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Interaction of Sulfonamides with Cyclic Polyether 18-Crown-6 in Solution and in Solid State[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 solubility of sulfonamides in organic solvents. In benzene solution, sulfamonomethoxine and sulfamethoxazole formed the respective crystalline complexes with 18-crown-6. The stability constant K for sulfamonomethoxine/18-crown-6 system was particularly large in comparison with the other systems. In chloroform solution, however, the solid complex was not obtained in any systems. K values in chloroform were smaller than those in benzene. Furthermore, when the complex formation of sulfamethomidine with 18-crown-6 was investigated in various dielectric constants of solvents, K value decreased with the increase in polarity of the solvent. These results indicated that the hydrogen bonding might be a primary force of the formation of these complexes.

Additionally, the complex formation in solid phase was confirmed in sulfamonomethoxine/18-crown-6 and sulfamethoxazole/18-crown-6 systems by powder X-ray diffractometry and differential scanning calorimetry.

From infra-red and nuclear magnetic resonance spectra, it was suggested that 4-amino group of sulfonamide might interact with the oxygen of ether ring of 18-crown-6.

Keywords——complex; 18-crown-6; sulfonamides; in solution; in solid state; powder X-ray diffractometry; differential scanning calorimetry; infra-red absorption spectrophotometry; nuclear magnetic resonance spectroscopy

Cyclic polyethers named crown ethers, which were first synthesized by Pederson,[3] usually form various kinds of inclusion compounds with such components as alkali metal, alkali earth metal, ammonium ions and organic cationic compounds. Accordingly, these ethers have widely been used in the field of organic synthesis,[4] and also applied in some bioorganic chemistry *e.g.*, as enzyme models and optical resolution reagents.[5] A very few toxicological investigation has been done.[3b,6]

In pharmaceutical field, however, any investigation of application has never been reported regarding such crown ethers. An interaction of drugs with these interesting reagents seems worth investigating with a view to applying to pharmaceutical dosage forms and processing and also to basic researches as some biopharmaceutical models.

The present study was attempted to investigate the interaction of 18-crown-6 (1,4,7,10,-13, 16-hexaoxacyclooctadecane), one of the most familiar crown ethers,[3b] with sulfonamides as the guest molecules on the basis of the effect of the former on the solubility of the latters in organic solvents. Sulfonamides were chosen because they bear primary amino group

1) This paper forms Part VI of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part V: K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **25**, 879 (1977).
2) Location: *Ebara-2-4-41, Shinagawa-ku, Tokyo, 142, Japan.*
3) *a*) C.J. Pederson, *J. Am. Chem. Soc.*, **89**, 2495 (1967); *b*) *Idem, ibid.*, **89**, 7017 (1967); *c*) *Idem, ibid.*, **92**, 386 (1970); *d*) *Idem, ibid.*, **92**, 391 (1970); *etc.*
4) D.J. Sam and H.E. Simmons, *J. Am. Chem. Soc.*, **94**, 4024 (1972); T. Matsuda and K. Koida, *Bull. Chem. Soc. Jp.*, **46**, 2259 (1973); J.N. Roitman and D.J. Cram, *J. Am. Chem. Soc.*, **93**, 2231 (1971); *etc.*
5) E.P. Kyba, K. Koga, L.R. Sousa, M.G. Siegel, and D.J. Cram, *J. Am. Chem. Soc.*, **95**, 2692 (1973); R.C. Helgeson, K. Koga, J.M. Timko, and D.J. Cram, *J. Am. Chem. Soc.*, **95**, 3021 (1973); *etc.*
6) B.K.J. Leong, O.T.T. Timothy, and M.B. Chenoweth, *Toxicol, Appl. Pharmacol.*, **27**, 342 (1974).

which is expected to interact with the oxygen of ether ring in the molecule of crown ether. The stoichiometry of complexes and the apparent stability constant of the complexes are discussed, and the binding mechanism of these complexes was also studied by infrared (IR) absorption spectrophotometry and nuclear magnetic resonance (NMR) spectroscopy. Moreover, an investigation was made to obtain the complexes with 18-crown-6 in solid state. Such complexes were confirmed by powder X-ray diffractometry and differential scanning calorimetry (DSC).

