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Ultraviolet Absorption Spectroscopy and Nuclear Magnetic Resonance Spectroscopy of Complexes of Sulfonamides with Cyclic Polyether 18-Crown-6[1]

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The interaction of sulfonamides with 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) was studied, observing the effect on the spectroscopic properties of sulfonamides in chloroform solution.

From the ultraviolet (UV) absorption spectra and the nuclear magnetic resonance (NMR) spectra, the stoichiometry and the stability constant K of the formation of complex were calculated. The measurement of K values according to the NMR method gives excellent results compared with that according to the UV method. On the other hand, it was observed that the binding mechanism was the inclusion of the primary amino group of 4-position of sulfonamides in the anionic cavity of 18-crown-6, and the hydrogen bonding might be a primary force of the formation of these complexes.

Keywords——complex; 18-crown-6; sulfonamides; UV absorption spectroscopy; NMR spectroscopy; hydrogen bonding; inclusion; stability constant; iteration method

In a previous paper,[3] an investigation of the stability constant of the complexes of 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane, 18-C-6), one of the most familiar crown ethers,[4] with sulfonamides in organic solvents by the solubility study[5] indicated that the hydrogen bonding might be a primary force of the formation of these complexes. In general, one of the factors of the hydrogen bonding is said to be based on the charge transfer type interaction which might result in various changes of the spectroscopic properties of acceptors by the addition of donors. In the complex formation of sulfonamides with 18-C-6, it might be predicted that the former acts as an electron acceptor and the latter as an electron donor.

Based on the above considerations, the present study was attempted to investigate the interaction of sulfonamides with 18-C-6 more closely in view of the charge transfer type complex according to the ultraviolet (UV) absorption spectroscopy and the nuclear magnetic resonance (NMR) spectroscopy.

Experimental

Materials——18-C-6, *p*-chloroaniline (PCA), *p*-aminobenzoic acid (PABA), and *p*-nitroaniline (PNA) used were of the reagent grade. Very pure compounds of sulfonamides supplied by the respective companies, which all conformed to the registered standards, were as follows: sulfamethoxypyridazine (SMP) by Yoshitomi Pharmaceutical Co., Ltd., mp 182°; sulfadimethoxine (SDO) by Chugai Pharmaceutical Co., Ltd., mp 202°; sulfamethomidine (SMD) by Tanabe Pharmaceutical Co., Ltd., mp 146°; sulfamethoxazole (SMO) by Shionogi Pharmaceutical Co., Ltd., mp 167°; sulfamonomethoxine (SMM) by Dai-ichi Pharmaceutical Co., Ltd., mp 205°; sulfisoxazole (SIO) and N^1-acetyl SIO (N^1-AcSIO) by Yamanouchi Pharmaceutical Co., Ltd., mp 194° and 192°. N^4-Acetyl SMP (N^4-AcSMP), N^4-acetyl SDO (N^4-AcSDO), and N^4-acetyl SMO (N^4-AcSMO) used

1) This paper forms Part XIV of "Pharmaceutical Interaction in Dosage Forms and Processing." The preceding paper, Part XIII: Y. Machida, H. Masuda, N. Fujisawa, S. Ito, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **27**, 93 (1979).
2) Location: *Ebara-2-4-41, Shinagawa-ku, Tokyo, 142, Japan.*
3) K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **25**, 2608 (1977).
4) C.J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
5) T. Higuchi and K.A. Connors, *Advan. Anal. Chem. Instr.*, **4**, 117 (1965).

were synthesized by the description in the annotated edition of J.P.IX,[6] and recrystallized in methanol: mp 222°, 215°, and 227°, respectively.

UV Absorption Spectroscopic Study——The solution in $CHCl_3$ was subjected to the study using a Hitachi 323 spectrophotometer.

NMR Spectroscopic Study——The solution in $CDCl_3$ was subjected to the study using a JEOL JNM-FX 100 NMR spectrometer, referring to tetramethylsilane as the internal standard.

