Enantioselectivity improvement induced by β-cyclodextrin in the $NaBH_4$ reduction of acetophenone through the formation of a three-component inclusion β-cyclodextrin–acetophenone–triethylamine complex

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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 $NaBH_4$ and to invert the face selectivity. The enantioselectivity obtained depends upon the molar ratio β-CD : ACPH : TEA and on the reaction temperature. For example, *R*(+)-1-phenylethanol was predominantly produced at −10 °C in 56% enantiomeric excess for a molar ratio β-CD : ACPH : TEA of 2 : 1 : 2 *vs*. the *S*(−) enantiomer in 5% enantiomeric excess in the absence of TEA, other experimental conditions remaining unchanged. Evidence for the formation of a three-component inclusion compound was obtained from detailed ^1H and ^2H NMR studies. TEA partially binds to the β-CD : ACPH molecular edifice in such a way that the conformational mobility of the acetyl group is reduced. The restriction of the rotational motion of the prochiral centre probably accounts for the strong enhancement of the chiral induction observed.

Introduction

Cyclodextrins (CDs) are cyclic molecules composed of several glucose units (6, 7 or 8 for α-, β- or γ-CD, respectively). The hydrophobic character of their internal cavity enables CDs to form inclusion complexes with organic compounds.[1] For this reason, many authors have proposed the use of CDs as nano-reactors to induce regio- and enantio-selectivity in organic reactions carried out in water.[2,3] Molecular size matching of the substrate with the host and geometry of binding in inclusion compounds are responsible for the selectivity observed. Regio-selectivity can be reached 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. Thus, *para*-selectivity is almost quantitative for substitution reactions performed in the presence of CDs as in the chlorination of anisole.[4] *meta*-Selectivity was observed in ester cleavage of substituted phenyl acetates,[5] and *ortho*-selectivity in the photo-Fries rearrangement of phenyl esters and anilides.[6] On the contrary, it appears more difficult to create a prochiral centre through the formation of CD complexes in an appropriate position such that an asymmetric reaction takes place. In fact, only a few examples of complete or nearly complete chiral induction have been reported in the literature.[7–10]

To explore whether a decrease in the degree of freedom of the included molecule can improve the face selectivity, we investigated the reduction of β-CD : aromatic ketones complexes in the presence of chemically inert species as potential co-guest.[11,12] The idea was to form three-component inclusion compounds in order to impose more steric constraints in the microenvironment of the prochiral site. We found that asymmetric inductions can be dramatically affected by adding third components (alcohol, tertiary amine or amide) in stoichiometric ratios with respect to the substrate. A pronounced increase of the enantioselectivity was obtained in certain cases although the opposite effect was generally observed. In addition, the selectivity changes can be associated with an inversion of the absolute configuration of the prevailing enantiomeric alcohol produced. Although it was not demonstrated, the formation of three-component inclusion compounds was suspected to be the explanation for these results.

Although this is the first report of an increase in chiral induction by chemically inert additives, the presence of third components, like certain alcohols, has also been shown to increase the reactivity of β-CD in the basic cleavage of *p*-nitrophenyl acetates.[13] In this case, the third components might play the role of an inert spacer, filling the CD cavity and allowing the substrate to occupy an appropriate position for esterolysis (so-called 'spectator catalysis'). Such ternary inclusion associations are well-documented in the case of CD : polyaromatic hydrocarbon systems.[14,15] Evidence for three-component complexes was obtained from changes of the spectroscopic properties of the binary systems in the presence of third species (alcohols, amines). It was concluded that the association proceeds by the binding of the co-guest in the residual spatial void volume remaining after complexation of the molecule having the higher affinity for the CD cavity.

The aim of the present work is to obtain evidence of the formation of three-component inclusion compounds in our systems and thereby to understand firstly how the third component can act to affect the face selectivity and secondly how it can modify the geometry of the preformed complex. For this purpose, NMR (1H and 2H nuclei) was used to obtain details of the structure and dynamics of the putative ternary complexes.

