MODIFICATION OF THE FACE SELECTIVITY IN ASYMMETRIC INDUCTION BY CYCLODEXTRINS THROUGH THE FORMATION OF THREE-COMPONENT INCLUSION COMPOUNDS

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ABSTRACT

Stoichiometric amounts of triethylamine (TEA) were found to enhance the chiral induction by β-cyclodextrin (β-CD) in the reduction of acetophenone (ACPH) by aqueous $NaBH_4$. The enantioselectivity obtained depends upon the molar ratio β-CD:ACPH:TEA. Evidence for the formation of a three-component inclusion compound was obtained from detailled ^1H and ^2H NMR studies. The restriction of the molecular motion of the prochiral center probably accounts for the strong enhancement of the chiral induction observed.

1. INTRODUCTION

Cyclodextrins are known to induce regio- and enantioselectivity in organic reactions carried out in water [1]. Molecular size matching of the substrate with the host and geometry of binding in inclusion compounds are responsible for the selectivity observed. Regioselectivity can be achieved in excellent yields since a part of the guest molecule is shielded by the walls of the CD cavity in such a way that the reagent attack is selectively directed towards the more accessible position. On the contrary, it appears more difficult to create an asymmetric micro-environment through the complexation by CDs so that an enantiofacial discrimination occurs. In fact, few exceptions of complete or nearly complete chiral induction have reported in the literature [2-5].
To explore whether a decrease of the degree of freedom of the included molecule can improve the face selectivity, the reduction of the β-CD:ACPH complexe was investigated in the presence of chemically inert species as potential co-guest. The idea was to form three-component inclusion compounds in order to impose more steric constraints in the micro-environment of the prochiral site. We found that asymmetric inductions can be dramatically affected by a adding third components (tertiary amines,

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amides or alcohols) in stoichiometric ratios with respect to the substrate [6]. The aim of this work is to demonstrate the formation of a ternary association when the reduction of ACPH included in β-CD was perfomed in the presence of TEA and to understand how the co-guest TEA can affect the enantioface selectivity.

2. MATERIALS AND METHODS

2.1. Reduction by $NaBH_4$

The three-component system β-CD:ACPH:TEA with 1:1:1 molar ratio was prepared by adding an equimolar amount (3mmol) of ACPH (0.35ml) and TEA (0.42ml) to a suspension of 3.4 g (3 mmol) of dry β-CD in 40 ml of 0.2M Na_2CO_3. After stirring overnight, the resulting slurry was reacted with $NaBH_4$ under vigourous stirring for further 24 h at room temperature. After neutralization (HCl), the mixture was extracted with diethyl oxide. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, 1-phenyl ethanol was purified by preparative TLC (CH_2Cl_2). Enantiomeric excesses (e.e.) were determined from the integral ratios of signals obtained by GLC analysis on chiral capillary column (CYDEX-B, Scientific Glass Engineering). Runs were triplicated. The reduction of other molar ratios were conducted according the same procedure using the desired amount of each compound.

2.2 NMR analysis

^1H NMR experiments were performed at 500MHz using a Brüker AMX 500 spectrometer. In all cases, the samples were prepared in D_2O and measurements carried out at 298K. Chemical shifts are given relative to external TMS (0ppm) and calibration was performed using the signal of the residual protons of the solvent as a secondary reference. ROESY experiments were obtained using the program provided by the Brüker library with a 300msec spin-lock time. ^2H NMR spectra were obtained in ^2H depleted water (Euriso-Top) using a Brüker MLS 300 spectrometer operating at 46 MHz for ^2H.

2.3 Molecular modelling

Molecular models were obtained using the Insight II software programme running on a Silicon Graphics Iris Indigo station.

3. RESULTS AND DISCUSSION

3.1 Chiral induction

Reductions of ACPH by $NaBH_4$ were carried out in carbonate buffer on the mixture of the three compounds β-CD, ACPH, and TEA in the desired molar ratio. It can be seen from Table 1 that a stoichiometric molar fraction of TEA dramatically affects the enantioselective formation of 1-phenyl ethanol induced by β-CD. The increase of e.e.

values was accompagnied by an inversion of the face selectivity. Both effects obviously reveal the contribution of TEA in the chiral induction mechanism.

TABLE 1. Enantioselectivities obtained for $NaBH_4$ reduction of β-CD:ACPH complexes in the presence of different amounts of TEA

Molar ratio β-CD:ACPH:TEA	1:1:0	1:1:1	2:1:0	2:1:1	2:1:2	2:1:3	2:1:10
Chemical yield (%)	60	55	61	50	54	48	49
E.e. (%)	6	15	5	43	48	39	6
Configuration	S(-)	R(+)	S(-)	R(+)	R(+)	R(+)	R(+)

In the absence of TEA, only low e.e. values of S(-) 1-phenyl ethanol were obtained. It can be noticed that better results were observed in the presence of two molar equivalents of β-CD. This is probably due to the lowering of the free ketone concentration by shifting the complexation equilibrium. The maximum e.e. value was reached for the molar ratio 2:1:2. Beyond this ratio, the e.e. decreased likely because TEA in excess competes with ACPH for inclusion.

