Studies on the Formation of β-Cyclodextrin/Alkylcobaloxime Inclusion Complexes by Using NMR Methods

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STUDIES ON THE FORMATION OF β-CYCLODEXTRIN/ ALKYLCOBALOXIME INCLUSION COMPLEXES BY USING NMR METHODS

Key Words: β-Cyclodextrin, Alkylcobaloxime, NMR

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ABSTRACT

It has been established that alkylcobaloxime($R=i$-C_4H_9, n-C_4H_9, n-C_5H_{11}, c-C_6H_{11}, $PhCH_2$) and β-cyclodextrin form a kind of 1:1 inclusion complexes in aqueous solution by ^1H NMR spectroscopy. Ka and $-\Delta G^\ominus$ were calculated according to chemical shift changes of different probe protons. The stability constant(Ka) has been found increasing in the order: $PhCH_2$ > n-C_5H_{11} > c-C_6H_{11} > i-C_4H_9 > n-C_4H_9.

Cyclodextrins(CDs) are known to provide hydrophobic environment in aqueous solution and are capable to include a variety of lipophilic guests in their cavities[1]. Recently they have been proposed as enzyme models for being due to their ability to show regiospecificity and stereospecificity with respect to the substrate and to the product during catalytic processing[2].

Coenzyme B_{12}, i. e. 5'-deoxyadenosylcobalamin, which acts as a cofactor to take part in over a dozen inner-molecular arrangement reactions, is a very important organometalic complex in nature[3]. In the past three decades, a significant effort has been devoted to the study on the factors that influence the Co-C bond homolysis, which is a key step in catalytic cycles. Unfortunately the question of exactly how enzymes weaken Co-C bond and accelerate the rate of the Co-C bond homolysis by a factor of 10^{13} remains unanswered[4]. Alkylcobaloxime which contains the $Co(DH)_2$ moiety, where DH is dimethylglyoxime, is one kind of the most extensively studied coenzyme B_{12} model[5]. Since inspection of space-filling molecular models revealed that the R groups of cobaloximes may fit snugly into the cavity of β-CD, we were encouraged to investigate the binding of cobaloximes($H_2OCo(DH)_2R$, R=i-C_4H_9, n-C_4H_9, n-C_5H_{11}, c-C_6H_{11}, $PhCH_2$) with β-CD in aqueous solution in order to realize the extent of the stability of formation the inclusion

complexes and the effect of environment on Co-C bond properties of cobaloxime.

Equimolar β-CD and cobaloxime were dissolved in D_2O at 30-40°C. A series of solutions of known concentrations(10^{-2}-10^{-4}M) were prepared by dilution of original stock solution. After recording the spectra at 25°C, the chemical shifts observed for the resonance of the probe protons were ascertained.

The spectra of β-CD, $H_2OCo(DH)_2i-C_4H_9$ and β-CD/$H_2OCo(DH)_2i-C_4H_9$ were shown in Fig.1. There were significant shift of some signals comparing the spectra of inclusion complexes with those of hostes or guestes (see Fig.1 and appendix).

(a) For β-CD, ~0.1ppm upfield shifts were induced for the H-3 and H-5, which are located within the cavity of β-CD. While the chemiacl shifts of the resonances of H-1,H-2,H-4, which are on the outer surface of the β-CD torus, and H-6, which is at the narrow opening of β-CD were unaffected.

(b) For planar ligand of $H_2OCo(DH)_2R$, the singlet of resonance of the methyl groups of oxime split into doublet. Moreover,they move down field by about 0.05ppm and 0.1ppm, respectively, indicating the unequivalent of the methyls.

