



Modification of Chemical Reactivity upon Cyclodextrin Encapsulation: Asymmetric Bromination of Chalcone and Benzylideneacetone

KASI PITCHUMANI,^{*,a} PONNUSAMY VELUSAMY, SANTHAMOORTHY SABITHAMALA
and CHOCKALINGAM SRINIVASAN^{*}

Department of Materials Science, Madurai Kamaraj University,
Madurai-625 021, India and ^aSchool of Chemistry,
Madurai Kamaraj University, Madurai- 625 021

Abstract: Asymmetric bromination of chalcone and benzylideneacetone (*trans*-isomers) in crystalline β -cyclodextrin complex was studied. While bromination of chalcone in the absence of β -cyclodextrin yields *erythro*-dibromide, bromination of β -cyclodextrin-chalcone complex results in the formation of a mixture of *erythro*- and *threo*-dibromides respectively in the ratio 80:20. Complexation does not induce any variation in the bromination pattern in the case of *trans*-benzylideneacetone. These observations have been accounted for in terms of different conformations of the enones in the β -cyclodextrin-enone complexes. Complex formation between the substrate and cyclodextrin has been confirmed by various physical methods.

Introduction

Cyclodextrins (CDs) are doughnut shaped cyclic oligosaccharides possessing a hydrophobic pocket capable of binding a variety of organic as well as organometallic molecules.¹ They are found to be excellent model systems for studying the nature of noncovalent bonding forces in aqueous solution and are good models for understanding the specificity of enzyme-substrate interaction.^{2,3} CDs have also been used as reaction vessels to control photochemical as well as thermal reactions of bound guest molecules.⁴

Asymmetric reactions employing CDs are of particular interest since they provide a quick and easy method for the synthesis of chiral compounds from achiral materials. Various attempts to use CD as a tool in asymmetric induction resulted in limited success⁵. Our interest in utilising the hydrophobic β -CD cavity for achieving selectivity in organic reaction,⁶ prompted us to investigate the bromination of α , β -unsaturated ketones such as chalcone and benzylideneacetone (BA)

(Figure 1) in free and in bound form with β -CD. The experiments are designed with a view to analysing the influence of β -CD encapsulation on the bromination of these enones. Complex formation between the host and guest molecules has been established by various physical methods. The interaction of enones with β -CD is also evidenced by the measurements of dissociation constants and host-guest ratio.

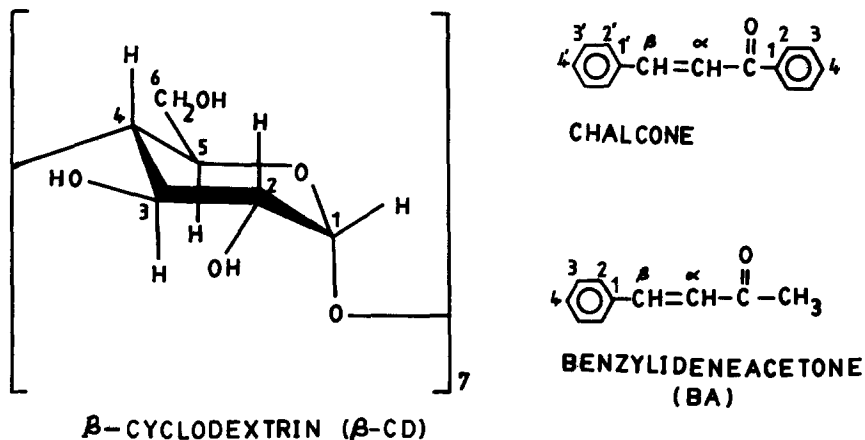


Figure 1. Structures of (a) β -cyclodextrin (β -CD), (b) chalcone and (c) benzylideneacetone (BA)

Experimental details

Materials. β -Cyclodextrin (Sigma), bromine (Merck) were used as such. Carbon tetrachloride (Qualigens; AR grade) was distilled and used. Chalcone and BA were synthesised and purified by reported procedure.⁷ The *trans*-isomers were obtained by separation using column chromatography.

