CHEMISTRY LETTERS, pp. 65 - 68, 1985.

SUPPRESSION OF THE CONVERSION OF 3-t-BUTYL-1-METHYL-1-NITROSOTHIOUREA TO 3-t-BUTYL-1-METHYLUREA BY β-CYCLODEXTRIN UNDER ACIDIC CONDITIONS

Masayoshi ISOBE
Department of Chemistry, Saitama Medical School,
Moroyama, Saitama 350-04

The denitrosation of 3-t-butyl-1-methyl-1-nitrosothiourea(1) was retarded by β-, and γ-cyclodextrins(CDs) at pH 4.70. Decomposition of 1 in the presence of β-CD produced selectively 3-t-butyl-1-methylthiourea(1a), which was remarkably different from the product ratio in the absence of β-CD. These results may be caused by both the protective and the microsolvent effect of β-CD.

Cyclodextrins(CDs) can form a great variety of inclusion complexes with substrates that range from hydrophobic to ionic in charactor, with subsequent reactivity changes. The catalytic actions of CD as a model of enzyme have been interpreted from the standpoint of the nucleophilic catalysis, the microsolvent effect, and/or the conformational effect.[1,2] There are few reports in which the effects of CDs on the product ratio are ascribed to the protective effect of CDs against the attack of reagents. The decomposition of 3-t-butyl-1-methyl-1-nitrosothiourea(1)[3] in acetate buffer solution(pH 4.6) was found to produce a mixture of 3-t-butyl-1-methylthiourea(1a) and 3-t-butyl-1-methylurea(1b) (1a:1b = 37:63)(Scheme 2), which was partly analogous to the decomposition product of 1,3-dipropyl-1-nitrosothiourea in acetone-HCl(1 mol dm^{-3}) solution reported by Lown and Chauhan.[4] In this report the effect of CDs on the conversion of 1 to 1a or 1b has been studied

Pseudo first-order rate constants for the denitrosation of 1 were measured in acetate buffer solution(pH 4.70 or 5.63) in the presence of α-, β-, or γ-CD(1-15 mM) at 37 °C.[5] The results are exhibited in Fig. 1. The denitrosation of 1 was retarded by the formation of the inclusion complexes with β-, or γ-CD and that of 1 in the presence of α-CD showed almost the same rate constants with that in the absence of α-CD. Protonation on N_1 position is necessary prior to the rearrangement of nitroso group. The suppression of protonation on N_1 and/or of rearrangement of nitroso group by β-, or γ-CD are considerd as the reason for the retardation. As for α-CD, it has been reported that the bulky t-butyl group is located outside the CD ring in the complex of p-t-butylphenolate and α-CD.[6]

In order to evaluate the dissociation constant(K_d) and the catalyzed rate constant(k_c) for the inclusion complex between CD and 1, the effect of the CD

concentration on the rate constant was examined by use of the Eadie-type plot.[7] On the assumption of the formation of the 1:1 CD-$\underset{\sim}{1}$ complex, the observed first-order rate constant(k_{obsd}) may be represented by Eq. 1 if the concentration of the CD is much higher than that of $\underset{\sim}{1}$: where $[CD]_0$ is the total concentration of the CD and k_{un} is the uncatalyzed rate constant, respectively.

$$k_{obsd}-k_{un} = -K_d(k_{obsd}-k_{un})/[CD]_0 + k_c-k_{un} \quad (1)$$

Figure 2(A) shows the plots of $(k_{obsd}-k_{un})$ vs. $(k_{obsd}-k_{un})/[CD]_0$ for the denitrosation of $\underset{\sim}{1}$ in the presence of β-CD. The plot was linear with a slope(=K_d) of $(1.24\pm0.04)\times10^{-3}$ M and with an intercept(k_c-k_{un}) of $(-15.87\pm0.03)\times10^{-4}s^{-1}$. Similar linear plots(Fig.2(B)) were obtained for the reaction in the presence of γ-CD, but no such a plot was obtained in the presence of α-CD indicating that $\underset{\sim}{1}$ may not sufficiently be included in the cavity of α-CD. The K_d and k_c values determined are summarized in Table 1. As anticipated, the K_d value for β-CD was much smaller than that for γ-CD.