(c) For R groups of $H_2OCo(DH)_2R$, the signals were shifted to higher frequency, espically for α-H at carbon connected with cobalt directly.
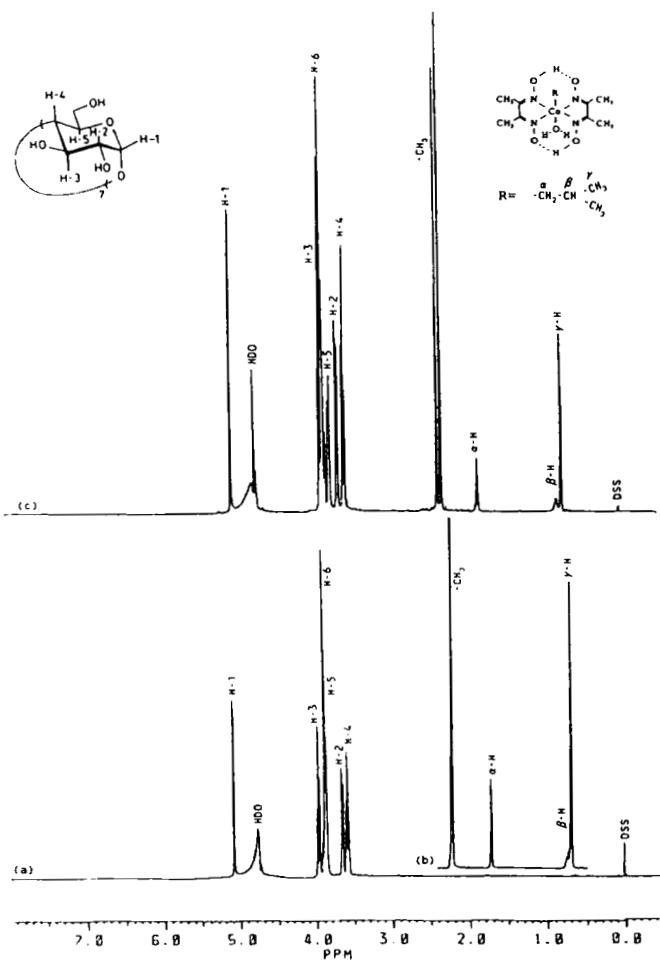
FIG. 1 The 500MHz ^{1}H NMR spectra of (a) β-CD (b) $H_2OCo(DH)_2i$-C_4H_9 (c) β-CD/$H_2OCo(DH)_2i$-C_4H_9 in D_2O at concentration of approximately $1.10\times10^{-2}M$

The results may indicat that R groups of $H_2OCo(DH)_2R$ were included within the cavities and planars involving Co atom and oxime ligand were placed near wider openings of β-CD. Evenmore, it was probably suggested that the electron density of the inner protons of β-CD increased and the electron density at equatorial ligand and Co atom decreased after inclusion.

Based on the fact that chemical shifts observed are different with changing the concentration of the 1:1 adducts, ^{1}H NMR spectroscopy is useful to quantatively determine the stability constant of formation of the inclusion complexes [6]. Equation (3) could be used for data analysis. Where the Δ's are the differences between the observed chemical shifts of the probe protons and those for the same protons in free components, the Δ_0's are the limiting chemical shifts, in which 1:1 adducts are assumed fully formed, and the x are the concentrations of 1:1 adducts.

$$H_2OCo(DH)_2R + \beta\text{-CD} \overset{Ka}{\rightleftharpoons} \beta\text{-CD}/H_2Co(DH)_2R \qquad \textbf{(1)}$$
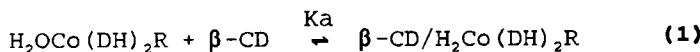
$$Ka = \frac{[\beta\text{-CD}/H_2OCo(DH)_2R]}{[H_2OCo(DH)_2R]\,[\beta\text{-CD}]} \qquad \textbf{(2)}$$

