

DYNAMIC MOLECULAR MOTIONS OF GUEST MOLECULE INCLUDED
 IN MODIFIED β -CYCLODEXTRINS

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

Upon inclusion in capped β -cyclodextrin, the overall reorientational motion of doubly deuterium labeled p-methylcinnamic acid slows down by a factor of 14 compared with that in an aqueous solution but the internal rotation of the methyl group still remains free.

In order to design sophisticated host molecules such as artificial receptors, it is important to understand the nature of "recognition" interactions between hosts and guests.¹⁾ Cyclodextrin is one of most interesting host molecules which are suitable for the investigation of such molecular recognitions, because cyclodextrin can be easily modified to introduce various types of recognition groups in addition to its basic hydrophobic cavity.²⁾ Although the static aspects of the molecular recognitions by cyclodextrins have been extensively investigated by measuring thermodynamic parameters,^{2,3)} little is still known about their dynamic aspects except those of unmodified cyclodextrins,⁴⁾ which suggest an guest molecule in the cyclodextrin cavity rotates relatively freely but highly anisotropically along the z axis (see Chart I). In this paper, we wish to report the effects of the modified β -cyclodextrin on the molecular motion of the guest molecule, which is measured directly by the deuterium quadrupolar relaxation method.⁵⁾ The data obtained here indicate that the additional recognition groups on β -cyclodextrin restrict the molecular motions of the benzene ring of the guest but not necessarily the internal rotation of its small substituent such as the methyl group.

Doubly deuterium labeled p-methylcinnamic acid (G) which was first applied by Lehn et al. to the estimation of the molecular motion in the α -cyclodextrin inclusion complex,^{4b)} was employed as the guest and β -, (Cy), 6-trimethylammonium- β -, (CyN⁺),⁶⁾ A,C-6,6'-bis(trimethylammonium)- β -, (CyN₂²⁺),⁷⁾ and A,C-carbazole capped- β -cyclodextrin, (Cap),⁸⁾ were chosen as

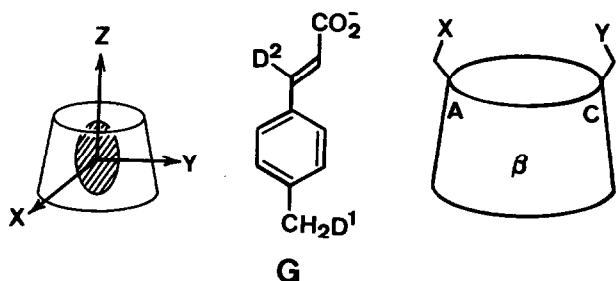
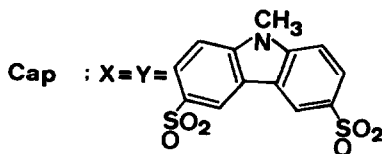
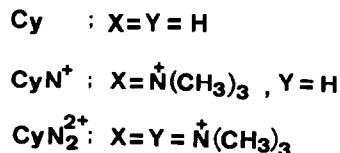


Chart 1.



hosts. The association constant of each host-guest couple (K) was determined spectroscopically by the competitive binding of G with methyl orange.⁹⁾ Since, in the case of α -cyclodextrin, the formation of the 1:2 complex (guest/host) was reported, the possibility of the similar 1:2 complexation in the present β -cyclodextrin host series was also checked by the conductometric measurement reported by Laufer et al.¹⁰⁾ The results, however, did not suggest the existence of such a 1:2 complex under the present condition, i.e., for example, the association constant between G and Cy was measured to be $440 \pm 50 \text{ M}^{-1}$ by spectroscopic measurement or $470 \pm 40 \text{ M}^{-1}$ by conductometric measurement and that for the 1:2 complex ($G \cdot Cy_2$) was less than 20 M^{-1} if existed. Therefore, only the 1:1 complexes were considered in the following analysis.

All $^1\text{H-NMR}$ data were collected by a JEOL GX-400 NMR spectrometer. The deuterium relaxation times (T_q) for D^1 and D^2 were obtained by the computer aided line shape analysis of ^1H nucleus of G coupled with the corresponding deuterium including the natural line width parameter¹¹⁾ (Fig 1). After correction of T_q with association constant according to eq. 1,^{4b,12)} two molecular correlation times of G , τ_q^M (for the overall reorientation) and τ_q^i (for the internal rotation of the methyl group in G), were calculated by the method employed by Lehn.^{4b)} Since it is well established that, at the present temperature, the rotational barrier between the double bond and the benzene ring is sufficiently high,^{4b)} the τ_q^M value thus obtained for D^2 is the good index of the molecular motion of the benzene ring. The association constants and molecular correlation times are summarized in Table 1.

$$1/T_q^{\text{obs}} = \alpha/T_q^{\text{complex}} + (1-\alpha)/T_q^{\text{free}} \quad (\alpha: \text{fraction of complexes}) \quad \text{eq.1}$$

