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^{1}H NMR Spectroscopy as a Probe of Intermolecular Interactions in β-Cyclodextrin Inclusion Compounds

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Abstract. ^{1}H NMR spectroscopy was used to probe the formation of inclusion compounds of permethylated and peracetylated β-cyclodextrins as host molecules and a variety of electronically very different guest molecules. Complexation, obtained only in water, was estimated quantitatively by means of chemical shift/concentration curves of relevant protons, and the intermolecular forces involved are criticially discussed.

Key words. β-cyclodextrins, inclusion compounds, intermolecular interaction, ^{1}H/^{13}C NMR, Hildebrand–Benesi equation.

1. Introduction

The reason why cyclodextrins (CDs) are of continuing scientific interest is their ability to form inclusion complexes (to act as a host) with many, often structurally very different molecules (guests), which are able to enter the CD cavity [1–6]. The nature of the host/guest intermolecular interactions is of particular interest. The aim of this paper is to study these interactions, which are preconditional for the formation of inclusion compounds, in the cases of β-CD, heptakis(2,3,6-tri-*O*-methyl)-β-CD (β-TMCD), and heptakis(2,3,5-tri-*O*-acetyl)-β-CD (β-TACD) as hosts and a variety of aromatic and heteroaromatic compounds as guest molecules in different polar solvents.

2. Experimental

2.1. SYNTHESES

β-CD was commercially available [7]. From it β-TACD was obtained by acetylation with acetic anhydride in dry pyridine [8]. The NMR data are in agreement with data already reported [9]. To prepare β-TMCD, β-CD was methylated at 40°C in the presence of NaH [10], or Ag_2O [11], but with no success. The methylation reaction succeeded only at low temperature in the presence of NaH [12] and methyliodide. The NMR data are the same as described previously [5, 12–14], except for the assignment problems described below.

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Table I. ^1H and ^{13}C NMR spectral data of β-TMCD in D_2O.

^1H chemical shifts		^{13}C chemical shifts	
(ppm)*	Atom No.	(ppm)	Atom No.
4.53(d)	1	97.4	1
3.12(m)	5,6	81.2	3
3.05(t)	4	80.3	2
3.00(t)	3	77.4	4
2.95(d)	6	71.0	6
2.90(s)	3-OMe	70.7	5
2.78(s)	2-OMe	60.0	3-OMe
2.66(s)	6-OMe	58.6	6-OMe
2.62(d)	2	58.3	2-OMe

[a] Multiplicity in brackets: s singlet, d doublet, dd double doublet, t triplet, m multiplet.

2.2. NMR SPECTRA

Different assignments of the ^{13}C NMR spectra of β-TMCD in D_2O have been published [12, 13]. By means of an H,C-correlated 2D-NMR spectrum, the APT (C(6)H_2 group) and a special H,C-correlated 2D-NMR spectrum with zero-quantum detection [15, 16], the correct assignment has been obtained (see Table I). ^1H assignments are in agreement with those reported [5, 14].

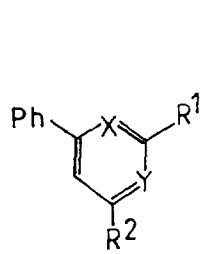
In order to study inclusion phenomena, the following procedure was used: the compounds (**1–12**) were dissolved in 0.5 ml of the solvent (D_2O, CD_3OD, CD_3CN, $(CD_3)_2CO$, $CDCl_3$), the ^1H NMR spectra were recorded at 80.13 MHz using a Bruker AC-80 NMR spectrometer and the chemical shifts determined relative to internal tetramethylsilane or 3-(trimethylsilyl)-propanesulfonic acid sodium salt (the latter in water only). The concentration of the guest compounds was generally 0.01 M. β-CD, β-TACD and β-TMCD, respectively, were added to these solutions in concentrations from 0 up to 0.06 mol/l giving host/guest ratios in the range 0–6.