Experimental

Materials——18-Crown-6, sulfathiazole and sulfanilamide used were of the reagent grade. Very pure compounds of the other sulfonamides supplied by the respective companies, which all conformed to the standards, were as follows: sulfamethomidine and sulfamerazine by Tanabe Pharmaceutical Co., Ltd., mp 146° and 236°; sulfamonomethoxine by Dai-ichi Pharmaceutical Co., Ltd., mp 205°; sulfamethoxazole by Shionogi Pharmaceutical Co., Ltd., mp 167°; sulfaphenazole and sulfisomidine by Dainippon Pharmaceutical Co., Ltd., mp 182° and 243°; sulfamethoxypyridazine by Yoshitomi Pharmaceutical Co., Ltd., mp 182°; sulfadimethoxine by Chugai Pharmaceutical Co., Ltd., mp 202°; sulfamethizole by Eisai Co., Ltd., mp 208°; sulfisoxazole by Yamanouchi Pharmaceutical Co., Ltd., mp 194°.

Phase Solubility Studies——A given excess amount of each sulfonamide over the solubility and the various amounts of 18-crown-6 in 10 ml of organic solvents (*i.e.*, benzene, chloroform, ether and methylene chloride) were sealed in vials and incubated for about 72 hr at 10° in a Taiyo M 1 type constant temperature incubator. Then, the solution was filtered rapidly through a Toyo filter paper No. 5B. In the case of chloroform solution, the concentration of sulfonamides in filtrates was determined directly according to ultraviolet (UV) absorption method using a Hitachi 124 spectrophotometer. In the cases of benzene, ether and methylene chloride solutions, 1 ml of the filtrate was evaporated with a Taiyo concentrator Model TC-8 at 40°, and then the residue was dissolved in chloroform to determine the concentration according to the same method as the above.

The stoichiometry and the stability constant were calculated from the solubility diagrams.[7]

Preparation of Complexes in Solid State

Sulfamonomethoxine/18-Crown-6 Complex——On referring to the solubility diagram in Fig. 1, 40 mg of sulfamonomethoxine and 632 mg of 18-crown-6 in 600 ml of benzene were sealed in a flask and stirred well for 24 hr at 10°. After the filtration, 888 mg of 18-crown-6 was added in the filtrate, being incubated for 72 hr at 10°. The microcrystalline particles formed were filtered out, washed with benzene and dried under vacuum.

Sulfamethoxazole/18-Crown-6 Complex——On referring to the solubility diagram in Fig. 2, 20 mg of sulfamethoxazole in 200 ml of benzene was sealed in a flask and stirred well for 24 hr at 10°. After the filtration, 527 mg of 18-crown-6 was added in the filtrate, being incubated for 72 hr at 10°. The microcrystalline particles formed were filtered out, washed with benzene and dried under vacuum.

IR Absorption Spectroscopic Study——This was done using a Shimadzu Model IR-400 infrared spectrophotometer in a sodium chloride cell of length 0.5 mm.

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

Powder X-Ray Diffraction Study——Powder X-ray diffractometry was carried out using a Rigaku Denki Geigerflex Model D-2 diffractometer by Ni-filtered Cu-Kα radiation.

DSC Study——This was done using a Perkin-Elmer Model 1B differential scanning calorimeter.

Result and Discussion

Phase Solubility Diagrams

As shown in Fig. 1, the solubility of sulfamonomethoxine in benzene was found to increase with the addition of 18-crown-6, reaching a certain value. Furthermore, the crystalline complex precipitated at the higher concentration of 18-crown-6. On the other hand, the solubility of sulfamethoxazole in benzene was found to decrease without any rise with the addition of 18-crown-6 as shown in Fig. 2. This result seemed strange, but the similar phenomenon had already been reported by Higuchi, *et al.*,[7] and such an explanation was given for this

7) T. Higuchi and K.A. Connors, *Advan. Anal. Chem. Instr.*, 4, 117 (1965).

