Pergamon

Tetrahedron Letters 43 (2002) 1871–1875

TETRAHEDRON LETTERS

Synthesis and intramolecular inclusion of β-cyclodextrins linked with a cyclohexyl group

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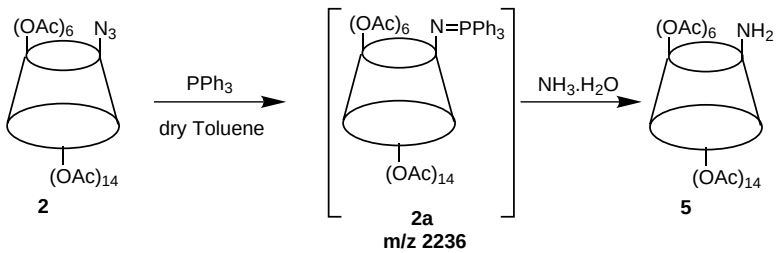
Received 12 November 2001; revised 11 December 2001; accepted 20 December 2001

Abstract—Cyclohexanecarboxylic acid (6^A-deoxy-β-cyclodextrin-6^A-*C*-yl)-amide (CHC-βCD) was synthesized via an aza-Wittig reaction and found to form in water, a temperature-independent intramolecular complex with its own cyclohexyl moiety. The analysis was based on data from 2D and variable-temperature NMR spectroscopy. The self-inclusion behavior of peracetylated CHC-βCD (PACHC-βCD) in chloroform was also investigated. © 2002 Elsevier Science Ltd. All rights reserved.

It is well known that a substituent of a modified cyclodextrin may be confined within its cavity and form an intramolecular complex in water.[1] Various investigations have shown that the extent of the complexation (also called inside–outside isomerism) depends on the complementary relationship between the substituent and the cyclodextrin cavity,[2] the nature of the link between the cyclodextrin and the substituent,[3,4] the chirality of the substituent,[5–7] temperature,[8–10] concentration[11] and even the extent of protonation of the substituent.[4] A number of β-cyclodextrins containing aromatic moieties, have been extensively examined by NMR, UV absorption, UV–CD and fluorescence spectroscopies. All the results from these measurements confirm the existence of the complexation and describe the potential importance of the modified cyclodextrins for the design of chemical sensors, molecular recognition and photochemistry.[1] Despite the extensive interest, there are a number of limitations associated with the synthesis and purification of the modified cyclodextrins. Furthermore, little is known about intramolecular inclusion of a cyclodextrin covalently linked with an alicyclic group in organic solvents and in water. We herein report the successful synthesis of β-cyclodextrins linked with a cyclohexyl group via an aza-Wittig reaction as well as the intramolecular complexation of the modified β-cyclodextrins and its substituents in non-aqueous solvents and in water.

The aza-Wittig reaction has been developed into an efficient method for amide bond formation and utilized in synthesis of small peptides.[12] In the reported methods[2,13] a carboxylic acid was directly coupled onto 6^A-amino-6^A-deoxy-α-, β- and γ-cyclodextrins to form an amide bond via a classical dicyclohexylcarbodiimide (DCC) procedure. However, the poor yield and tedious purification procedure preclude its application as a suitable coupling strategy for the modification of cyclodextrins. Peracetylated 6^A-azido-6^A-deoxy-β-cyclodextrin (**2**)[14] makes it possible to utilize the aza-Wittig reaction as an alternative coupling strategy



Scheme 1.

