

# COMPLEXATION OF SPIROPYRANS WITH CYCLODEXTRINS: EFFECTS OF $\beta$ - AND $\gamma$ -CYCLODEXTRINS ON THE THERMAL ISOMERIZATION OF 6-SO<sub>3</sub><sup>-</sup>-SPIROPYRAN

YOSHIMI SUEISHI\* AND TOMONORI NISHIMURA

Department of Chemistry, Faculty of Science, Okayama University, Tsushima-naka 3-1-1, Okayama 700, Japan

The thermal isomerizations of 1',3',3'-trimethyl-spiro[2*H*-1-benzopyran-2,2'-indoline]-6-sulphonic acid (6-SO<sub>3</sub><sup>-</sup>-SP) between its spiro (SP) and merocyanine (MC) forms were followed spectrophotometrically in the presence of cyclodextrins ( $\beta$ - and  $\gamma$ -CDs) at various pressures. From the pressure dependence of the isomerization rate, the activation volumes for the thermal isomerization of 6-SO<sub>3</sub><sup>-</sup>-SP were estimated to be 17.1 cm<sup>3</sup> mol<sup>-1</sup> for MC → SP and 8.5 cm<sup>3</sup> mol<sup>-1</sup> for SP → MC. The equilibrium constants (*K*) for the inclusion complex formation of CDs with 6-SO<sub>3</sub><sup>-</sup>-SP were determined at various pressures. It was found that the stability of the 1:1 inclusion complex between 6-SO<sub>3</sub><sup>-</sup>-SP and CDs decreases in the order  $\beta$ - >  $\gamma$ - >  $\alpha$ -CD. From the pressure dependence of *K*, the reaction volumes were estimated to be -0.9 cm<sup>3</sup> mol<sup>-1</sup> for the 6-SO<sub>3</sub><sup>-</sup>-SP- $\beta$ -CD system and 4.0 cm<sup>3</sup> mol<sup>-1</sup> for the 6-SO<sub>3</sub><sup>-</sup>-SP- $\gamma$ -CD system. Based on the activation volumes, the structure of the transition state for the thermal isomerization is discussed and an explanation for the effect of CDs on the reaction rate is given. The difference in the reaction volumes for the inclusion complex formation of  $\beta$ - and  $\gamma$ -CDs is explained in terms of the difference in the number of water molecules excluded from the CD cavity.

## INTRODUCTION

Cyclodextrins (CDs) are extensively used in the pharmaceutical and food industries.<sup>1</sup> Owing to their large cavities and hydrophobic nature, CDs form inclusion complexes with a large number of organic and inorganic molecules. The stability of the inclusion complex depends on the hydrophobicity, size and shape of the guest molecules. The conformation and the dynamic properties of inclusion complexes have been studied by numerous workers.<sup>1,2</sup> One of the important applications of inclusion complexes is in the control of chemical reactions. For example, the protective effects of CDs against the oxidation of guests by oxygen have been reported.<sup>3</sup>

The isomerization of spiropyrans has attracted much attention because of their reversible photochromic and thermochromic behaviour.<sup>4</sup> We have previously examined the pressure and solvent effects on the thermal isomerizations of different kinds of spiropyrans, and discussed the reaction mechanism.<sup>5</sup> Spiropyrans can

exist in the colourless spiro form (SP) and the coloured merocyanine form (MC). The MC form has a dipolar planar structure with delocalized  $\pi$ -electrons of indoline and pyran fragments, and the SP form a less polar structure with reciprocally orthogonal fragments. Since the stability of a CD inclusion complex depends on the hydrophobicity of the guest, the difference in the stabilities of inclusion complexes, formed with the dipolar MC form or the less polar SP form, can be utilized for the control of the isomerization reaction. It is of interest to know how the volume changes during the process of complex formation, because CDs have large cavities.

This study was aimed at examining how CDs affect the isomerization reaction of spiropyrans. We examined the pressure dependence of the inclusion complex formation of CDs with spiropyrans and undertook a volumetric study to clarify the inclusion phenomena.