3. Results

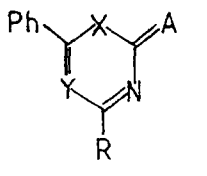
^1H NMR spectroscopy, which has proved to be very useful in the study of inclusion phenomena [1–6, 17], has been used to probe the intermolecular interactions which are required for the formation of the β-CD, β-TMCD, and β-TACD inclusion complexes. For this, the chemical shifts of the protons of the host molecules and various guest molecules **1–12** (see Scheme 1) have been measured at various host/guest molar ratios in the different organic solvents CD_3OD, CD_3CN, $(CD_3)_2CO$, $CDCl_3$ and in D_2O. The following points are notable:

(i) In the case of β-TACD and β-TMCD as host molecules and **1–10** as guest molecules in solvents other than D_2O, the ^1H chemical shift changes observed are equal to zero.

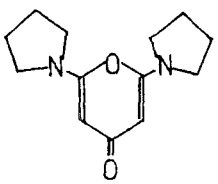
(ii) If D_2O is the solvent used, chemical shift changes of both the host as well as the guest protons have been obtained for β-TMCD and guests **1–10**; however, the solubility of **1–10** in water is too low to obtain quantitative data. Because



	X	Y	R^1	R^2	
1	$O^{\oplus}$	CH	-N⬡	-N⬡	$ClO_4^{\ominus}$
2	$O^{\oplus}$	CH	$-NMe_2$	$-NMe_2$	$ClO_4^{\ominus}$
3	$O^{\oplus}$	N	$-NMe_2$	$-NMe_2$	$ClO_4^{\ominus}$
4	N	$S^{\oplus}$	-N⬡O	-H	$ClO_4^{\ominus}$



	X	Y	A	R
5	O	N	S	-N⬡
6	S	N	O	-N⬡
7	O	N	S	$-NMe_2$
8	O	CH	S	-N⬡
9	O	CH	O	-N⬡



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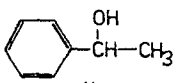

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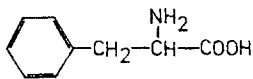

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Scheme 1. Chemical structure of guest molecules used for complexation with cyclodextrins in D_2O and common solvents, respectively.

of the low solubility of β-TACD in D_2O, experiments with this host molecule were not performed.

(iii) For DL-1-phenylethanol, **11**, and DL-phenylalanine, **12**, which have been used as model compounds, remarkable chemical shift variations have been obtained in D_2O but not in CD_3OD and other solvents – see Figures 1 and 2; due to the low operating frequency of only 80 MHz, no splitting of the racemic mixture in the chiral β-CD cavity was observed.

For the estimation of the association/dissociation constants of the β-CD and β-TMCD inclusion complexes with **11** and **12**, a Hildebrand–Benesi equation was used, modified for NMR applications [18] – see Figures 1 and 2. From the shape of these curves, molar ratios of 1:1 for the complexes were assumed.

Therefore, ^1H chemical shift changes of **11** and **12**, respectively, at different host concentrations were used to obtain association constants and, inversely, the validity of the latter values were tested by calculating theoretical ^1H chemical shift changes from the association constants and the actual concentrations; the error obtained was ± 0.002 ppm.

The association constants, K_{ASS}, obtained by the method described, are given in Table II.