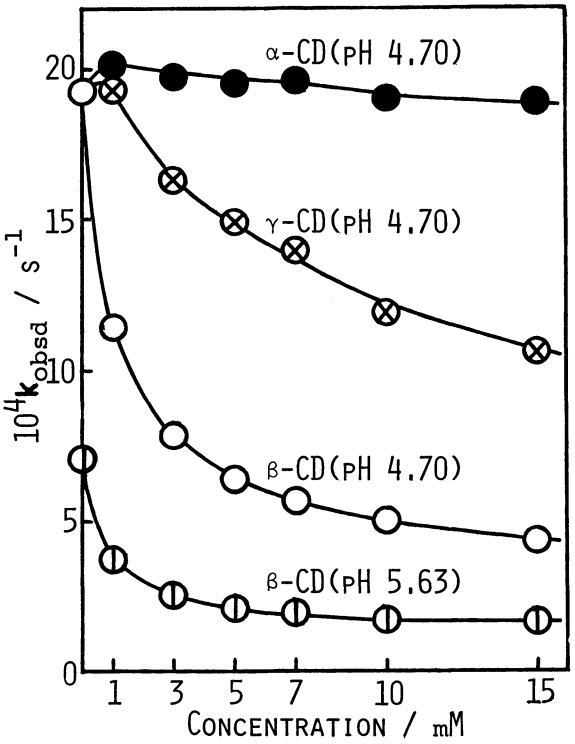


Fig. 1. Effects of cyclodextrins on the denitrosation rate constants of $\underset{\sim}{1}$; $[\underset{\sim}{1}] = 8.28 \times 10^{-5}$ M, μ= 0.2(NaCl).

Table 1. The dissociation constant(K_d) and the catalyzed rate constant(k_c) of the cyclodextrin-$\underset{\sim}{1}$ complex at 37 °C(pH 4.70)

Cyclodextrin	K_d / mM	$k_c \times 10^4$ / s^{-1}
α	———	———
β	1.24 ± 0.04	3.24 ± 0.10
γ	16.1 ± 0.4	1.36 ± 0.03

To examine the effect of α-, β-, or γ-CD on the conversion of $\underset{\sim}{1}$ to $\underset{\sim\sim}{1a}$ or $\underset{\sim\sim}{1b}$, the product analysis in the presence of α-, β-, or γ-CD were performed and the decomposition products were analyzed by the use of ^{1}H NMR.[8] In addition, to know the effect of oxygen or sodium nitrite on the conversion of $\underset{\sim}{1}$ the product analysis under nitrogen atmosphere or with the addition of sodium nitrite under nitrogen atmosphere was also performed. The results were shown in Table 2 with the per cent of $\underset{\sim}{1}$ bound at the different cyclodextrin concentrations. These results may be caused by the different protection of protonated intermediate of $\underset{\sim}{1}$ due to inclusion in the cavity of α-, β-, or γ-CD against the attack of nitrous acid formed by oxygen (Scheme 1)[9] and they suggest that it is almost impossible for $\underset{\sim}{1}$ to be converted to $\underset{\sim\sim}{1b}$ in the cavity of β-CD but it is possible in the larger cavity of γ-CD to a small extent or outside the ring of α-CD. Product ratio of $\underset{\sim\sim}{1b}$ decreased and that of $\underset{\sim\sim}{1a}$ increased with the increase in the concentration of β-CD(Table 2). The similar protective effect against a reagent by β-CD has been observed in the reaction of

$$2NO + O_2 = 2NO_2$$
$$NO_2 + NO = N_2O_3$$
$$N_2O_3 + H_2O = 2HNO_2$$

Scheme 1.

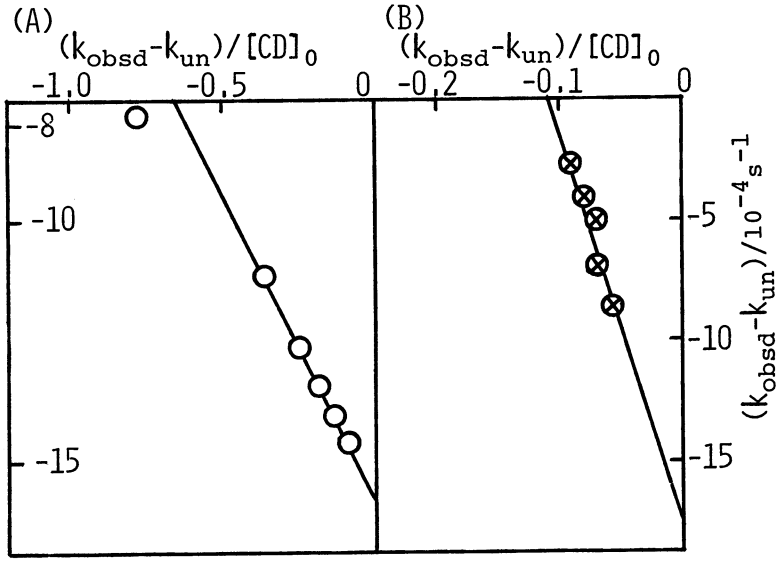


Fig. 2. The plots of $(k_{obsd}-k_{un})$ vs. $(k_{obsd}-k_{un})/[CD]_0$ for the denitrosation of 1 in the presence of β-CD((A)) or γ-CD((B)).