## EXPERIMENTAL

1',3',3'-Trimethylspiro[2*H*-1-benzopyran-2,2'-indoline]-6-sulphonic acid (6-SO<sub>3</sub><sup>-</sup>-SP) was prepared according to the method of Sunamoto *et al.*<sup>6</sup> and recrystallized from

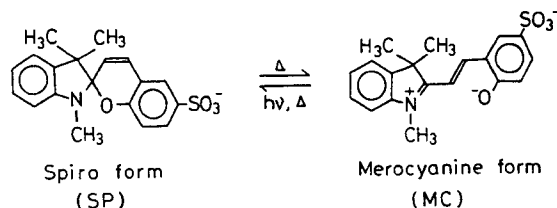
\* Author for correspondence.

methanol: m.p.  $\sim 513$  K, decomp. (lit.<sup>6</sup>  $\sim 513$  K, decomp.). Cyclodextrins ( $\alpha$ ,  $\beta$  and  $\gamma$ ) were purchased from Wako Pure Chemicals and used as received. Phosphate buffer solution of 0.1 M prepared from phosphate salts and distilled water was used as the solvent throughout.

The instrumentation for the kinetic measurements under high pressures has been described elsewhere.<sup>7</sup> A sample solution deoxygenated by bubbling with nitrogen was irradiated with a projection lamp through a  $\text{CuCl}_2$  solution to produce the SP form. Photo- and thermal isomerizations could be carried out reproducibly. The thermal isomerization between SP and MC was followed by monitoring the absorbance in the vicinity of 510 nm using a Hitachi Model 139 spectrophotometer, and the first-order rate constants obtained agreed within 5% error. Circular dichroism spectra were obtained at 298 K with a JASCO J-720 spectropolarimeter.

## RESULTS AND DISCUSSION

$6\text{-SO}_3^-$ -SP exists as an equilibrium mixture of the colourless SP form and the coloured MC form (Scheme 1).<sup>6</sup> Figure 1 shows the absorption spectra of  $6\text{-SO}_3^-$ -SP in the presence of  $\beta$ -CD. The peak in the vicinity of 220 nm increases at the expense of the peak at 510 nm as the CD concentration increases. With increasing CD concentration, the equilibrium between MC and SP favours the SP form. This sug-



Scheme 1

gests that the inclusion complex between the SP form and CD is more stable than that between the MC form and CD. In the presence of a 50-fold excess CD concentration,  $6\text{-SO}_3^-$ -SP molecules exist almost entirely as the SP form, and may be included in CDs. Further, the isomerization reaction of  $6\text{-SO}_3^-$ -SP included in the CD cavity did not occur, even if the solution was irradiated with light. As reported previously,<sup>5</sup> the absorption band position of the MC form of spiropyrans is sensitive to the solvent polarity. Thus, if the MC form of  $6\text{-SO}_3^-$ -SP is included in the CD cavity, a large spectral shift can be expected. However, in the presence of CD, no change in the spectral shapes in the vicinity of 510 nm is observed, suggesting that the MC form of  $6\text{-SO}_3^-$ -SP is not included in the CD cavity, as shown by examination of the electronic spectrum.  $6\text{-SO}_3^-$ -SP and CD did not show any circular dichroism by themselves. Hirai *et al.*<sup>8</sup> indicated that circular dichroism is induced by the