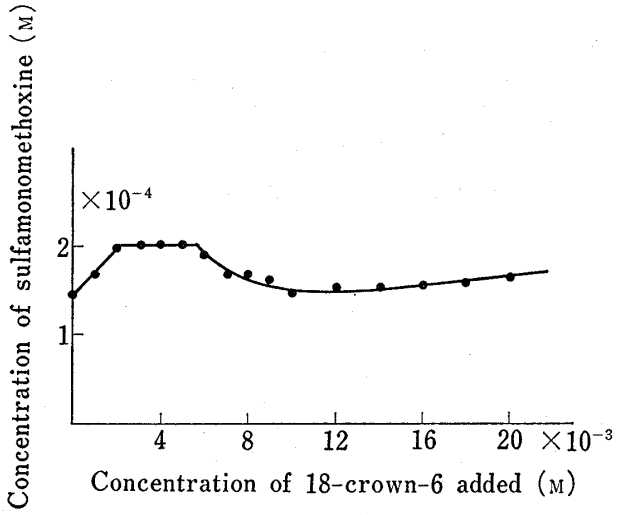

Fig. 1. Solubility of Sulfamonomethoxine in Benzene as a Function of 18-Crown-6 Added

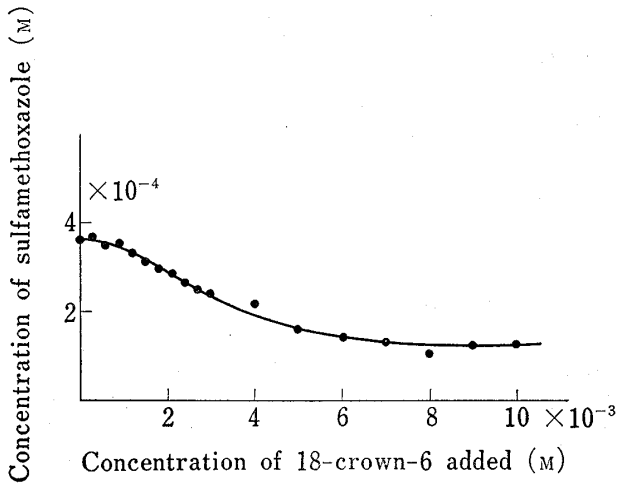

Fig. 2. Solubility of Sulfamethoxazole in Benzene as a Function of 18-Crown-6 Added

that the solid solution was probably formed between the solid substrate and the precipitated complex. These complexes obtained in solid state were analyzed chemically according to UV absorption method, giving the result that both systems contained sulfonamide and 18-crown-6 in molecular ratio 1:1. Furthermore, from the data in the plateau region of the diagram in Fig. 1, the stoichiometry of sulfamonomethoxine/18-crown-6 complex was also determined to be 1:1. For the other systems, the solubility of sulfonamides increased linearly with the increase of the concentration of 18-crown-6. Therefore, the stability constants were calculated assuming the formation of 1:1 complex. The data are summarized in Table I. K values in benzene were larger than those in chloroform. Furthermore, when the complex formation of sulfamethomidine with 18-crown-6 was investigated in various dielectric constants of solvents, K value decreased with increase in the polarity of solvent, as shown in

Table I. Stability Constants for Complexes of Sulfonamides with 18-Crown-6 in Benzene and in Chloroform at 10°

Sulfonamides	Stability constant K (M^{-1})	
	In benzene	In chloroform
Sulfamethomidine	34.30	20.52
Sulfamonomethoxine	166.0	14.11
Sulfamethoxazole	*a*)	10.00
Sulfaphenazole	41.95	6.68
Sulfamethoxypyridazine	29.71	10.60
Sulfadimethoxine	50.38	10.52
Sulfamethizole	*b*)	11.21
Sulfisoxazole	80.71	13.35
Sulfisomidine	*b*)	5.44
Sulfamerazine	*b*)	22.38
Sulfathiazole	*b*)	21.08
Sulfanilamide	*b*)	48.54

a) Referring to the solubility diagram shown in Fig. 2, on which there was found no increase of the solubility with the addition of 18-crown-6.

b) Could not be determined with accuracy, because of the poor solubility of sulfonamides in benzene.