Preparation of β -CD complexes. Reported procedures⁸ were employed for the preparation of cyclodextrin complexes of chalcone and BA. To 5 mL of an aqueous solution containing β -CD (3×10^{-1} M) were added equimolar amounts of the guest molecule and mixed by stirring continuously for 24 hours at room temperature. The complex was filtered off, washed mildly with diethyl ether to remove any uncomplexed guest molecule and dried in an air oven at 60°C for about 150-180 minutes. The white crystalline powders obtained were used as such for further studies.

Bromination of enones. The bromination of enone was carried out following the general procedure.⁹ To 5 g of pure enone dissolved in 15 mL of CCl_4 kept at 0°C was added 5.5 g (1.72 mol) of bromine dissolved in

6mL of CCl_4 . The slow, careful addition was carried out with constant stirring for about 30 min. in dark. After completion of the reaction, the dibromide was collected in a Buckner funnel, washed with 75% ethanol and dried.

Bromination in solid β -CD complexes. The β -CD complex of enone (2g) was dissolved in 5 mL of CCl_4 in dark at 0°C . Equimolar amount of Br_2 in CCl_4 was admitted dropwise for a duration of 10 minutes. After completion of the reaction, the excess bromine was removed and the complex was dissolved in excess of water. The product was then extracted with diethyl ether, the organic layer was dried over anhydrous sodium sulphate and on removal of the solvent yielded a white solid.

Analytical Methods. The reaction products formed in both the conventional and complex bromination were identified as follows:

The infrared absorption spectra (neat or KBr disc) were measured in the region $4000\text{--}200\text{ cm}^{-1}$ on a Perkin-Elmer 577 IR spectrophotometer. The ^1H - and ^{13}C -NMR spectra were recorded at a 200/400 MHz NMR spectrometer (in $\text{DMSO-d}_6/\text{CDCl}_3$ or D_2O) with TMS (tetramethylsilane) as the internal reference standard. The X-ray diffraction patterns of the powdered samples were measured in the region of $0\text{--}57^\circ$ employed with $\text{CuK}\alpha$ radiation (1.54 \AA) from Mabe Joel Model JDX-830 powder diffractometer. Dissociation constant (K_D) values for the β -CD complexes of the enones were determined spectrophotometrically. A UV/VIS JASCO 7800 spectrophotometer was employed (concentration of β -CD varied from $5 \times 10^{-4}\text{ M}$ to $5 \times 10^{-3}\text{ M}$ measured in the region of 200-320 nm, using spectroscopic grade methanol as the solvent at 25°C). Optical rotations were measured in acetonitrile (AR grade) on a JASCO DIP 370 Digital Polarimeter with 1 dm cell at 25°C .

Results and Discussion

Characterisation of CD complexes. To establish the complex formation, physical methods such as IR, ^1H - and ^{13}C -NMR, X-ray powder diffraction have been employed.

Infrared spectra. IR techniques are not generally utilised for the detection of inclusion compounds because the resultant spectra have superposition of host and guest bands. However, in this study chalcone and BA have some characteristic IR absorptions in regions where β -CD does not absorb and this is used to identify the host-guest interaction. The two bands due to carbonyl group observed at 1590 and 1650 cm^{-1} in free chalcone have been shifted to 1580 and 1640 cm^{-1} respectively in its β -CD complex. Similarly, the C-H bending frequencies (for trans-disubstituted alkene) observed in chalcone at 1010 and 1325 cm^{-1} are shifted to 1005 and 1350 cm^{-1} respectively in the complex. The aromatic bending at 740 cm^{-1} moves over to 730 cm^{-1} . In addition, decrease in intensities of many bands are observed in CD complex of chalcone compared

to a physical mixture of chalcone and β -CD. No such shift in C=C and C=O peaks are observed in physical mixture. In the case of BA, though the C=C and C=O bands and the aromatic C-H bending frequencies are not affected, considerable shift to lower frequencies in the case of aromatic C-H stretching and olefinic bands (*trans*-disubstituted) from 3000 and 960 cm^{-1} to 2880 and 950 cm^{-1} respectively has been observed in the spectrum of the complex. Here also, as a result of complexation considerable decrease in intensities are observed in many bands in the β -CD complex (in comparison with physical mixture and the pure compounds).

