCOCH$_2$CH*(OH)Ph	92.5–94.0	68.00(68.29)	5.83(5.39)
2	FcCOCH$_2$CH*(OH)Pho–CH$_3$	101.5–102.5	68.93(68.98)	5.96(5.79)
3	FcCOCH$_2$CH*(OH)Php–CH$_3$	93.0–94.5	68.60(69.98)	5.77(5.79)
4	FcCOCH$_2$CH*(OH)Pho–Cl	128.5–130.0	62.10(61.90)	4.60(4.65)
5	FcCOCH$_2$CH*(OH)Phm–Cl	84.5–85.0	62.52(61.90)	4.47(4.65)
6	FcCOCH$_2$CH*(OH)Phm–F	102.5–103.0	64.27(64.79)	5.03(4.87)
7	FcCOCH$_2$CH*(OH)C$_4$H$_3$S-2	82.5–83.5	58.50(58.64)	4.83(4.63)

Table 2
Spectral data of the synthesized compounds

Entry	IR (cm^{-1})	^{1}H NMR δ (solvent, CDCl$_3$ ppm)
1	3361.3, 2943.0, 1630.5, 1384.4, 1228.5	3.10(d, 2H), 3.87(d, 1H), 4.17(s, 5H), 4.54(m, 2H), 4.77(m, 2H), 5.13(m, 1H), 7.23–7.60(m, 5H)
2	3418.7, 2926.7, 1638.7, 1376.2, 1228.5	3.07(d, 2H), 3.80(d, 1H), 4.23(s, 5H), 4.56(m, 2H) 4.80(m, 2H), 5.60(m, 1H), 7.20–7.73(m, 4H), 2.40(s, 3H)
3	3476.2, 2960.9, 1646.9, 1380.0, 1236.7	2.33(s, 3H), 3.08(d, 2H), 3.73(d, 1H), 4.16(s, 5H), 4.50(m, 2H), 4.76(m, 2H), 5.26(m, 1H), 7.03–7.46(m, 4H)
4	3369.5, 2926.6, 1638.7, 1376.2, 1269.5	3.62(d, 2H), 4.13(d, 1H), 3.90(s, 5H), 4.47(m, 2H), 5.05(m, 2H), 5.67(m, 1H), 7.11–7.48(m, 4H)
5	3435.2, 2901.9, 1646.9, 1384.4, 1236.7	3.07(d, 2H), 3.87(d, 1H), 4.20(s, 5H), 4.54(m, 2H), 4.80(m, 2H), 5.27(m, 1H), 7.27–7.43(m, 4H)
6	3385.9, 2959.4, 1646.9, 1400.8, 1261.3	3.10(d, 2H), 3.96(d, 1H), 4.20(s, 5H), 4.58(m, 2H), 4.78(m, 2H), 5.30(m, 1H), 6.88–7.52(m, 4H)
7	3484.4, 2860.9, 1646.9, 1376.2, 1236.7	3.20(d, 2H), 3.94(d, 1H), 4.14(s, 5H), 4.50(m, 2H), 4.74(m, 2H), 5.48(m, 1H), 6.88–7.26(m, 3H)

rotation of the reaction was obtained at lower temperatures.

5. Effect of the solid state condition on enantioselectivity

Asymmetric synthesis in the solid state has become currently a new and developing area [7]. With the ability to provide both a chiral receptor and reactive sites, CDs have been demonstrated to catalyze a few asymmetric reactions. Here the effect of the solid state condition on asymmetric induction is shown in Table 6. It was found that the solid state reaction condition is more favorable for the production of the optically active products.

Table 3
Asymmetric aldol condensation product FcCOCH$_2$CH*(OH)Ar from acetyl ferrocene and ArCHO (reaction temperature, 14–16°)

Ar	$[\alpha]_{578}^{14}$ (°)	ee (%)
Ph	+4.69 (CH$_2$Cl$_2$, c = 0.192)	21.4
o-CH$_3$C$_6$H$_4$	+1.59 (CH$_2$Cl$_2$, c = 0.504)	6.0
o-ClC$_6$H$_4$	−6.82 (CH$_2$Cl$_2$, c = 0.176)	30.4
m-FC$_6$H$_4$	−6.63 (CH$_2$Cl$_2$, c = 0.166)	26.6
2-C$_4$H$_3$S	+4.97(CH$_2$Cl$_2$, c = 0.201)	12.7

Surprisingly enough, the product was found to have the opposite specific rotation and a larger specific rotation value.

