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STUDIES ON THE REACTION OF ACETYLFERROCENE WITH AROMATIC ALDEHYDES IN THE PRESENCE OF β-CYCLODEXTRIN

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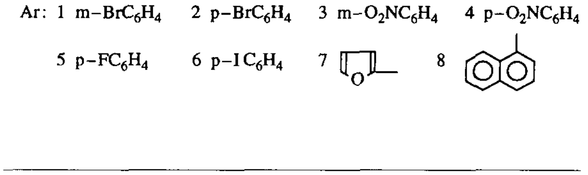
Abstract—The condensation reaction of acetylferrocene with aromatic aldehydes was investigated by the formation of the β-cyclodextrin (β-CD) inclusion complexes. Eight novel and optically active compounds were synthesized and characterized by IR, ^{1}H NMR spectroscopies and elemental analysis. The data of $[\alpha]_{578}^{16}$ of the compounds were determined. From their esters with D-camphor-β-sulfonic chloride the optical yields (e.e.%) of some compounds were determined by HPLC. Copyright © 1996 Elsevier Science Ltd

β-Cyclodextrin (β-CD) is a cyclic oligosaccharide consisting of seven glucose units. Due to the characteristic doughnut-like shape of β-CD, various types of organic compounds are incorporated into the β-CD, forming inclusion complexes. The utilization of inclusion complexes of cyclodextrins in the modification of the chemical reactivity of organic molecules has been of much interest.[1]

In recent years, some efforts have been made using CDs in asymmetric synthesis. For example, using CD, an asymmetric reaction in a solid crystaline complex by Sakuraba *et al.* gave 91% e.e. in one case.[2]

Harada and Takahashi reported the preparation and properties of inclusion complexes of ferrocene and its derivatives with cyclodextrins.[3] The β-CD formed 1 : 1 complexes with the mono-substituted ferrocenes in high yields.

Recently, we prepared the complex of acetylferrocene with β-CD and have studied the reaction of the complex with aromatic aldehydes, as follows:



EXPERIMENTAL

^{1}H NMR spectra were recorded on JEOLFT-90X and BRUKER AC-P-200 spectrometers, IR on a Nicolet-FT IR 5DX spectrometer. Diastereomers were separated and measured on a Varian-5000 HPLC; optical activity was observed on a Perkin–Elmer 240C MC automatic polarimeter.

A typical reaction procedure

To a suspension of the inclusion complex (70 cm^3) formed by β-CD (4 mmol) and acetyl ferrocene (2 mmol), which was saturated with potassium chloride, excess of ArCHO and 10% sodium hydroxide aqueous solution were added, respectively. The reaction mixture was then stirred at room temperature and monitored by TLC. After the reaction, the reaction mixture was extracted with ethyl acetate (50 cm^3). The separated organic layer was dried over anhydrous sodium sulfate and then evaporated under a reduced pressure below 40°C, the residual crude product was purified by TLC on silica gel.

Product **1**. Yield 38.7%, red crystals, m.p. 129–131.5°C. Found: C, 55.3; H, 4.1. Calc. for $C_{19}H_{17}FeBrO_2$: C, 55.2; H, 4.1%. IR (Nujol), 3419, 1639, 1097, 999 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.08 (2H,d), 3.89 (1H,d), 4.19 (5H,s), 4.78 (2H,m), 4.58 (2H,m), 5.25 (1H,m), 7.24–7.61 (4H,m).

Product **2**. Yield 19.6%, yellow crystals, m.p. 106–108°C. Found: C, 55.2; H, 4.2. Calc. for

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$C_{19}H_{17}FeBrO_2$: C, 55.2; H, 4.1%. IR (Nujol), 3484, 1647, 1089, 1007 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.08 (2H,d), 3.88 (1H,d), 4.21 (5H,s), 4.79 (2H,m), 4.59 (2H,m), 5.29 (1H,m), 7.28–7.60 (4H,m).

Product **3**. Yield 55.4%, yellow crystals, m.p. 132–134°C. Found: C, 59.7; H, 4.4, N, 3.4. Calc. for $C_{19}H_{17}FeNO_4$: C, 60.2; H, 4.5; N, 3.7%. IR (KBr), 3419, 1630, 1524, 1343, 1089, 999 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.12 (2H,d), 4.20 (1H,d), 4.22 (5H,s), 4.83 (2H,m), 4.59 (2H,m), 5.39 (1H,m), 7.57–8.33 (4H,m).

