

2,3,6,6-PERDEUTERO-CYCLODEXTRINS
POWERFUL NEW FAMILY OF CYCLODEXTRIN FOR NMR SPECTROSCOPY

Yasuhisa Kuroda*, Masahiko Yamada and Iwao Tabushi†
Department of Synthetic Chemistry, Kyoto University, Sakyo-ku Kyoto, 606 Japan

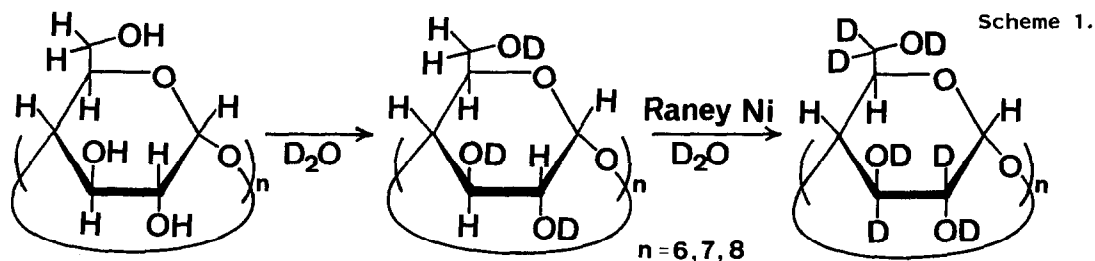
α -, β - and γ - Cyclodextrins are deuterated at the C2, C3 and C6 positions by the Raney nickel catalyzed H-D exchange reaction in D₂O. ¹H- and ¹³C-NMR of these cyclodextrins are highly simplified and, therefore, expected to provide one of strong means for the structure determination of cyclodextrin derivatives.

In host-guest chemistry, cyclodextrins are undoubtedly one of the most important host molecules because of their versatile binding abilities, easiness of modifications, high solubilities in water and etc.¹⁾ Especially, various types of modified cyclodextrins have been demonstrated to show a variety of functions mimicking biological processes and mono-, di-, and tri-substituted cyclodextrins have actually been utilized as highly sophisticated enzyme and/or receptor models.²⁾ In these extensive investigations, the NMR spectroscopy has been used as one of the essential techniques for determination of intricate structures of modified cyclodextrins. The structural determinations, however, require a tough work, i.e., it is sometimes difficult to fully analyze the heavily overlapped C2-, C3-, C4-, C5- and C6-H's signals of unsymmetrically substituted cyclodextrins even by using a recent high resolution NMR spectrometer and appropriate two dimensional NMR techniques.

In this article, we wish to report the preparation of 2,3,6,6-perdeutero-cyclodextrins which show highly simplified NMR patterns and, therefore, are expected to be useful for studying structural and geometrical features of cyclodextrin derivatives by NMR spectroscopy. The compounds are also interesting from viewpoints of deuterium relaxation measurements of their complexes³⁾ and the isotope effects on their guest binding.

The deuteration reactions of cyclodextrins were carried out by Raney nickel catalyzed H-D exchange reaction (see Scheme 1)⁴⁾. In the typical reaction, 200mg of α -cyclodextrin was converted to the corresponding deuterioxy compound by dissolving in 1mL of D₂O followed by evaporation and treatment with deuterated W4 Raney nickel⁵⁾ (1mL, settled volume) in 5mL of D₂O. The resultant suspension was heated under reflux for 48h and cooled at room temperature. The residual nickel was filtrated off and washed with 20mL of hot water. The combined filtrate was concentrated to ca.5mL and passed through a short CM-Sephadex(C-25) column (NH₄⁺ form, 0.5×20cm) and then, after concentrating the appropriate fractions, through a short DEAE-Sephadex(A-25) column (Cl⁻ form, 0.5×20cm). Since the NMR spectrum of the crude sample in

* To whom correspondence should be addressed. † Deceased in March 22, 1987.



this stage usually showed the partial deuteration of α -cyclodextrin⁶⁾, the sample was treated again with D_2O and Raney nickel under the same conditions with those described above and similarly purified by successive CM- and DEAE-Sephadex column chromatographies. The final product was recrystallized from aqueous ethanol to afford 120mg of 2,3,6,6-perdeutero- α -cyclodextrin. β - and γ -Perdeutero-cyclodextrin were also prepared by the same procedures.