$$\Delta = \Delta_0 - (\Delta/x)^{(1/2)} (\Delta_0/Ka)^{(1/2)} \qquad \textbf{(3)}$$
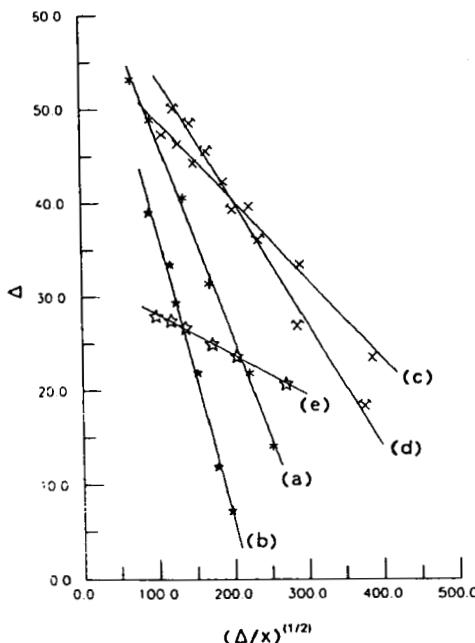
FIG. 2 Plots of Δ against $(\Delta/x)^{(1/2)}$ for $-CH_3$ at dimethylglyoxime in the quantitative ^1H NMR experiment

(a) $H_2OCo(DH)_2i-C_4H_9$ (b) $H_2OCo(DH)_2n-C_4H_9$ (c) $H_2OCo(DH)_2n-C_5H_{11}$

(d) $H_2OCo(DH)_2c-C_6H_{11}$ (e) $H_2OCo(DH)_2PhCH_2$

In this paper, H-5(at β-CD), $-CH_3$(at oxime), α-H(at carbon connected with cobalt directly) were chosen as probe protons. All plots of Δ against $(\Delta/x)^{(1/2)}$ gave good straight lines as required by equation(3). Plots in which $-CH_3$ was probe protons were shown in Fig. 2. LogKa, Δ_0 and $-\Delta G^\ominus$ were calculated and listed in Table.

Values of LogKa and $-\Delta G^\ominus$ are in acceptable agreement with each other for all β-CD/cobaloxime adducts according

TABLE

Data of LogKa, $-\Delta G^{\circ}$(KJ/mol), Δ_0(Hz) for Inclusion
Compound Formation Involving $H_2OCo(DH)_2R$ and β-CD

R	H-5			$-CH_3$			α-H		
	LogKa	$-\Delta G^{\circ}$	Δ_0	LogKa	$-\Delta G^{\circ}$	Δ_0	LogKa	$-\Delta G^{\circ}$	Δ_0
i-C_4H_9	3.07	17.5	80.6	3.18	18.1	68.6	3.13	17.9	66.2
n-C_4H_9	2.70	15.4	106.0	2.85	16.2	68.8	2.87	16.4	74.3
n-C_5H_{11}	3.78	21.6	96.1	3.90	22.3	57.5	3.93	22.5	47.3
c-C_6H_{11}	3.58	20.5	67.9	3.58	20.5	67.9			
$PhCH_2$	4.12	23.5	36.9	4.24	24.2	32.5	4.20	24.0	162.2

to different probe protons. Moreover we found that the ability for formation of β-CD/$H_2OCo(DH)_2R$ adducts was $PhCH_2$ > n-C_5H_{11} > c-C_6H_{11} > i-C_4H_9 > n-C_4H_9 . It probably revealed that the bigger size of the R groups and the deeper inclusion of the groups into the β-CD cavity enhanced hydrophobic and Vander Waals interactions[7].

Single crystals suitable for X-ray crystallography have been achieved. The work are in progress.

ACKNOWLEDGEMENT

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APPENDIX

Table 1 Data of quantitive analysising inclusion compound formation involving $H_2OCo(DH)_2i-C_4H_9$ and β-CD

Concen.	H_5		CH_3		α-H	
	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$
1.10×10^{-2}	61.28	74.59	53.11	69.44	50.16	67.49
5.51×10^{-3}	54.04	99.06	48.88	94.22	46.92	92.30
2.20×10^{-3}	44.05	141.41	40.57	135.72	38.20	131.70
1.10×10^{-4}	34.50	176.99	31.46	169.00	29.56	163.83
4.41×10^{-4}	22.05	223.73	21.86	222.74	18.99	207.65
2.20×10^{-4}	14.16	253.55	14.09	252.88	13.12	244.06