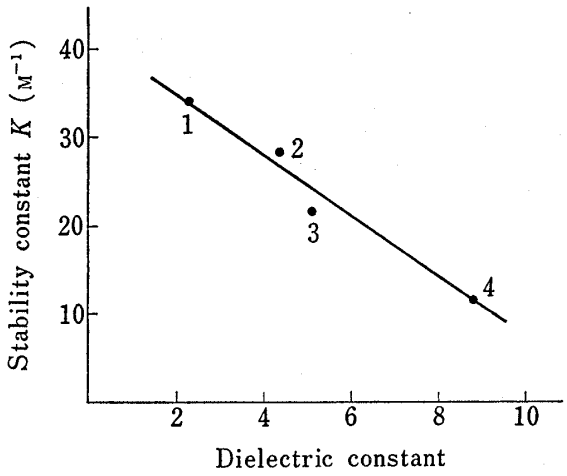

Fig. 3. Relationship between Stability Constant K of Sulfamethomidine/18-Crown-6 Complex at 10° and Dielectric Constant of Solvent

1, C_6H_6; 2, $(C_2H_5)_2O$; 3, $CHCl_3$; 4, CH_2Cl_2.

Fig. 3. These results indicated that the electrostatic interaction might be a primary force of the formation of these complexes.[8] Additionally, it was found that K value for sulfamonomethoxine/18-crown-6 complex in benzene was larger than the other complexes, suggesting that only the systems of a large K value might be formed as crystalline complexes in solid state.

Formation of Complexes in Solid State

As an example, Fig. 4 shows the powder X-ray diffraction patterns of sulfamethoxazole/18-crown-6 complex and physical mixture. These patterns were different from each other, and indicated that the interaction of sulfamethoxazole with 18-crown-6 gave a new solid phase.

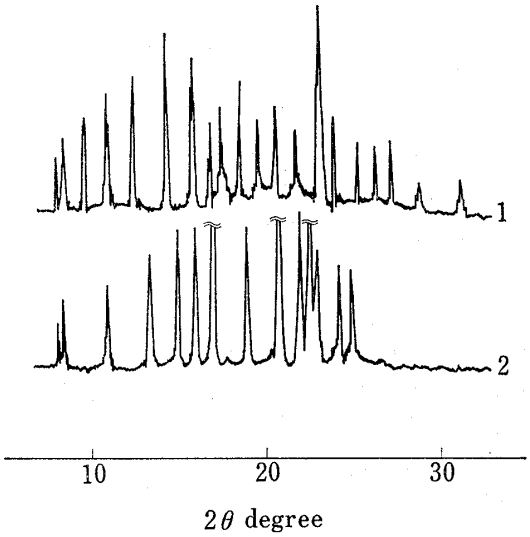

Fig. 4. Powder X-Ray Diffraction Patterns of Sulfamethoxazole/18-Crown-6 Physical Mixture and Complex by Cu-Kα Radiation

1, sulfamethoxazole/18-crown-6 physical mixture.
2, sulfamethoxazole/18-crown-6 complex.

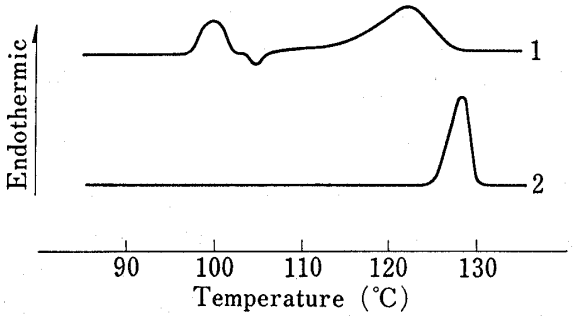

Fig. 5. DSC Curves of Sulfamethoxazole/18-Crown-6 Physical Mixture and Complex at Scanning Speed of 8°/min

1, sulfamethoxazole/18-crown-6 physical mixture.
2, sulfamethoxazole/18-crown-6 complex.

The DSC curves of sulfamethoxazole/18-crown-6 system as an example are shown in Fig. 5. Three peaks were observed on the curve in the case of the physical mixture, while only one in the case of the complex prepared. The three peaks in the case of the physical mixture were considered as follows: the endothermic one near 100° due to the eutectic point of sulfamethoxazole with 18-crown-6, the exothermic one near 105° due to the complex formation involving subsequent solidification, and the endothermic one near 122° due to the melting of complex. Regarding the solid complex of sulfamonomethoxine with 18-crown-6, a similar tendency was observed. Moreover, it was recognized that these complexes were stable in solid state when kept in a desiccator.

