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Spectroscopic Studies on Molecular Interactions. IV.[1] Charge-Transfer Properties and Antibacterial Activity of Sulfonamides[2]

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Charge-transfer properties of 12 sulfonamides, together with diaminodiphenyl sulfone, *p*-aminobenzoic acid, and aniline, were investigated by their interactions with *p*-chloranil. The equilibrium constant was determined and the ionization potential (I_D) was estimated by utilizing the charge-transfer band arising in the 500—550 mμ region. The relation of $h\nu_{CT}$ (charge-transfer transition energy) or I_D to the Michaelis constant for the acetylation of sulfonamides with liver extract indicated that the affinity of the drugs to acetylation enzymes increased as the ability of the charge-transfer of the drugs increased. The relationships between $h\nu_{CT}$ or I_D and *in vitro* bacteriostatic activities were expressed with parabolic curves, which indicated the optimum value of I_D being about 2.37 eV for the potent sulfonamides. The relationships were explained from the dependence of the affinity to enzymes on the charge-transfer ability of the drugs.

Various properties of sulfonamide molecules have been demonstrated to relate to the antibacterial activity of the drugs.[4] Although these relations present different explanations of the mechanism of sulfonamide action, they are all based on the original suggestion of Woods[5] and Fildes[6] that sulfonamides interfere with the utilization of *p*-aminobenzoic acid (PABA) in enzyme systems through competitive enzyme inhibition. Recently, from the quantum-chemical point of view, Yomosa[7] suggested that enzyme-substrate complexes may generally be charge-transfer complexes formed under the influence of the local field in the living body. Accordingly, in this paper, charge-transfer properties of sulfonamides were spectroscopically determined by their interactions with *p*-chloranil, and the relations to the bacteriostatic activities were investigated.

Experimental

Materials——Aniline, PABA, and *p*-benzoquinone and its derivatives were of JIS special grade or the like, and purified by redistillation or recrystallization. Xyloylsulfanilamide was kindly supplied by Hujisawa Yakuhin Kogyo Co., Ltd. All other sulfonamides and diaminodiphenyl sulfone were from commercial sources and recrystallized from methanol. Purified methanol was used as the solvent throughout the investigation. Melting points and boiling points were found to be similar to those listed in chemical handbooks and literatures.

Measurements of Absorption Spectra——The spectra were measured in 1 cm cells at room temperature (17—20°) with a Hitachi model EPS-2 recording spectrophotometer about one week after preparing the test solutions.

1) Part III: I. Moriguchi and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **17**, 2173 (1969).
2) Presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April, 1969.
3) Location: *Hatanodai, Shinagawa-ku, Tokyo.*
4) *a*) P.H. Bell and R.O. Roblin, *J. Am. Chem. Soc.*, **64**, 2905 (1942); *b*) I. Moriguchi, S. Wada, and T. Nishizawa, *Chem. Pharm. Bull.* (Tokyo), **16**, 601 (1968); *c*) W.D. Kumler and T.C. Daniels, *J. Am. Chem. Soc.*, **65**, 2190 (1943); I.M. Klotz, *ibid.*, **66**, 459 (1944); J. Seydel, E. Krügel-Thiemer, and E. Wempe, *Z. Naturforsch.*, **15b**, 628 (1960); S. Yamabe, *Chemotherapy*, **9**, 220 (1961); J. Seydel, *Arzneimittel-Forsch.*, **16**, 1447 (1966); A. Cammarata and R.C. Allen, *J. Pharm. Sci.*, **56**, 640 (1967); I. Moriguchi and S. Wada, *Chem. Pharm. Bull.* (Tokyo), **16**, 734 (1968).
5) D.D. Woods, *Brit. J. Exp. Pathol.*, **21**, 74 (1940).
6) P. Fildes, *Lancet*, **1940, I**, 955.
7) S. Yomosa, "Seitai-Kobunshi to Ion," ed. by N. Imai T. Ooi, U.Kisimoto, M. Nagasawa, and S. Yomosa, Kagakudojin, Kyoto, 1968, p. 45.