* C:M Δ:Hz

Table 2 Data of quantitive analysising inclusion compound formation involving $H_2OCo(DH)_2n-C_4H_9$ and β-CD

Concen.	H_5		CH_3		α-H	
	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$
4.67×10^{-3}	54.84	108.38	38.99	91.38	42.68	95.60
2.43×10^{-3}	44.55	135.45	33.47	117.40	37.02	123.47
1.87×10^{-3}	40.60	147.43	29.36	125.39	32.59	132.10
9.34×10^{-4}	26.55	168.61	21.87	153.03	24.23	161.06
3.74×10^{-4}	14.94	199.95	11.90	178.48	13.07	187.08
1.88×10^{-4}	8.31	210.99	7.21	196.40	8.28	210.61

* C:M Δ:Hz

Table 3 Data of quantitive analysising inclusion compound formation involving $H_2OCo(DH)_2n-C_5H_{11}$ and β-CD

Concen.	H_5		CH_3		α-H	
	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$
3.93×10^{-3}	78.60	141.43	47.29	109.71	39.47	100.22
2.75×10^{-3}	74.30	164.35	46.30	129.74	38.66	118.55
1.96×10^{-3}	72.25	191.76	44.26	150.09	36.13	135.61
1.18×10^{-3}	66.32	237.20	42.31	189.44	35.22	172.86
7.86×10^{-4}	60.86	278.29	39.62	224.54	32.72	204.06
3.93×10^{-4}	52.09	364.09	33.48	291.92	28.26	268.18
1.57×10^{-4}	35.38	474.44	23.52	386.83	19.97	356.44

● C:M Δ:Hz

Table 4 Data of quantitive analysising inclusion compound
        formation involving $H_2OCo(DH)_2c-C_6H_{11}$ and β-CD

Concen.	H_5		CH_3		$\alpha-H^\#$	
	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$
3.26×10^{-3}	51.39	125.56	50.17	124.06		
2.28×10^{-3}	47.71	144.60	48.62	145.97		
1.63×10^{-3}	45.12	166.38	45.63	167.33		
9.78×10^{-4}	41.03	204.84	39.40	200.72		
6.52×10^{-4}	36.93	238.01	36.23	235.72		
3.26×10^{-4}	29.32	299.90	27.01	287.87		
1.30×10^{-4}	17.62	367.60	18.45	376.10		

* C:M Δ:Hz
#: It partly overlapped with the peak of $-CH_3$ at dimethylglyoxime

Table 5 Data of quantitive analysising inclusion compound
        formation involving $H_2OCo(DH)_2PhCH_2$ and β-CD

Concen.	H_5		CH_3		$\alpha-H$	
	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$	Δ	$(\Delta/C)^{(1/2)}$
2.81×10^{-3}	31.68	106.12	27.99	99.74	138.10	221.56
1.97×10^{-3}	30.21	123.84	27.51	118.18	135.20	262.01
1.41×10^{-3}	29.05	143.70	26.74	137.87	132.61	307.03
8.44×10^{-4}	27.38	180.11	25.02	172.17	124.86	384.62
5.63×10^{-4}	25.77	214.02	23.71	205.27	117.11	456.20
2.81×10^{-4}	22.13	280.43	20.74	271.48	100.50	597.65

* C:M Δ:Hz

Table 6 Data of chemical shifts of $H_2OCo(DH)_2R$, β-CD
1:1 β-CD/$H_2OCo(DH)_2R$(ppm)

		Host	R=i-C₄H₉ Guest	Complex	R=n-C₄H₉ Guest	Complex
R	α-H		1.72	1.82	1.76	1.85
	β-H		0.73	0.80	1.16	1.17
	γ-H		0.69	0.73	0.78	0.78
	δ-H				0.77	0.77
CH₃			2.24	2.34	2.23	2.31
				2.29		2.27
β-CD	H-1	5.06		5.05		5.06
	H-2	3.64		3.64		3.64
	H-3	3.96		3.88		3.90
	H-4	3.58		3.56		3.57
	H-5	3.86		3.74		3.75
	H-6	3.87		3.87		3.86

