Carbohydrate Research, 147 (1986) 205–209
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

INDUCED CIRCULAR DICHROISM OF CONJUGATED CYCLOHEXENONES INCLUDED IN NATIVE OR MODIFIED CYCLOMALTOOLIGOSACCHARIDES

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(Received July 15th, 1985; accepted for publication, September 19th, 1985)

ABSTRACT

The mode of insertion of conjugaed cyclohexenones into native cyclomaltooligosaccharides (cyclodextrins) and heptakis(2,6-di-*O*-methyl)cyclomaltoheptaose, heptakis(2,3,6-tri-*O*-methyl)cyclomaltoheptaose, and heptakis[6-deoxy-6-(*N*-methylacetamido)]cyclomaltoheptaose has been inferred from induced c.d. spectra. Depending on the presence of methyl substituents in the cyclohexenone moiety and on the size of the cyclodextrin, the carbonyl group may be forced to penetrate the cavity. The induced c.d. spectra of complexes with heptakis[6-deoxy-6-(*N*-methylacetamido)]cyclomaltoheptaose show that the carbonyl group of the 6-substituent penetrates into the cavity and, as a result of the cyclohexenone inclusion, it is forced out.

INTRODUCTION

In recent years, the rapidly growing interest in inclusion phenomena[1] has stimulated a large number of investigations on cyclomalto-oligosaccharides (cyclodextrins, CDs) which are toroidal shaped molecules composed of six or more D-glucosyl residues. Most studies have focussed upon their ability to influence reactivity[2] and, in particular, to catalyse hydrolyses[3]. More recently, inclusion complexes have been reported to undergo selective reactions[4]. Reactivity and selectivity effects depend on the strength of binding and on the orientation of the substrate in the cavity of the CD.

Circular dichroism is one of the most useful techniques[5] for determining the mode of insertion into the cavity of a CD in solution of substrate molecules bearing a suitable chromophore. Thus, it has been shown[6] that, depending on the length of

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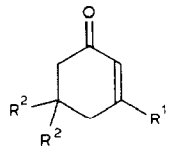
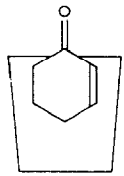


1a $R^1 = R^2 = H$
1b $R^1 = Me, R^2 = H$
1c $R^1 = R^2 = Me$



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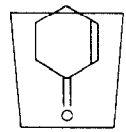

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the alkyl group, either the aromatic or the aliphatic moiety of *p*-acyloxynitrobenzene can be included in the chiral cavity of a CD.

Following on from an investigation[7] on the regioselectivity of the borohydride reduction of cycloalkenones in the presence of a CD and a ^{1}H-n.m.r. study of their inclusion complexes, we now report on the induced circular dichroism (c.d.) of the complexes of cyclohexenones **1a–c** with cyclomaltohexaose (α-CD) and cyclomaltoheptaose (β-CD) and of the complexes of **1c** and the modified CDs, heptakis(2,6-di-*O*-methyl)cyclomaltoheptaose (2,6-Me_2-β-CD), heptakis(2,3,6-tri-*O*-methyl)-cyclomaltoheptaose (2,3,6-Me_3-β-CD), and heptakis[6-deoxy-6-(*N*-methylacetamido)]cycloheptaose (6-NMeAc-β-CD) in aqueous solution.

RESULTS AND DISCUSSION

The formation of inclusion complexes between native or modified CDs in aqueous solutions is based[7] on chemical and spectroscopic evidence. Binding constants in the ranges 20–35 and 120–620 M^{-1} for the complexes of α-CD and β-CD, respectively, were obtained for solutions of **1a–c** in D_2O in the presence of excess of α-CD and β-CD.

For β-CD in aqueous 2% methanol, only **1c** showed a well-defined induced c.d. band in the absorption region corresponding to the n→π^* transition of conjugated enones (Fig. 1A). This finding clearly indicated that only **1c** binds to the

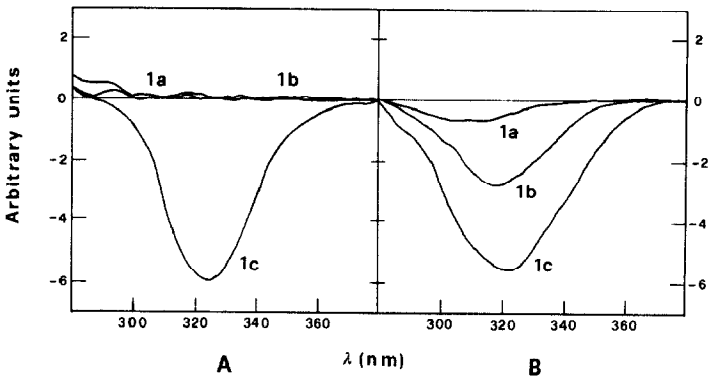

Fig. 1. C.d. spectra of cyclohexenones **1a–c** with A, β-CD; B, α-CD; [CD] = 10mM, [**1**] = 20mM, in aqueous 2% methanol

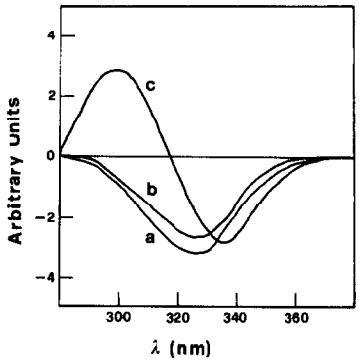

Fig. 2. C.d. spectra of cyclohexenone **1c** with *a*, 2,3,6-Me_3-β-CD; *b*, 2,6-Me_2-β-CD; *c*, 6-NMeAc-β-CD; [modified CD] = 5mM, [**1c**] = 15mM, in aqueous 1.5% methanol.