Determination of Equilibrium Constants——A Hitachi–Perkin Elmer model 139 spectrophotometer with 1 cm cells was employed for measurements of absorbances at the wave length listed as λ_{CT} in Table I. The initial concentrations of sulfonamides, diaminodiphenyl sulfone, aniline, and PABA were kept constant at 10^{-3}M, and the concentrations of *p*-chloranil were varied between 2.4×10^{-3}M and 5.6×10^{-3}M. The measurements were made at $25\pm0.2°$ about one week after preparing the test solutions. The evaluation of the equilibrium constants was made by the method previously described.[1]

Results and Discussion

p-Chloranil known as a good electron–acceptor[8] has an absorption maximum at 363 mμ in methanol, but in the presence of a sulfonamide a new absorption band arises in the 500—550 mμ region (Fig. 1). Such a new band was also observed in the mixed solutions of *p*-chloranil with aniline and PABA (See Fig. 1) but not observed with N^4-acetylsulfanilamide, *p*-toluenesulfanilamide, and benzenesulfanilamide. And a linear relationship between the electron affinity[9] of *p*-benzoquinones and the transition energy for the new absorption bands of the mixed solutions of the benzoquinones with sulfanilamide is recognized (Fig. 2). These results seem to indicate that the new absorption bands are charge–transfer bands due to the formation of charge–transfer complexes, and that the free amino group of sulfonamides, aniline, and PABA plays an important role of electron-donating in the complexation with the acceptors.

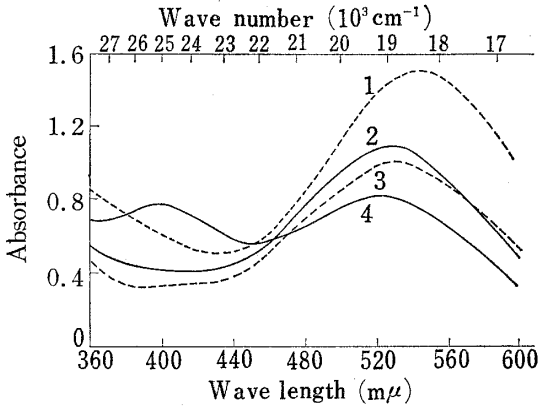

Fig. 1. Spectra of Mixed Solution of *p*-Chloranil with Sulfonamides, Aniline, and PABA *vs.* *p*-Chloranil

5×10^{-3}M *p*-chloranil with 1.25×10^{-3}M aniline (1), sulfanilamide (2), PABA (3), and sulfadimethoxine (4) in methanol

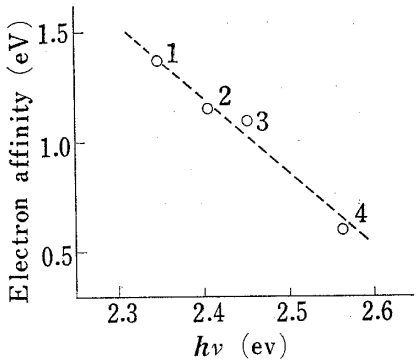

Fig. 2. Relation of Electron Affinity of Benzoquinones to $h\nu$ of the New Absorption Bands of Sulfanilamide–Benzoquinone Systems

benzoquinones: 1. *p*-chloranil, 2. 2,6-dichloro-*p*-benzoquinone, 3. 2,5-dichloro-*p*-benzoquinone, and 4. *p*-benzoquinone

The equilibrium constant, K, and the molar absorptivity, ε_{CT}, of the complexes with *p*-chloranil were determined from the absorbance data at the wave length of the charge–transfer, λ_{CT}, by means of the improved Benesi-Hildebrand method proposed in the previous paper.[1] The spectroscopic analysis confirmed the occurrence of 1:1 complexes.

