^{1}H NMR STUDY ON THE INCLUSION OF BICYCLO[3.3.1]NONANES IN CYCLODEXTRINS

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ABSTRACT

α- and ß-cyclodextrins were found to form 1:1 inclusion complexes with 2,6- and 2,9-substituted bicyclo[3.3.1]nonanes. The binding constants and the structure of the complexes were estimated from titration studies and 2D ROESY experiments.

1. INTRODUCTION

The relatively hydrophobic cavities of the doughnut-shaped cyclodextrins (CDs) are known for their ability to bind organic molecules in solution and in the crystalline state. The shape and the internal diameter of the CDs cavity and the size of the guest molecules, i.e. the close match is of primary importance for the complex formation and this may provide useful tools in molecular recognition, substrate-receptor interactions, etc. The interaction of CDs with a number of organic structures has been studied in recent years [1] and among the organic compounds exhibiting the strongest binding to the CDs are substituted adamantanes [2]. The investigation on the interaction of CDs with bicyclo[3.3.1]nonanes which are conformationally flexible structures and have one carbon atom less than adamantane was carried out seeking to gain insight into the bicyclononanes-CDs complex formation and structure.

2. MATERIALS AND METHODS

2.1. Materials

α- and β-Cyclodextrins (Aldrich) were used as received and freeze dried before use. Literature methods were used to prepare bicyclo[3.3.1]nonane-2,6-dione (**1**), endo,endo-bicyclo[3.3.1]nonane-2,6-diol (**2**) and endo-2-anti-9-bicyclo[3.3.1]nonanediol (**4**) [3,4]. Monoacetate **3** was prepared by acetylation of **2** with an equimolar amount of acetic anhydride.

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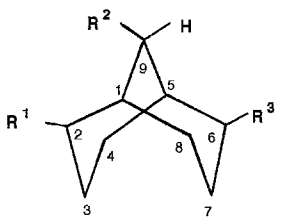
2.2. **Proton NMR spectra**

^{1}H NMR spectra were recorded at 303K on a Bruker AMX500 spectrometer equipped with Eurotherm controller for temperature regulation. The complexes were obtained and the titrations were performed by adding variable amounts of the substrates to a cyclodextrin solution in D_2O and *vice versa* at 33 ^oC. The concentration of substrates and the CDs varied between 1-5x10^{-3} M. The solutions were thoroughly mixed and allowed to equilibrate for several minutes in the probe before the spectrum was acquired. The inclusion stability constants K and the estimated associated errors were calculated from ^{1}H NMR titration data using a non-linear least squares fit of the data to a modified version of the Benessi-Hildebrand equation [5] within the program SigmaPlot (Jandel Sci.). For the ROESY spectra the standard pulse sequence was used.

3. RESULTS AND DISCUSSION

The complex formation is expected to induce shifts of the ^{1}H NMR resonances of the cyclodextrin protons, especially of H-3 and H-5, which are directed towards the interior of the cavity. The inclusion of guest bicyclo[3.3.1]nonane molecules **1-4** in the α- and ß-CD cavity in aqueous solution was supported by the changes in the ^{1}H NMR spectra of both partners. The occurrence of chemical shift changes without line broadening allows to characterize the interaction as being fast on the NMR time scale. Furthermore, the fact that significant chemical shift changes occur only for hydrogens on the inner surface (H-3 and H-5) of the CDs, and not for those on the outer surface (H-1, H-2, H-4) allows to establish unambiguously that these changes are the result of inclusion complex formation and not the result of non-specific interactions between both partners.



$R^1=R^3=-O, R^2=H$

$R^1=R^3=OH, R^2=H$

$R^1=OH, R^2=H, R^3=OCOCH_3$

$R^1=H, R^2=R^3=OH$

An addition of α-CD to the solution of dione **1** resulted in an upfield shift (0.064 ppm) for H-3 proton of the α-CD which is located in the wide opening of the truncated cone. Practically no induced shift was observed for the H-5 proton which is at the narrower side. Downfield shifts for the protons of the included dione **1** were observed (Table I). From these data it follows that substrate molecule does not penetrate deeply into the α-CD cavity. Because of the closer match of the ß-CD cavity size and the shape of bicyclo[3.3.1]nonane (both *ca.*7 Å), a stronger host-guest interaction was expected in this case. Significant chemical shift changes were

