Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Identification of the inclusion complexation between phenyl β-d-($^{13}C_6$)glucopyranoside and α-cyclodextrin using 2D ^{1}H or ^{13}C DOSY spectrum

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To cite this Article Oda, Yoshiki , Matsuda, Sho , Yamanoi, Takashi , Murota, Akihiko and Katsuraya, Kaname(2009) 'Identification of the inclusion complexation between phenyl β-d-($^{13}C_6$)glucopyranoside and α-cyclodextrin using 2D ^{1}H or ^{13}C DOSY spectrum', Supramolecular Chemistry, 21: 7, 638 — 642
To link to this Article: DOI: 10.1080/10610270802709345
URL: http://dx.doi.org/10.1080/10610270802709345

Supramolecular Chemistry
Vol. 21, No. 7, October–November 2009, 638–642

Identification of the inclusion complexation between phenyl β-D-($^{13}C_6$)glucopyranoside and α-cyclodextrin using 2D ^{1}H or ^{13}C DOSY spectrum

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(*Received 9 July 2008; final version received 22 December 2008*)

This study describes the 2D ^{1}H and ^{13}C diffusion-ordered NMR spectroscopy (DOSY) experiments using the mixed sample of α-cyclodextrin (α-CyD) and phenyl β-D-($^{13}C_6$)glucopyranoside (**1**). Both the 2D ^{1}H and ^{13}C DOSY spectra showed the component with a diffusion coefficient different from those of α-CyD and **1**, which suggested the inclusion complexation of α-CyD with **1**.

Keywords: diffusion-ordered NMR spectroscopy; DOSY; inclusion complexation; α-cyclodextrin; phenyl β-D-($^{13}C_6$)glucopyranoside

Introduction

The diffusion-ordered NMR spectroscopy (DOSY) method can conveniently separate the NMR spectra of components that may differ in molecular weight, geometry or complexation by the difference in their diffusion coefficients (*1*). The 2D DOSY spectrum displays the conventional chemical shifts in one dimension and the diffusion coefficients in the other dimension.

Recently, several groups have reported that the complexation between a host molecule and a guest molecule could be analysed by the 2D ^{1}H DOSY technique (*2–12*). We have also succeeded in observing the inclusion complexation of a β-cyclodextrin (β-CyD) derivative with doxorubicin by the measurement of the 2D ^{1}H DOSY spectrum (*13*, *14*).

This study involves the 2D ^{1}H DOSY, 2D ^{13}C DOSY and 2D rotating-frame Overhauser enhancement (ROESY) experiments using the mixed sample of α-CyD and **1** in order to analyse the inclusion complexation of α-CyD with **1**. D-($^{13}C_6$)Glucose was used for the purpose of differentiating between the ^{1}H NMR spectral pattern of the glucose moiety from **1** and that of the glucose moiety from α-CyD. The use of D-($^{13}C_6$)glucose was also expected to increase the sensitivity of the 2D ^{13}C DOSY measurement.

Experimental section

General

The optical rotations were recorded on a JASCO DIP-360 digital polarimeter. Melting points were measured on a B-545 (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected. The HR-MS was obtained using a Mariner spectrometer (PerSeptive Biosystems, Inc., Framingham, MA, USA). The preparative TLC was performed using Merck 60GF254 silica gel. Column chromatography was conducted using 60 N silica gel (40–50 μm; Kanto Chemical Co., Inc., Tokyo, Japan). All anhydrous solvents were purified according to the standard methods. The ^{1}H and ^{13}C NMR spectra were obtained using a JEOL ECA-600 spectrometer with 5-mm tubes in $CDCl_3$ using TMS as the internal standard. The sample concentrations were about 0.8% (w/v) in D_2O (Kanto Chemical Co., 99.8% minimum in *D*). The ^{1}H NMR spectra were recorded at 600 MHz. The chemical shifts were referenced to the solvent values (δ 4.70 ppm for HOD). The ^{13}C NMR spectra were recorded at 150 MHz. The chemical shifts were referenced to the solvent values (δ 29.9 ppm for acetone in D_2O). The 2D ROESY experiment was carried out at 25°C using a mixing time of 500 ms. The 2D ^{1}H and ^{13}C DOSY experiments were performed at 25°C using the bipolar pulse pair and longitudinal eddy current delay (BPPLED) sequence and stimulated echo and insensitive nuclei enhanced by polarisation transfer (STEINEPT) sequence. The spectral analyses were processed by Delta NMR processing software version 4.3.4. (JEOL USA, Inc., Peabody, MA, USA).

