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Note

Chiral recognition of 1-*O*-allyl- and 1-*O*-benzyl-D- and -L-*myo*-inositol by cyclomalto-hexaose and -heptaose (α- and β-cyclodextrin)

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Recent interest in inositol phosphate chemistry[1] and in the synthesis of inhibitors of the phosphatidyl inositol cycle has emphasised the need for efficient procedures for the synthesis of functionalised *myo*-inositol intermediates. There are three main challenges, namely, regioselective protection, efficient phophorylation, and optical resolution.

We have developed an efficient one-step regioselective preparation of 1-*O*-alkyl-DL-*myo*-inositol[2], which is an intermediate in a projected synthesis of phosphorylated *myo*-inositol-containing aminoglycosides[3]. We have found that cyclomaltohexaose (αCD, α-cyclodextrin) and cyclomaltoheptaose (βCD, β-cyclodextrin) can be used as chiral complexing agents[4] of 1-*O*-allyl- and 1-*O*-benzyl-DL-*myo*-inositol in water to produce diastereomers that are observable by ^{1}H-n.m.r. spectroscopy. This method allows a rapid and facile analysis of the efficacy of procedures for optical resolution. Chemical shift and n.O.e. data allow structures for the inclusion complexes to be proposed. The isolation of drug stereoisomers by chromatography[5] of inclusion complexes with βCD and chiral recognition of some diastereomers by CDs, using n.m.r. spectroscopy[6], have been reported.

The ^{1}H-n.m.r. data for 0.010M solutions of 1-*O*-benzyl- (**1**) and 1-*O*-allyl-DL-*myo*-inositol (**2**) in D_2O in the absence and presence of 0.01M αCD or βCD are given in Table I. The spectrum of **1** + βCD showed an upfield shift of the resonances of H-3 (0.02 p.p.m.) and H-5 (0.03 p.p.m.) of the βCD, indicating the formation of an inclusion compound that probably involved the narrower rim of βCD (Table II). The signals for H-5,6 and the benzylic protons of the guest shifted downfield (Table I) and those for H-1,3,5 were split ($\Delta\delta$ 0.003, 0.003, and 0.006 p.p.m., respectively), indicating the formation of diastereomeric host–guest complexes (Fig. 1). The isolated signal for H-2 of **1**, at ~4.01 p.p.m., was also split, depending on the concentration of βCD. These results indicate an interaction of the α-side of the inositol derivative with βCD. The

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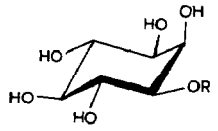