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PII: S0040-4039(02)00019-9

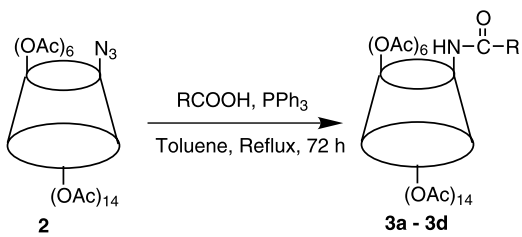
because our initial studies proved that it can be reduced readily by treatment with triphenylphosphine and subsequent addition of concentrated ammonium hydroxide to give peracetylated 6^A-amino-6^A-deoxy-β-cyclodextrin (**5**) in good yield (Scheme 1). Since it is known that organic azides react under very mild conditions with trivalent phosphines to afford iminophosphoranes, which are key intermediates in aza-Wittig reactions,[12d] the reduction of **2** was monitored by ESI mass spectroscopy, which showed a peak with m/z 2236 (100%) corresponding to the protonated iminotriphenylphosphorane ionic species formed in the reaction mixture. Hence, coupling between **2** and cyclohexanecarboxylic acid in the presence of triphenylphosphine in dry toluene was employed and the expected peracetylated cyclohexanecarboxylic acid (6^A-deoxy-β-cyclodextrin-6^A-*C*-yl)-amide (PACHC-βCD) (**3**) was obtained in 53% yield. Deacetylation of **3** conveniently afforded the pure cyclohexanecarboxylic acid (6^A-deoxy-β-cyclodextrin-6^A-*C*-yl)-amide (CHC-βCD) (**4**) (without any need for purification) in 89% yield (Scheme 2).

We further investigated the application of this coupling strategy for the synthesis of a series of peracetylated β-cyclodextrin derivatives and the results of these additional studies have been summarized in Table 1. In addition, the direct aza-Wittig coupling between 6^A-azido-6^A-deoxy-β-cyclodextrin (**1**)[15] and cyclohexanecarboxylic acid in the presence of triphenylphosphine in dry DMF was also examined, but proved unsuccessful. The failure to obtain the corresponding product, may be explained due to the highly polar DMF solvent which precludes coupling between the acid and the formed iminotriphenylphosphorane intermediate.[12b] The latter was observed by ESI mass spectroscopy, which showed a peak at m/z 1394 (100%) corresponding to the protonated ionic species (Scheme 3).

2D NMR techniques have become indispensable in the study of interactions between cyclodextrin and its substituents, since one can conclude that two protons are closely located in space if an NOE cross-peak is detected between the relevant protons in the ROESY or NOESY spectra. To determine the position of the cyclohexyl group in CHC-βCD (**4**), a ^{1}H ROESY NMR measurement was performed. The region of the ^{1}H ROESY NMR spectrum illustrated in Fig. 1 shows clear NOE interactions between the protons of the cyclohexyl moiety and the H-3 and H-5 protons of the cyclodextrin (comparable intensities). Although the complete assignment of the cyclodextrin hydrogens between δ 3.0 and 4.0 ppm and the cyclohexyl hydrogens is difficult due to insufficient resolution, the cross-peaks in the ^{1}H ROESY spectrum definitely indicate that in **4** the cyclohexyl moiety is enclosed within the β-cyclodextrin cavity from the primary hydroxyl side as illustrated in Scheme 2.

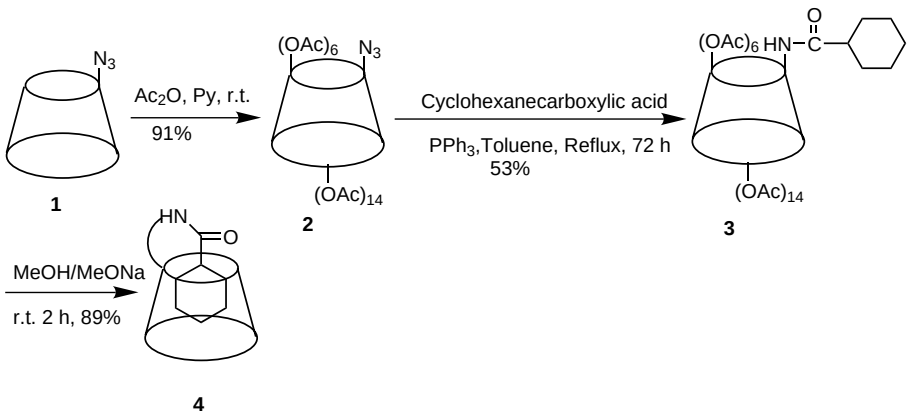
Furthermore, to study the conformational change of **4** which may be induced by temperature, a variable-temperature ^{1}H NMR experiment was performed. The ^{1}H NMR spectrum of the cyclohexyl region of **4** (Fig. 2) is virtually unaffected by temperature variations in the range 25–80°C. It appears that the self-inclusion of **4** is not a function of temperature and the position of equilibrium (Fig. 2) for conformational inside–outside isomerism of **4** is not affected by temperature. This observation can be related to the fact that the amide bond,[2] which links the cyclohexyl group to β-cyclodextrin, is not flexible enough to allow the cyclohexyl