3.2 Evidences for the formation of a three-component complex

^1H NMR spectra show the formation of an inclusion compound in the binary ACPH:β-CD (Fig. 1a) and in the ternary system ACPH:β-CD:TEA (Fig. 1b). Upfield shifts of CD protons were observed upon addition of ACPH, the most important being those of protons H-3 and H-5 located in the CD cavity. The presence of TEA did not induced significant variations of these signals. On the other hand, the signal of the ACPH methyl group was changed into a very complex multiplet. The most probable explanation is to consider that a strong immobilization of the methyl group at the time scale of the NMR analysis. ^2H NMR technique was used to determine unambigously the molecular dynamics. In the binary system, ACPH retains a large mobility in the cavity (Fig.2a, sharp signal). In the presence of TEA, the linewidth increased to a value very similar to that obtained for β-CD (Fig. 2b). This implies that the included ACPH molecule has no or very little internal mobility in the cavity when TEA is present.

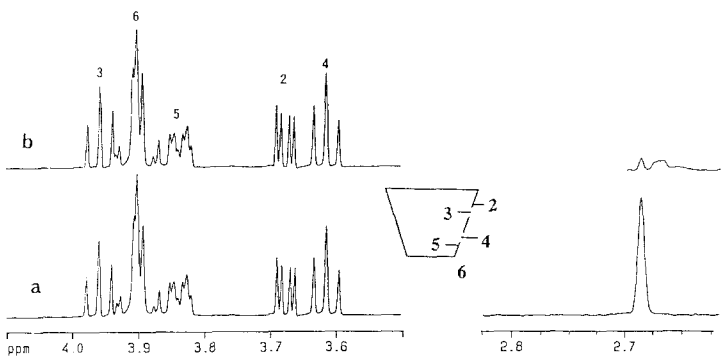

Fig. 1. 500 MHz ^1H NMR spectra (D_2O, 298 K) (a) β-CD 4 mM, ACPH 5 mM; (b) + TEA 12.5mM

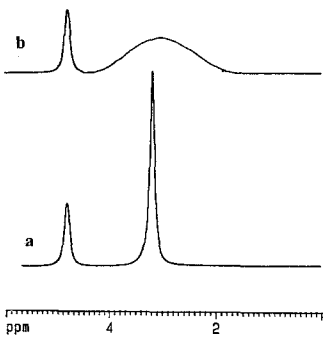

Fig. 2. 46 MHz ^{2}H NMR spectra

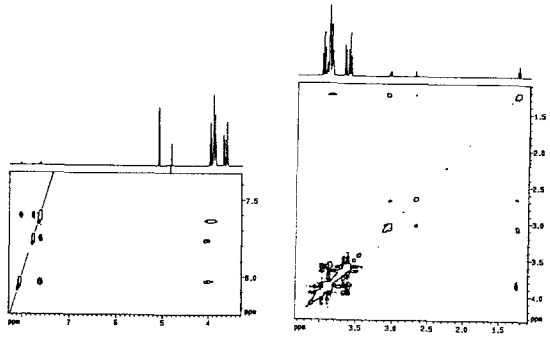

Fig. 3. ROESY (a) aromatic protons; (b) non-aromatic protons

To get a deeper insight in the possible structure of the ternary complex, a two-dimensional ^{1}H NMR experiment was performed (Fig. 3). All non-diagonal peaks are indicative of spatial proximities between protons. Dipolar interactions can be observed between the ortho protons of ACPH and H-5, H-6 protons of β-CD. This result indicates that inclusion proceeds by the primary hydroxyl side. Besides, it can be seen interactions between the methyl group of TEA and H-6 protons of β-CD and, at the same time, the methyl group of ACPH. From these data, we propose a possible structure for the ternary association ACPH:β-CD:TEA where TEA partially binds to β-CD, the ethyl group included strongly limiting the mobility of ACPH within the cavity.

4. CONCLUSION

Chemically inert species were demonstrated to affect the chiral induction mediated by CDs. The locking effect of TEA can be related to a simple model of allosteric effect in enzyme catalysis. It can be supposed that dramatic improvements of selectivity could be achieved with a co-guest of the appropriate shape and structure. The powerful combination of NMR experiments and molecular modelling provides an useful way for the screening of the appropriate co-guest molecule.

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