Results and Discussion

UV Absorption Spectroscopic Study

As an example, Fig. 1 shows the UV absorption spectrum of SMD under the various concentrations of 18-C-6 in $CHCl_3$. The spectrum of SMD shifted to long wavelength region

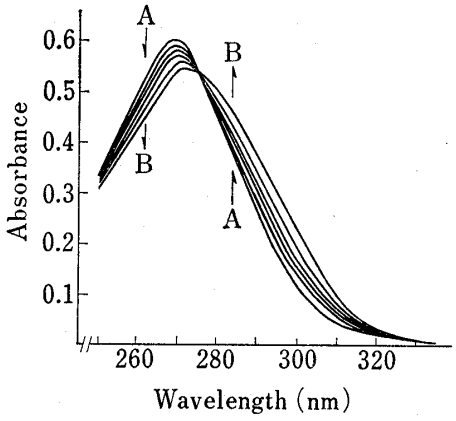


Fig. 1. UV Absorption Spectrum of SMD in Various Concentrations of 18-C-6 in $CHCl_3$ at 25±1°

SMD concentration (M); 3.041×10^{-5}: 18-C-6 concentrations (M); 0, 1.492×10^{-2}, 2.522×10^{-2}, 3.661×10^{-2}, 5.913×10^{-2}, and 9.680×10^{-2}, read from A to B

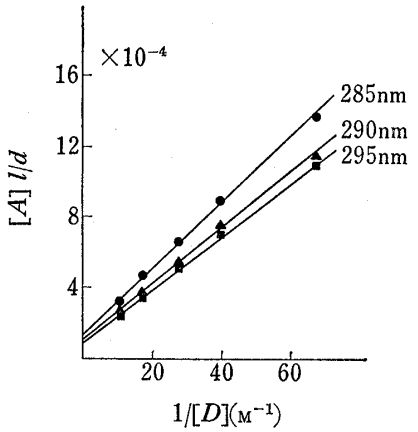


Fig. 2. Relation between $1/[D]$ and $[A]l/d$ Values of SMD/18-C-6 System in $CHCl_3$ at 25±1° obtained according to Equation 1

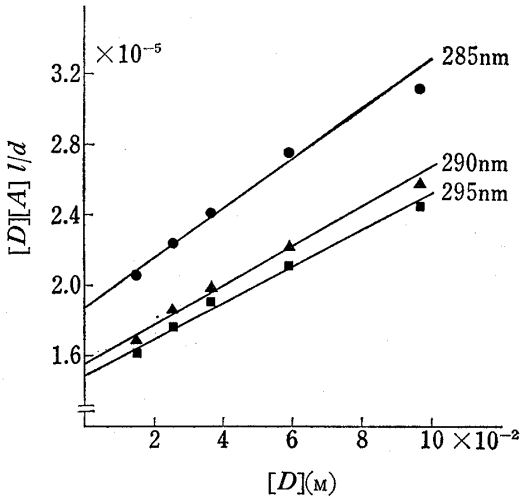


Fig. 3. Relation between $[D]$ and $[D][A]l/d$ Values of SMD/18-C-6 System in $CHCl_3$ at 25±1° obtained according to Equation 2

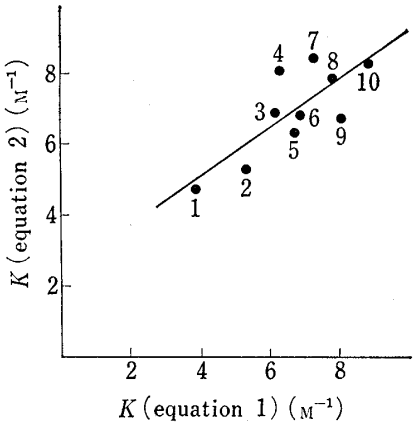


Fig. 4. Relation between Stability Constant, K, obtained according to Equation 1 and That according to Equation 2

1: SMP; 2: SPZ; 3: SIO; 4: PABA; 5: SDO; 6: N^1-AcSIO; 7: PNA; 8: SMD; 9: SMM; 10: SMO.
$y=0.681x+2.36$.
$r=0.769$.