6. Experimental details

^{1}H NMR was measured on a JEOL FX-90X spectrometer and IR on a Shimadzu IR-435 and Nicolet, FT-IR 50X spectrometer. Diastereomers were separated

Table 4
The effect of the alkli metal halides on the enantioselectivity

Ar	MCl	$[\alpha]_{578}^{14}$ (°)	ee (%)
o-ClC$_6$H$_4$	None	−4.43 (CH$_2$Cl$_2$, c = 0.271)	19.7
o-ClC$_6$H$_4$	KCl	−6.82 (CH$_2$Cl$_2$, c = 0.176)	30.4
o-ClC$_6$H$_4$	NaCl	−6.17 (CH$_2$Cl$_2$, c = 0.308)	27.5

Table 5
Effect of reaction temperature on enantioselectivity

Ar	Temperature (°C)	$[\alpha]_{578}^{14}$ (°)	ee (%)
o-ClC$_6$H$_4$	14–16	−6.82 (CH$_2$Cl$_2$, c = 0.176)	30.4
o-ClC$_6$H$_4$	0	−10.45 (CH$_2$Cl$_2$, c = 0.268)	46.6

Table 6
Effect of the solid state condition on enantioselectivity

Ar	Reaction condition	$[\alpha]_{578}^{14}$ (°)	ee (%)
C_6H_5	Aqueous suspension	+ 4.69 (CH_2Cl_2, $c = 0.192$)	21.4
C_6H_5	Solid state	− 14.20 (CH_2Cl_2, $c = 0.317$)	64.8

and measured on a HP-1090 high performance liquid chromatograph. The optical activity was observed on a Perkin–Elmer 241 MC automatic polarimeter.

6.1. The typical reaction procedure

To the 140 ml suspension of the inclusion complex formed by β-CD (8.8 mmol) and acetyl ferrocene compounds $FcCOCH_3$ (4.0 mmol), which was saturated with potassium chloride, excess ArCHO and 18 ml NaOH aqueous solution were added. The reaction mixture was then stirred violently for 2 h, and pyridine in appropriate amount was added. After 4–6 h, the mixture obtained was partitioned between water and ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After concentration of the solution, the residual crude product was purified by thin layer chromatography (TLC) on silica gel.

6.2. The solid state reaction procedure

After the inclusion procedure, the resultant yellow precipitate from $Fc-COCH_3$ and β-CD was filtered and dried in air. Then NaOH (4.0 g) and PhCHO (4.0 ml) were added in dried form. The mixture was ground for about 20 min and was then extracted with ethanol. After the concentration of the solution, the residual crude product was purified by TLC.

All the products were characterized by ^1H NMR, IR and C, H analysis.

6.3. The determination of the enantio excess percentage

After the product had been purified, it was weighed and dissolved in an appropriate solvent for determination of $[\alpha]_{578}^{14}$ in an automatic polarimeter, accurate to a thousandth of a degree.

The optical purity was determined by two methods:

the ^1H NMR method by means of chemical shift reagent $Eu(tfc)_3$; high performance liquid chromatography (HPLC) separation of the diastereoisomers, whose isomeric components were determined through the UV absorption peak area. The latter method is more efficient. (1R)-(-)-10-Camphor sulfonic acid chloride was reacted with the optically active product to form the diastereomer sulfonic ester:
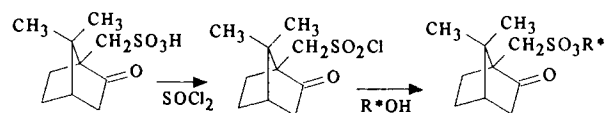
($[\alpha]_D^{20} = -20°$; $c = 2$; H_2O). HPLC analysis of the diastereomers provided the isomeric ratio.

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