Table 1. Peracetylated β-cyclodextrin derivatives prepared by an aza-Wittig coupling method (Eq. (1))

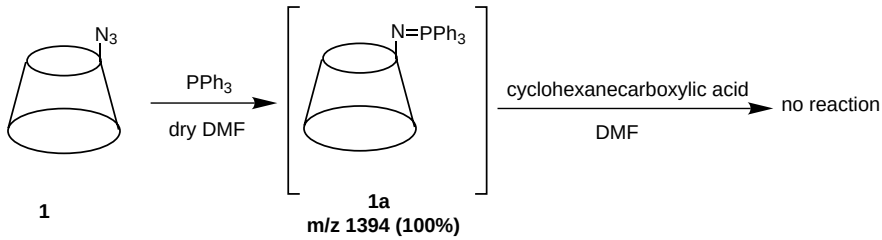


2 3a - 3d (1)

Compd	RCO_2H	Yield (%)	Mp (°C)
3a	CH_3COOH	52	123–124
3b	$ClCH_2COOH$	90	129–131
3c	$Cl(CH_2)_4COOH$	72	136–137
3d	$Br(CH_2)_{10}COOH$	82	144–145



Scheme 2.



Scheme 3.

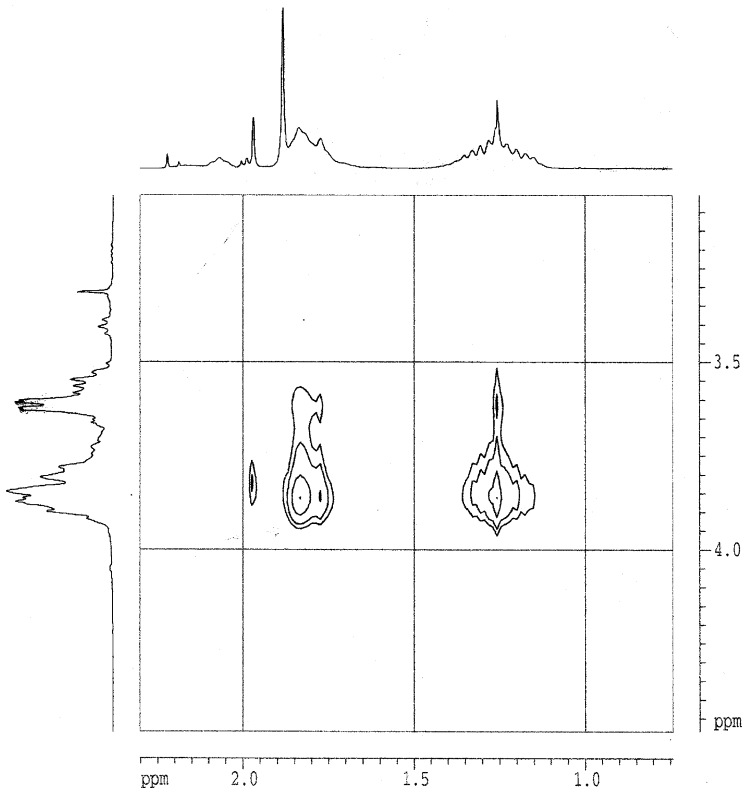
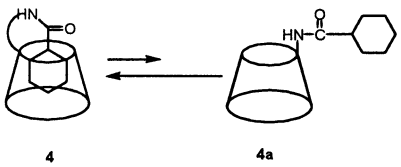