From our preliminary results,[12] the β-CD : acetophenone (ACPH) : triethylamine (TEA) system shows an important association in terms of chiral induction and face selectivity. Therefore, it was chosen for this study.

Table 1 Dependence of the enantioselectivities obtained for $NaBH_4$ reduction of β-CD : ACPH complexes on 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*(+)

Table 2 Dependence of the enantioselectivities obtained for $NaBH_4$ reduction of β-CD–ACPH–TEA systems in 3 mol dm^{-3} NaC1 solutions upon temperature

Molar ratio β-CD–ACPH–TEA	*T*/°C	Chemical yield (%)	e.e. (%)	Configuration
2:1:0	−10	65	5	*S*(−)
2:1:1	+25	—	39	*R*(+)
2:1:1	−10	58	54	*R*(+)
2:1:2	+25	50	46	*R*(+)
2:1:2	−10	52	56	*R*(+)

Results and discussion

1. Chiral induction

Reduction by $NaBH_4$ was carried out in a carbonate buffer on a mixture of the three compounds β-CD, ACPH, TEA in the desired molar ratio. It can be seen from Table 1 that TEA in a molar ratio as small as 1 : 1 with respect to ACPH dramatically affects the enantioselective formation of 1-phenylethanol induced by β-CD. In the absence of TEA, only a low e.e. of *S*(−) enantiomeric alcohol was obtained. The increase of enantiomeric excess (e.e.) values is furthermore accompanied by an inversion of the face selectivity. Both effects obviously reveal the contribution of TEA in the chiral induction mechanism.

Tertiary amines are known to complex BH_3. It has been previously reported that high enantioselective reductions of ACPH can be achieved using a crystalline β-CD complex of pyridine–BH_3 as reducing agent [8% yield and 91% e.e. (*S*(−)].[9] Since such an effect was not observed with pyridine in our conditions [56% yield, 3% e.e. (*S*(−)],[12] we consider that TEA does not act as a TEA–BF_3 intermediate and that the origin of the enhancement of the chiral induction should be found elsewhere.

We investigated the dependence of enantioselectivity on the variation of the molar ratio β-CD : ACPH : TEA. We noticed that better results were obtained through the addition of at least 2 molar equivalents of β-CD. This is probably due to the lowering of the free ketone concentration in the reduction medium by shifting the complexation equilibrium, since inclusion is strictly required for chiral induction.[3] As mentioned above, the presence of TEA gave predominantly the *R*(+) enantiomer with much higher face selectivities. The maximum e.e. value was reached for the molar ratio β-CD : ACPH : TEA of 2 : 1 : 2. Beyond this ratio, the enantioselectivity decreased, probably because TEA competes with ACPH for inclusion.

The inclusion compounds formed with aromatic ketones are only poorly soluble in water.[16] Reductions were therefore conducted under heterogeneous conditions on crystalline CD complexes in aqueous $NaBH_4$. Guest molecules included in the CD cavity were shown to have a large mobility even in the solid state.[17] The poor selectivity generally observed for CD-mediated asymmetric reactions can be in part ascribed to excessive molecular motion of the substrate. In order to slow down the mobility of the different components, reductions were carried out at −10 °C in 3 M NaCl solutions. As expected, the reaction rate was drastically reduced since it took more than 100 h for the reaction to go to completion compared with about 12 h at 25 °C.

The comparison for the selectivities obtained at 25 °C and at −10 °C in this reaction medium is given in Table 2 for various β-CD : ACPH : TEA ratios. The comparison with data in Table 1 shows that the presence of NaCl does not significantly affect the enantioselectivity. Decreasing the temperature results in a significant improvement in the chiral induction but only when TEA is added to the reaction medium. Two major conclusions can be drawn from this Table. Firstly, the mobility of the substrates appears to be an important factor in the control of the face selectivity in β-CD mediated asymmetric reductions. Secondly, the molecular motion of the included ACPH seems to be reduced in the presence of inert additives such as TEA. This observation provides further support for the formation of a three-component inclusion complex.