*: [β-CD/$H_2OCo(DH)_2$i-C₄H₉]=~1.1×10⁻²M
[β-CD/$H_2OCo(DH)_2$n-C₄H₉]=~4.67×10⁻³M

		R=n-C₅H₁₁ Guest	Complex	R=c-C₆H₁₁ Guest	Complex	R=PhCH₂ Guest	Complex
R	α-H	1.75	1.83	2.29	2.38	2.92	3.19
							3.05
	β-H	1.20	1.20	1.40	1.54		
					1.48		
	γ-H	1.14	1.20	1.27	1.28	6.99	7.17
				1.08	0.91		
	δ-H	0.80	0.84	0.84	0.88	7.08	7.11
	ε-H	0.79	0.73			7.32	7.22
CH₃		2.23	2.32	2.24	2.34	2.10	2.16
			2.28		2.30		2.10
β-CD	H-1		5.05		5.05		5.08
	H-2		3.64		3.66		3.66
	H-3		3.88		3.88		3.98
	H-4		3.56		3.55		3.60
	H-5		3.70		3.76		3.79
	H-6		3.87		3.85		3.86

*: [β-CD/$H_2OCo(DH)_2$n-C₅H₁₁]=~3.93×10⁻³M
[β-CD/$H_2OCo(DH)_2$c-C₆H₁₁]=~3.26×10⁻³M
[β-CD/$H_2OCo(DH)_2$PhCH₂]=~2.81×10⁻³M
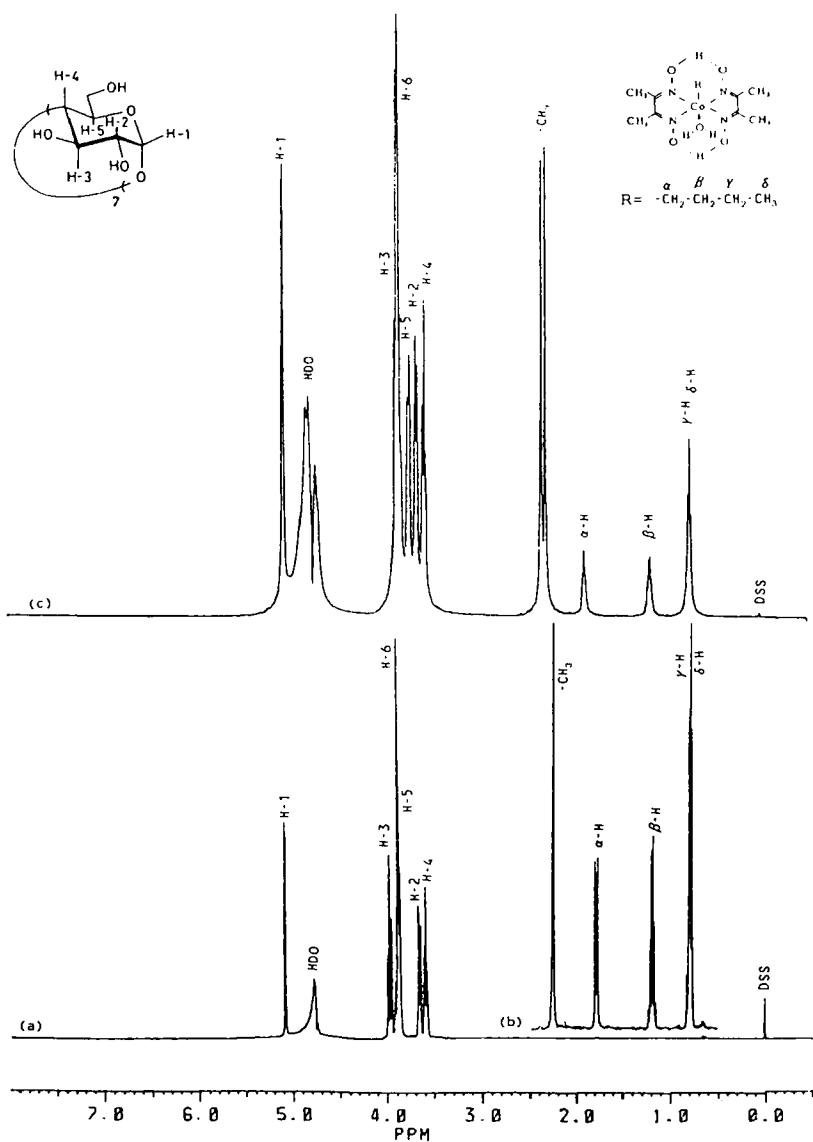
Fig. 1 The 500MHz ^{1}H NMR spectra of (a)β-CD (b) $H_2OCo(DH)_2n$-C_4H_9
(c)β-CD/$H_2OCo(DH)_2n$-C_4H_9 in D_2O at concentration of
approximately 4.67×10^{-3}M
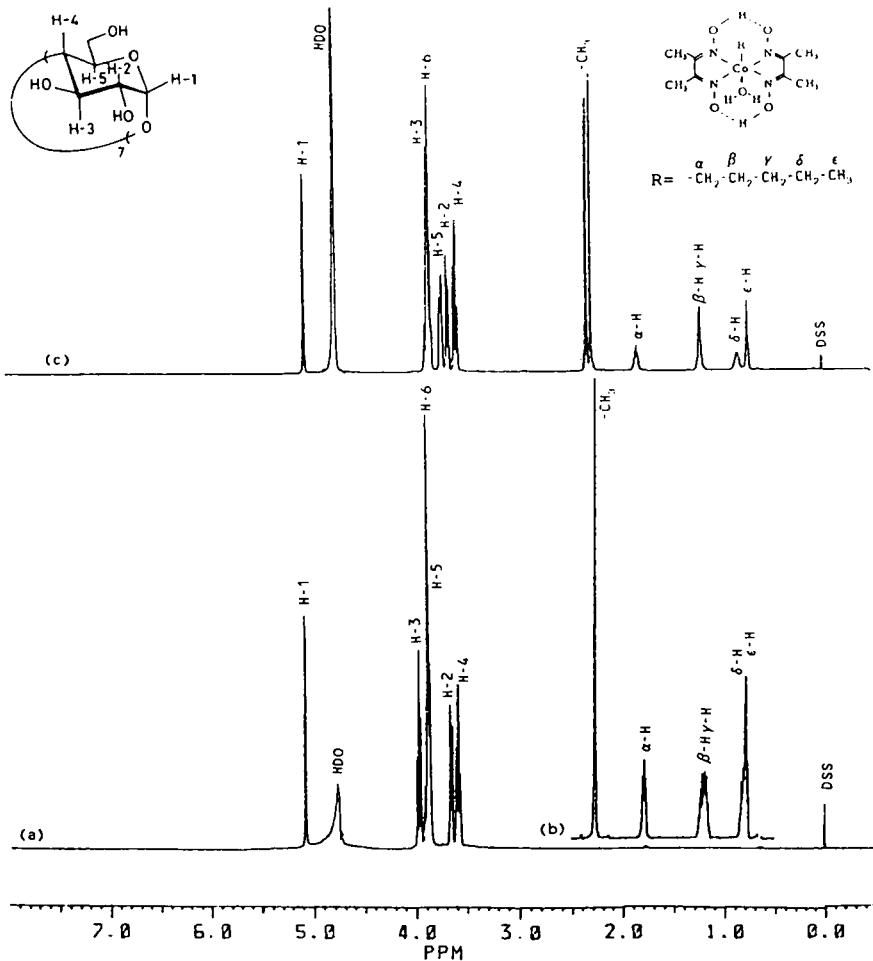
Fig. 2 The 500MHz ^{1}H NMR spectra of (a)β-CD (b) $H_2OCo(DH)_2n$-C_5H_{11}