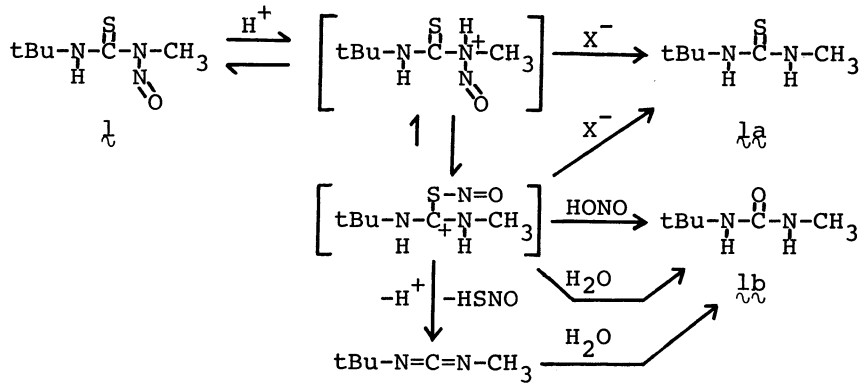
vitamine K analogues against the attack of hydrogen peroxide in the presence of β-CD.[10] Moreover, decomposition of 1 in 50% ethylene glycol-acetate buffer(pH 4.60) produced predominantly 1a. This result suggests that the microsolvent effect of cyclodextrin may be affecting the product ratio by depressing the approach of the nitrous acid into the apolar cavity which possesses the character of space alkalinity[11] or topochemical base.[12]

In conclusion, the conversion of 1 to 1b was most suppressed by β-CD among those three CDs leading to produce selectively 1a(Scheme 2).

Table 2. Decomposition product ratio(%) of 1 under acidic conditions[a]

Catalyst	Concentration 10^{-3} mol dm^{-3}	Product ratio, 1a : 1b	Yield/% 1a	Yield/% 1b	% 1 bound
None		37 : 63	24	40	-
None(N_2)[b]		83 : 17	22.5	4.5	-
None(N_2,$NaNO_2$)[c]		50 : 50	37	37	-
α-CD	5.70	36 : 64	29	52	-
β-CD	2.85	69 : 31	50	22	37
	5.70	87 : 13	56	8	63
	8.55	82 : 18	60	13	77
γ-CD	5.70	66 : 34	51	26	22
Sucrose	20.0	42 : 58	28	38	-
Ethylene glycol[d]		77 : 23	60	18	-

a)Acetate buffer(pH 4.60), μ= 0.2(NaCl). [1]= 5.70 X 10^{-3}mol dm^{-3}. b)Under nitrogen atmosphere. c)With sodium nitrite(an equimolar amount with 1) under nitrogen atmosphere. d)50%(vol%).



Scheme 2.

The author wishes to thank Professor Kazuo Nagamatsu and Dr. Kazuyuki Yano at Saitama Medical School for their helpful comments and useful discussions.

References

1) D. W. Griffiths and M. L. Bender, Adv. Catal., 23, 209(1973).
2) M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag, Berlin(1978).
3) 1: Found: C, 41.07; H, 7.46; N, 23.92; S, 18.39%. Calcd for $C_6H_{13}N_3OS$: C, 41.12; H, 7.48; N, 23.98; S, 18.30%.
4) J. W. Lown and S. M. S. Chauhan, J. Org. Chem., 48, 3901(1983).
5) 20 μl of 1(0.87 mg/0.4 ml-MeOH) in the acetate buffer solution(3 ml) in a thermostated UV cell, the progress of the reaction was monitored spectrophotometrically by following the disappearance of the absorption maximum at 266-272 nm.
6) J. P. Behr and J. M. Lehn, J. Am. Chem. Soc., 98, 1743(1976).
7) G. S. Eadie, J. Biol. Chem., 146, 85(1942).
8) A solution of 1(10 mg, 0.057 mmol) in 0.5 ml of MeOH was added to 10 ml of acetate buffer solution(pH 4.6, 0.05 M, μ=0.2(NaCl)) containing β-CD(64.8 mg, 0.057 mmol) and stirred for 1 h at 37 °C. After cooling, the contents were extracted with chloroform(10 ml X 4). The combined extracts were washed with saturated NaCl solution, dried($MgSO_4$), and evaporated to give a white solid (5.2 mg, 64%, 1a:1b = 87:13 by ^1H NMR analysis comparing the integrated value of the peak of $N-CH_3$). 1a: NMR($CDCl_3$) δ 6.14(br, 2H, NH), 3.02(d, 3H, J=4.8 Hz, $N-CH_3$), 1.42(s, 9H, $-C(CH_3)_3$); 1b: NMR($CDCl_3$) δ 5.21(br, 1H, NH), 5.01(br, 1H, NH), 2.65(d, 3H, J=4.8 Hz, $N-CH_3$), 1.30(s, 9H, $-C(CH_3)_3$).
9) D. L. H. Williams, J. Chem. Soc., Perkin Trans. 2, 1977, 128.
10) I. Tabushi, K. Yamamura, K. Fujita, and H. Kawakubo, J. Am. Chem. Soc., 101, 1019(1979).
11) F. Cramer, Ann. Chem., 579, 17(1953).
12) J. Szejtli and E. Bánky-Elöd, Acta Chim. Acad. Sci. Hung., 91, 67(1976).

(Received October 16, 1984)