Materials

D-($^{13}C_6$)Glucose ($^{13}C_6 = 99\%$) was purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). Compound **1** was prepared from D-($^{13}C_6$)glucose as shown in Scheme 1.

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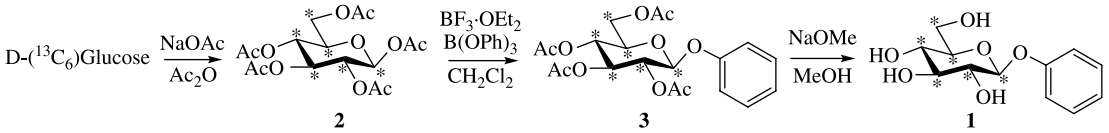
ISSN 1061-0278 print/ISSN 1029-0478 online

DOI: 10.1080/10610270802709345
http://www.informaworld.com



Scheme 1. Preparation of **1** from D-($^{13}C_6$)glucose.

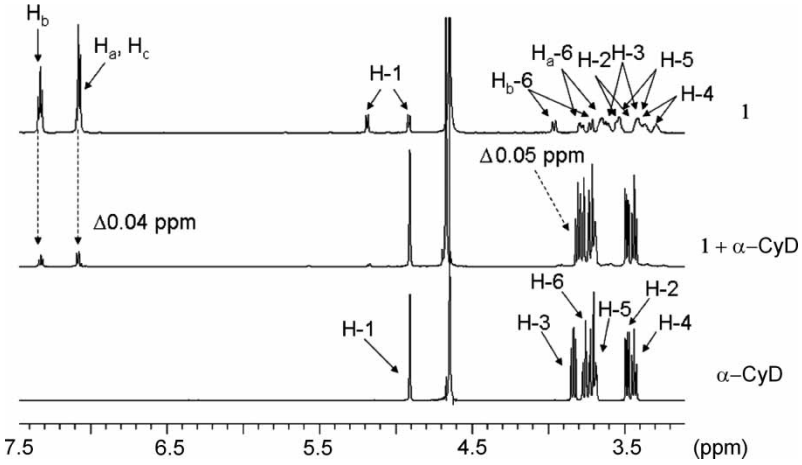


Figure 1. The ^{1}H NMR spectra (600 MHz, D_2O at 25°C) of **1** (upper), **1** and α-CyD (middle) and α-CyD (bottom).

***Penta*-O-*acetyl*-β-D-($^{13}C_6$)*glucopyranose* 2**

β-D-($^{13}C_6$)Glucopyranose (1.02 g, 5.48 mmol) was added to a solution of sodium acetate (500 mg, 6.10 mmol) in acetic anhydride (7 ml). The resulting mixture was stirred for 15 min on heating. The reaction was then quenched by the addition of iced water (20 ml) and a saturated $NaHCO_3$ solution (10 ml). The reaction mixture was extracted with CH_2Cl_2. The crude product was purified by flash column chromatography (silica gel, EtOAc/hexane: 1/3) to give **2** (*15*) (2.14 g, 99% yield) as white crystals.