1 R = Bn
2 R = allyl
3 R = *p*MeO Bn

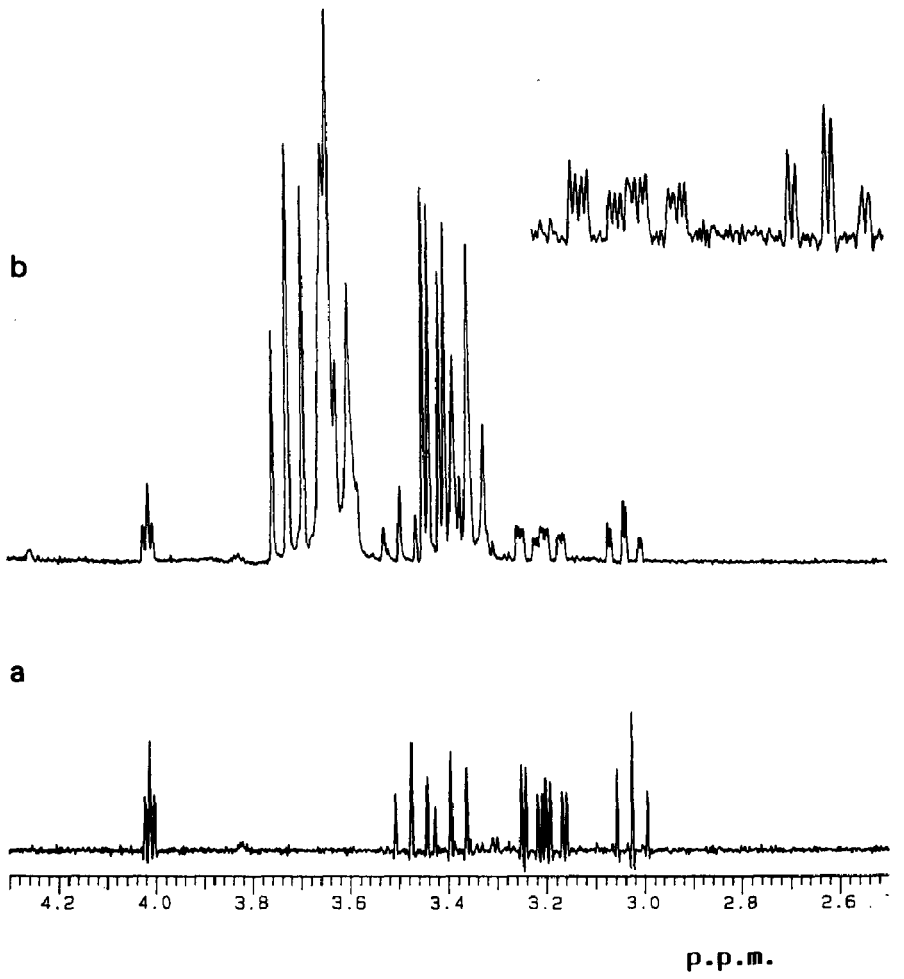

Fig. 1. Partial ^{1}H-n.m.r. spectra (D_2O, 300 MHz) of (*a*) 1-*O*-benzyl-DL-*myo*-inositol (**1**) and (*b*) **1** in the presence of 1 equiv. of βCD.

TABLE I

Chemical shifts (δ) of the ^{1}H resonances of **1** and **2** in the absence and presence of αCD and βCD

Atom	**1**	**2**	**1** + *βCD*	**2** + *αCD*
H-1	3.180	3.133	3.179/3.182[a]	3.120
H-2	4.013	4.018	4.012	4.004
H-3	3.230	3.258	3.232/3.235[a]	3.260
H-4	3.394	3.391	N.d.	N.d.
H-5	3.026	3.044	3.033/3.039[a]	3.041/3.044[a]
H-6	3.475	3.443	3.494	3.445/3.449[a]
OCH_{2a}	4.525	3.986	4.546	4.009
OCH_{2b}	4.405	3.860	4.428	3.900/3.904[a]
OCH_2CH	–	5.753	–	5.765

[a] Split signals. [b] Not determined.

TABLE II

Chemical shifts (δ) of the ^{1}H resonances of αCD and βCD in the absence and presence of **1** and **2**

Atom	*βCD*	*βCD* + **1**	*αCD*	*αCD* + **2**
H-1	4.846	4.841	4.824	4.809
H-2	3.425	4.423	3.402	3.390
H-3	3.731	3.711	3.753	3.726
H-4	3.357	3.354	3.350	3.339
H-5	3.612	3.582	N.d[a]	N.d.[a]
H6a,6b	3.650–3.625	3.640	3.651–3.590	N.d.[a]

[a] Not determined.

upper-field region (inset in Fig. 1) could be used to determine the optical purity of these inositol derivatives. 1D-NOE and 2D-NOESY experiments showed cross-relaxation between the aromatic protons of **1** and H-3, and, to a lesser extent, H-5 of βCD, supporting also the formation of the inclusion compound.

No complex formation could be detected, between **1** and αCD. However, for **2** + αCD, the signal for H-3 of αCD was shifted upfield (0.027 p.p.m.) and those for H-5,6 and the allylic protons of **2** were split ($\Delta\delta$ 0.003, 0.004, and 0.004 p.p.m., respectively), indicating the formation of diastereomeric complexes (Fig. 2). No complex formation of **2** with βCD, and **1** or **2** with γCD (cyclomalto-octaose), could be observed and the same results were obtained when methylated βCD was used. Thus, the structural requirements for the formation of complexes appear to be specific. Hydrogen bonding, besides hydrophobic interactions, could be responsible for the observed complexations. Attempts to substantiate this hypothesis, using methyl sulfoxide-d_6 instead of D_2O, were not successful, as complex formation did not occur in this solvent. The influence of the solvent on the complexation behaviour of CDs has been reported[7].