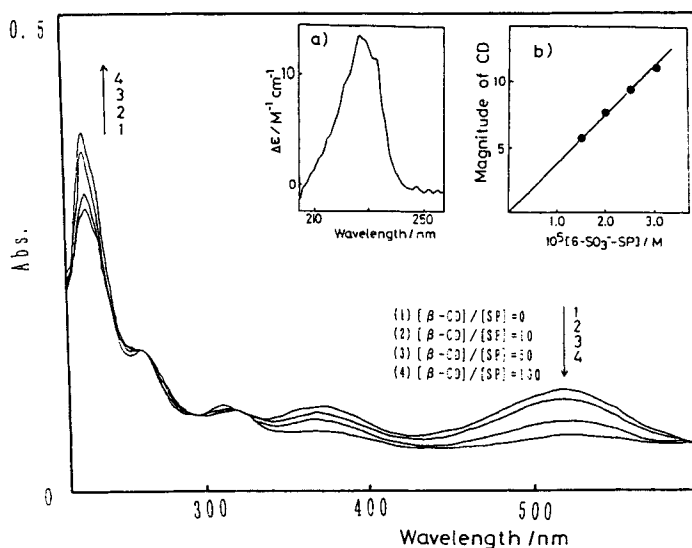


Figure 1. Absorption spectra of  $6\text{-SO}_3^-$ -SP in aqueous solution in the presence of  $\beta$ -CD at 313 K, 1 h after mixing the aqueous solutions of  $6\text{-SO}_3^-$ -SP and  $\beta$ -CD. Insets: (a) Circular dichroism spectrum of the inclusion complex between  $6\text{-SO}_3^-$ -SP and  $\beta$ -CD,  $[\beta\text{-CD}]/[6\text{-SO}_3^-\text{-SP}] = 67$ ; (b) The plot of the magnitude of circular dichroism induced at 227 nm against the initial concentration of  $6\text{-SO}_3^-$ -SP.  $[\beta\text{-CD}] = 1.0 \times 10^{-3}$  M

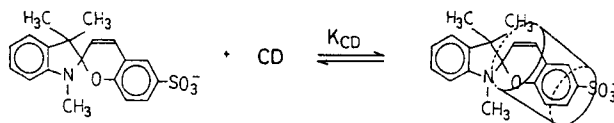
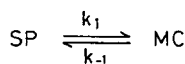
inclusion of a guest molecule in the CD cavity. As shown in Figure 1(a), new circular dichroism appears in the vicinity of 220 nm. Further, the magnitude of the circular dichroism increases linearly with increase in the initial concentration of 6-SO<sub>3</sub><sup>-</sup>-SP [Figure 1(b)]. This linear relationship is evidence of 1:1 complex formation of β-CD with 6-SO<sub>3</sub><sup>-</sup>-SP.<sup>8</sup> Similar results were obtained with γ-CD.

Taking the information obtained so far into account, a reaction scheme for isomerization in the presence of CDs can be proposed as shown in Scheme 2. Here,  $K_{CD}$  denotes the equilibrium constant for the formation of the inclusion complex. In order to depict the inclusion complexes of CDs with 6-SO<sub>3</sub><sup>-</sup>-SP, the Corey–Pauling–Koltun (CPK) space-filling models of these systems were examined. The CPK models show that the indoline fragment of 6-SO<sub>3</sub><sup>-</sup>-SP (8.6 Å diameter) is too large to pass through the CD cavity since β- and γ-CDs have internal diameters of *ca.* 7 and 8.5 Å, respectively.<sup>1</sup> Therefore, inclusion from the indoline side would not occur. On the other hand, the cavity diameter of β- and γ-CDs may allow the pyran fragment of 6-SO<sub>3</sub><sup>-</sup>-SP to be included. The pyran fragment of 6-SO<sub>3</sub><sup>-</sup>-SP, however, is too long to be included completely inside the cavity of CD and therefore a part of the 6-SO<sub>3</sub><sup>-</sup>-SP may be located outside the cavity. The sulphonato group of 6-SO<sub>3</sub><sup>-</sup>-SP may be exposed to an aqueous environment owing to the hydrophobic nature of the CD cavity (Scheme 2). On addition of α-CD to 6-SO<sub>3</sub><sup>-</sup>-SP solution, we did not observe a shift of the equilibrium from MC to SP, which suggests incomplete inclusion, if any, of 6-SO<sub>3</sub><sup>-</sup>-SP in α-CD.