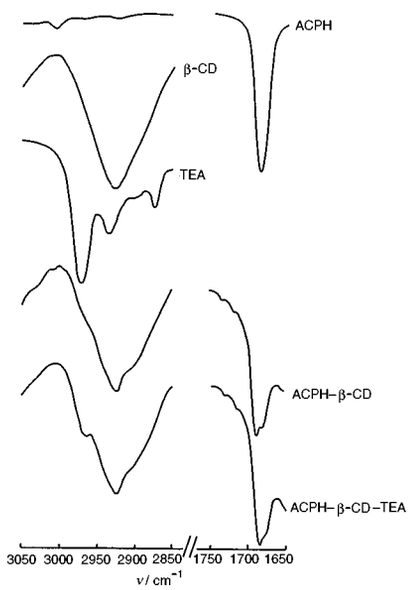

Fig. 1 IR diffuse reflectance spectra in KBr of the precipitates obtained from binary β-CD–ACPH and ternary β-CD–ACPH–TEA systems compared to those of the separate compounds

2. Evidence for the formation of a three-component complex

2.1 Solid state IR spectroscopy. The β-CD–ACPH inclusion compounds prepared as described in the experimental section, possessed low water solubility (*ca.* 10^{-3} mol dm^{-1}). Therefore, we tried to obtain information on the formation of the ternary complex using IR spectroscopy in the solid state.

The position of the carbonyl stretching vibration occurs in the 1650–1750 cm^{-1} region where there is no absorption from either cyclodextrin or TEA, and this can therefore provide information on possible host–guest and guest–co-guest interactions. Diffuse reflectance spectra in KBr are reported in Fig. 1 for the binary and ternary systems with comparison to the free ketone. The carbonyl absorption of the included ACPH appears as a broad band with two contributions (1686 and 1678 cm^{-1}) indicative of the formation of a host–guest complex, the highest frequency corresponding to the free ACPH. The shift of the carbonyl stretching vibration to lower frequency appears to be the result of strong intramolecular interactions such as hydrogen bonding. Unfortunately, no significant variations were observed between the binary and ternary systems in this region.

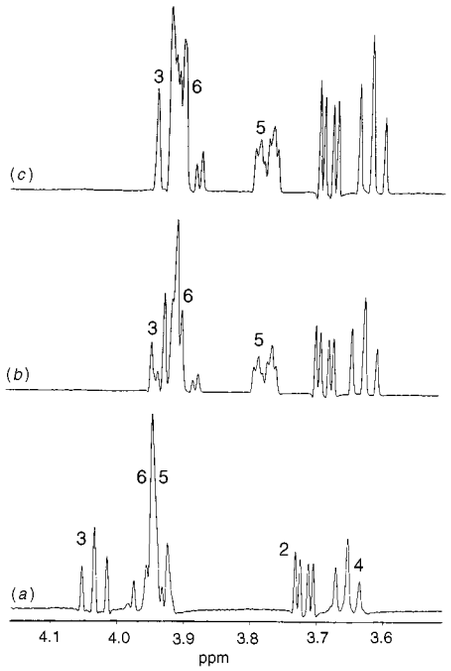

Fig. 2 Partial ^{1}H NMR spectra (500 MHz, D_2O, 298 K) of β-CD 4 mmol dm^{-3} alone (*a*), in the presence of ACPH (*b*) and in the presence of ACPH : TEA (*c*)

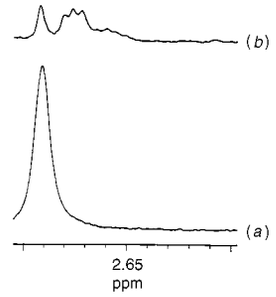

Fig. 3 Partial ^{1}H NMR spectra (500 MHz, D_2O, 298 K) of ACPH in the presence of β-CD (*a*) and in the presence of β-CD : TEA (*b*)