Figure 1. Region of the ^{1}H ROESY NMR spectrum (500 MHz) of CHC-βCD (**4**) in D_2O at 298 K with a mixing time of 300 ms, covering the protons of the cyclohexyl group.

group to move freely in and out of the β-cyclodextrin cavity on the NMR time scale, within the experimental temperature range. Furthermore, compared with coplanar aromatic groups, the cyclohexyl moiety is non planar and roughly spherical.[16] Therefore it can touch a large part of the hydrophobic cavity of **4** and fit snuggly into it and become 'trapped'. Since the β-cyclodextrin cavity is fairly rigid with an internal diameter of ca. 6.6 Å and since van der Waals forces are strongly influenced by separation distances, we would expect that strong van der Waals forces would contribute to the intramolecular inclusion and complex formation. A combination of the steric and known hydrophobic effects would limit further movement of the cyclohexyl moiety within the cyclodextrin cavity. This may rationalize the fact that the stability of the intramolecular inclusion complex is not strongly influenced by temperature. These interpretations are consistent with the structural features of **4** as suggested by the described ^{1}H ROESY NMR spectrum.

Finally, since little is known about the intramolecular inclusion of a cyclodextrin and its substituent in non-aqueous solvent, we utilized the CHC-βCD (**4**) precursor, PACHC-βCD (**3**), as an example on which to study its conformation in chloroform-d_3 using ^{1}H ROESY NMR spectroscopy. As shown in Fig. 3, the ^{1}H ROESY spectrum shows clear and numerous NOE cross-peaks between the methyl protons of the acetyl groups in **3** and the protons of the β-cyclodextrin cavity. The cross-peaks between some methyl protons of the acetyl groups and H-3 and H-5 of the cyclodextrin indicate that **3** includes the acetyl groups in the cavity of itself from both primary and secondary sides, while the cross-peaks between other methyl protons of the acetyl groups and H-1, H-2, H-4 and H-6 of the cyclodextrin indicate that the acetyl groups are closely located in the outer layer of the β-cyclodextrin cavity. Interestingly, there is no NOE effect between the protons of the cyclohexyl moiety and any of the cyclodextrin annual protons, which suggests that the



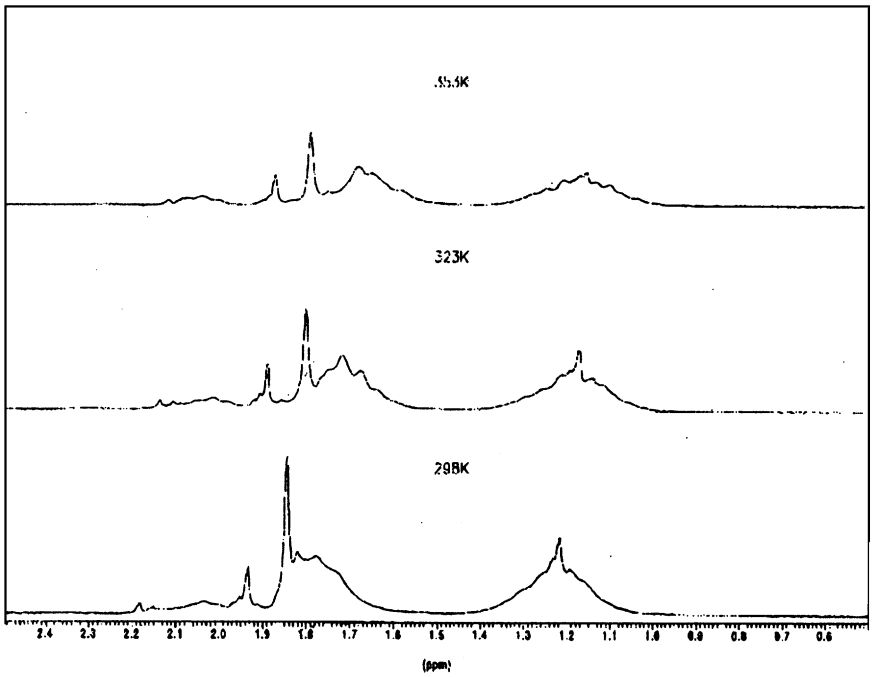


Figure 2. Equilibrium mode for inside–outside isomerism of CHC-βCD (**4**) and ^{1}H NMR (300 MHz, D_2O) spectra of the cyclohexyl region of CHC-βCD (**4**) at 298, 323 and 353 K.