6) Nippon Koteishokyokai, "J.P.IX Kaisetsusho," Hirokawashoten, Tokyo, 1976, p. C-851.

about 3 nm with the addition of 18-C-6. Moreover, the isosbestic point at 275 nm indicates the formation of 1:1 complex. For the other sulfonamides, spectral shifts and isosbestic points were also observed with the addition of 18-C-6.

The stability constants of these complexes could be calculated according to the Benesi-Hildebrand equation[7] (1) and the modified equation (2) reported by Scott.[8]

$$[A]l/d = 1/K\varepsilon[D] + 1/\varepsilon \quad (1)$$

$$[D][A]l/d = [D]/\varepsilon + 1/K\varepsilon \quad (2)$$

where $[A]$ and $[D]$ are the concentrations of sulfonamides and 18-C-6, respectively, K the stability constant of the complex, ε the difference of the molar extinction coefficients for free and complexed sulfonamides, d the change in the absorbance of the sulfonamides solution with the addition of 18-C-6, and l the cell length.

The data for SMD/18-C-6 complex in Fig. 1 are plotted according to the equations 1 and 2 as shown in Fig. 2 and 3, respectively, showing a linear relationship. For the other complexes also, a linear relationship was obtained in $CHCl_3$. Therefore, K values were obtained from the slope and the intercept, as summarized in Table I.

Table I. Stability Constants of Sulfonamides/18-C-6 Complexes in $CHCl_3$ at 25±1° according to UV Method

Sulfonamides	Stabilityconstant (M^{-1})	
	By equation 1	By equation 2
SMP	3.87	4.69
SPZ	5.32	5.26
SDO	6.71	6.31
SMD	7.81	7.85
SMO	8.90	8.27
SMM	8.06	6.72
SIO	6.17	6.90
N^1–AcSIO	6.89	6.80
PCA[a]	—	—
PABA	6.25	8.11
PNA	7.34	8.49
N^4–AcSMP[a]	—	—
N^4–AcSDO[a]	—	—
N^4–AcSMO[a]	—	—

a) No change was observed by the addition of 18-C-6.

The K value of N^1-AcSIO/18-C-6 complex was almost the same as that of SIO/18-C-6 complex. Moreover, an interaction similar to the cases of sulfonamides/18-C-6 systems were also observed in both systems of PABA/18-C-6 and PNA/18-C-6. However, the interaction of PCA/18-C-6 system could not be observed with an accuracy. On the other hand, neither spectral shifts nor isosbestic points were observed in N^4-acetyl sulfonamides/18-C-6 systems in this experimental condition.

The above results indicated that 4-amino group of sulfonamides might bind to the anionic cavity of 18-C-6 in the complex formation, and 1-amino group has no participation in the interaction in this experimental condition. These specurations are well coincided with the results which reported in the previous paper.[3]

Figure 4 shows the relation of K values calculated by equations 1 and 2. The correlation coefficient was 0.769. The regression line ($y=0.681x+2.36$) deviated largely from the theoretical one ($y=x$), as might be due to the experimental error derived from the smallness of the d value in equations 1 and 2.

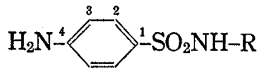
7) H.A. Benesi and J.H. Hildebrand, *J. Am. Chem. Soc.*, **71**, 2703 (1949).
8) R.L. Scott, *Rec. Trav. Chim.*, **75**, 787 (1962).

NMR Spectroscopic Study

The NMR spectra of benzene ring protons of sulfonamides consist of two doublet lines corresponding to the 2 and 3-positions, respectively. These spectra were not disturbed with those of 18-C-6.

As an example, the changes of chemical shifts in the 2-position (δ_a and δ_b) and the 3-position (δ_c and δ_d) of SMD in $CDCl_3$ with the addition of 18-C-6 were shown in Table II.

