Pergamon

Tetrahedron Letters, Vol. 35, No. 46, pp. 8661-8664, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01834-0

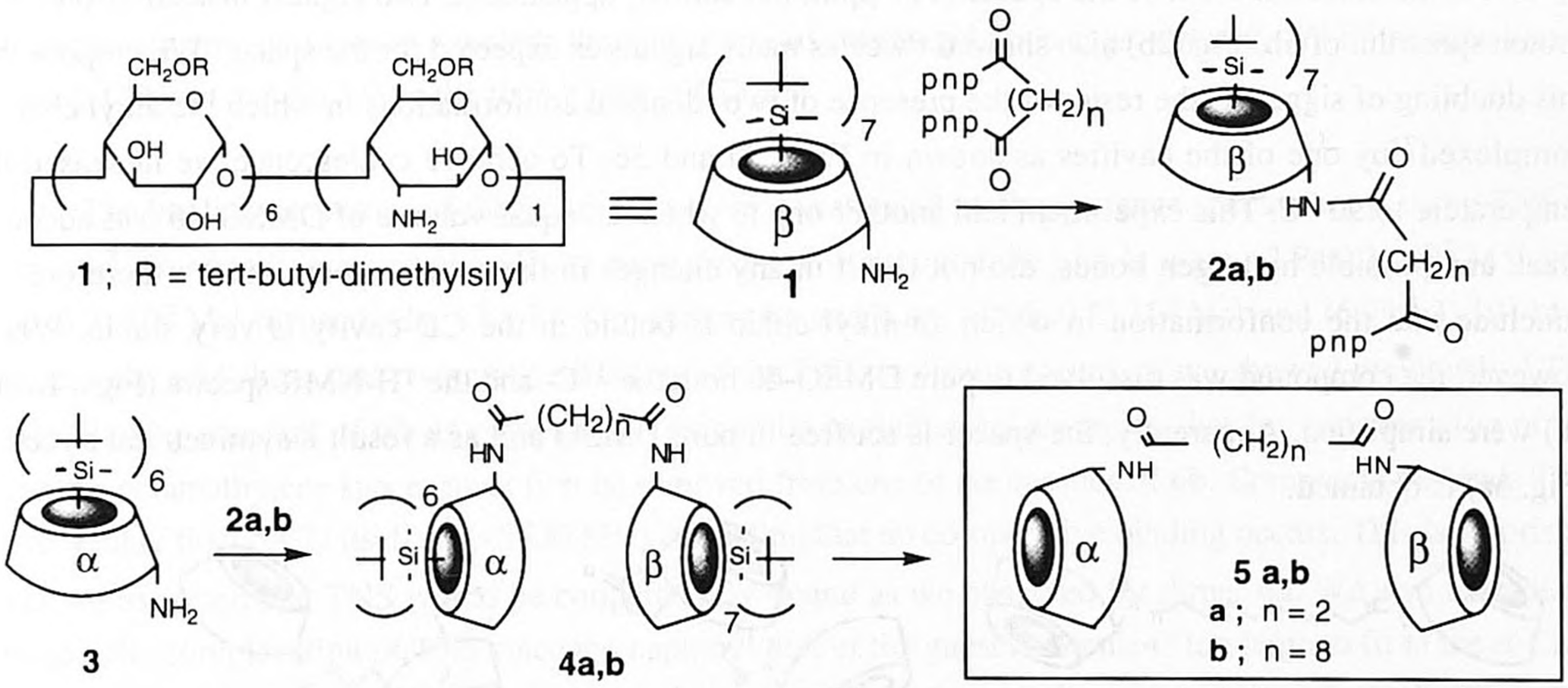
Synthesis and Conformational Behaviour of Novel Cyclodextrin Hetero-Dimers

Fokke Venema, Chantal M. Baselier, Martinus C. Feiters, and Roeland J.M. Nolte*

Department of Organic Chemistry, NSR-Center, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

Abstract: *The synthesis of two novel cyclodextrin heterodimers derived from α- and β-cyclodextrin is reported. The cyclodextrin molecules are linked via alkyl spacers on their secondary sides. NMR-studies indicate that the spacer is bound in one of the two cavities of the dimer, which results in lower affinities for guest molecules.*

We are interested in the synthesis of cyclodextrin (CD)-dimers[1] for catalytic purposes, in particular, dimers capable of binding substrates in a site-specific way, which can lead to regioselective or enantioselective reactions. Recently the first example of site-specific binding by a CD hetero-dimer was reported.[2] This dimer consists of an α-CD which is covalently linked to a β-CD, both via their primary sides. In this paper we describe the synthesis of two novel CD hetero-dimers, as well as the conformational behaviour and the binding properties of these compounds.