X-ray powder diffraction. The X-ray powder patterns for β -CD, chalcone, β -CD-chalcone complex and the physical mixture of host and guest are given in Figure 2. A comparison of X-ray diffraction patterns of β -CD and chalcone with that of the complex revealed marked

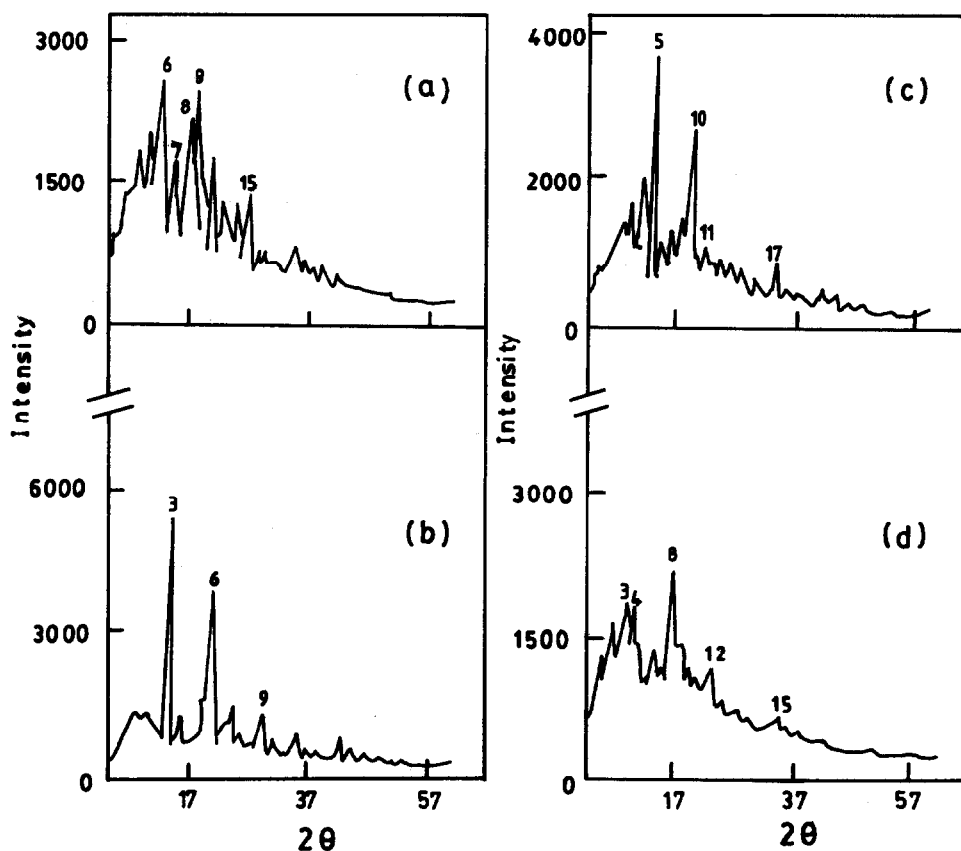


Figure 2. X-ray powder diffraction patterns of (a) β -CD, (b) chalcone, (c) β -CD-chalcone complex and (d) β -CD-chalcone physical mixture

differences. The sharp peaks in the 2θ region of 8.9° , 12.3° and 19.6° for β -CD and 13.7° for chalcone are absent in the complex pattern. However, these peaks are observed in the physical mixture and this can be interpreted as an approximate superposition of the components namely β -CD and chalcone. The major peaks in chalcone pattern (at 2θ) values of 13.7° and 20.3° are the prominent ones in the physical mixture also. But this is not the case with the β -CD-chalcone complex. The medium peaks at 19.6° for β -CD and 19.1° for chalcone are just superimposed to give a peak at 19.0° in the physical mixture. But the complex pattern is markedly different. These observations reinforce the evidence from IR spectral analysis that the precipitated solid obtained from β -CD and chalcone is a microcrystalline inclusion complex formed between β -CD and chalcone. X-ray diffraction studies has not been extended to BA as it is a liquid.