The NMR measurements of the reaction mixtures at appropriate time intervals indicate that the orders of the H-D exchange reaction rates may be roughly estimated to be C2-H > C6-H > C3-H and γ -> β -> α -cyclodextrin. These observations suggest that the reaction rates are mainly dominated by the steric surroundings around the corresponding protons. In any cases, however, the procedures described above are enough for the complete H-D exchange reactions (>95%) of α -, β - and γ -cyclodextrins.

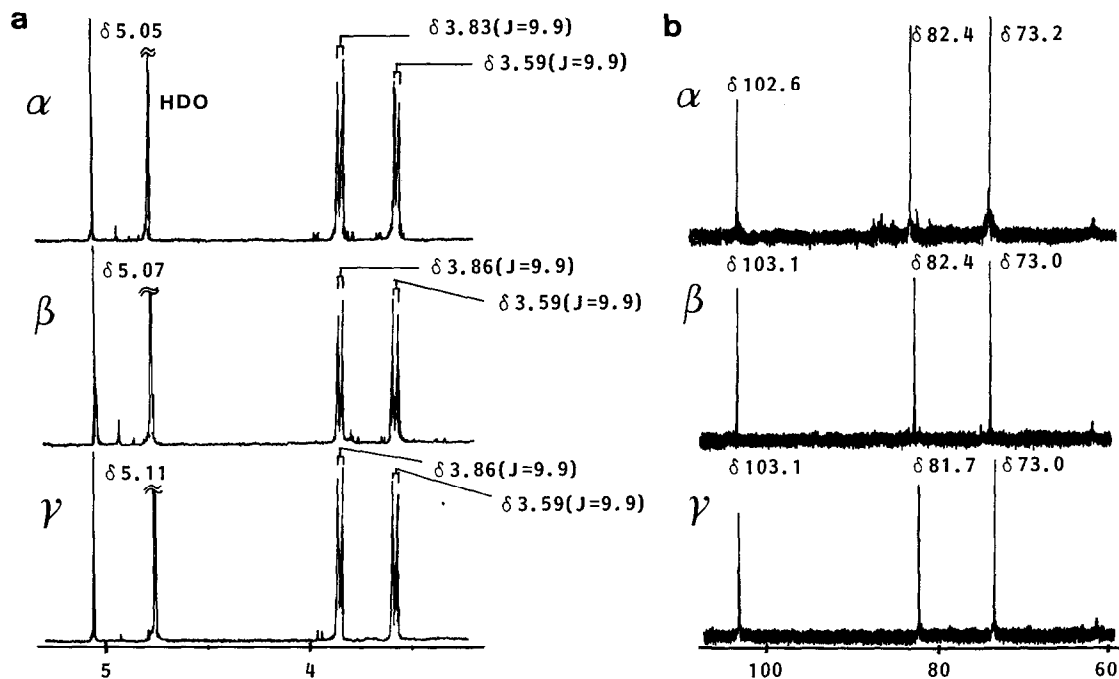


Fig. 1 a) 1H - (400MHz) and b) ^{13}C - (100MHz) NMR spectra of 2,3,6,6-perdeutero-cyclodextrins in D_2O (δ (ppm) from TSP external reference, J(Hz)).

The data of NMR spectra of these deuterated cyclodextrins are summarized in Fig.1. The ^1H -NMR spectra of these cyclodextrins are dramatically simplified as expected (Fig.1a). Thus, for example, signals of C1-, C4- and C5-H's of deuterated α -cyclodextrin are observed at δ 5.05, 3.59 and 3.83 as singlet, doublet($J=9.9\text{Hz}$) and doublet($J=9.9\text{Hz}$), respectively. Based on these observations, these deuterated compounds are concluded to maintain the original configurations of corresponding cyclodextrins. Interestingly, ^{13}C -NMR spectra obtained under the conditions of the complete proton decoupling are also apparently simplified as shown in Fig.1b, i.e., for example, only C1-, C4- and C5-carbons of α -cyclodextrin are observed at δ 102.6, 82.4 and 73.2ppm, respectively and the signals of C2-(72.6), C3-(74.0) and C6-(61.3ppm) carbons are strongly diminished because of the lack of the NOE effect due to the proton decoupling and the line broadening effect due to the deuterium quadrupolar interaction.