Sunamoto *et al.*<sup>6</sup> suggested that the equilibrium between SP and MC shifts to the SP form on irradiation with visible light, and it returns to the original state in the dark. We found that the thermal isomerizations of 6-SO<sub>3</sub><sup>-</sup>-SP obey first-order kinetics regardless of the concentration of CD. Under the condition [CD] ≫ [6-SO<sub>3</sub><sup>-</sup>-SP], the rate constant ( $k_{obsd}$ ) observed for the thermal isomerization can be given as follows:

$$k_{obsd} = k_{-1} + k_1 / (1 + K_{CD}[CD]_0) \quad (1)$$

Here [CD]<sub>0</sub> denotes the initial concentration of CD.



Scheme 2

When the aqueous solutions of 6-SO<sub>3</sub><sup>-</sup>-SP and CD were mixed, the peak at 220 nm due to the SP form gradually increased with time at the expense of the peak at 510 nm and eventually reached an equilibrium state. Many kinetic studies of inclusion processes of CD with various kinds of molecules have shown that the processes are very rapid.<sup>9</sup> Therefore, the observed change in the absorption band can be ascribed to the thermal isomerization of 6-SO<sub>3</sub><sup>-</sup>-SP from MC to SP. The observed rate constant can be expressed by equation (1). Figure 2 shows the dependence of the β-CD concentration on the rate constants observed for the thermal MC → SP isomerization. As predicted by equation (1), the rate constants observed in the presence of a large excess of CD ([CD]<sub>0</sub>/[6-SO<sub>3</sub><sup>-</sup>-SP] ≫ 100) correspond to the rate constant ( $k_{-1}$ ) for the thermal MC → SP isomerization.

As can be seen in Figure 1, the addition of CD causes a shift of the position of the equilibrium between SP and MC. Under the condition [CD]<sub>0</sub>/[6-SO<sub>3</sub><sup>-</sup>-SP] = 10–25, 6-SO<sub>3</sub><sup>-</sup>-SP exists as free and complex species. Free 6-SO<sub>3</sub><sup>-</sup>-SP can be converted into the SP form by the irradiation with visible light, and in the dark we can follow the apparent SP → MC isomerization. The rate constants ( $k_{obsd}$ ) estimated at various concentrations of CDs are given in Table 1. Equation (1) can be rewritten as

$$1/(k_{obsd} - k_{-1}) = 1/k_1 + K_{CD}[CD]_0/k_1 \quad (2)$$

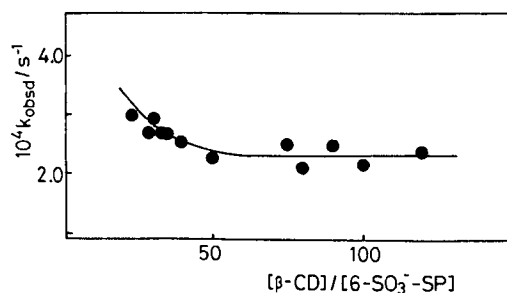


Figure 2. Effect of β-CD concentration on the rate constants observed for the MC → SP isomerization of 6-SO<sub>3</sub><sup>-</sup>-SP at 313 K

Table 1. Observed rate constants for the thermal isomerization of 6-SO<sub>3</sub><sup>-</sup>-SP (1.0 × 10<sup>-5</sup> M) in the presence of CDs at 313 K

CD	10 <sup>4</sup> [CD] <sub>0</sub> /M	10 <sup>3</sup> k <sub>obsd</sub> /s <sup>-1</sup>			
		1 kgf cm <sup>-2</sup> <sup>a</sup>	200 kgf cm <sup>-2</sup>	500 kgf cm <sup>-2</sup>	800 kgf cm <sup>-2</sup>
β-CD	0	5.25	4.93	4.28	3.70
	1.00	4.89	4.39	3.81	3.27
	1.56	4.55	4.06	3.62	3.07
	2.03	4.25	3.88	3.34	2.82
	2.51	4.04	3.56	3.03	2.72
γ-CD	0	5.25	4.93	4.28	3.70
	1.01	4.89	4.39	3.79	3.42
	1.54	4.49	4.29	3.76	3.17
	2.02	4.24	3.93	3.39	2.95
	2.47	4.17	3.91	3.39	2.92

<sup>a</sup> 1 kgf cm<sup>-2</sup> = 0.981 × 10<sup>5</sup> Pa.