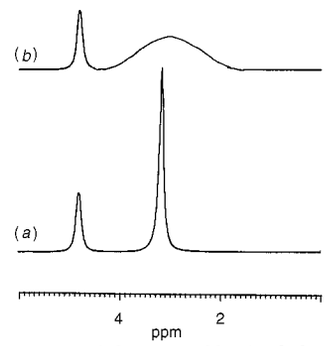

Fig. 4 ^{2}H NMR spectra (46 MHz, 298 K) of the methyl groups of ACPH in the presence of β-CD (*a*) and in the presence of β-CD : TEA (*b*)

On the other hand, a comparison of the IR spectra in the 2850–3050 cm^{-1} region revealed the presence of an additional shoulder at 2966 cm^{-1} in the spectrum of the ternary system. This shoulder can be attributed to the C–H stretching vibration in TEA. Since the carbonyl absorption for both the binary and the ternary systems was the same it was concluded that if a ternary complex is formed, the TEA molecule cannot be located in close proximity of the carbonyl group. This implies that TEA is probably only partially included, in agreement with a preliminary evaluation of CPK models. NMR investigations will therefore be used to obtain a deeper insight into the nature and structure of this complex in the absence and in the presence of TEA.

2.2 NMR spectroscopy. *^{1}H NMR experiments.* In a first step, ^{1}H NMR spectroscopy was used to evidence the formation of a binary inclusion complex and to estimate the possible effects of TEA on the nature and structure of this complex. It must be borne in mind that all data presented here were obtained in solution. The conclusions drawn will therefore be representative of the interfacial system (solid–solution interface) such as the one used in the reduction process. Fig. 2 shows a partial ^{1}H NMR spectra of the cyclodextrin alone and in the presence of ACPH and ACPH–TEA.

The first information obtained from a comparison of the spectra in Figs. 2(*a*) and 2(*b*) concerns the formation of the inclusion complex in the binary system. The spectrum in Fig. 2(*a*) was obtained in the presence of TEA but comparison with data obtained in pure deuterium oxide shows no variations indicating that TEA does not interact with the cyclodextrin. The spectrum presented in Fig. 2(*a*) can therefore be considered as a reference spectrum for the free β-CD.

Addition of ACPH induced large shifts in the signals of the β-CD. The most important are those due to protons H-3 and H-5 which are located in the β-CD cavity.

These upfield shifts are induced by ring-current effects and are considered as proof for the formation of an inclusion complex.[18]

The spectrum presented in Fig. 2(*c*) was obtained with the ternary system. A simple observation of the signals from the cyclodextrin moiety shows that no important variations are produced indicating that the complex between the β-CD and ACPH is not affected significantly, at least as far as the stability is concerned. However, a very important observation can be made concerning the signal of the methyl group of ACPH. This group normally appears as a singlet at 2.7 ppm [see Fig. 3(*a*)]. In the present case, this gives rise to a very complex multiplet.

The structure of this complex signal is shown in Fig. 3(*b*) along with that of the TEA. The only possible explanation for this structure is to consider that the three protons of the methyl group of ACPH are now non-equivalent and therefore give rise to a complex coupled system. This can be ascribed to a very strong immobilization of the methyl group leading to the observation of a non-averaged signal for each proton.

Since ^{1}H NMR is not a suitable method with which to investigate molecular dynamics, because a variety of mechanisms contribute to the definition of the line-shape and the line width observed, the more appropriate ^{2}H NMR technique was used. This method enables the molecular motions in solution to be determined unambiguously because only quadrupolar relaxation occurs.[19]

Deuterium NMR experiments. Fig. 4 shows the deuterium NMR spectra corresponding to the methyl groups of partially deuteriated ACP–[$^2H_3$]methyl in the presence of β-CD and in the presence of β-CD and TEA in conditions similar to those presented in Fig. 3. The most striking observation concerns the linewidth of the signal which is directly related to molecular motion.