Cyclodextrins **2a** and **b** which are appended by an active ester were obtained by reaction of the previously reported[3] 3-amino-3-deoxy-heptakis(6-O-*tert*-butyldimethylsilyl)-β-cyclodextrin **1** with a tenfold excess of the 4-nitrophenyl (pnp)-ester of the appropriate dicarboxylic acid in refluxing THF. Purification by column chromatography yielded **2a** and **b** in 51 % and 63 % yield, respectively.[4] These compounds were

treated in refluxing THF with the mono-functionalised α-CD **3**[5] yielding the corresponding dimers **4a** (61 %) and **4b** (80 %). Desilylation of these products was achieved with tetrabutylammonium fluoride in refluxing THF (15 hrs). After work-up the compounds were dissolved in a small volume of water and precipitated by addition of acetone. Repeating this precipitation twice afforded compounds **5a** and **5b** in 50 and 71 % yield, respectively. Their structures were confirmed by FAB-MS, ^{1}H- and ^{13}C-NMR spectra.[6]

The conformation of dimer **5b** was studied by NMR. For comparison we also studied the previously reported[3] symmetrical dimer **6b** whose NMR-spectra in DMSO-d6 (Fig. 1a) and in D_2O (Fig. 1b) will be discussed first. In the ^{13}C-NMR spectrum of compound **6b** in D_2O eight distinct signals for the octamethylene

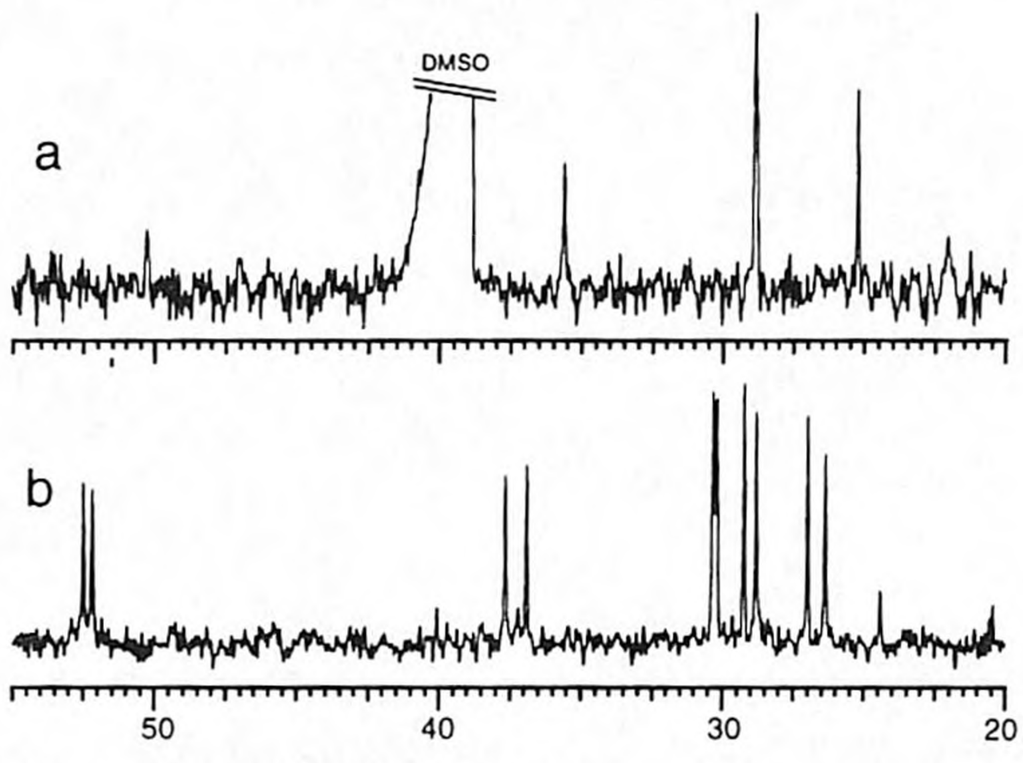


Fig 1: ^{13}C-NMR of **6b** in DMSO-d6 (a) and in D_2O (b)