$^1\text{H-NMR}$ spectra. Additional evidence for complex formation is provided by the $^1\text{H-NMR}$ spectra of β -CD complexes of chalcone and BA in D_2O . The CD protons are identified by their specific coupling pattern.¹⁰ The chemical shifts of β -CD protons in the uncomplexed and complexed forms given in Table 1 indicate that H-1, H-2 and H-4 protons are unaffected as a result of complexation. The H-3 and H-5 protons which are oriented towards the interior of the β -CD cavity, have considerable upfield chemical shifts in both the complexes. In the case of chalcone complex, H-6 protons move downfield while in BA complex, it is unchanged. These observations are consistent with the reasoning of Demarco and Thakkar¹¹ that, if inclusion occurs the screening environment should be sensed only by the hydrogens on the inner surface (H-3 and H-5) but not by the hydrogens on the outer surface. The above chemical shift behaviour for the β -CD protons establishes clearly that the aryl ring in both the cases is positioned within the CD cavity.¹⁰⁻¹²

Table 1. 200 MHz $^1\text{H-NMR}$ Chemical Shifts of β -CD Protons in Complexes.^a

Compound	H-1	H-2	H-3	H-4	H-5	H-6
β -CD	1007.1	722.7	784.9	709.9	763.0	769.7
β -CD/chalcone complex ^b	1007.0	726.0	768.0	710.0	758.0	782.0
β -CD/BA complex ^b	1007.0	726.9	765.1	708.4	753.3	770.6

^a Chemical shifts are expressed in Hz; solvent D_2O .

^b Recorded in a 400 MHz instrument.

¹³C-NMR spectra. The ¹³C-NMR chemical shifts for the various carbon atoms of β-CD, chalcone and its β-CD complex are presented in Table 2. The data reveal that the shielding of carbon atoms C₁, C₅, and C₆ of β-CD in the complex are significant. The carbon atoms of chalcone exhibit a significant deshielding, the shift being larger in the case of carbonyl, α- and β-carbon atoms (non-phenyl carbon atoms). The smallest shifts are observed in the *ipso*-carbon atom (1 and 1'). These results corroborate the inclusion of either of phenyl group into the cavity.

Table 2. ¹³C-NMR Chemical Shifts (Hz) of β-CD, Chalcone and the β-CD-Chalcone Complex. ^{a,b}

β-CD			β-CD-Chalcone		
Carbon atoms	(δ)	(Δδ) ^c	Carbon atoms	(δ)	(Δδ) ^c
1 ^d	102.018	-0.046	carbonyl	189.131	+0.045
2	72.419	-0.016	β	143.973	+0.030
3	72.905	-0.016	α	130.479	+0.060
4	81.648	-0.031	1 ^d	137.568	+0.014
			2	128.809	+0.045
5	71.933	-0.016	3	128.749	+0.029
6	59.912	-0.031	4	132.953	+0.045
			1'	134.608	+0.014
			2'	128.642	+0.045
			3'	128.445	+0.014
			4'	121.963	+0.030

^a Chemical shift values are assigned with DMSO signals as the base in both the complexes and the free substrate as well as β-CD; ^b At room temperature; ^c + and - signs indicate deshielding and shielding respectively; ^d Numbering of carbon atoms of β-CD and chalcone is given in Figure 1.