In the presence of the β-CD alone, a sharp signal is observed (*ca.* 3 Hz linewidth) indicating that although complexed to β-CD, the ACPH molecule retains a large mobility in the cavity. This is a common observation since the degree of dynamic coupling between host and guest molecules is generally low. On the contrary, in the presence of TEA, the linewidth is increased to a value very similar to that obtained for the β-CD itself[19] (40 Hz linewidth) indicating that, in terms of molecular mobility, the ACPH molecule behaves like the host. This implies that the included ACPH molecule has no—or very little—internal mobility in the cavity when TEA is present. This observation fully supports the locking effect of TEA for the guest molecule and is further proof for the presence of a ternary complex. This immobilization process accounts therefore for the abnormal proton signals in ^{1}H NMR as displayed in Fig. 3.

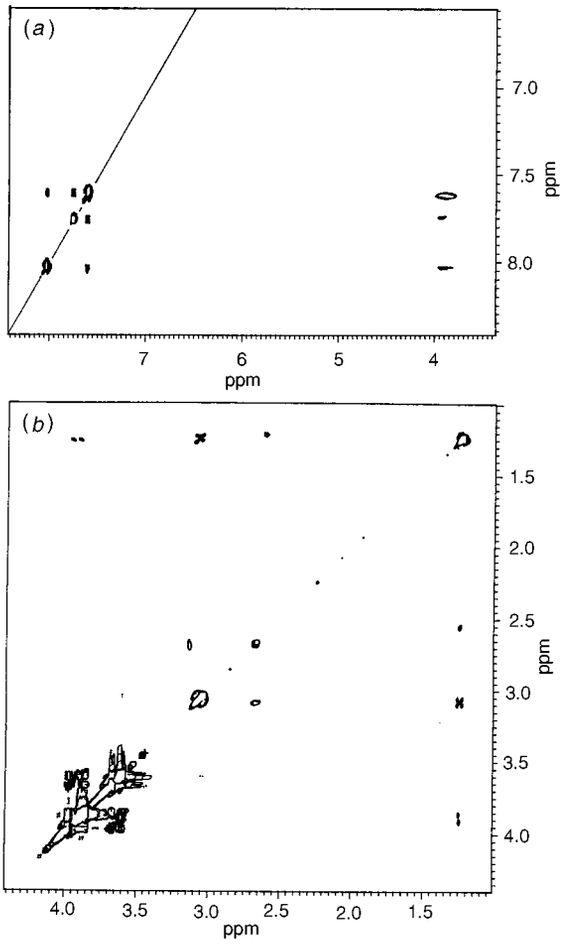

Fig. 5 Partial contour plots of a ROESY experiment (spinlock: 300 ms, attenuation 22 dB) performed at 500 MHz in the ternary complex in D_2O at 298 K: areas of aromatic protons (*a*) and aliphatic protons (*b*)

^1H ROESY experiments. To get a deeper insight in the possible structure of the ternary complex, a two-dimensional ^1H NMR experiment was performed to probe the spatial distance environment in the putative ternary complex. The ROESY sequence[20] was used for this purpose since it was shown that this provides the most sensitive approach to the structural analysis of inclusion complexes with cyclodextrins.[21] A partial contour plot is presented in Fig. 5.

All non-diagonal peaks are indicative of spatial proximities between protons. The main features are the following:

All cross-peaks between the β-CD protons and the ACPH molecule are indicative of the presence of an inclusion complex. For instance, dipolar interactions are observed between the *ortho*-protons of the ACPH and H-5 H-6 of the β-CD, as expected for the inclusion process involving proximity of the carbonyl group and the primary hydroxy side of the β-CD. It has been noted that no dipolar interactions are seen between the methyl group of ACPH and the β-CD protons meaning that it is located outside of the cavity.

The methyl group of the ACPH molecule lies in the vicinity of at least one ethyl group of TEA. The presence of dipolar interactions between the ethyl group(s) of TEA and H-6 protons of the β-CD further supports the presence of a three-component complex β-CD–ACPH–TEA where one ethyl group of TEA is partially included.