Product **4**. Yield 60.0%, yellow crystals, m.p. 80°C (dec.). Found: C, 55.2; H, 4.3; N, 3.2. Calc. for $C_{19}H_{17}FeNO_4 \cdot 0.5CH_2Cl_2$: C, 55.4; H, 4.3; N, 3.3%. IR (KBr) 3427, 1650, 1516, 1343, 1089, 1015 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.30 (2H,d), 4.20 (1H,d), 4.28 (5H,s), 4.84 (2H,m), 4.64 (2H,m), 5.40 (1H,s) 5.44 (1H,m), 7.64–8.30 (4H,m).

Product **5**. Yield 37.0%, red crystals, m.p. 123–124°C. Found: C, 64.2; H, 5.0. Calc. for $C_{19}H_{17}FeFO_2$: C, 64.3; H, 5.0%. IR (KBr) 3402, 1650, 1089, 1015 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.06 (2H,d), 4.79 (1H,d), 4.19 (5H,s), 4.80 (2H,m), 4.56 (2H,m), 5.28 (1H,m) 7.03–7.41 (4H,m).

Product **6**. Yield 16.3%, red crystals, m.p. 117–118°C. Found: C, 50.1; H, 4.0. Calc. for $C_{19}H_{17}FeIO_2$: C, 49.6; H, 3.7%. IR (Nujol) 3460, 1650, 1097, 999 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.08 (2H,d), 3.98 (1H,d), 4.22 (5H,s), 4.78 (2H,m), 4.58 (2H,m), 5.28 (1H,m), 7.21–7.81 (4H,m).

Product **7**. Yield 18.5%, red crystals, m.p. 75–76°C. Found: C, 62.9; H, 4.8. Calc. for $C_{17}H_{16}FeO_3$: C, 63.0; H, 5.0%. IR (KBr) 3501, 1650, 1097, 999 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.24 (2H,d), 4.76 (1H,m), 4.22 (5H,s), 4.82 (2H,m), 4.56 (2H,m), 5.30 (1H,m), 6.36–7.44 (4H,m).

Product **8**. Yield 11%, yellow crystals, m.p. 111–113°C. Found: C, 71.8; H, 5.0. Calc. for $C_{23}H_{20}FeO_2$: C, 71.9; H, 5.2%. IR (Nujol) 3427, 1630, 1089, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.20 (2H,d), 4.00 (1H,m), 4.09 (5H,s), 4.68 (2H,m), 4.47 (2H,m), 6.00 (1H,m), 7.40–8.00 (7H,m).

Determination of e.e.% value

In a dried tube, the synthesized compound (0.04 mmol) and (*R*)-(−)-10-camphor sulfonic acid chloride (0.4 mmol) were added and then CH_2Cl_2 (2 cm^3) as well as anhydrous pyridine (0.1 cm^3) was added to the mixture. The mixture was sealed and monitored by TLC. After the reaction, products were separated and purified by TLC on silica gel, then dissolved in the appropriate solvent for the determination of e.e.% value through HPLC.

RESULTS AND DISCUSSION

The aldol condensation is an important method in organic synthesis, for increasing carbon chains; however, its application is greatly restricted by a series of side reactions, such as dehydrolysis and polymerization. The condensation of the aldehydes and ketones with high molecular weight is very difficult to obtain the β-hydroxylcarbonyl compounds. However, in the presence of β-CD, we had obtained the β-hydroxylcarbonyl compounds through the reaction of acetyl ferrocene with aromatic aldehydes.

It is our purpose to investigate the asymmetric inductive effect to the β-CD. When β-CD was used as a inductive agent, the aldol condensation of acetylferrocene with aromatic aldehydes produced optically active products. It is indispensable that the substrate be included through the hydrophobic interaction into the β-CD cavity. The ferrocenyl ring penetrates the cavity of the β-CD tightly and entirely by axial inclusion mode;[3] the acetyl group points out of the cavity of β-CD and interacts with the hydroxyl group of β-CD by hydrogen bonding. The rotation of the ferrocenyl group might be inhibited. The factors presented here became the chief cause for this chiral induction of β-CD. However, how the substituents of benzene affect the optic active yield of the reaction is not yet clear.