Table II. Effect of 18-C-6 on Chemical Shifts of SMD in $CDCl_3$ at 24.5±0.5° (concentration of SMD: 0.005 M)



Concentration of 18-C-6 (M)	Chemical shifts (Hz)			
	2-Position		3-Position	
	δ_a	δ_b	δ_c	δ_d
0.0	771.7	762.9	666.0	657.2
0.1931	766.1	757.3	662.8	654.1
0.2392	765.9	756.8	662.6	653.6
0.2752	765.1	756.3	662.1	653.3
0.4587	764.2	755.4	661.6	652.6
0.8325	763.2	754.4	661.1	652.6

The changes of chemical shifts to higher magnetic field in the 2-position were larger than those in the 3-position. It seemed difficult to explain completely from these limited experimental data the difference in the changes in chemical shifts between the 2 and 3-positions. However, the stability constants of sulfonamides/18-C-6 systems might be obtainable by the changes of chemical shifts in the 2-position with the addition of 18-C-6 according to the Hanna equation[9] (3) and the modified equation (4) reported by Foster *et al.*[10]

$$1/\Delta = 1/K\Delta_c[D] + 1/\Delta_c \quad (3)$$

$$\Delta/[D] = -\Delta K + \Delta_c K \quad (4)$$

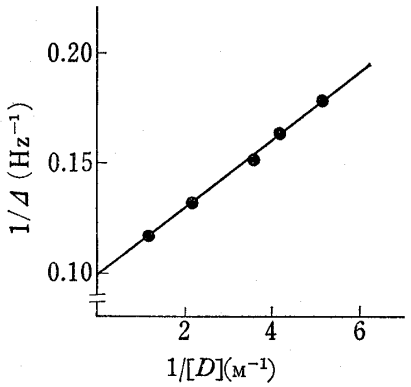


Fig. 5. Relation between $1/[D]$ and $1/\Delta$ Values of SMD/18-C-6 System in $CDCl_3$ at 24.5±0.5° obtained according to Equation 3

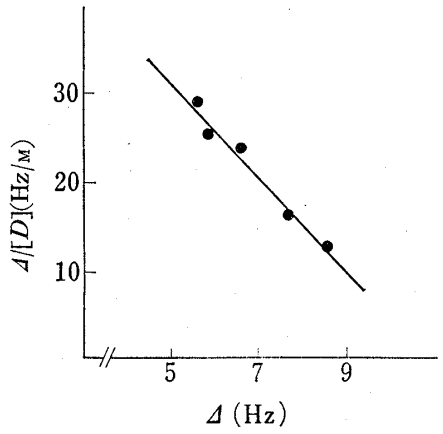


Fig. 6. Relation between Δ and $\Delta/[D]$ Values of SMD/18-C-6 System in $CDCl_3$ at 24.5±0.5° obtained according to Equation 4

9) M.W. Hanna and A.L. Ashbaugh, *J. Phys. Chem.*, **68**, 811 (1964).
10) R. Foster and C.A. Fyfe, *Trans. Faraday Soc.*, **61**, 1626 (1965).

where $[D]$ is the concentration of 18-C-6, K the stability constant of the complex, Δ the change in the chemical shift of the sulfonamides solution with the addition of 18-C-6, and Δ_c the shift for the pure complex.

The data for SMD/18-C-6 complex in Table II are plotted according to the equations 3 and 4 as shown in Fig. 5 and 6, respectively. K values obtained were summarized in Table III.

Table III. Stability Constants of Sulfonamides/18-C-6 Complexes in $CDCl_3$ at $24.5\pm0.5°$ according to NMR Method

Sulfonamides	Stability constant (M^{-1})		
	By equation 3	By equation 4	By equations 5 and 6
SMP	3.22	3.15	3.17
SPZ	5.34	5.30	5.49
SDO	7.28	7.04	7.44
SMD	6.25	6.19	6.61
SMO	7.86	7.46	7.74
N^1–AcSIO	6.00	6.01	6.32
PCA	0.463	—	—
PABA	2.06	2.07	2.14
PNA	7.40	7.20	7.25

The iteration method to obtain more refined values of K according to the equations 5 and 6 was reported by T. Higuchi, *et al.*[11]

$$[D]/\Delta = ([A]+[D]-[AD])/\Delta_c + 1/K\Delta_c \quad (5)$$

$$[AD] = [A]\Delta/\Delta_c \quad (6)$$

where $[A]$ and $[AD]$ are the concentrations of sulfonamides and complex, respectively. The first calculations start as $[AD]=0$ in equation 5, and then, the values of Δ_c obtained are substituted into equation 6. The $[AD]$ values thus obtained are then used in equation 5 to calculate an improved value of the slope. In this paper, these steps were repeated to