3. Molecular modelling

In order to evaluate the possibility of the formation of a ternary complex, molecular modelling was used to derive a realistic model for the complex. We proceeded by minimization of energy between a structure for the binary β-CD–ACPH complex inferred from the ROESY data and TEA. The model reported in Fig. 6 gives a probable picture of the ternary complex. It should be emphasized that all spatial proximities (internuclear distances lower than 5 Å) defined on this model are evidenced as cross-peaks in the ROESY experiment. The aromatic ring of ACPH docks within the β-CD cavity from the primary hydroxy side. The penetration of the guest molecule is not very deep so that the carbonyl group is exposed to the primary hydroxy rim of the host. This location shows that no hydrogen bonding occurs either in the binary or ternary complexes, which is supported by the IR data. Moreover, this model agrees with the chemical results observed for the binary complex where a central position inside the CD cavity cannot induce an enantioface selectivity.

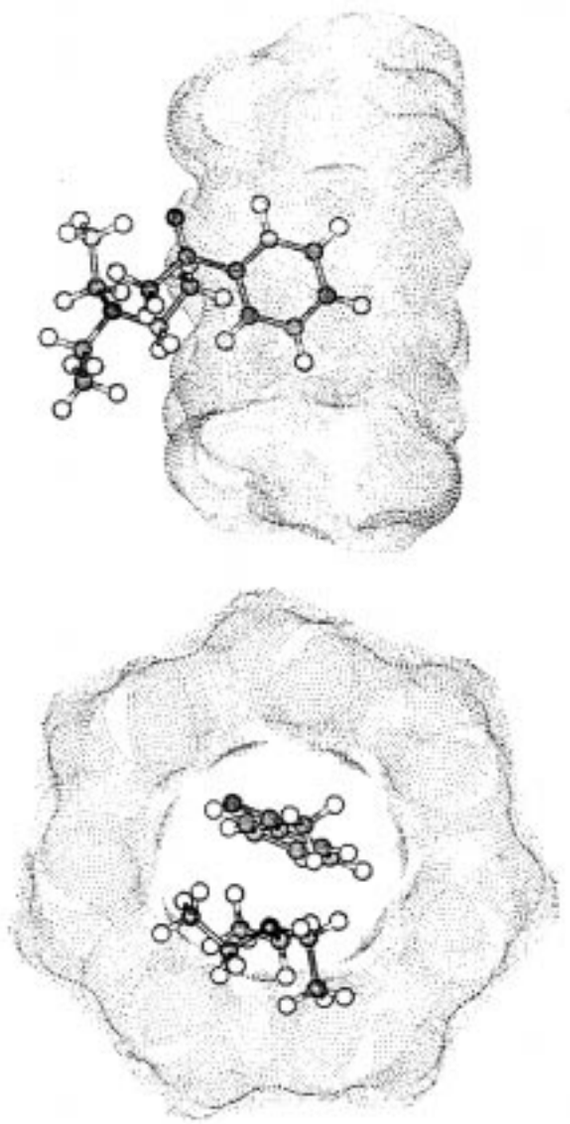

Fig. 6 Proposed structure for the ternary β-CD–ACPH–TEA inclusion complex displayed by CPK drawings for the guests and the solvent-accessible surface for β-CD

The methyl group is then located outside the cavity in agreement with the ROESY experiment. One ethyl group of TEA can be partially included in the residual void volume, the methyl group being at the same level as the carbonyl group of ACPH. As illustrated in the model, the methyl group of ACPH is surrounded by two ethyl groups of TEA. The relative spatial disposition of the three components in the ternary complex accounts for the strong decrease of mobility observed in the deuterium NMR experiments for the included ACPH molecule when TEA is present. The structure proposed clearly demonstrates that the increase of the enantiofacial attack of hydride anions is due to a locking effect of TEA.

