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^{1}H-NMR Study of the Inclusion Reactions of Charged Derivatives of α-Cyclodextrin with Sodium p-(3-t-Butyl-4-hydroxyphenylazo)benzenesulfonate

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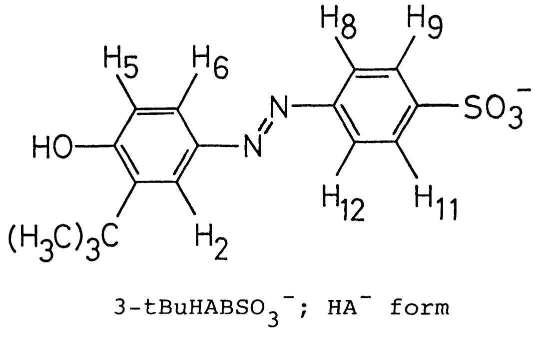
Presence of an intermediate inclusion species is demonstrated by 270 MHz ^{1}H-NMR spectroscopy in the system of the title azo compound and the charged derivatives of α-cyclodextrin. The ^{1}H-NMR peaks due to the sulfanilate moiety of the guest molecule are distinctly split into two peaks upon binding to the positively charged cyclodextrin, suggesting the formation of an intermediate species.

The mode of interaction of cyclodextrin with a variety of aromatic guest molecules in solution has been extensively studied mainly by proton magnetic resonance spectroscopy (^{1}H-NMR).[1)] α-Cyclodextrin, the smallest member in the series of cyclic oligosaccharides composed of six or more α-(1,4)-linked D-glucopyranose units, forms regioselective inclusion complexes with rod-like organic compounds such as the title azo guest molecule (3-tBuHABSO_3^-).[2)] In these systems, NMR spectroscopy was proved to be a powerful tool to clarify the interaction site of the formed regioselective inclusion complex.

Recently, we have demonstrated the following two-step mechanism for the inclusion reaction of a positively charged α-cyclodextrin, an ethylenediamine monosubstituted α-cyclodextrin ($((C_6H_{10}O_5)_5O_4H_7C_5H_2C\text{-}NH_2^+CH_2CH_2NH_3^+$; $\alpha\text{-CDxenH}_2^{2+}$) and a negatively charged title guest molecule in aqueous solution.[3)]

$$\text{Guest(G)} + \alpha\text{-CDxenH}_2^{2+} \underset{}{\overset{\text{fast}}{\rightleftarrows}} \text{G-}\alpha\text{CDxenH}_2^{2+*} \overset{\text{slow}}{\rightleftarrows} \text{G-}\alpha\text{CDXenH}_2^{2+} \qquad (1)$$

Despite such an impressive detection by kinetic method of an intermediate species ($\text{G-}\alpha\text{CDxenH}_2^{2+*}$), its structure was still not elucidated.



3-tBuHABSO_3^-; HA^- form

In the present paper, we propose the structure of the intermediate species, reporting the ^{1}H-NMR evidence for the two-step inclusion process (Eq. 1) of 3-tBuHABSO$_3^-$ with a positively charged α-cyclodextrin.

The ^{1}H-FT NMR spectra of the degassed sample ([guest] = (0.8 - 3.8) x 10^{-2} mol dm^{-3}, [α-CDx] = [α-CDxen] = (0.6 - 6) x 10^{-2} mol dm^{-3}, and [Zn^{2+}] = 8.4 x 10^{-2} mol dm^{-3}) were taken on a JEOL JNM GX-270 spectrometer (270 MHz) in a 5mm spinning tube at 25 °C. Deuterium oxide (99.9%), 40% sodium hydroxide-d$_1$ (NaOD), and 20% hydrochloric acid-d$_1$ (DCl) were purchased from E. Merck, Ltd. Chemical shifts were referred to external tetramethylsilane (1% TMS in $CDCl_3$) with an accuracy of 0.001 ppm.

Figure 1 shows the ^{1}H-NMR spectra of an acid form (HA$^-$) of 3-tBuHABSO$_3^-$ in the absence and the presence of α-CDx and α-CDxen in D_2O (pD = 3.2). The assignments of the ^{1}H-NMR spectra of 3-tBuHABSO$_3^-$ are based on coupling constants, peak heights, substituents effect, and additivity rule. The coupling constants of the sulfanilate moiety ($H_{8,12}$ and $H_{9,11}$) and the phenol moiety (t-Bu, and $H_{2,5,6}$) are determined to be $J_{8,12} = J_{9,11}$ = 8.43 Hz, $J_{5,6}$ = 8.43 Hz, and $J_{2,6}$ = 2.19 Hz. In α-CDx system (Fig. 1B), the protons of $H_{9,11}$ and $H_{8,12}$ show an appreciable downfield shift ($\Delta\delta(H_{9,11}) = \delta(\text{complex}) - \delta(\text{free})$ = 0.546 ppm and $\Delta\delta(H_{8,12})$ = 0.629 ppm) as compared with those of $H_{2,5,6}$ and t-Bu substituent. This fact indicates that α-CDx interacts regioselectively with the sulfanilate moiety (-PhSO$_3^-$) of 3-tBuHABSO$_3^-$. A large steric hindrance occurs between the rim of α-CDX and the t-Bu substituent.$^{4)}$ Figure 1B shows only the presence of one inclusion complex.