Equation (2) predicts a linear relationship between  $1/(k_{\text{obsd}} - k_{-1})$  and  $[\text{CD}]_0$  with a slope of  $K_{\text{CD}}/k_1$  and an intercept of  $1/k_1$ . As shown in Figure 3, such a linear relationship can be obtained for β-CD. The linearity of the plots indicates that the assumption of 1:1 stoichiometry for the inclusion complex is valid. Using the slope and intercept of the plots, we can estimate the  $k_1$  and  $K_{\text{CD}}$  values for the 6-SO<sub>3</sub><sup>-</sup>-SP-β-CD system.

The  $k_1$  and  $k_{-1}$  values estimated in the presence of β-CD at various pressures are given in Table 2. The thermal SP→MC and MC→SP isomerizations are retarded by external pressure. The activation volumes ( $\Delta V_1^*$  and  $\Delta V_{-1}^*$ ) for the SP→MC and MC→SP

isomerizations at atmospheric pressure were estimated according to the following equations (Table 2):

$$\ln k = ap + b \quad (3)$$

$$\Delta V^* = -RT(\partial \ln k / \partial p)_T \quad (4)$$

The thermal MC→SP isomerization has a positive activation volume, which is attributed to the decrease in solvation on going from the dipolar initial state to the less polar transition state. In the previous papers,<sup>5</sup> similar results were reported for the thermal isomerization (MC→SP) of 6-NO<sub>2</sub>-spiropyran, for which the structure of the transition state was discussed. The positive activation volume obtained for the SP→MC isomerization may be explained in terms of the increase in the intrinsic volume accompanied by the stretching of the C<sub>spiro</sub>-O bond on activation.<sup>5</sup>

Since the volume profile affords useful information on the nature of the transition state, we depicted the volume profile for the thermal isomerization of 6-SO<sub>3</sub><sup>-</sup>-SP by using  $\Delta V_1^*$  and  $\Delta V_{-1}^*$ -values (Figure 4). The volume of reaction can be estimated to be -8.6 cm<sup>3</sup> mol<sup>-1</sup> ( $=\Delta V_1^* - \Delta V_{-1}^*$ ). As can be seen in Figure 4, the volume profile has a maximum. Such a maximum has been also observed for the thermal isomerization of 6-COOH-8-NO<sub>2</sub>-spiropyran.<sup>10</sup> Accordingly, we conclude that the thermal isomerization of 6-SO<sub>3</sub><sup>-</sup>-SP proceeds via a similar transition state to that of 6-NO<sub>2</sub>- and 6-COOH-8-NO<sub>2</sub>-spiropyran, which isomerize by homolytic bond fission or bond formation.

The  $K_{\text{CD}}$ -values at high pressures in the 6-SO<sub>3</sub><sup>-</sup>-SP-γ-CD system were obtained in a similar manner and are given in Table 3. The  $K_{\text{CD}}$  value at atmospheric pressure in the 6-SO<sub>3</sub><sup>-</sup>-SP-β-CD system is larger than that in the 6-SO<sub>3</sub><sup>-</sup>-SP-γ-CD system. The stability of an inclusion complex may be determined by the fit of a guest in the