***Phenyl* 2,3,4,6-*tetra*-O-*acetyl*-β-D-($^{13}C_6$)*glucopyranoside* 3**

BF_3·OEt_2 (72.4 μl, 0.57 mmol) was added to a solution of **2** (113.2 mg, 0.29 mmol) and triphenyl borate (42 mg, 0.14 mmol) in CH_2Cl_2 (2 ml) at 0°C (*16*). The resulting mixture was stirred for 40 h at room temperature. The reaction was then quenched by the addition of a saturated $NaHCO_3$ solution (10 ml). The reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a saturated NaCl solution. After the organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, EtOAc/hexane: 1/1) to give **3** (71.4 mg, 58% yield) as a colourless oil. $[\alpha]_D^{23}$ + 9.2° (c = 1.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.02–2.14 (m, 12H, CH_3 × 4), 3.86 (m, 1H, H-5), 4.17 (d, J = 12.4 Hz, 1H, H_a-6), 4.29 (dd, J = 4.8 Hz, J = 12.3 Hz, 1H, H_b-6), 5.09 (d, J = 7.6 Hz, 1H, H-1), 5.17 (m, 1H, H-4), 5.27–5.30 (m, 2H, H-2, H-3), 6.99 (d, J = 8.3 Hz, 2H, Ph), 7.08 (t, J = 7.5 Hz, 1H, Ph) and 7.27–7.31 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ = 20.56–20.64 (*C*H_3 × 4), 61.27–62.10 (C-6), 67.54–72.99 (C-2, C-3, C-4, C-5), 99.27 (C-1), 116.95, 123.33, 129.56, 156.83 (Ph), 169.26, 169.36, 170.21 and 170.54 (C═O × 4); HR-MS (ESI) *m/z*: calcd for $^{13}C_6C_{14}H_{24}O_{10}$ [M + Na^+]: 453.1463; found: 453.1490.

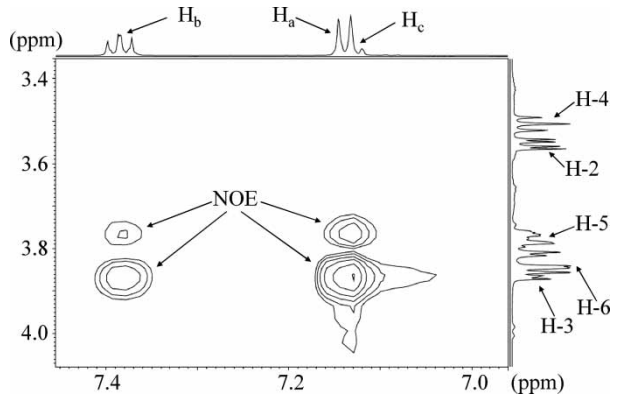
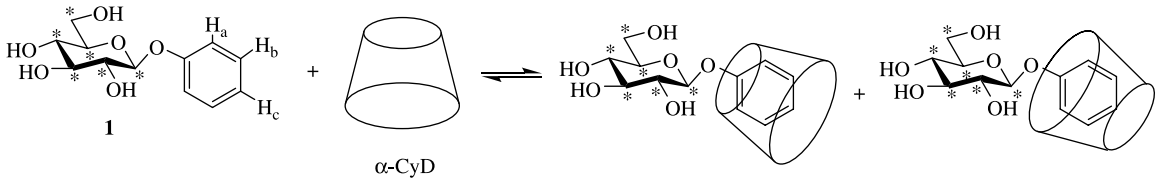


Figure 2. The 2D ROESY spectrum (600 MHz, D_2O at 25°C) of the mixed sample of **1** and α-CyD.



Scheme 2. Proposed complexes of α-CyD with **1**.

Phenyl β-D-($^{13}C_6$)glucopyranoside 1

A 28% sodium methylate methanol solution (0.3 ml, 0.0016 mmol) was added to a solution of **3** (131.4 mg, 0.31 mmol) in MeOH (5 ml). The resulting mixture was stirred for 14 h. The solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC (silica gel, MeOH/$CHCl_3$: 1/5) to give **1** (73 mg, 91% yield) as white crystals. $[\alpha]_D^{23}$ −58.6° (c = 3.65, MeOH); mp: 169.0–169.6°C; ^{1}H NMR ($CDCl_3$): δ = 3.42–3.46 (m, 5H, H-2, H-3, H-4, H-5, H_a-6), 3.88 (d, J = 11.7 Hz, 1H, H_b-6), 4.90 (d, J = 6.9 Hz, 1H, H-1), 6.99 (t, J = 7.5 Hz, 1H, Ph), 7.09 (d, J = 7.6 Hz, 2H, Ph) and 7.27 (t, J = 6.9 Hz, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ = 62.51 (C-6), 71.41 (C-4), 74.70 (C-5), 77.67–78.31 (C-2 and C-3), 102.26 (C-1), 117.72, 123.34, 130.39 and 159.11 (Ph); HR-MS (ESI) *m/z*: calcd for $^{13}C_6C_6H_{16}O_6$ [M + Na^+]: 285.1040; found: 285.1050.