(c)β-CD/$H_2OCo(DH)_2n$-C_5H_{11} in D_2O at concentration of
approximately 3.93×10^{-3}M
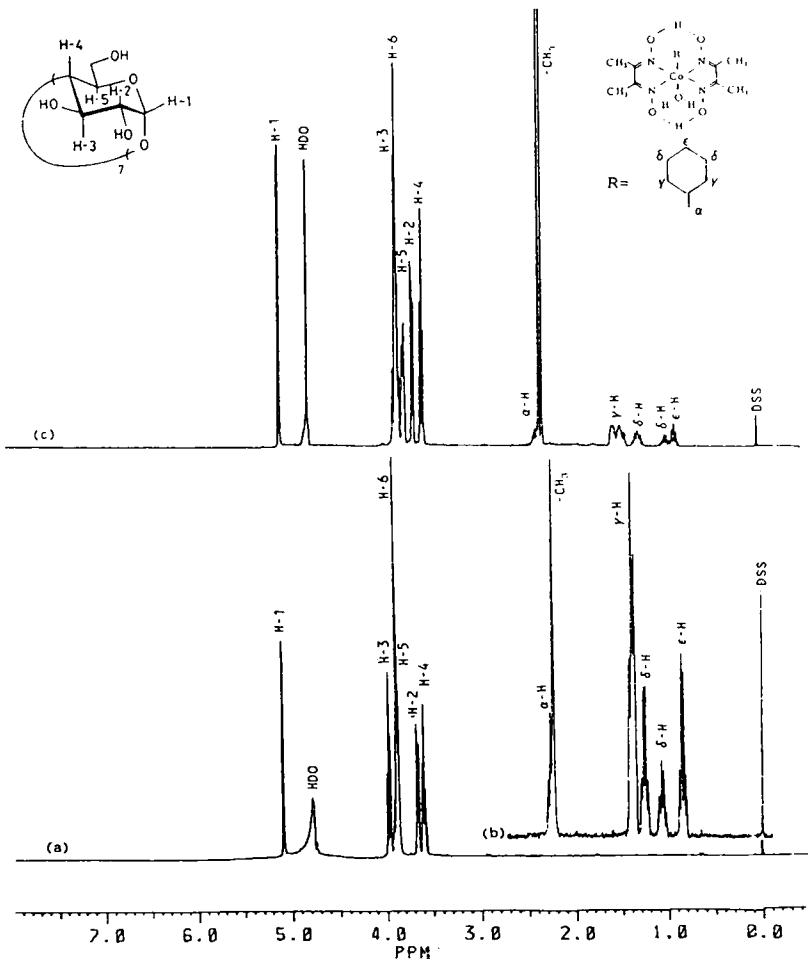
Fig. 3 The 500MHz ^{1}H NMR spectra of (a)β-CD (b) $H_2OCo(DH)_2c$-C_6H_{11}
(c)β-CD/$H_2OCo(DH)_2c$-C_6H_{11} in D_2O at concentration of
approximately 3.26×10^{-3}M
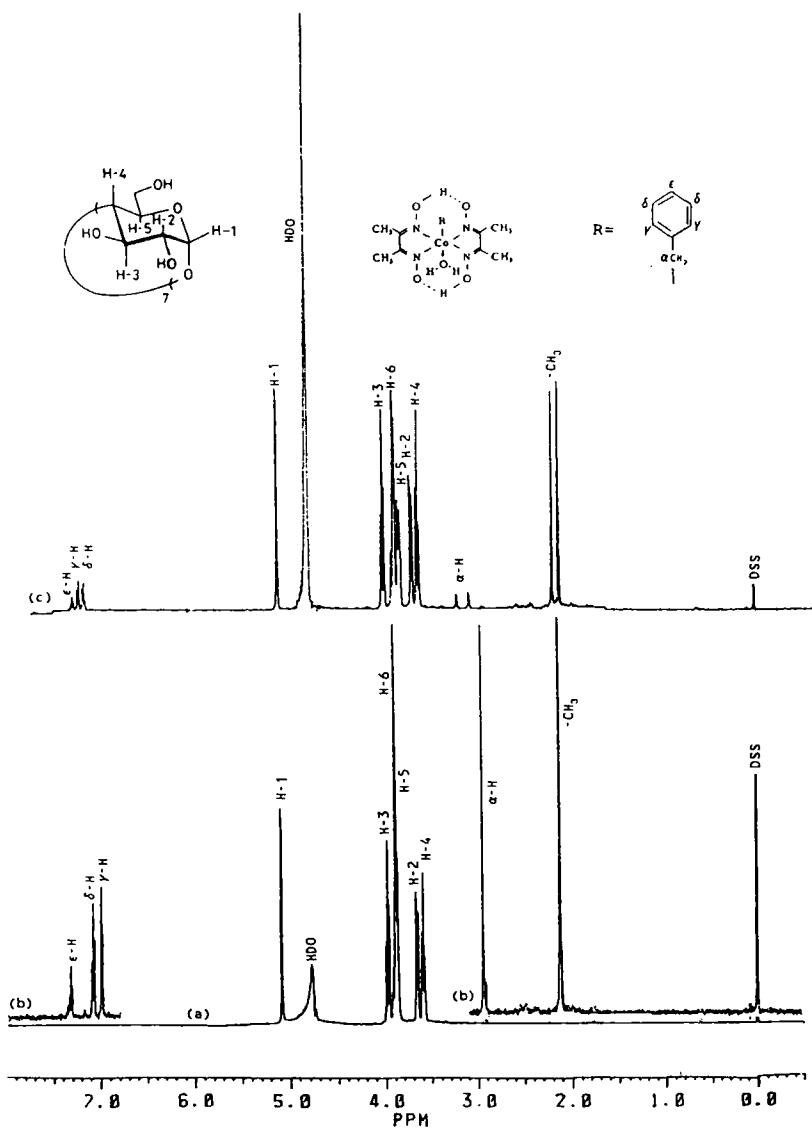
Fig. 4 The 500MHz ^{1}H NMR spectra of (a)β-CD (b) $H_2OCo(DH)_2PhCH_2$
         (c)β-CD/$H_2OCo(DH)_2PhCH_2$ in D_2O at concentration of
       approximately $2.81×10^{-3}$M
