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Studies on the Biological Activity. II.[1] Discussions on the Biological Activity of *para*- and *meta*-Substituted Benzene Derivatives

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Partition coefficients and biological activities of substituted benzene derivatives have been analysed with respect to the substituent constants σ_i and σ_π, and suggested that they are essentially dependent on the molecular electronic conditions.

Introduction

Recently, several attempts have been carried out for the analyses of the biological activities, and one of which is the so-called *sigma-rho-pi* analysis.[3] This treatment signifies that the Hammett relationship is a reliable measure of biological response. In the preceding papers of our study,[4,5] it is proved that substituent constants σ_i and σ_π proposed by Yukawa and Tsuno[6] has practical utility in the estimation of *pi*-electron charge density distributions. In this study, the biological activities of several *para*- and *meta*-substituted benzene series have been discussed with respect to above view points, and tried to deduce reasonable results.

General Consideration

In the present step, the biological activity is expressed in the linear combination of several factors as below.

$$\log 1/c = k\pi + \rho\sigma + k'E_s + k'' \qquad (1)^{7}$$

where c = molar concentration of the derivative with substituent producing an equivalent biological response, for example, LD_{50}, ED_{50}, *etc.* in a fixed time under standard condition

ρ and σ = Hammett constants

π[8,9] = free energy related constant from the partition coefficient of the parent drug (P_H) and it's derivative (P_X) $\pi = \log P_X - \log P_H$

E_s = Taft's steric constants

k, k', k'' = constants in a given system

On the several contributing factors cited above, the following considerations have been explored as below.

1) Part I: Y. Sasaki and M. Susuki, *Chem. Pharm. Bull.* (Tokyo), **16**, 958 (1968).
2) Location: *Toneyama 5–6, Toyonaka, Osaka.*
3) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
4) Y. Sasaki and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **16**, 1187 (1968).
5) Y. Sasaki and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **17**, 1090 (1969).
6) Y. Yukawa and Y. Tsuno, *J. Chem. Soc. Japan*(*Pure Chemistry Section*), **86**, 873 (1965).
7) C. Hansch and E.W. Deutsch, *Biochem. Biophys. Acta*, **112**, 381 (1966).
8) T. Fujita, J. Iwasa and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).
9) J. Iwasa, T. Fujita and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965).

1. The revised Hammett's substituent constants σ_i and σ_π proposed by Yukawa and Tsuno[6] are reliable for the estimation of *pi*-electron charge density distribution in aromatic systems.

2 Steric factor operating between biological active molecule and receptor site has long been overestimated, but an "induced fit" proposed by Belleau[10] has liberated our confidence from steric factors.

3. The free energy related terms concerning the partition coefficient has long been accepted that they are independent of the electronic contribution. Recently, the linear free energy relationship has been acknowledged between partition coefficient and the aqueous solubility of organic solvent by Hansch, *et al*,[11] then, it is assumed that partition constant could be analysed with respect to the substituent constants σ_i and σ_π.

4. As is illustrated in 1., 2. and 3, the linear combination of two factors without steric condition are both controled from electronic condition, and eventually, we are able to analyse the biological response with respect to the substituent constant, in other words, to electron charge density distribution.

Results and Discussion

In this study, the partition coefficients of monosubstituted benzenes are analysed in the first place, and, in the next, several observed biological responses have been treated with respect to the linear combination of the substituent constants.

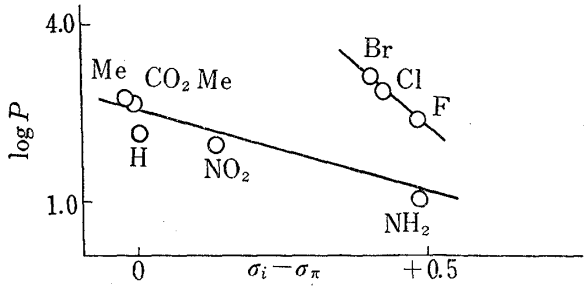


Fig. 1. Partition Coefficient of Monosubstituted Benzenes[11]

P=partition coefficient

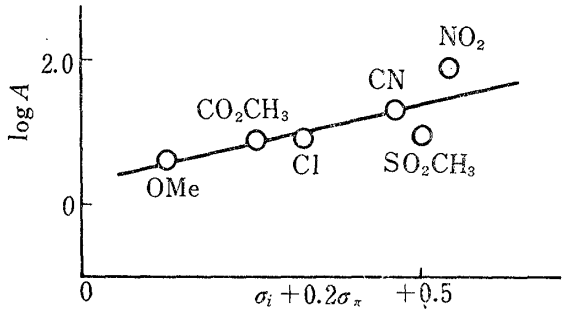
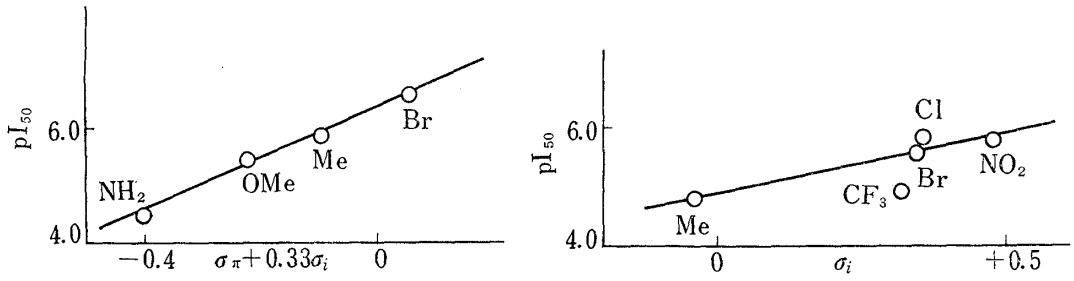