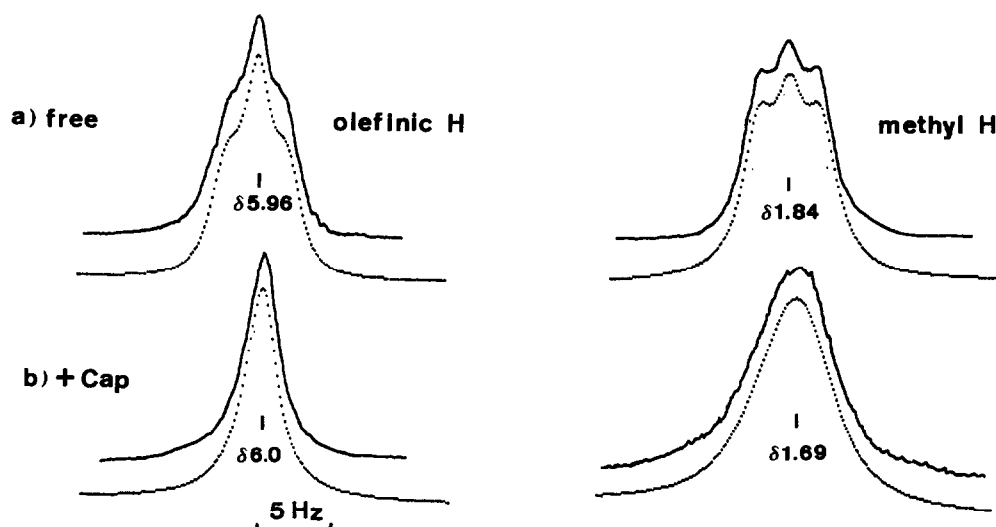


Fig.1. $^1\text{H-NMR}$ spectra of G : (—) observed and (.....) simulated line shapes. $\text{pD}=7.0$, 35°C , $[G]=3 \times 10^{-3} \text{ M}$, $[\text{Cap}]=5 \times 10^{-3} \text{ M}$.

Table 1 Molecular Correlation Times (τ_q) and Association Constants of Deuterium Labeled p-Methylcinnamic Acid (G).^{a)}

Host	K (M ⁻¹)	τ_q^M (ps)	τ_q^i (ps)
_____ b)	_____	20 ± 1	< 1 c)
Cy	440 ± 50	73 ± 2	19 ± 5
CyN ⁺	720 ± 60	106 ± 10	53 ± 10
CyN ₂ ²⁺	790 ± 100	150 ± 8	< 1 c)
Cap	3200 ± 500	270 13	< 1 c)

a) 35 ± 1°C, pD 7.0 in D₂O. b) without the host molecule.

c) the values smaller than the experimental error limits.

The association constants for CyN⁺·G, CyN₂²⁺·G and Cap·G, as expected, are 1.6, 1.8 and 7.3 times larger than that for Cy·G, due to the additional recognition interactions, e.g., the Coulombic interaction between ammonium and carboxylate ions in CyN⁺·G, CyN₂²⁺·G and the expanded hydrophobic interaction in Cap·G,¹³⁾ respectively. The most striking result in the present work is that the stronger host in the sense of the association constant restricts the overall reorientation of the guest molecule more significantly. Thus, the correlation times, τ_q^M , of G included by Cy, CyN⁺, CyN₂²⁺ and Cap become ca. 2.2, 3.6, 8 and 14 times larger, respectively, than that in the free state. Since the correlation time for the overall reorientation of the β -cyclodextrin inclusion complex usually lies in 400-700ps,^{4c-f)} the dynamic coupling coefficients for the benzene ring of G and Cap ($\tau_q^M(\text{G in Cap})/\tau_q^M(\text{Cap})$) may be estimated to be larger than ca. 0.4, which indicates the existence of the appreciable coupling between the molecular motions of G and Cap.

In contrast, the unexpected free internal rotation of the methyl moiety of G included by Cap (small τ_q^i for Cap·G) are observed,¹⁴⁾ though those for Cy·G and CyN⁺·G are significantly restricted (see Table 1). Although the situation is still too complicated for the definite conclusion, in the case of Cap, the low local dielectric constant in the cavity is one of possible answers which explain this free internal rotation of the methyl moiety in Cap·G.¹⁵⁾

The relationship between K and τ_q^M found in this work indicate that, in the present case, the rotational barriers of benzene ring in hosts ($\Delta G_{\text{rot}}^{\ddagger}$) are almost proportional to the free energy changes for the complexation between hosts and G ($\Delta G_{\text{ass}}^{\circ}$).¹⁶⁾ This new finding is very important for the design of the artificial receptor, because this type of the information makes it possible to estimate the degree of the entropy loss due to the restriction of the molecular motion of the guest upon inclusion. Further detailed

investigations, including the determination of activation energies for molecular motions of guests in a wide variety of hosts, are now under way.