β-CD preferentially with the carbonyl group inserted into the chiral cavity. Two limiting insertion modes (**2** and **3**) may be envisaged. Thus, for enones **1a** and **1b**, mode **2** is preferred, and mode **3** is allowed for enone **1c**. Inspection of CPK molecular models indicates that mode **2** is not possible for **1c** because of the steric requirements of the three methyl groups.

Such a clear-cut distinction was not found for the α-CD complexes (Fig. 1B), but the trend from a preferential mode **2** to mode **3** is evident on going from **1a** to **1c**. Apparently, for **1b**, steric factors become important in the smaller cavity of α-CD, thus favouring mode **3**, although this argument can hardly apply to **1a**. There seems to be a more random penetration into the cavity of α-CD, other modes of insertion between **2** and **3** being possible at least for enones **1a** and **1b**.

In the presence of 2,6-Me_2-β-CD or 2,3,6-Me_3-β-CD, enone **1c** displayed induced c.d. bands similar to that observed with β-CD (Fig. 2). Measurements made at different substrate-modified CD ratios showed that, whereas saturation conditions were reached with 2,6-Me_2-β-CD and β-CD at relatively low host–guest ratios (3–4:1, [CD] = 10mM), saturation with 2,3,6-Me_3-β-CD was attained, presumably, at much higher ratios that were inaccessible experimentally due to the strong absorbance of highly concentrated solutions of 2,3,6-Me_3-β-CD in this spectral region. This finding indicated the binding constant of the inclusion complex with 2,3,6-Me_3-β-CD to be substantially lower than that with 2,6-Me_2-β-CD or β-CD, a fact, although unexplained, which accords with the lower stability of the permethylated-β-CD complexes observed[8] also with other substrates.

The induced c.d. spectra with 6-NMeAc-β-CD (Fig. 2c) showed two bands of opposite sign at 300 and 338 nm. Such behaviour could be due to different conformations of the complexed cyclohexenone within the CD, owing to the presence of the 6-methylacetamido groups which also penetrate into the cavity (see below). The Cotton effect of the α,β-unsaturated ketone chromophore in the 300–340 nm region is extremely sensitive[9] to conformational alterations in the ring containing the chromophore. It is noteworthy that this bisignate behaviour was not shown by

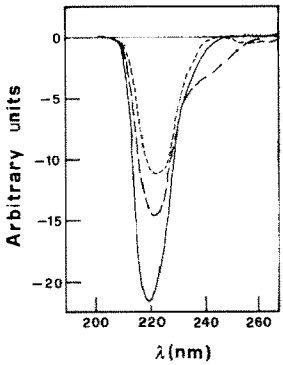

Fig. 3. C.d. spectra of 6-NMeAc-β-CD: ———, alone; — — —, with **1c**; – – –, with **1b**, ..., with **1a**; [CD] = 5mM, [enones **1**] = 3mM, in aqueous 1.5% methanol.

the complex of 3,5,5-trimethylcyclohexanone with 6-NMeAc-β-CD, which displayed a negative induced c.d. band at ~290 nm. Since the two bands have comparable areas and the cross-over at 318 nm corresponds to the λ_{max} of the conjugated enone chromophore, an exciton coupling[10] between two enone chromophores cannot be ruled out. However, such an effect would require two molecules of **1c** inside 6-NMeAc-β-CD or the formation of a dissymmetric dimer in which two enone chromophores are in close proximity, a situation which can hardly be envisaged when the steric requirements of these molecules are taken into account. This phenomenon is being investigated further.

Conclusive evidence of the insertion of the amide carbonyl group of 6-NMeAc-β-CD into the chiral cavity is given by the strong induced c.d. band at 219 nm, the intensity of which decreased on addition of the enones **1a–c** (Fig. 3). Such a decrease of the band, which virtually disappeared at higher concentrations of **1a** and **1b**, indicated that the inclusion of a guest molecule forced the amide carbonyl to move out of the cavity particularly when, as suggested for **1a** and **1b**, a mode **2** insertion is involved. On the other hand, the induced c.d. band at 220 nm is due to an intramolecular chiral interaction as demonstrated by the linear dependence of the band intensity on the concentration of 6-NMeAc-β-CD (from 0.5 to 5mM).

It is concluded that the more polar or less hydrophobic sections of a guest molecule, such as the carbonyl group of the cyclohexenones, can be accommodated in the cavity of a CD when steric factors prevent inclusion of the more hydrophobic portion. Thus, the cavity of a CD appears not to be so hydrophobic as often claimed and should be considered as a possible inclusion site for weakly hydrophilic molecules.

EXPERIMENTAL

2-Cyclohexen-1-one (**1a**), 3-methyl-2-cyclohexen-1-one (**1b**), 3,5,5-trimethyl-2-cyclohexen-1-one (**1c**), and 3,5,5-trimethylcyclohexanone were commercial

products and were purified by distillation. α-CD and β-CD (Sigma) were used without further purification. 2,6-Me_2-β-CD[11] and 6-NMeAc-β-CD[7] were synthesised by the reported procedures, whereas 2,3,6-Me_3-β-CD[11] was obtained by methylating[12] 2,6-Me_2-β-CD.

C.d. spectra were recorded with a JASCO J-500 A spectropolarimeter equipped with a DP-501 N data processor and cylindrical, 1-cm fused-quartz cells, for solutions prepared by mixing 5 or 10mM solutions (1.9 mL) of CD or modified CD in twice-distilled water and methanolic M cyclohexenone (10–100 μL).

ACKNOWLEDGMENTS

We thank E. Castiglione and V. Moretto for technical assistance, and the Ministry of Public Education (Italy) for financial support.

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