Results and discussion

^{1}H NMR and 2D ROESY experiments

Figure 1 shows the ^{1}H NMR spectra of **1**, α-CyD and the mixed sample of **1** and α-CyD (20 mM:20 mM). Compound **1** indicated the specific spectrum attributable to D-(^{13}C$_6$)glucose. In the ^{1}H NMR spectrum of the mixed sample, the shifts (0.01–0.05 ppm) of some protons of α-CyD and **1** were observed. Figure 2 shows the 2D ROESY spectrum of the mixed sample. The NOE interactions were observed between each of the H_a and H_b protons of the phenyl group of **1** and each of the interior H-3 and H-5 protons of α-CyD. These observations suggest that the phenyl group of **1** enters the α-CyD's cavity from both the α-CyD's primary and secondary sides as shown in Scheme 2 (*17–19*).

2D ^{1}H DOSY experiment

Figure 3 shows the 2D ^{1}H DOSY spectrum of the mixed sample of α-CyD and **1** (20 mM:20 mM). The spectrum indicated three components with different diffusion coefficients (D), two of which corresponded to the α-CyD ($D = 3.12 \pm 0.14 \times 10^{-10}$ m^2/s, lit. $D = 3.46 \pm 0.01 \times 10^{-10}$ m^2/s, 10 mM (*20*)) and **1** ($D = 4.36 \pm 0.11 \times 10^{-10}$ m^2/s), and one of which suggested the inclusion complexation of α-CyD with **1** ($D = 3.73 \pm 0.13 \times 10^{-10}$ m^2/s). The D value of α-CyD in this experiment almost corresponded to the literature value. Thus, the inclusion complexation of **1** with α-CyD was successfully analysed by the measurement of the 2D ^{1}H DOSY spectrum. This spectrum indicated the apparent signal separations of each component, α-CyD and **1**, and their inclusion complex showed the following findings. (i) Although the 2D ROESY spectrum suggested that two kinds of inclusion complexes were formed in the mixed sample, the 2D ^{1}H DOSY spectrum could not distinguish them. This may be because the diffusion coefficients of the two inclusion complexes are

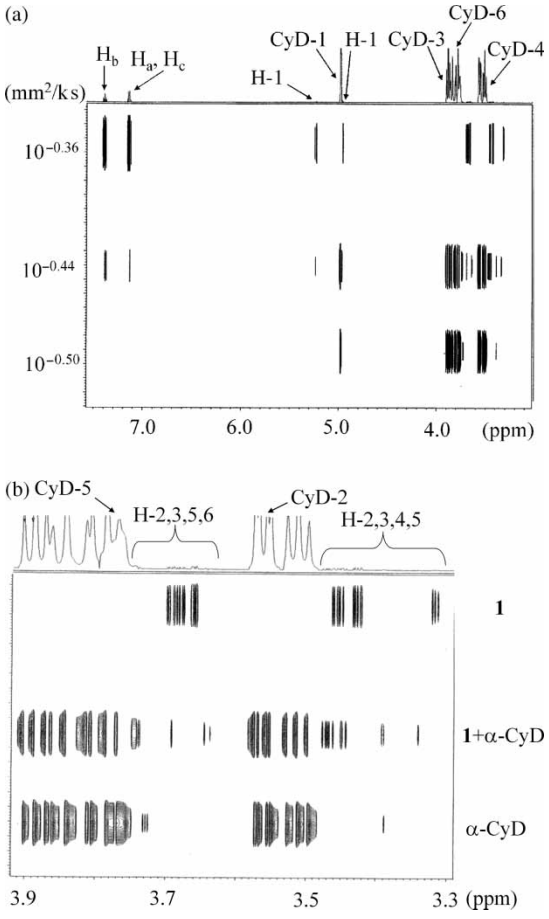


Figure 3. (a) The 2D ^{1}H DOSY spectrum (600 MHz, D_2O at 25°C) of the mixed sample of **1** and α-CyD. (b) Its expansion. Sequence = BPPLED; diffusion time = 0.2 s; grad 1 = 2 ms; grad 1 amp = 20–247 mT/m; 19 points; relaxation delay = 7 s; scans = 64 times.