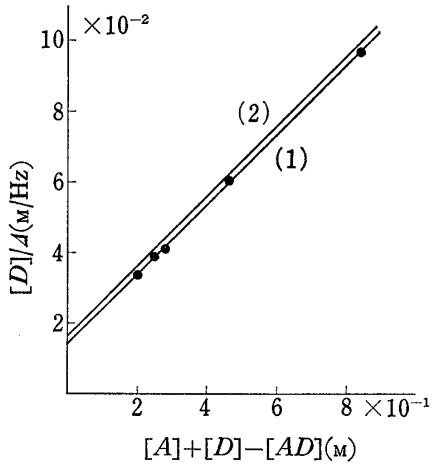


Fig. 7. Relation between $[A]+[D]-[AD]$ and $[D]/\Delta$ Values of SMD/18-C-6 System in $CDCl_3$ at $24.5\pm0.5°$ obtained according to Equation 5

(1): the first approximation line with $[AD]$ set equal to 0.
(2): the final convergent line with iteration method.

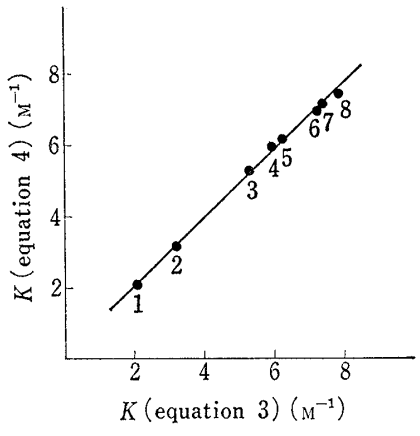


Fig. 8. Relation between Stability Constant, K, obtained according to Equation 3 and That according to Equation 4

1: PABA; 2: SMP; 3: SPZ; 4: N^1–AcSIO; 5: SMD; 6: SDO; 7: PNA; 8: SMO.
$y=0.950x+0.164$.
$r=0.999$.

11) M. Nakano, N.I. Nakano, and T. Higuchi, *J. Phys. Chem.*, **71**, 3954 (1967).

obtain essentially identical convergent values for the slope and the intercept in the equation 5 by the use of computer.

The data for SMD/18-C-6 system are plotted according to the equation 5 as shown in Fig. 7. K values obtained in this iteration method were also summarized in Table III.

These data were well correlated with those obtained by the UV method. However, K value of PABA/18-C-6 system was very small in comparison with that obtained by the UV method, as might be due to the relatively high concentration of PABA solution in the NMR measurement, that is, the formation of the dimer structure of PABA. On the other hand, the chemical shifts of the 2 and 3-positions of N^4-acetyl sulfonamides moved to lower magnetic field with the addition of 18-C-6, as was contrary to the cases in the other systems. It seemed difficult to explain these lower magnetic field shifts in these limited experimental data. However, this result might indicate that the primary amino group in the 4-position of sulfonamides is indispensable to bind with 18-C-6. An interaction similar to that observed by the UV method was obtained in the cases of N^1-AcSIO/18-C-6 and PNA/18-C-6 systems. The above results also indicate that 4-amino group of sulfonamides might bind to the anionic cavity of 18-C-6.

Figure 8 shows the relation of K values calculated by the equations 3 and 4. The correlation coefficient was 0.999. The regression line ($y=0.950x+0.164$) almost coincided with the theoretical one ($y=x$). Moreover, K values calculated by the equations 3 and 4 well coincided with those obtained by the iteration method. Therefore, it might be considered that the measurement of K value according to the NMR method gives excellent results compared with that according to the UV method in the case of the relatively weak interaction in the complex formation.

Based on the above spectral considerations, it was recognized that the binding mechanism was the inclusion of the primary amino group of 4-position of sulfonamides in the anionic cavity of 18-C-6, and the hydrogen bonding might be a primary force of the formation of these complexes.

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