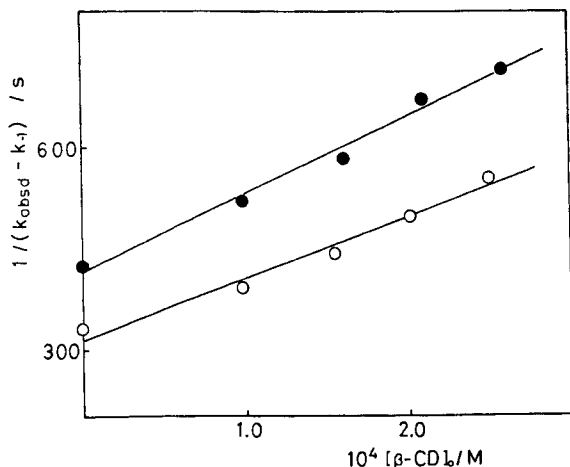


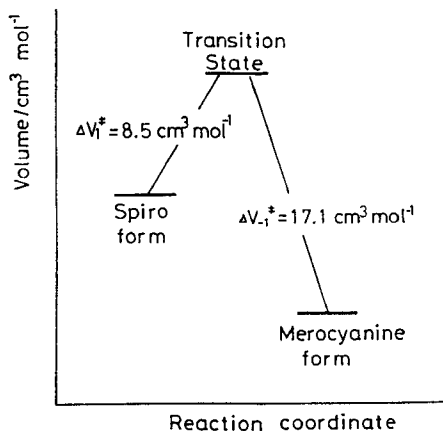
Figure 3. Plots of  $1/(k_{\text{obsd}} - k_{-1})$  against  $[\beta\text{-CD}]_0$  at 313 K: (○) at 1 kgf cm<sup>-2</sup>; (●) at 800 kgf cm<sup>-2</sup>

Table 2. Rate constants and activation volumes for the thermal isomerization of 6-SO<sub>3</sub><sup>-</sup>-SP at 313 K in water

Isomerization	Parameter	$p/\text{kgf cm}^{-2}$				$\Delta V_{-1}^*, \Delta V_1^*/\text{cm}^3 \text{ mol}^{-1}$
		1	200	500	800	
MC → SP	$10^3 k_{-1}/\text{s}^{-1}$	2.27	1.93	1.63	1.34	$17.1 \pm 0.5$
SP → MC	$10^3 k_1/\text{s}^{-1}$	3.09	3.02	2.67	2.42	$8.5 \pm 0.6$

Table 3. Equilibrium constants at various pressures and volumes of reaction for inclusion complex formation at 313 K

CD	$10^{-3} K_{\text{CD}}/\text{M}$				$\Delta V/\text{cm}^3 \text{ mol}^{-1}$
	1 kgf cm <sup>-2</sup>	200 kgf cm <sup>-2</sup>	500 kgf cm <sup>-2</sup>	800 kgf cm <sup>-2</sup>	
$\beta$ -CD	2.93	3.36	3.56	2.91	$-0.9 \pm 3.6$
$\gamma$ -CD	2.56	2.19	2.13	2.15	$4.0 \pm 2.0$


 Figure 4. Volume profile for the isomerization of 6-SO<sub>3</sub><sup>-</sup>-SP in aqueous solution

CD cavity. Hence the above finding suggests that the fit of 6-SO<sub>3</sub><sup>-</sup>-SP in the cavity space of  $\beta$ -CD is better than that of  $\gamma$ -CD.

The reaction volume ( $\Delta V_{\text{CD}}$ ) for the formation of the inclusion complex was estimated according to the equation

$$\Delta V_{\text{CD}} = -RT(\partial \ln K_{\text{CD}}/\partial p)_T + \Delta n \kappa_T RT \quad (5)$$

where  $\kappa_T$  is the isothermal compressibility of solvent and the  $\kappa_T RT$  value was calculated from available data for water;<sup>11</sup>  $\Delta n$  is the difference between the numbers of species in the final and initial states. From the pressure dependences of  $K_{\text{CD}}$ , the volumes of reaction were estimated to be  $-0.9 \text{ cm}^3 \text{ mol}^{-1}$  for  $\beta$ -CD and  $4.0 \text{ cm}^3 \text{ mol}^{-1}$  for  $\gamma$ -CD. These values cannot be