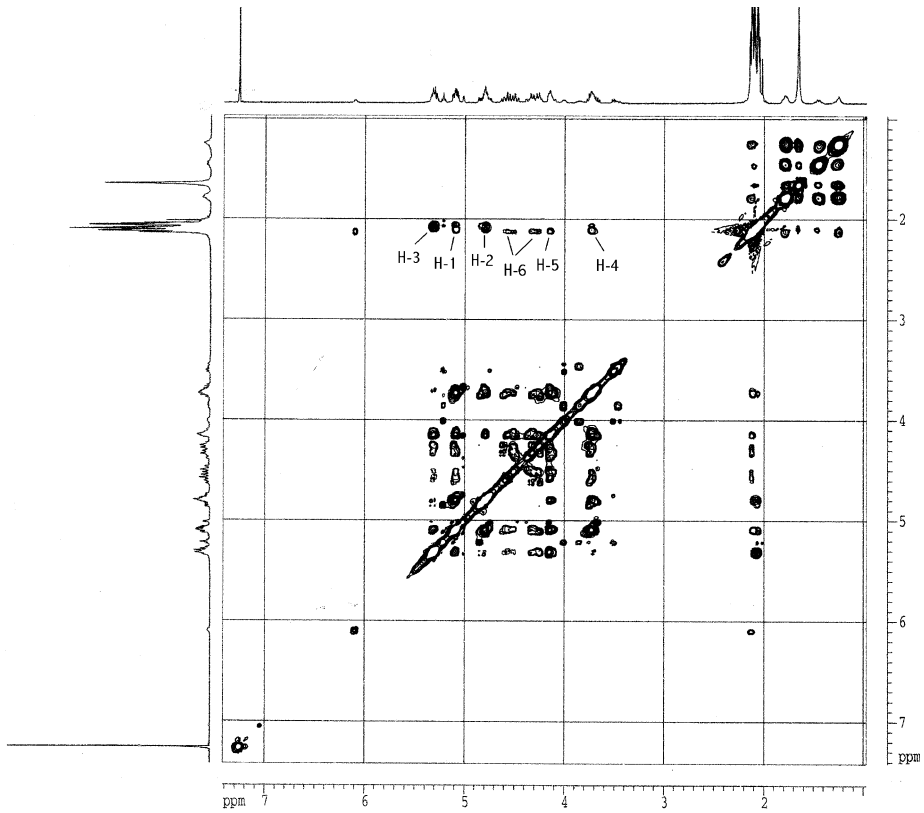


Figure 3. ^{1}H ROESY NMR spectrum (500 MHz) of PACHC-βCD (**3**) in $CDCl_3$ at 298 K with a mixing time of 350 ms. Assignments of cross-peaks are also shown.

β-cyclodextrin cavity occupied by acetyl groups becomes too small to accommodate the cyclohexyl moiety and the intramolecular inclusion complexation mode is thermodynamically favorable in chloroform.

In conclusion, the analyses of the ^{1}H NMR spectra of Figs. 1 and 2 demonstrate the existence of an intramolecular interaction between the modified cyclodextrin and its alicyclic substituent in water. However, the intramolecular interaction was not observed in a nonaqueous solvent due to the competition from the other substituents. Further investigation of binding between external guests and CHC-βCD, PACHC-βCD, respectively, is in progress.

Acknowledgements

We gratefully acknowledge the National University of Singapore for generous financial support. We also wish to thank Madam Yan-Hui Han for 2D NMR (500 MHz) assistance.

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