^{13}C-N.m.r. spectroscopy was less valuable for detecting the formation of the

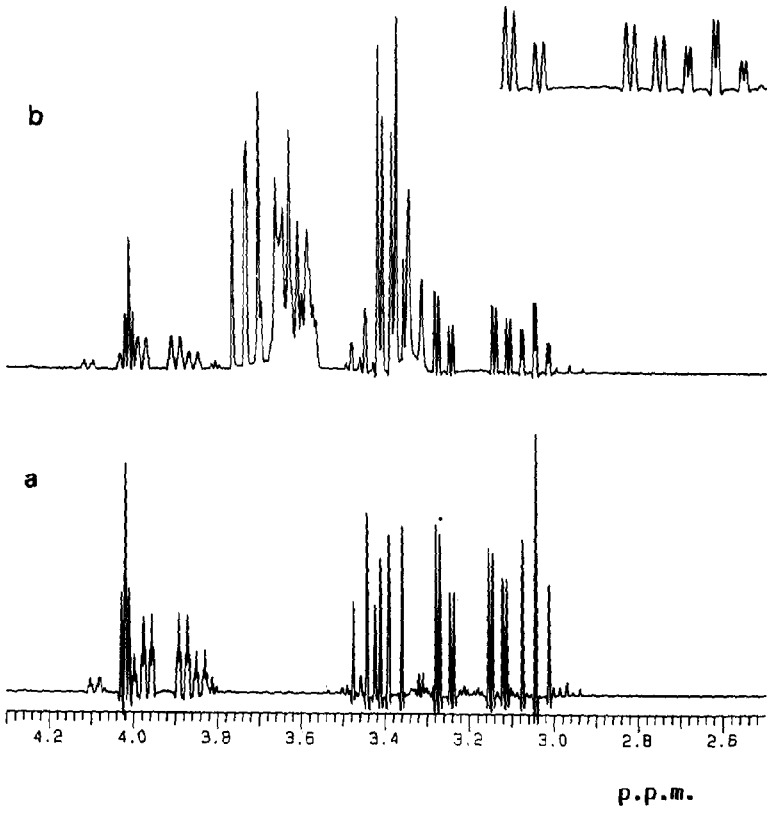

Fig. 2. Partial ^{1}H-n.m.r. spectra (D_2O, 300 MHz) of (*a*) 1-*O*-allyl-DL-*myo*-inositol (**2**) and (*b*) **2** in the presence of 1 equiv. of αCD.

diastereomeric complexes. Only changes up to 0.1 p.p.m. were observed for the ^{13}C resonances of the (βCD + **1**) and (αCD + **2**) complexes, and only the resonances of the guest in the latter complex showed splitting.

On the basis of $\Delta\delta$ observed for the resonance of H-3 of βCD on the addition of increasing amounts of **1** or for that of the lowest-field benzylic proton of **1** on addition of βCD, the binding constants for the 1:1 complex could be estimated[8] from double reciprocal plots of $1/\Delta\delta$ against 1/[L] (K_a 88 ±14 or 58 ±15 M^{-1}, respectively).

Diastereomeric complexes were also formed when 1-*O*-*p*-methoxybenzoyl-DL-*myo*-inositol (**3**) was treated with 1 equiv. of βCD; thus splitting of the signals for H-1,2,5 and the aromatic protons ($\Delta\delta$ 0.051 p.p.m.) was also observed.

EXPERIMENTAL

^{1}H-N.m.r. spectra (300 MHz) were obtained with a Varian XL-300 spectrometer at 30° (external acetone, 2.0 p.p.m.). The resonances of the inositol protons were assigned by COSY experiments, using 128 t_1 experiments and a relaxation delay of 1 s. N.O.e. effects were measured using a differential technique. A pre-irradiation time of 7 s was used with a decoupler intensity of ~30 Hz and an observation pulse of 90°. NOESY experiments were carried out using the phase-sensitive mode, with 256 t_1 increments and two different mixing times of 500 and 750 ms. A relaxation delay of 2 s was used. ^{13}C-N.m.r. spectra (50 MHz) were recorded with a Bruker AM-200 spectrometer. A line broadening of 0.5 Hz was used in order to increase the signal-to-noise ratio.

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