explained in terms of the primitive idea of a decrease in volume accompanied by inclusion of spirocyanine in the cavity of CD. Previously, we have discussed the contributions of different factors to the volume change for the inclusion complex formation of CDs with di-*tert*-butyl nitroxide.<sup>12</sup> Similarly, the volume change in the present cases can be expressed as follows:

$$\Delta V_{\text{CD}} = \Delta V_{\text{inclu}} + \Delta V_{\text{desolv}} + \Delta V_{\text{push}} \quad (6)$$

where  $\Delta V_{\text{inclu}}$  and  $\Delta V_{\text{desolv}}$  are the volume changes related to inclusion of spirocyanine in the CD cavity and accompanying desolvation around 6-SO<sub>3</sub><sup>-</sup>-SP upon inclusion, respectively.

In the  $\beta$ -CD cavity, 6.5 water molecules are known to be involved on average.<sup>13</sup> The vacancy of the  $\beta$ -CD cavity may be almost fully occupied by spirocyanine,<sup>1</sup> and hence all water molecules in  $\beta$ -CD must be excluded from the CD cavity on inclusion complex formation. The 6.5 water molecules excluded cause an increase in volume of  $\Delta V_{\text{push}} = 117 \text{ cm}^3 \text{ mol}^{-1}$ . From the CPK model,  $\Delta V_{\text{inclu}}$  was estimated to be  $-130 \text{ cm}^3 \text{ mol}^{-1}$ .<sup>12</sup> Accordingly, the  $\Delta V_{\text{desolv}}$  value can be calculated to be  $12.1 \text{ cm}^3 \text{ mol}^{-1}$  from equation (6). In the cation-crown ether complex, the volume change due to the release of water molecules electrostricted around guest ions has been estimated to be  $8\text{--}25 \text{ cm}^3 \text{ mol}^{-1}$ .<sup>14</sup> The above value of  $\Delta V_{\text{desolv}}$  seems to be reasonable.

Twelve water molecules are originally situated in the cavity of  $\gamma$ -CD.<sup>15</sup> Judging from the sizes of  $\gamma$ -CD and spirocyanine, some of them must be excluded on complex formation. Since the depths of the cavities of  $\beta$ - and  $\gamma$ -CDs are the same, the sum of  $\Delta V_{\text{desolv}} + \Delta V_{\text{inclu}}$  in the 6-SO<sub>3</sub><sup>-</sup>-SP- $\gamma$ -CD system can be approximated to be  $-117.9 \text{ cm}^3 \text{ mol}^{-1}$ , which is as obtained in the 6-SO<sub>3</sub><sup>-</sup>-SP- $\beta$ -CD system. The  $\Delta V_{\text{push}}$  value in the 6-SO<sub>3</sub><sup>-</sup>-SP- $\gamma$ -CD system therefore can be calculated to be

121.9 cm<sup>3</sup> mol<sup>-1</sup> from equation (6). Of the 12 water molecules, 6·8 are replaced by 6-SO<sub>3</sub><sup>-</sup>-SP upon complex formation. We have reported similar results for inclusion complex formation between di-*tert*-butyl nitroxide and  $\gamma$ -CD, and obtained evidence that part of the water molecules remain in  $\gamma$ -CD on complex formation by using an ESR technique.<sup>12</sup> These results are in accord with our expectation and support the proposed mechanism.

In the present study, it was found that  $\beta$ - and  $\gamma$ -CDs form a 1:1 inclusion complex with the SP form of 6-SO<sub>3</sub><sup>-</sup>-SP, and this is consistent with the examination of CPK models. The preferential inclusion of the SP form causes the retardation of the apparent SP→MC isomerization reaction. Although the present volumetric study is a simplified model, the above findings show that the water molecules excluded from the CD cavity play an important role in inclusion complex formation.

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