Upon binding to α-CDxen in acid pD region, the ^{1}H-peaks of 3-tBuHABSO$_3^-$, particularly those of the sulfanilate moiety, split into two peaks. This shows clearly the formation of a new inclusion species which is not detected in the α-CDx system. The chemical shifts (δ) designated as A in Fig. 1C coincide almost with those observed in α-CDx system (Fig. 1B); the structure of this state (state A) closely resembles that of the α-CDx inclusion complex. On the other hand, the δ of state A* in Fig. 1C differs considerably from that of state A. The ^{1}H-peaks of H_5 and t-Bu in state A* appear always more upfield as compared with those in state A except for H_2 and H_6.$^{5)}$ Particularly, as for $H_{8,12}$ and $H_{9,11}$, more upfield positioning of δ are observed,$^{6)}$ indicating that the inclusion in state A* is to some extent shallower than that in state A. This shallow inclusion would be due to the strong electrostatic interaction in state A* operating between the positive charge (-NH$_2^+$CH$_2$CH$_2$-NH$_3^+$) and the negative charge (-SO$_3^-$). The state A* is not observed in alkaline pD region.$^{7)}$ All the interesting ^{1}H-NMR features observed in α-CDxen system appear also in α-CDxen Zn^{2+} system (See Fig. 1D).$^{8)}$

Figure 2 shows the dependence of δ of 3-tBuHABSO$_3^-$ on the concentration of α-CDxenH$_2^{2+}$.$^{9)}$ There are two characteristic tendencies as for the concentration-dependence of δ, corresponding to the two states, A and A*. The peaks (δ_A) ascribed to the state A appear always at the same position irrespectively of the bound(%), suggesting the chemical exchange is slow as compared with the NMR time scale.$^{10)}$ However, the signals (δ_{A^*}) due to A* appear in the intermediate region between δ(free) and δ(intermediate); their position and peak areas are proportional to the bound(%), i.e., the ratio of the population of the intermediate

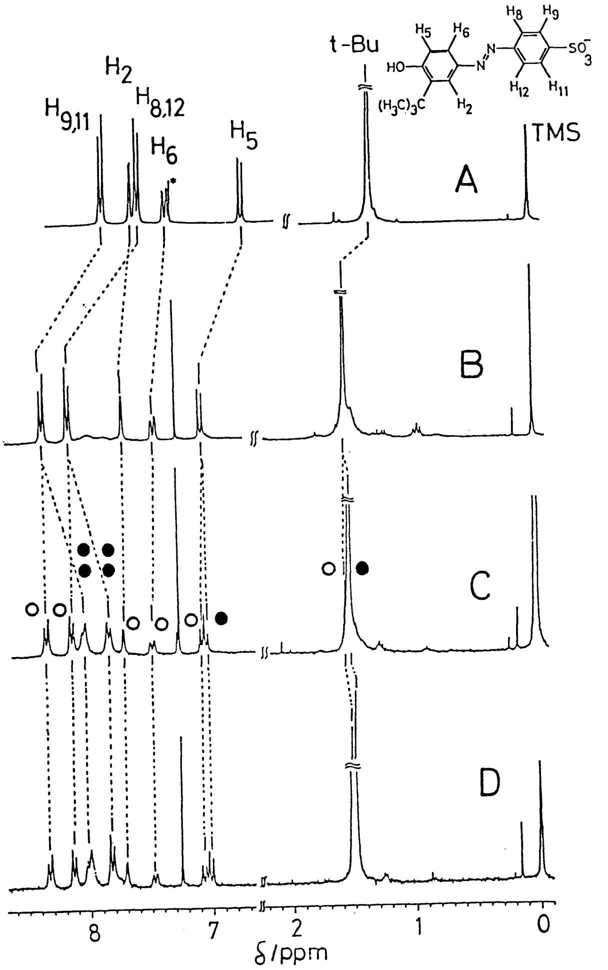


Fig. 1. ^{1}H-NMR Spectra of t-BuHAB-SO_3^- in the Absence and the Presence of α-CDx and α-CDxen in D_2O (pD = 3.4). The symbols, o and ●, denote the states, A and A^*, respectively.

A: 3-tBuHABSO_3^- alone,
B: α-CDx system,
C: α-CDxen system,
D: α-CDxen + Zn^{2+} system.