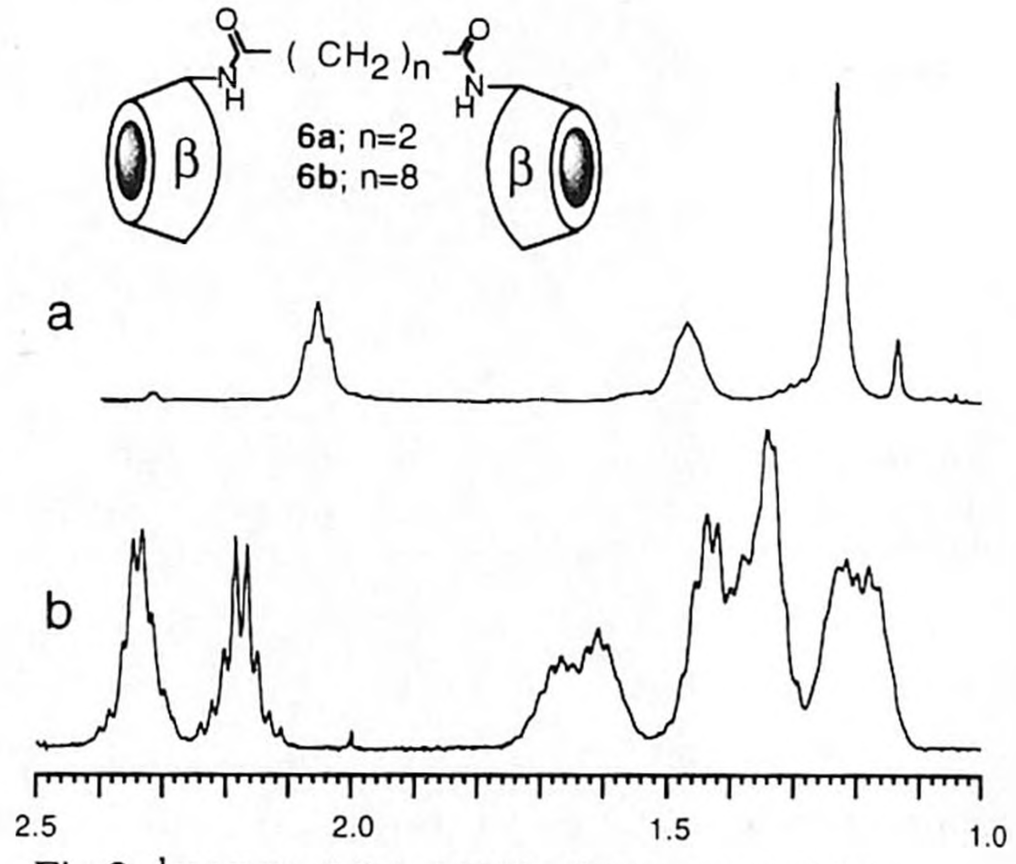


Fig 2: ^{1}H-NMR of **6b** in DMSO-d6 (a) and in D_2O (b)

spacer were observed in the region of 20-40 ppm (see Fig. 1b). Because the molecule is symmetrical (Fig. 3a) only four signals were expected. Also the CD-carbon atom (C-3', next to the amide bond), which resonates at 52 ppm, and the carbonyl atom of the spacer (177 ppm, not shown) appeared as two signals instead of one. The proton spectrum of **6b** (Fig. 2b) also showed twice as many signals as expected for the spacer. We propose that this doubling of signals is the result of the presence of two identical conformations in which the alkyl chain is complexed[7] by one of the cavities as shown in Figs. 3b and 3c. To achieve coalescence we increased the temperature to 90 ^{0}C. This experiment and another one in which an equal volume of DMSO-d6 was added to break any possible hydrogen bonds, did not result in any changes in the proton spectrum. We therefore can conclude that the conformation in which an alkyl chain is bound in the CD-cavity is very stable. When, however, the compound was dissolved in pure DMSO-d6 both the ^{13}C- and the ^{1}H-NMR spectra (Figs. 1a and 2a) were simplified. Apparently, the spacer is set free in pure DMSO and as a result a symmetrical structure (Fig. 3a) is obtained.