Similarly, the ¹³C-NMR spectral data for β-CD complex of BA presented in Table 3 indicate that while the carbon atoms of β-CD are shielded (again the largest shieldings are observed at C₁, C₅ and C₆), the carbon atoms of BA exhibit significant deshielding. Here also, by analogy with chalcone, the largest deshieldings are observed at the non-phenyl carbon atoms (carbonyl, methyl, α- and β-) and a slight deshielding is observed at the *ipso*-carbon atom. This trend also compares with chalcone spectrum, wherein the smallest shifts are observed at the *ipso*-positions.

Table 3. ^{13}C -NMR Chemical Shifts (Hz) of β -CD, BA and the β -CD-BA Complex. ^{a,b}

β -CD			β -CD-BA		
Carbon atoms	(δ)	($\Delta\delta$) ^c	Carbon atoms	(δ)	($\Delta\delta$) ^c
1 ^d	102.018	-0.031	carbonyl	197.813	+0.167
2	72.419	-0.016	β	143.078	+0.121
3	72.905	-0.016	α	130.373	+0.091
4	81.648	-0.016	1 ^d	134.456	+0.026
			2	128.900	+0.076
5	71.933	-0.030	3	128.339	+0.060
			4	127.215	+0.076
6	59.912	-0.031	methyl	27.307	+0.121

^a Chemical shift values are assigned with DMSO signals as the base in both the complexes and the free substrate as well as β -CD; ^b At room temperature; ^c + and - signs indicate deshielding and shielding respectively; ^d Numbering of carbon atoms of β -CD and BA is given in Figure 1.

Thus the results of the ^{13}C -NMR spectral data clearly indicate the formation of an inclusion complex between β -CD and the substrate. Similar results are also obtained in an earlier study in the ^{13}C -NMR spectra of β -CD-phenylpropionic acid complex.¹²

Dissociation constants. Dissociation constants (K_D), estimated spectrophotometrically using the method of Benesi and Hildebrand,¹³ yielded values of $1.4 \times 10^{-4}\text{M}$ and $5.8 \times 10^{-4}\text{M}$ for β -CD complexes of chalcone and BA respectively. The K_D values are quite low suggesting that the β -CD forms strong complexes with these two substrates.

Complex formation is also evidenced from the determination of host-guest ratio by a gravimetric method. The ratios are 1:0.71 and 1:0.88 for β -CD-chalcone and β -CD-BA complexes respectively.

Bromination. Stereospecific addition of bromine to carbon-carbon double bond of α, β -unsaturated ketones is well documented by several examples.¹⁴ The reaction proceeds by electrophilic attack of the halogen on the double bond to form an intermediate cyclic bromonium ion followed by attack of halide ion on the cyclic intermediate. The overall result is an *anti*-addition of the two halogen atoms to the double bond. The reaction is altered by electron-donating substituents in the olefin and

also by the use of polar solvents.¹⁴ However, there appears to be no systematic investigation of the effect of an organised media as cyclodextrin on the addition of bromine to an olefin. Asymmetric halogenation and hydrohalogenation have been reported in a crystalline α -CD complex of *trans*-2-butenoic acid.¹⁵ Exposure to gaseous HBr at 20°C and to HCl at 0°C gave (S)-(+)-3-bromobutanoic acid in 58% and (S)-(-)-3-chlorobutanoic acid in 64% enantiomeric excess respectively. At 45-50°C, the guest in the cavity of CD reacted with gaseous bromine or chlorine to produce *erythro*-dihalides with extremely low optical activities.

Herein we report the addition of bromine to *trans*-isomers of chalcone and BA in free as well as in their β -CD complexed form using a mixture of Br₂/CCl₄. Conventional bromination of chalcone and BA results⁹ in the formation of only *erythro*-dibromides (characterised by their IR and NMR spectra). We also studied bromination of the above enones in their β -CD complexed form. The β -CD-BA complex upon bromination yields exclusively *erythro*-dibromide as in the case of conventional bromination. However, a mixture of *erythro*- and *threo*-dibromides are obtained in the ratio of 80:20 respectively in the bromination of β -CD-chalcone complex. This is evidenced by a comparison of the NMR chemical shifts of the dihalides and also from chromatographic techniques.