Finally, as a typical example of the modification of these deuterated cyclodextrins, 6-mono-tosylation of α -cyclodextrin under the usual conditions was attempted⁷⁾. The NMR spectrum of the product purified by a Merck RP-8 column was shown in Fig.2. The C4- and C5-protons of tosylated glucose are easily assigned as the signals appearing at δ 3.51 and 4.01ppm, respectively, as separated peaks. Thus, the present deuterated cyclodextrins seem to be highly promising as the probe compounds for the structure determination of substituted cyclodextrins by NMR spectroscopy.

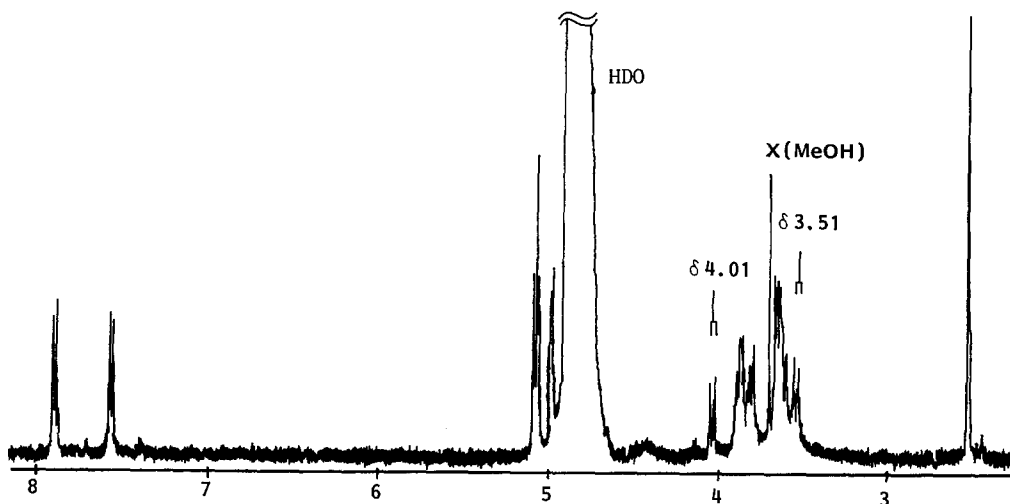


Fig. 2 ^1H -NMR (400MHz) spectrum of 6-tosyl-2,3,6,6-perdeutero- α -cyclodextrin in D_2O (δ (ppm) from TSP external reference).

References and Notes.

- 1) a) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer Verlag: New York, 1978.
- b) Tabushi, I., Acc. Chem. Res. 1982, 15, 66.

- c) Breslow, R., Science 1982, 218, 532.
- 2) a) Tabushi, I.; Kuroda, Y., Adv. Catal. 1983, 32, 417.
b) Tabushi, I.; Kuroda, Y.; Yamada, M.; Higashimura, H.; Breslow, R.,
J. Am. Chem. Soc. 1985, 107, 5545.
c) Tabushi, I.; Kuroda, Y.; Mizutani, T., ibid. 1986, 108, 4514.
- 3) a) Behr, J. P.; Lehn, J. M., J. Am. Chem. Soc. 1976, 98, 1743.
b) Tabushi, I.; Kuroda, Y.; Yamada, M., Tetrahedron Lett. 1988, 29, 1413.
c) Tabushi, I.; Kuroda, Y.; Yamada, M., J. Inclusion Phenomena 1988,
in press.
- 4) The Raney nickel catalyzed H-D exchange reaction was well established for the various types of non-cyclic saccharides, see, for example, Koch, H. J.; Stuart, R. S., Carbohydrate Res. 1978, 64, 127.
The reactions for cyclodextrins, however, were not reported except the brief and obscure description in the following communication, Balza, F.; Hamer, G. K.; Perlin, A. S.; Koch, H. J.; Stuart, R. S., Carbohydrate Res. 1977, 59, c7.
- 5) a) Pavlic, A. A.; Adkins, H., J. Am. Chem. Soc. 1946, 68, 1471
b) Adkins, H.; Billica, H. R., ibid. 1948, 70, 695.
- 6) The reaction was confirmed to completely stop at this first step based on the NMR measurement and simple addition of Raney nickel without following column purifications resulted in no reactions. The reason for this stoppage of the reaction is not clear but the formations of oxidized nickel and/or acetic acid converted from ethanol contained in Raney nickel are most probable candidates for the present catalytic poison.
- 7) Melton, L. D.; Slessor, K. N., Carbohydrate Res. 1971, 18, 29.

(Received in Japan 2 June 1988)