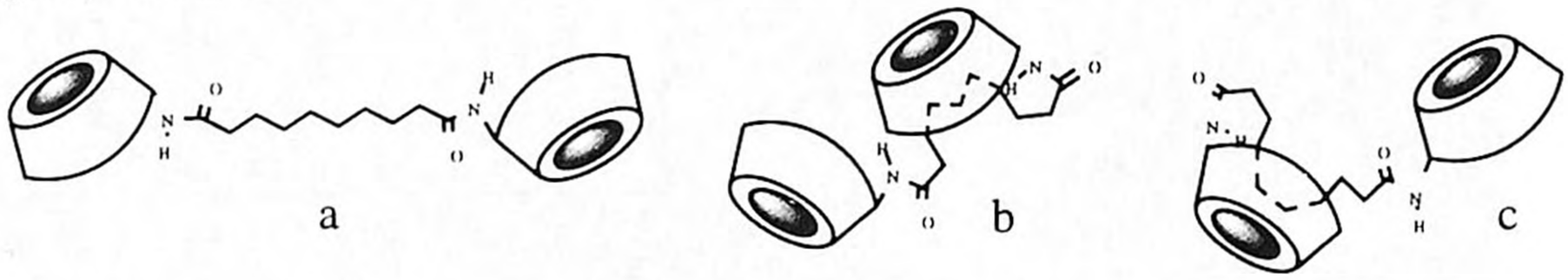


Figure 3: Possible conformations of cyclodextrin dimers in solution.

The ^{13}C-NMR spectrum of the asymmetrical CD-hetero-dimer **5b** in D_2O appeared to be more complex than the spectrum in DMSO-d6 (see Figs. 4a and 4b). In the region of 20-40 ppm sixteen signals for the

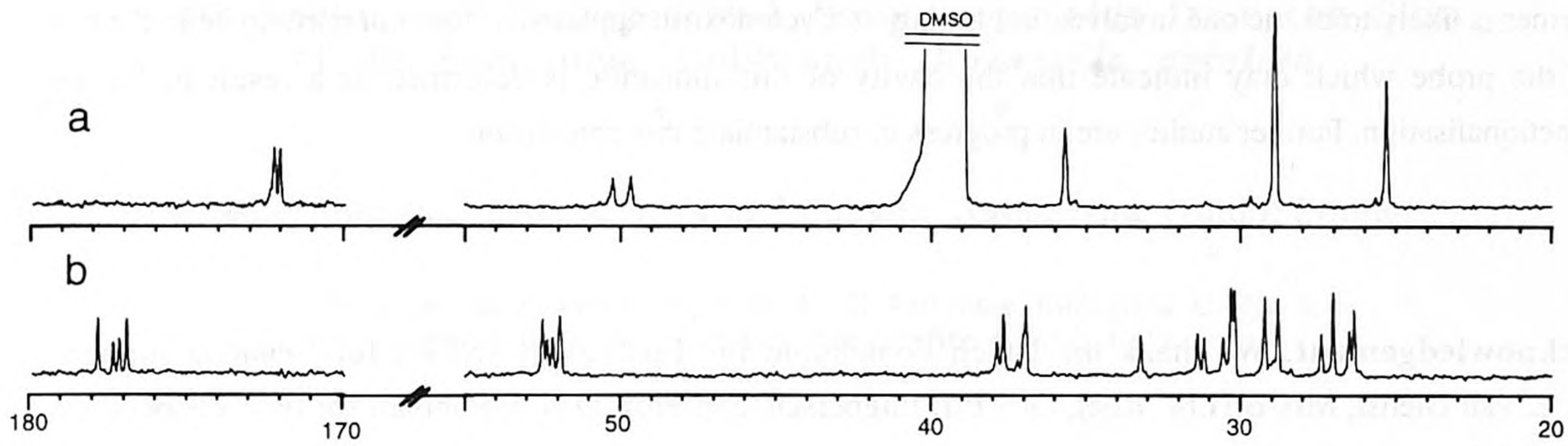


Fig 4: ^{13}C-NMR of **5b** in DMSO-d6 (a) and in D_2O (b)