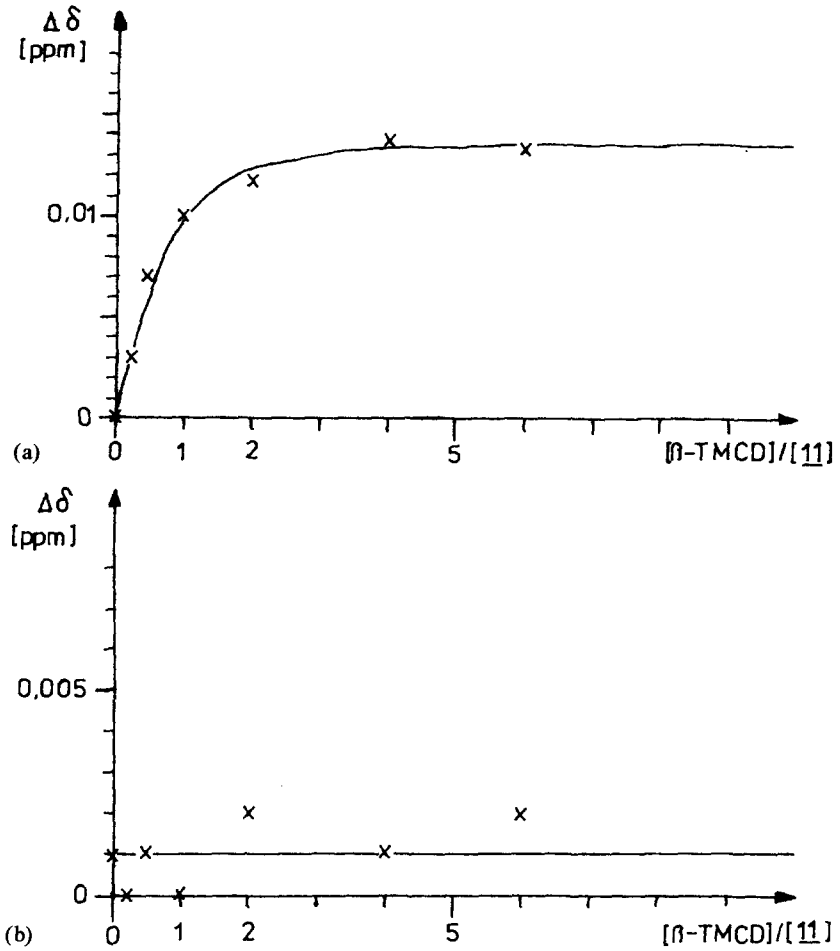

Fig. 1. Plot of ^1H chemical shift changes of the aromatic protons of **11** on complexation with β-TMCD (a) in D_2O, and (b) in CD_3OD vs the host/guest molar ratios; × experimental values, solid lines are the fitted Hildebrand–Benesi equations.

Table II. Calculated association constants for complexes of **11** and **12** with various cyclodextrins

Host	Guest	Solvent	$K_{ASS}(M^{-1})$
β-TMCD	**11**	D_2O	392
		CD_3OD	0.00001
β-TMCD	**12**	D_2O	13.6
		CD_3OD	0
β-CD	**12**	D_2O	131