Fig. 2. Action of Chloromycetin Analogs on *Staphylococcus aureus*[12]

A=activity relative to chloromycetin (in mole%)



4-Substituted series 3-Substituted series

Fig. 3. Inhibition of Monoamine Oxidase by N-(Phenoxyethyl)cyclopropylamines[13]

pI_{50}=negative logarithm of the inhibitor concentration producing 50% inhibition

10) B. Belleau, *J. Med. Chem.*, 7, 776 (1964).
11) C. Hansch, J.E. Quinlan and G.L. Lawrence, *J. Org. Chem.*, 33, 347 (1968).
12) M.M. Shemyakin, M.N. Kosolov, M.M. Levitov, K.I. Germanova, M.G. Karapetyan, Yu.B. Shvetsov and E.M. Bamdas, *J. Gen. Chem. U.S.S.R.*, **26**, 885 (1956).
13) R.W. Fuller, M.M. Marsh and J. Mills, *J. Med. Chem.*, **11**, 397 (1968).

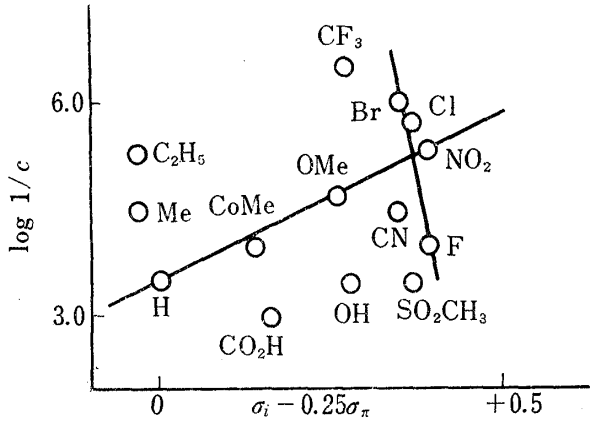


Fig. 4. Plant Growth-promoting Activitites of *meta*-Substituted Phenoxyacetic Acids[14]

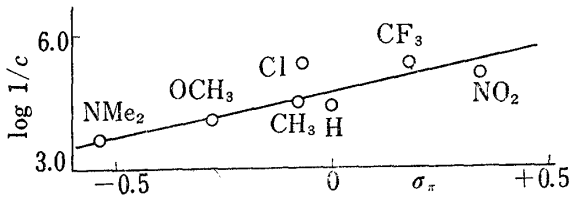


Fig. 5. Inhibition of Hill Reaction by *para*-Substituted Phenyldimethylureas[15]

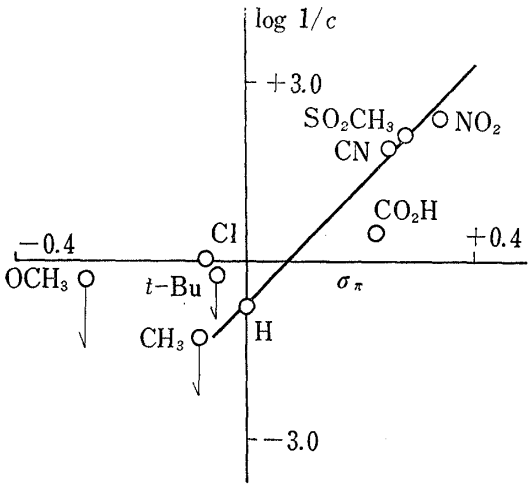


Fig. 6. Cholinesterase Inhibition of *para*-Substituted Diethyl Pheanyl Phosphates[16]

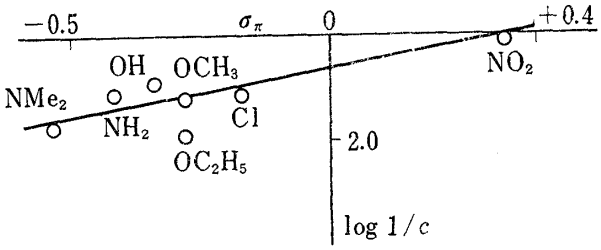


Fig. 7. Local Anesthetic Action of 2-Diethylaminoethyl Benzoates on Guinea Pigs[17]

As is shown in the foregoing example, the correlations among biological response and substituent constant have been observed in all examples, and following results were acknowledged.

1) *pi*-Electronic contribution is a dominant factor in *para*-substituted series, whereas *sigma*-electronic effect in *meta*-substituted ones.

2) In the examples 5 and 7, the biological response is correlated with *pi*-electron charge density distribution of the *meta* position from substituent group.[1)]

14) C. Hansch, R.T. Muir, T. Fujita, P.P. Maloney, F. Geiger and M. Streich, *J. Am. Chem. Soc.*, **85**, 2817 (1963).
15) N.E. Good, *Plant Physiol.*, **36**, 788 (1961).
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