The reaction conditions

Many factors affect the rate and the yield of the reaction. We found if the substituted aromatic aldehydes had the electron-withdrawing substituents, the condensation reaction became easy. Moreover, the stronger electron-withdrawing effects of the substituents resulted in better yields and shorter reaction times. With *p*-nitrobenzaldehyde, the chemical yield reached 60% because of the strong electron-withdrawing effect and conjugation of the nitro group.

It is well-known that the temperature has a definite influence upon the optical yield of the product. Generally, in an asymmetrically selective reaction the difference of the free energy of the reactions between enantiomers increases at lower temperature.[4] Furthermore, the molecular complex is stable at low temperature[5] and the dissociation constant is very small. Low temperature favours high asymmetric selectivity for two aspects, i.e. the facile formation of the inclusion complex and a large difference in free energy of the enantiomeric differentiating reaction. However, if the reaction temperature was too low, such as below 0°C, the reaction failed. At a temperature greater than 30°C, only the dehydrated compounds were isolated. Therefore, the experiments were carried out at around 14–16°C. The choice of catalyst and its concentration are extremely important factors in determining a successful condensation. We used sodium hydroxide as the catalyst, its concentration was varied with respect to the different reactivity of the aromatic aldehydes.

The IR spectra and ^1H NMR spectra

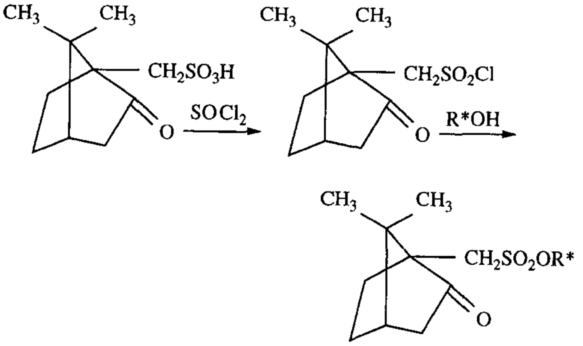
The bands at 1080–1105 and 999–1015 cm^{-1} were the characteristic absorption of the mono-substituted ferrocenes, in accordance with the 9–10 μm rule. The carbonyl group stretching vibration was at a lower frequency region (1630–1647 cm^{-1}), because of the conjugation of the carbonyl group with the cyclopentadienyl ring and intramolecular hydrogen bonds. When the alcohols became esters, the hydrogen bond disappeared and the carbonyl group stretching vibration rose to 1663 cm^{-1}. The average shift discrepancy was *ca* 20 cm^{-1} between the two frequencies.

The hydroxyl protons varied from 3.88 to 4.79 ppm and were near to the unsubstituted cyclopentadienyl ring protons. Therefore, it showed a multiplet. The methylene protons showed a triplet in the down field region because of the electron-withdrawing effect of the hydroxyl and aryl group. When these alcohols became esters with (R)-(−)-10-camphor sulfonic acid chloride, the separation of the methylene proton was not clear. However, the proton signals shift downfield for 1.0 ppm, because the electron-withdrawing effect of the ester group is greater than that of the hydroxyl group.

The determination of e.e.% value

After the product was purified, it was weighed and dissolved in an appropriate solvent for the determination of its $[\alpha]_{578}^{16}$ in an automatic polarimeter, accurate to a thousandth degree.

The optical purity was determined by HPLC. (*R*)-(−)-10-camphor sulfonic acid chloride was used to react with the optically active product to form diasteromeric sulfonic ester:



The diastereomer on the HPLC column showed the proportion of its components from the recorder. Table 1 gives the data of $[\alpha]_{578}^{16}$ and e.e.% of some compounds.

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Table 1. The data of $[\alpha]_{578}^{16}$ (CH_2Cl_2, g 100 cm^{-3}) and e.e.% of compounds

No.	$[\alpha]_{578}^{16}$	e.e.%	No.	$[\alpha]_{578}^{16}$	e.e.%
1	-5.25 ($c = 0.40$)	34.3	5	-11.7 ($c = 0.18$)	31.2
2	-7.03 ($c = 0.29$)	21.4	6	$+11.1$ ($c = 0.25$)	16.0
3	$+1.56$ ($c = 0.80$)	2.0	7	$+4.51$ ($c = 0.24$)	/
4	-14.9 ($c = 0.30$)	/	8	$+1.98$ ($c = 0.30$)	/