octamethylene spacer were visible. In addition, four signals were observed for the carbon atoms at C-3' and for the carbonyl carbon atoms in the spacer (Fig. 4b). This multitude of signals can be explained by assuming that the spacer is bound in one of the two CD-cavities resulting in two conformations (see Fig. 3b and 3c) that do not exchange on the NMR time-scale. Since the dimer is asymmetrical the two conformations are no longer equivalent, resulting in a doubling of the signals observed for compound **6b**. The ^{13}C-NMR spectrum of **5b** in DMSO-d6 (Fig. 4a) is simple as it was in the case of **6b** and in accordance with the structure shown in Fig. 3a. The two signals that remain for both the carbon at C-3' and for the carbonyl atoms of the spacer are the result of the asymmetry in the heterodimer. All corresponding signals in the ^{13}C-NMR spectrum in D_2O appear in the same ratio, viz. 2:1, supporting the presence of two conformers. The fact that this ratio is the same for all pairs of signals indicates that relaxation-effects can be ignored. The carbonyl signals at 176.9 and 177.8 ppm in the ^{13}C-spectrum of **5b** in D_2O resonate at exactly the same frequency as the carbonyl signals of compound **6b** in D_2O. We therefore ascribe these signals to the conformation in which the alkyl chain is bound in the β-CD unit. Given this assignment we may conclude that the spacer of compound **5b** is approximately 2/3 of the time bound by the β-CD unit and for 1/3 of the time by the α-CD unit.

The binding properties of the CD dimers were investigated by fluorescence spectroscopy, using TNS as a probe.[8] The binding constants (K_b's) measured for compound **5a** and **b** were $(2.8\pm0.3).10^3\ M^{-1}$ and $(0.6\pm0.2).10^3\ M^{-1}$,respectively. The K_b's for dimers **6a** and **b** are $(10.5\pm0.2).10^3\ M^{-1}$ and $(6.7\pm0.3).10^3\ M^{-1}$, respectively, and show that cooperative binding of the TNS molecule occurs, as we showed previously.[3] The lower binding constant of **6b** as compared to **6a** can be explained by assuming that for complexation of the guest the octamethylene spacer must first be removed from one of the cavities of **6b**. Compound **5a** binds TNS more weakly than β-CD itself (K_b=3500 M^{-1}) indicating that no co-operative binding occurs. This is surprising since we expected that TNS would be cooperatively bound as we observed for dimer **6a.** We also expected a site-specific complexation of TNS since the naphthyl unit of the guest molecule is too large to fit in the α-CD.[9] The very low binding of TNS by dimer **5b** suggests that the alkyl spacer is strongly bound in the β-CD part of the molecule and is not easily removed by the guest. The emission maximum (λ_{max}) of TNS provides information on the extent of shielding of the TNS molecule from the water environment. In the case of **6a** and **b**

the λ_{max}-values (440 and 436 nm respectively) are similar to the values reported[10] for a 2:1 complex between β-CD and TNS. The values found for **5a** and **b** (for both dimers 453 nm) indicate that only one CD unit is involved in the complexation of the probe. Since the larger β-CD is a better host for TNS than α-CD , the former is likely to be the one involved in binding. α-Cyclodextrin apparently does not participate in the binding of the probe which may indicate that the cavity of this molecule is deformed as a result of the mono-functionalisation. Further studies are in progress to substantiate this conclusion.

Acknowledgement: We thank the Dutch Foundation for Technology (STW) for financial support and Dr E. van Dienst, Mrs B.H.M. Ruël, Dr J.F.J. Engbersen, and Prof. D.N. Reinhoudt for their cooperation and helpful discussions.