The ionization potential, I_D, of the donors was calculated by utilizing the following equation,[10]

$$h\nu_{CT}=I_D-C_1+C_2/(I_D-C_1)$$

8) L.J. Andrews and R.M. Keefer, "Molecular Complexes in Organic Chemistry," Holden–Day, Inc., San Francisco, 1964.
9) G. Briegleb, *Angew. Chem.*, **76**, 326 (1964).
10) S.H. Hastings, J.L. Franklin, J.C. Schiller, and F.A. Matsen, *J. Am. Chem. Soc.*, **75**, 2900 (1953).

where $h\nu_{CT}$ is the charge-transfer transition energy which can be obtained from λ_{CT}, and the constants C_1 and C_2 are 5.70 eV and 0.44 (eV)^2, respectively, for *p*-chloranil complexes.[11] The values of λ_{CT}, ε_{CT}, $h\nu_{CT}$, I_D, and log K are listed in Table I.

Table I. Charge-Transfer Properties of Sulfonamides, Diaminodiphenylsulfone, PABA, and Aniline with *p*-Chloranil

	λ_{CT} (mμ)	ε_{CT} (10^3)	$h\nu_{CT}$ (eV)	I_D (eV)	log K[a] at 25°
1. Sulfanilamide	528.5	4.08	2.346	7.840	1.91
2. Sulfamethoxazole	522.5	4.17	2.373	7.870	1.81
3. Sulfadimethoxine	523	4.35	2.371	7.868	1.87
4. Xyloylsulfanilamide	520.5	3.85	2.382	7.880	1.81
5. Sulfadiazine	525	3.70	2.362	7.858	1.93
6. Sulfisoxazole	521.5	3.57	2.378	7.876	1.64
7. Sulfamonomethoxine	523.5	3.28	2.369	7.866	1.95
8. Sulfaphenazole	522.5	3.33	2.373	7.870	1.79
9. Sulfamethomidine	525.5	3.21	2.360	7.856	2.23
10. Sulfamethoxypyridazine	526.5	2.87	2.355	7.850	2.17
11. Sulfamerazine	525.5	4.20	2.360	7.856	1.93
12. N^1-*p*-Tolylsulfanilamide	526	2.09	2.357	7.853	2.08
13. Diaminodiphenylsulfone	521	3.36	2.380	7.878	2.29
14. PABA	532.5	3.64	2.329	7.822	1.93
15. Aniline	545	3.73	2.275	7.762[b]	2.14

a) Unit of K is liter/mole.
b) 7.70 by photoionization method (K. Watanabe and J.R. Mottl, *J. Chem. Phys.*, **26**, 1773 (1957))

Fig. 3 is the plot of $h\nu_{CT}$ against log K, showing a linear relationship except with sulfanilamide and diaminodiphenyl sulfone. This may indicate that the charge-transfer forces are

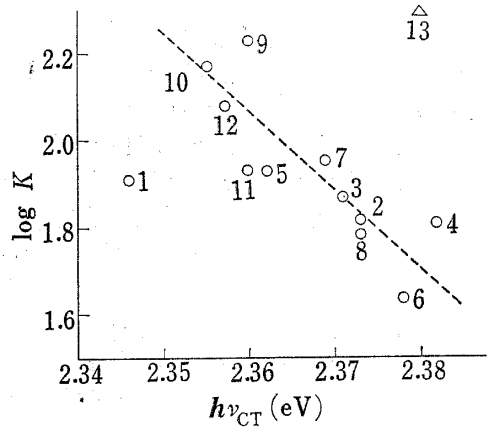

Fig. 3. Correlation of log K with $h\nu_{CT}$
○: sulfonamides △: sulfone
For numbering, see Table I.

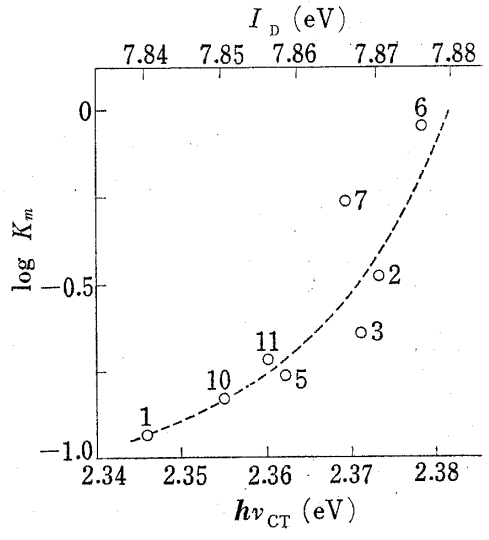

Fig. 4. Relationship between Michaelis Constant, K_m, for Enzymatic Acetylation and $h\nu_{CT}$ or I_D of Sulfonamides
For numbering, see Table I.

dominant in the complexations, but that the contribution of Van der Waals' forces or the like is not so small.