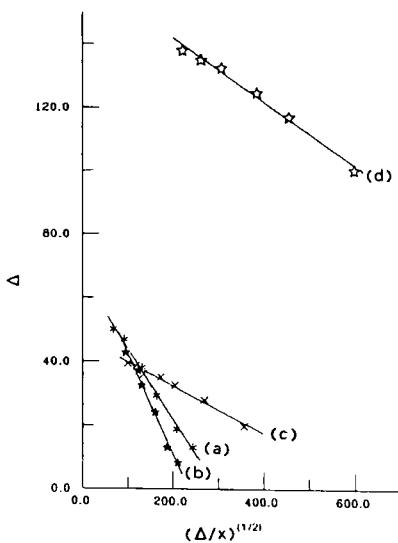
Fig. 5 Plots of Δ against $(\Delta/x)^{(1/2)}$ for α-H at R groups in the
quantitative ^{1}H NMR experiment
(a) $H_2OCo(DH)_2i$-C_4H_9 (b) $H_2OCo(DH)_2n$-C_4H_9 (c) $H_2OCo(DH)_2n$-C_5H_{11}
(d) $H_2OCo(DH)_2PhCH_2$

Fig. 6 Plots of Δ against $(\Delta/x)^{(1/2)}$ for H-5 at β-CD in the
quantitative ^{1}H NMR experiment
(a) $H_2OCo(DH)_2i$-C_4H_9 (b) $H_2OCo(DH)_2n$-C_4H_9 (c) $H_2OCo(DH)_2n$-C_5H_{11}
(d) $H_2OCo(DH)_2c$-C_6H_{11} (e) $H_2OCo(DH)_2PhCH_2$