This difference in the bromination of the two β -CD-enone complexes may be explained on the basis of specific modes of complexation of the substrate into the CD cavity. As a consequence of the restriction on rotational and translational motion of the guest molecule inside the CD cavity, differences in bromination pattern arise.

In the case of *trans*-BA, the structure of the complex may be visualised as given below (Figure 3), in which the phenyl ring being more hydrophobic resides inside the CD cavity and the rest of the molecule will be protruding away from CD. This mode of complexation accounts for the observed ¹³C-NMR data in which the non-phenyl carbon atoms (carbonyl, α and β -carbon atoms) have the largest deshielding (Table 3). This indicates clearly that two sets of carbon atoms in different environments are present and this supports the suggested structure of the complex.

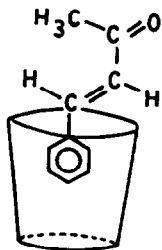


Figure 3. Conformation of β -CD-BA complex

In the case of β -CD-chalcone complex, the conformation of chalcone in the complex in the light of ^{13}C -NMR data, may be visualised as shown in Figure 4 (A to B).

In structure A, the phenyl group attached to the carbon-carbon double bond resides inside the cavity while the benzoyl group moves away. In structure B, the phenyl group attached to the carbonyl group resides inside the cavity while the styryl group moves away. In structure C also, the phenyl group attached to carbon-carbon double bond enters into the cavity as in structure A, but the benzoyl group tends to remain near the wider mouth of torus.

Structures B and to some extent A do not experience any hindrance to anti-addition of bromine as there is free rotation about the carbon-carbon single bond between the olefinic and the carbonyl groups. This is not the case with structure C in which anti-addition is difficult since

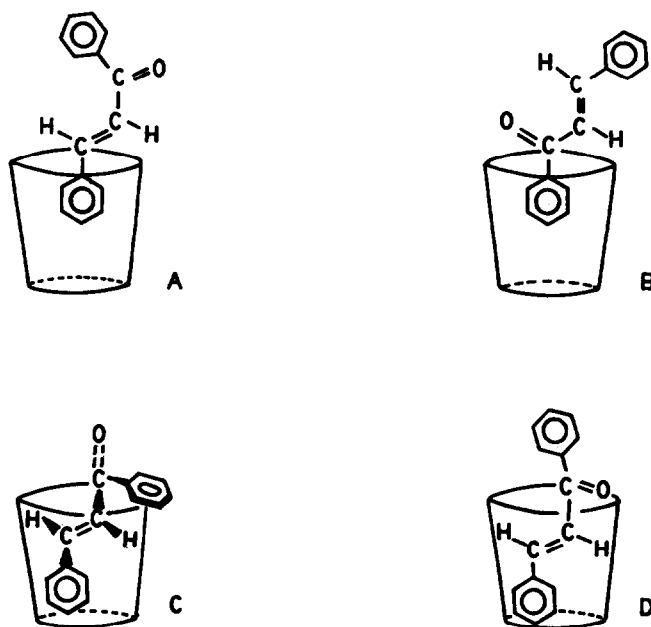


Figure 4. (A to D) Conformations of β -CD-chalcone complex

the addition of second bromine atom has to come from the more crowded side of CD molecule. Thus a perusal of the structure of the complexes reveal that while bromination of structures A and B results in anti-addition leading to erythro-dibromide, bromination of C leads to syn-addition across carbon-carbon double bond yielding threo-dibromide.

Deeper penetration of aryl ring in structure A leads to structure D which only one face of the double bond is exposed for bromination and

threo-dibromide is expected to be the major product in this conformation also.

Additional evidence for the formation of a mixture of dibromides in the case of chalcone complex can be obtained from optical rotation studies. $[\alpha]_D^{25}$ for brominated chalcone in the presence of β -CD, is $+1.15^\circ$ whereas in the absence of β -CD, the observed specific rotation is -12.6° (concentration 0.27 M ; solvent: CH_3CN).

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