11) G. Briegleb and J. Czekalla, *Z. Elektrochem.*, **63**, 6 (1959).

For the purpose of ascertaining the Yomosa's suggestion previously described, the relation of Michaelis constant, K_m, for acetylation of sulfonamides with pigeon liver extract[12] to $h\nu_{CT}$ or I_D was investigated. Fig. 4 shows the relation exhibiting that the values of log K_m remarkably increases with increasing of $h\nu_{CT}$ or I_D. This seems to indicate that the affinity of sulfonamides to acetylation enzymes in the liver extract increases with an increase of charge-transfer ability of the drugs. This may support the Yomosa's suggestion.

Bacteriostatic activities of 12 sulfonamides[4b] and diaminodiphenyl sulfone[4a] against gramm-negative *Escherichia coli* and gramm-positive *Staphylococcus aureus* are plotted against $h\nu_{CT}$ or I_D (Fig. 5). The relationships are generally expressed with parabolic curves, which indicate the optimum value of I_D being about 2.37 eV for the potent sulfonamides. If

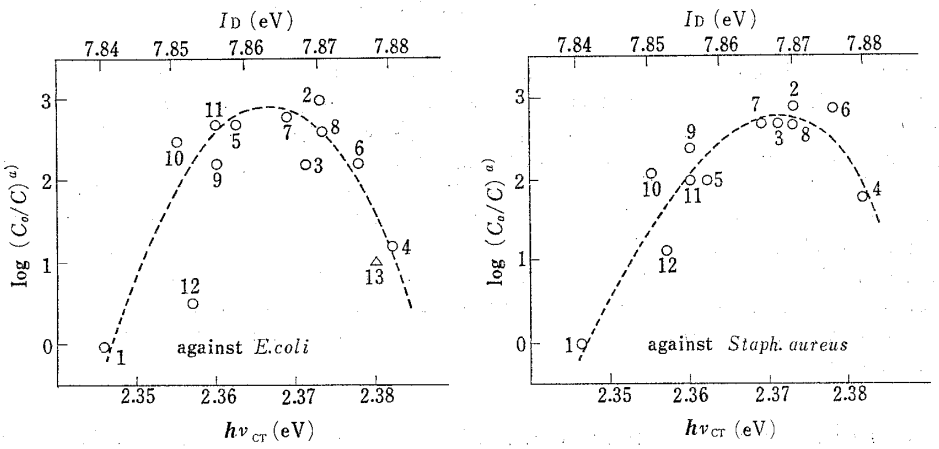

Fig. 5. Relationships between *in Vitro* Bacteriostatic Activities and $h\nu_{CT}$ or I_D

○: sulfonamides △: sulfone
For numbering, see Table I.
a) *C* is the minimum bacteriostatic concentration, and C_0 is that for sulfanilamide.

differences of permeabilities through bacterial cell walls are assumed to be negligible with many sulfonamides, a possible explanation for the relationships would be that too high ability of the charge-transfer accelerates the metabolism of sulfonamides by their combining with drug-metabolizing enzymes such as acetylation enzymes, and that too low ability of the charge-transfer dose not enable the drugs to bind so strongly with the target enzymes in the competition with PABA to reveal their bacteriostatic action. Because the value of I_D can be estimated by the quantum-chemical calculation,[13] the relationships, together with other physico-chemical knowledge, may be usefull for predicting the antibacterial activity of new sulfonamides.

12) K. Kakemi, T. Arita, and T. Koizumi, *Yakuzaigaku*, **25**, 22 (1965).
13) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, New York, 1963.