References and Notes:

1. For other CD dimers see for example: a) Tabushi, I.; Kuroda,Y.; Shimokawa, K., J. Am. Chem. Soc. **1979**, 101, 1614. b) Harada, A.; Furue, M.; Nozakura, S.I., Polymer J. **1980**, 12, 29. c) Fujita, K.; Ejima, S.; Imoto, T., J. Chem. Soc. Chem. Commun. **1984**, 1277. d) Fujita, K.; Ejima, S.; Imoto, T., Chem. Lett. **1985**, 11. e) Breslow, R.; Greenspoon, N.; Guo, T.; Zarzycki, R., J. Am. Chem. Soc. **1989**, 111, 8296. f) Coates, J.H.; Easton, G.J.; van Eyk, S.J.; Lincoln, S.F.; May, B.L.; Whalland, C.B.; Williams, M.L., J. Chem. Soc. Perkin Trans. **1990**, 1, 2619. g) Breslow, R.; Chung, S., J. Am. Chem. Soc. **1990**, 112, 9659. h) Breslow, R.; Zhang, B., J. Am. Chem. Soc. **1992**, 114, 5882. i) Breslow, R.; Zhang, B., J. Am. Chem. Soc. **1993**, 115, 9353. j) Deschenaux, R.; Greppi, A.; Ruch, T.; Kriemler, H.-P.; Raschdorf, F.; Ziessel, R., Tetrahedron Lett. **1994**, 35, 14, 2165.
2. Wang, Y.; Ueno, A.; Toda, F., Chem. Lett. **1994**, 167.
3. Venema, F.; Baselier, C.M.; van Dienst, E.; Ruël, B.H.M.; Feiters, M.C.; Engbersen, J.F.J.; Reinhoudt, D.N.; Nolte, R.J.M., Tetrahedron Lett. **1994**, 35, 11, 1773.
4. Purification of all the silylated compounds was achieved by flash chromatography on silicagel (particle size < 0.063 nm) with the following eluent systems : ethyl acetate-ethanol-water, 50:2:1 v/v, for compounds **2** and **4**, and ethyl acetate-ethanol-water, 25:2:1 v/v, followed by 16:2:1 v/v, for compounds **1** and **3**. Compound **2a** decomposed during purification. This might be due to a self catalysed hydrolysis of the active ester or to an acyl transfer to one of the secondary hydroxyl groups. See Tee, O.S.; Mazza, C.; Du, X.-X., J. Org. Chem. **1990**, 55, 3603.
5. 3-Amino-3-deoxy-hexakis(6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin **3** was synthesised in the same way as reported[3] for compound **1**, the only difference being the solvent used for silylating the α-CD: DMF/pyridine, 10/1, v/v instead of pyridine.
6. **5a** ^{1}H-NMR (D_2O) δ : 5.08-4.88 (5 x m, 13H), 4.17-4.13 (m,4H), 3.93-3.77 and 3.64-3.52 (2 x m, 74H), 2.56 (m, 4H). ^{13}C-NMR (D_2O) δ : 176.1, 105.5,105.0,103.2-101.6, 82.8-81.2, 79.7, 77.3, 74.4-72.4, 71.4, 71.1, 62.0-60.9, 59.4, 52.2, 52.0, 32.3. FAB-MS (glycerol): 2189 (M+1).
5b ^{1}H-NMR (DMSO-d6) δ : 4.90-4.57 (5 x m, 13H), 4.02 (m, 2H), 3.91 (m, 2H), 3.76-3.52 and 3.46-3.25 (2 x m, 74H), 2.06 (t, 4H), 1.48 (m, 4H), 1.24 (m, 8H). ^{13}C-NMR: see figures in text FAB-MS (glycerol): 2272 (M+1).
7. The complexation of alkyl chains by cyclodextrins is known to be an energetically favourable proces. See: Tee, O.S.; Gadosy, T.A.; Giorgi, J.B., J. Chem. Soc. Perkin Trans. **1993**, 2, 1705.
8. Fluorescence experiments using 6-(p-toluidino)-2-naphthalenesulfonic acid (TNS) were performed in a 0.1 M phosphate buffer (pH=7.0) at 25 ^{0}C. The fluorescence enhancement of TNS (1.10^{-5} M^{-1}) on addition of various amounts of CD-dimer (up to 5.10^{-4} M^{-1}) was followed at the emission maximum (453 nm). From these data the binding constants were determined as described previously.[3]
9. Kondo, H.; Nakatani, H.; Hiromi, K., J. Biochem. **1976**, 79, 393.
10. Harada, A.; Furue, M.; Nozakura, S.I., Macromolecules **1977**, 10, 676. See also ref. 1b.

(*Received in UK* 3 *August* 1994; *revised* 8 *September* 1994; *accepted* 16 *September* 1994)