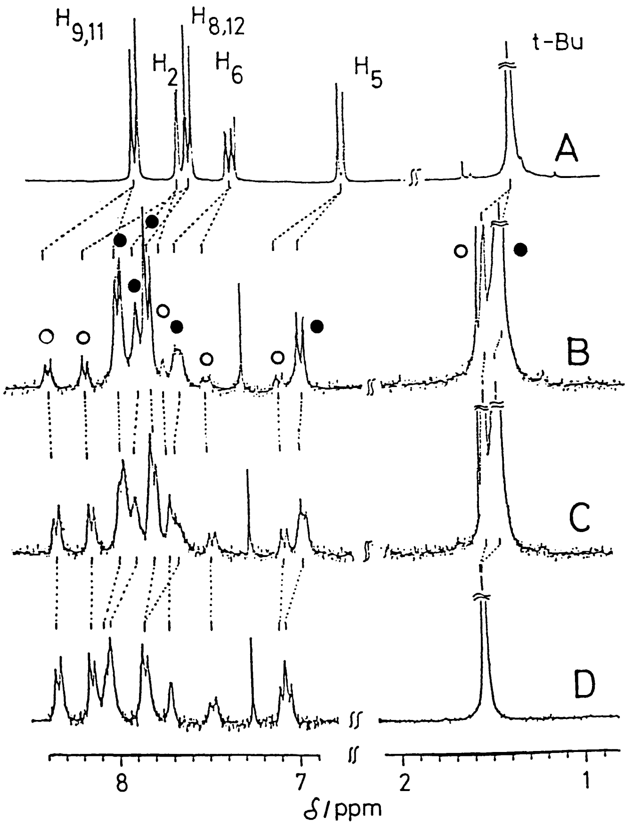
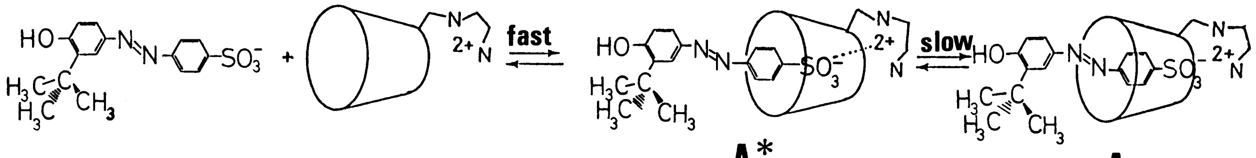


Fig. 2. Dependence of the Chemical Shifts (δ) of 3-tBuHABSO_3^- on the Concentration of α-CDxen (pD = 3.4). As for the symbols, o and ●, see Fig. 1.

Bound(%)	
A:	0,
B:	23.2,
C:	49.2,
D:	95.1.

species increases. This fact indicates that the chemical exchange of the type G + α-CDxenH_2^{2+} $\rightleftarrows$ G-αCDxenH_2^{2+*} proceeds rapidly compared with the NMR time scale,[1, 11] which is in line with the result of the stopped-flow data.[3]

In conclusion, we could propose the following reaction mechanism for the inclusion reaction of α-CDxenH_2^{2+} with 3-tBuHABSO_3^-.[12]



A* A

In the first step, the negatively charged guest molecule forms an unstable intermediate inclusion complex with the positively charged α-cyclodextrin in such a way that the electrostatic interaction is operative.[13] The second step would be assigned to the intramolecular motion of the intermediate species, such a process being responsible for the final rearrangement of the interacting site.

References

1) D. J. Wood, F. E. Hruska, and W. Saenger, J. Am. Chem. Soc., 99, 1735 (1977).

2) N. Yoshida, A. Seiyama, and M. Fujimoto, Chem. Lett., 1985, 1013.

3) H. Monzen, N. Yoshida, and M. Fujimoto, Chem. Lett., 1988, 1129.

4) This type of steric hindrance has been already observed. See Refs. in N. Yoshida and M. Fujimoto, J. Chem. Res., 1985, 224; J. Phys. Chem., 91, 6691 (1987). The inclusion from the sulfanilate moiety has been proved. Introduction of methyl group at 2, 6, and/or 9 positions inhibits the inclusion from the sulfanilate moiety.

5) The chemical shifts of H_2 and H_6 are very sensitive to the change of the electronic state of the guest molecule. Therefore, these protons are not the useful probes for an indication of the inclusion state.

6) This phenomenon was also observed in G-βCDxenH_2^{2+} system. H. Monzen, N. Yoshida, and M. Fujimoto, J. Coord. Chem., Sect. B, in press (1988).

7) The loss of an unusual ^{1}H-NMR feature upon increasing the pD value of the solution indicates that an electrostatic interaction derived from the host and the guest is not present in alkaline pD region.

8) α-CDxen can form the 1 : 1 zinc complex in a large excess of $ZnCl_2$.

9) The value of %(bound) which is the ratio of the complexed guest and the free guest can be evaluated using the formation constant.

10) Only this type of concentration-independent peaks are observed in α-CDx system, since the reaction between α-CDx and 3-tBuHABSO_3^- is very slow.

11) N. Yoshida and M. Fujimoto, Bull. Chem. Soc. Jpn., 55, 1038 (1982).

12) Although the electrostatic interaction between the -SO_3^- moiety and the -$NH_2^+CH_2CH_2NH_3^+$ moiety could be conceivable in the exterior part of the host molecule, α-CDxenH_2^{2+}, such a type of interaction would not be detectable by electronic absorption spectroscopy and ^{1}H-NMR spectroscopy.

13) The intermediate species would be unstable because of the location of the -SO_3^- group at the periphery of the cavity.

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