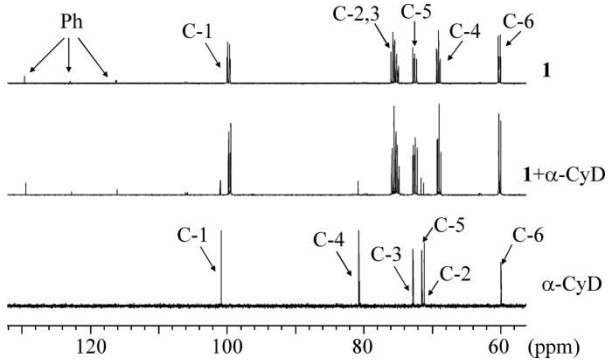


Figure 4. The ^{13}C NMR spectra (600 MHz, D_2O at 25°C) of **1** (upper), **1** and α-CyD (middle) and α-CyD (bottom).

very close. (ii) The complex of α-CyD and **1** stably exists on the DOSY time scale (*3*, *21*). (iii) The diffusion coefficient value of the complex, in spite of the increase in the molecular weight, was larger than that of α-CyD.

^{13}C NMR and 2D ^{13}C DOSY experiments

Figure 4 shows the ^{13}C NMR spectra of **1**, α-CyD and the mixed sample of α-CyD and **1** (20 mM:20 mM). Compound **1** provided the specific spectrum, which is attributable to D-($^{13}C_6$)glucose. Figure 5 shows the 2D ^{13}C DOSY spectrum of the mixed sample. It was found that the sensitivity of the 2D ^{13}C DOSY measurement increased by the effect of the ^{13}C-enriched carbon atoms of **1**, and the signals of only the ^{13}C-enriched carbon atoms were observed by the measurement of an appropriate accumulation number. The 2D ^{13}C DOSY spectrum with 64 scans showed only two components with different diffusion coefficients ($D = 4.09 \pm 0.24 \times 10^{-10}\,m^2/s$ and $D = 3.62 \pm 0.18 \times 10^{-10}\,m^2/s$), one of which suggested

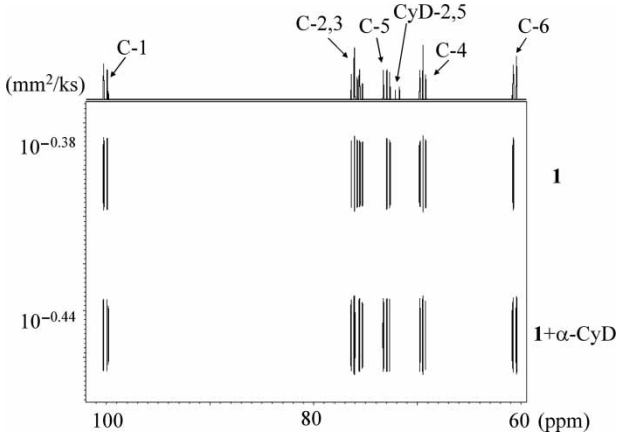


Figure 5. The 2D ^{13}C DOSY spectrum (600 MHz, D_2O at 25°C). Sequence = STEINEPT; diffusion time = 0.2 s; grad 1 = 1.5 ms; grad 1 amp = 20–247 mT/m; 19 points; relaxation delay = 7 s; scans = 64 times.

the inclusion complexation of α-CyD with **1**. The *D*-value of the complex in this experiment corresponded to that of the 2D ^1H DOSY experiment. To the best of our knowledge, this is the first observation of the host–guest complexation using the 2D ^{13}C DOSY NMR technique.

Conclusion

In this study, we conducted the 2D ^1H DOSY, 2D ^{13}C DOSY and 2D ROESY experiments using the mixed sample of α-CyD and **1** in order to analyse the inclusion complexation of α-CyD with **1**. The 2D ^1H and ^{13}C DOSY spectra successfully showed the inclusion complexation of α-CyD with **1** by revealing the component with a diffusion coefficient different from those of α-CyD and **1**. The use of D-($^{13}C_6$)-glucose made it possible to differentiate between the ^1H NMR spectral pattern of the glucose moiety from **1** and that of the glucose moiety from α-CyD. It also contributed to the increased sensitivity of the 2D ^{13}C DOSY measurement.

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