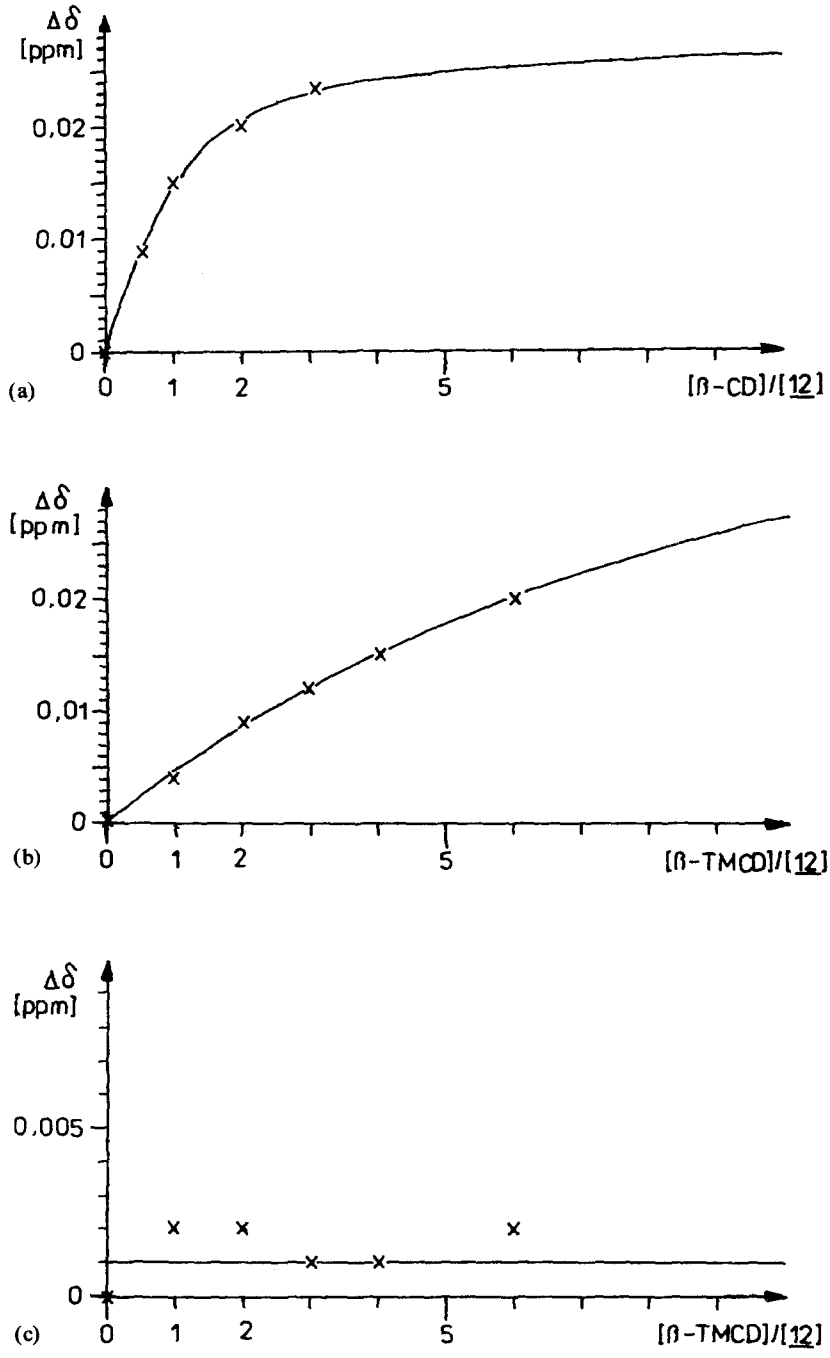

Fig. 2. Plot of ^1H chemical shift changes of the aromatic protons of **12** on complexation (a) with β-CD in D_2O, (b) with β-TMCD in D_2O, and (c) with β-TMCD in CD_3OD *vs* the host/guest molar ratios; × experimental values, solid lines are the fitted Hildebrand–Benesi equations.

4. Discussion

The aim of probing the intermolecular interactions within the hydrophobic cavity of inclusion compounds of β-TACD and β-TMCD (readily soluble in the usual organic solvents) in solvents other than water using guest molecules of very different electronic structure (charged (**1–4**), strongly dipolar (**5–10**), and neutral (**11–12**)) was not achieved due to the absence of complexation. Actually, complexation was obtained only in water and even there the guests **1–10** are not very useful due to their very low solubility. Therefore, polar effects are of negligible influence on the intermolecular interactions between the host and guest. Also **11** and **12** are not included into the β-CD cavity in solvents less polar than water, corroborating the dominating role of the latter solvent in the formation of inclusion compounds. Possible reasons for this are:

(i) Less polar solvents are already firmly fixed within the β-CD cavity, thus preventing the entry of potential guest molecules.
(ii) Host/guest hydrophobic interactions. The driving force for the formation of β-CD inclusion compounds is then the potential energy gain for the system if water, situated within the hydrophobic cavity of β-CD compounds, is replaced by new (for this purpose more useful) guest molecules. Another and alternative driving force is the unfavored interaction between the apolar guest and polar water molecules.
(iii) Finally, hydrogen bonds between host and guest may be useful in the formation of stable inclusion complexes.

In D_2O, the inclusion complex stability of **12** and β-CD ($K_{ASS} = 131\ M^{-1}$) is much greater than for **12** and β-TMCD ($K_{ASS} = 13.6\ M^{-1}$). This implies that permethylation decreases the complex stability of β-CD compounds as already observed for the α-TMCD analogues [5]. One explanation for this is that the hydrogen bonds formed between the CO group of **12** and the secondary OH groups of β-CD are no longer possible in β-TMCD. Additionally, the interactions between the CO group of **12** and the OMe groups of β-TMCD are now repulsive.

The corresponding hydrogen bond between the OH group of **11** as a potential guest molecule and the OMe groups of β-TMCD is still achievable. Accordingly, the association constant for this complex is, as expected, relatively large ($K_{ASS} = 392\ M^{-1}$).

5. Conclusions

The investigation of the ability of β-TMCD to form inclusion compounds was only possible in D_2O. For the common organic solvents, the energy gain in forming inclusion compounds with guests of very different electronic structure in the β-TMCD and the β-TACD cavity, respectively, could not be obtained. ^1H chemical shift variations could be used to follow and probe the inclusion process. The complexation curves can be used to calculate the association constants via a modified Hildebrand–Benesi equation.

The driving forces for the formation of inclusion compounds are probably hydrophobic interactions (the gain in potential energy of the system if the water

molecules within the β-CD or β-TMCD cavities are replaced by potential guest molecules) and in some cases hydrogen bonds.

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