Experimental

All chemicals were used as purchased from Aldrich Chemical Co. β-CD was a gift from the Ringdex Company. Analyses were performed using IR spectroscopy (Perkin-Elmer 1760), gas chromatography (Varian 3700) and polarimetry (Perkin-Elmer 241MC).

Preparation of the three-component systems

The β-CD : ACPH : TEA system with 1 : 1 : 1 molecular ratio was prepared according to the following procedure: an equimolar amount (3 mmol) of ACPH (0.350 cm^3) and TEA (0.420 cm^3) was added to a suspension of 3.4 g (3 mmol) of dried β-CD in 40 cm^3 of 0.2 mol dm^{-3} sodium carbonate. The mixture was stirred at room temperature overnight and the resulting slurry was used without further processing.

General procedure for the reduction by $NaBH_4$

A two-fold excess of $NaBH_4$ (227 mg) with respect to ACPH was added to the slurry obtained previously and the mixture was stirred at room temperature for 24 h. After neutralization with 6 mol dm^{-3} HCl, the resulting mixture was extracted with diethyl ether (5 × 5 cm^3) and the combined extracts were washed with water and dried (anhydrous $MgSO_4$). After evaporation of the solvent, the resulting 1-phenylethanol was purified by preparative TLC in methylene dichloride. Enantiomeric excesses (e.e.) were derived from the integral ratio of signals obtained by gas chromatography on a chiral capillary column (Cydex-B, Scientific Glass Engineering) and are given as a mean value of triplicate determinations. The reduction of other molar ratios were conducted according to the same procedure using the desired amount of each compound.

NMR analysis

^{1}H NMR experiments were performed at 500 MHz using a Bruker AMX500 spectrometer. In all cases, the samples were prepared in deuterium oxide (Euriso-Top, Saclay, France) and measurements were performed at 298 K under careful temperature regulation. The length of the 90° pulse was *ca*. 6.5 μs. 1D NMR spectra were collected using 16K data points. Chemical shifts are given relative to external tetramethylsilane (TMS = 0 ppm) 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 Bruker library with a 300 ms spin-lock time. These bidimensional experiments were acquired using 2K data points and 256 time increments. The phase sensitive (TPPI) sequence was used and processing resulted in a 1K.1K (real–real) matrix.

Deuterium spectra were obtained using a Bruker MSL300 spectrometer operating at 300 MHz for proton and 46 MHz for deuterium. Spectra were collected in deuterium-depleted water (Euriso-Top, Saclay France).

All NMR data were processed and plotted on a Bruker X32 data station.

Molecular modelling

Molecular models were obtained using the Insight II software program running on a Silicon Graphics Iris Indigo station according to a procedure described elsewhere.[22] The three-component inclusion complex was constructed by manually docking TEA and the binary β-CD–ACPH complex. The docking energy was minimized and all atoms were kept farther apart than the sum of their Van der Waals radii. For the sake of clarity, inclusion complexes were displayed by CPK drawings for the guest molecules and the solvent-accessible surface (Conelly surface) for β-CD.

Conclusions

It has been demonstrated that the presence of a chemically inert species can strongly affect the face selectivity in the chiral induction by CDs through the formation of a three component inclusion complex. The locking effect of TEA can be related to a simple model of the allosteric effect such as those observed in enzyme catalysis. It can be assumed that dramatic improvements in selectivity can be achieved with co-guests of the appropriate shape and structure to optimize the fitting in the constrained space of the CD cavity.

This opens the way to a more accurate control of the stereoselectivity of these reactions as far as the structure of the ternary complex is properly evidenced. In this respect, NMR experiments allow a confident analysis of the molecular structures in solution. ROESY experiments are clearly highly informative but, if deuterium labelled derivatives are available, ^{2}H NMR can provide very detailed information about the dynamics of the complex in solution. A clear insight into the molecular structures involved can be derived from the powerful combination of NMR spectroscopy and molecular modelling.

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