REFERENCES

- 1) Vögtle, F. "Host Guest Complex Chemistry I, II"; Springer Verlag: New York, 1982.
- 2) a) Breslow, R. Science 1982, 218, 532.
 b) Tabushi, I. Acc. Chem. Res. 1982, 15, 66.
 c) Tabushi, I.; Kuroda, Y. Adv. Catal. 1983, 32, 417.
 d) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer Verlag: New York, 1978.
- 3) a) Gelb, R. I.; Schwartz, L. M.; Candelino, B.; Fuhrman, H. S.; Johnson, R. F.; Laufer, D. A. J. Am. Chem. Soc. 1981, 103, 1750.
 b) Bergeron, R. J.; Channing, M. A. Ibid. 1978, 100, 2878.
 c) Uekama, K.; Otagiri, M.; Kanie, Y.; Tanaka, S.; Ikeda, K. Chem. Pharm. Bull. 1975, 23, 1421.
- 4) a) Flohr, K.; Paton, R. M.; Kaiser, E. T. J. Am. Chem. Soc. 1975, 97, 1209.
 b) Behr, J. P.; Lehn, J. M. J. Am. Chem. Soc. 1976, 98, 1743.
 c) Uekama, K.; Hirayama, F.; Koinuma, H. Chem. Lett. 1977, 1393.
 d) Bergeron, R. J.; Brown, P. S. J. Am. Chem. Soc. 1982, 104, 3664.
 e) Inoue, Y.; Okuda, T.; Miyata, Y. Carbohydrate Res. 1982, 101, 187.
 f) Okazaki, M.; Kuwata, K. J. Phys. Chem. 1984, 88, 4181.
 g) Tabushi, I.; Kiyosuke, Y.; Sugimoto, T.; Yamamura, K. J. Am. Chem. Soc. 1978, 100, 916.
- 5) Mantsch, H. H.; Saito, H.; Smith, I. C. P. Prog. NMR Spectro. 1977, 11, 211.
- 6) Matsui, Y.; Okimoto, A. Bull. Chem. Soc. Japan, 1978, 51, 3030.
- 7) a) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C. J. Am. Chem. Soc. 1981, 103, 711.
 b) Tabushi, I.; Shimokawa, K.; Fujita, K. Tetrahedron Lett. 1977, 18, 1527.
- 8) Tabushi, I.; Yamamura, K.; Nabeshima, T. J. Am. Chem. Soc. 1984, 106, 5267.
- 9) Tabushi, I.; Kuroda, Y.; Mizutani, T. Tetrahedron 1984, 40, 545.
- 10) Gelb, R. I.; Schwarz, L. M.; Laufer, D. A. J. Am. Chem. Soc. 1978, 100, 5875.
- 11) The most striking advantages of the deuterium relaxation analysis by the line shape analysis are; a) the deuterium quadrupolar relaxation may be directly associated with the molecular motions without considering other relaxation mechanisms such as dipole-dipole and spin-rotational interaction, b) the line shape analysis makes it possible to measure the relaxation time under the relatively low concentration of the target molecule, because only the ^1H -nucleus, not deuterium, which couples with the adjacent deuterium is necessary to be measured, see,
 a) Kintzinger, J. P.; Lehn, J. M.; Williams, R. L. Mol. Phys. 1969, 17, 135.
 b) Brevard, C.; Kintzinger, J. P.; Lehn, J. M. Tetrahedron 1972, 28, 2429.
- 12) Anderson, J. E.; Fryer, P. A. J. Chem. Phys. 1969, 50, 3784.
- 13) a) Tabushi, I.; Shimokawa, K.; Shimizu, N.; Shirakata, H.; Fujita, K. J. Am. Chem. Soc. 1976, 98, 7855.
 b) Tabushi, I.; Fujita, K.; Yuan, L. C. Tetrahedron Lett. 1977, 18, 2503.
 c) Fujita, K.; Shinoda, T.; Imoto, T. J. Am. Chem. Soc. 1981, 103, 1161.
- 14) Upon inclusion in Cap, the ^1H -NMR signals of methyl and olefinic protons of G show the large upfield shift ($\Delta\delta = -0.15$) and the small downfield shift ($\Delta\delta = +0.01$) respectively. Based on these observations, the methyl moiety in Cap·G is reasonably estimated to locate in the position near from the carbazole moiety.
- 15) Govil, G.; Bernstein, H. J. J. Chem. Phys. 1968, 48, 285.
- 16) It should be noted that the relationship between K and T_g^M may not be necessarily held in the different series of the host-guest complex. Indeed, the data reported by Lehn (see ref. 4b) and our preliminary result show that T_g^M of G in α -cyclodextrin is larger than that in β -cyclodextrin (Cy), though the former association constant is only one third of the latter one.

(Received in Japan 23 December 1987)