Consideration of the Binding Mechanism of Complex

Figure 6 shows the IR absorption spectra of sulfamethoxypyridazine/18-crown-6 system in $CHCl_3$. The intensities of the NH stretching at 3500—3250 cm^{-1} increased and a new band appeared at 3350 cm^{-1} with the addition of 18-crown-6, suggesting that the NH group might participate in hydrogen bonding. On the contrary, a band due to ether ring of 18-crown-6 at 1110 cm^{-1} hardly changed in the presence of sulfamethoxypyridazine. This result indicated that the steric situation of 18-crown-6 might be scarcely changed by the interaction of sulfamethoxypyridazine.

8) M. Otagiri, K. Uekama, K. Ikeda, and S. Onodera, *Chem. Pharm. Bull.* (Tokyo), **23**, 3228 (1975).

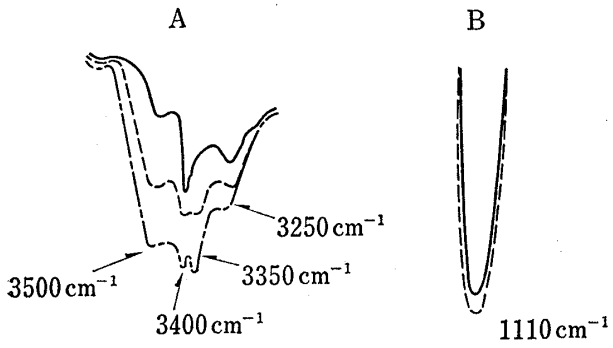

Fig. 6. IR Absorption Spectra of Sulfamethoxypyridazine/18-Crown-6 System in $CHCl_3$ according to Sodium Chloride Cell Method

A: ——, sulfamethoxypyridazine (0.016M) alone;
----, sulfamethoxypyridazine (0.016M)+18-crown-6 (0.032M);
——, sulfamethoxypyridazine (0.016M)+18-crown-6 (0.064M).
B: ——, 18-crown-6 (0.016M) alone;
----, 18-crown-6 (0.016M)+sulfamethoxypyridazine (0.016M).

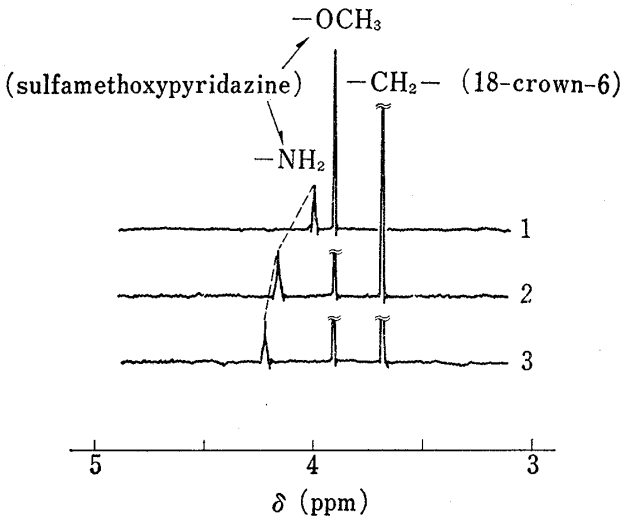

Fig. 7. Effect of 18-Crown-6 on ^{1}H-NMR Spectra of Sulfamethoxypyridazine in $CDCl_3$

1, sulfamethoxypyridazine (0.01M) alone.
2, sulfamethoxypyridazine (0.01M)+18-crown-6 (0.02M).
3, sulfamethoxypyridazine (0.01 M)+18-crown-6 (0.04M).

Figure 7 shows the effect of 18-crown-6 on ^{1}H-NMR spectrum of sulfamethoxypyridazine at 24.5°. The proton signal of 4-amino group shifted to lower field in the presence of 18-crown-6. This shift also indicated that 4-amino group might participate in hydrogen bonding. On the other hand, the proton signal of 18-crown-6 hardly shifted in the presence of sulfamethoxypyridazine, supporting the above speculation based on IR spectra.

Accordingly, it was suggested that 4-amino group of sulfonamide might be included in the cavity of 18-crown-6 in the complex formation.

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