observed for the substrates **1-4** and ß-CD protons. The upfield shift of the H-5 was larger than of the H-3 proton in dione **1**, i.e. 0.12 and 0.064 ppm, respectively. This observation is consistent with a deeper insertion of the bicyclic framework in the ß-CD cavity than in α-CD cavity. The protons of the guest dione **1** showed also significant downfield shifts of 0.11-0.12 ppm (Table 1). The inclusion of the diol **2** has a larger effect on the H-3 shift than on H-5 shift of ß-CD (0.054 and 0.03 ppm, respectively) showing that presumably the penetration of diol **2** is less deep in the CD cavity compared to the insertion of dione **1**. The proton signals of the bicyclic framework display comparatively large shifts of >0.1 ppm. In the case of 2,9-diol **4** the resonances of the H-3 and H-5 of CD showed small induced shifts (0.045 and 0.01 ppm, respectively), however relatively large shifts were observed for the H_1 proton and some other protons of the bicyclic molecule (Table 1).

TABLE 1. ^{1}H NMR chemical shifts (ppm) displacements ($\Delta\delta_{lim}$) resulting from the inclusion of **1-4** in α- and ß-cyclodextrins and inclusion stability constantsK

	$\Delta\delta_{lim}$				
	Guest+host				
Nucleus	**1**+αCD	**1**+ßCD	**2**+ßCD	**3**+ßCD	**4**+ßCD
Guest					
H_1	0.05	0.12	0.21		0.21
H_4	0.05				0.12
H_9	0.02	0.11	0.105		
H_2				0.07	
H_6				0.08	
CDs					
H-3	-0.64	-0.064	-0.054	-0.07	-0.045
H-5	-0.01	-0.12	-0.03	-0.13	-0.01
K(M^{-1})	60±11	345±12	71±14	195±10	13.5±4

The molar ratios and the stability constants K for the inclusion complexes formed between bicyclononanes and the CDs were determined from ^{1}H NMR titrations. The limiting changes in the chemical shifts of the CD proton resonances upon inclusion of the guest were determined by a titration of CDs with an excess of substrates and *vice versa*. To determine the stoichiometry of the CD-substrate complexes we have plotted the induced shift Δδ values for the ß-CD and bicyclic structures as a function of guest to host molar ratio (R). The changes of Δδ are observed until the value of R=1 for protons of CDs and of substrates when adding the CD to the solution of **1-4**. The variation of the ^{1}H chemical shifts over the range of R values considered is consistent with the formation of a 1:1 inclusion complex. The Δδ data were used to estimate K for the substrate-CD adducts. In the absence of any information about the activity coefficients, only an apparent association constant can be determined [5b] (Table 1).

The inclusion of the guest molecules were further studied by 2D ROESY spectroscopy. No intermolecular NOE's could be detected in 2D NOESY spectra recorded with various mixing times, while intramolecular NOE's were weak and positive and weak and negative for the guest and host molecules, respectively. The observation of weak negative NOE's for CD is mainly the result of the high ß-CD concentration and the degeneracy of the glucopyranose resonances. Therefore, 2D rotating frame NOE spectroscopy was used as ROE is always positive irrespective of τ_C. In the case of the dione **1** the intramolecular cross peaks within the substrate molecule and intermolecular cross peaks with the H-3 and H-5 protons of the CD are observed. The intermolecular NOE's are found between H-3 and $H_{1(5)}$ as well as between H-3 and $H_{9syn(anti)}$. The same NOE's although weaker are found to occur with H-5 of the ß-CD. Thus the protons at carbon atoms 1(5) and 9 are closer to H-3 than they are to H-5. In the case of **2** essentially all ß-CD protons display intermolecular NOE's of more or less equal intensity with the most of the 2,6-diol resonances. Although the ROESY spectra support the formation of inclusion complexes and allow delineate the location of the guest molecules in the host, the pseudo C_7 symmetric cavity of the ß-CD as well as the C_2 symmetry of the guest molecules **1** and **2** does not allow a more quantitative elaboration of the intermolecular distances and lead to the only conclusion that the guest molecules enter into the ß-CD cavity from the large hole to give a symmetrical location of the guest molecule.

4. CONCLUSION

An inclusion complex formation between bicyclo[3.3.1]nonanes and cyclodextrins has been demonstrated on the basis of the ^{1}H NMR titration experiments. The structure and the binding constants of the complexes have been estimated and the insertion into the cavity relative to one another have been discussed on the basis of chemical shift arguments and the observation of intermolecular NOE's.

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