of the pyrimidines in the solvents. The values in each of the solvents could be lineally correlated with the pKa (H_2O) values and the Hammett's σ_m for the 5-substituents. Some of the pyrimidines which deviated considerably from these linear relationships were discussed. Moreover, it was found that the differentiating titration of a mixture of pyrimidines might be facilitated with increasing of the reaction constant of the Hammett's equations. On the other hand, it was indicated by the Hammett's equations and by comparison of ultraviolet absorption spectra that these pyrimidines existed largely as the amino form in the solvents as well as in water and the actual proton acceptor in these molecules was the 1-position of pyrimidine ring.

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178. Yoshikazu Kondo, Kazue Kondo, Tsunematsu Takemoto,[*1] **and Tsuneo Ikenoue**[*2] :

Application of the Infinite Dilution Shifts in Acid-Base System to Organic Chemistry. I. Relation between the Infinite Dilution Shifts of Monosubstituted Benzoic Acids in Pyridine and the Hammett δ Values.[*3]

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Since the nuclear magnetic resonance (NMR) spectrum responds sharply to the electron density, it is an effective means to detect the electronegativity of a substituent. The effect of a substituent on chemical reactivity often depends on the change of electron density surrounding a reactive center and a relation is found between the chemical shift in NMR and chemical reactivity. Many studies have been carried out on the close correlation between the Hammett σ value, which is a parameter of reactivity, and the chemical shift of a proton shielding.

Gutowsky and his co-workers1) first measured the chemical shifts of fluorine (^{19}F) for a series of substituted fluorobenzenes and proved that there is a linear relation δ_F and electronegativity of the substituents. In recent years, a number of studies have been reported on effect of substituents on the magnetic shielding of a proton bound directly to the benzene ring.2~10) In this case, the relation between the Hammett σ values and δ_H was not quite so simple.[*4] In contrast to the aromatic proton, the

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[*3] Communication : Y. Kondo, K. Kondo, T. Takemoto, T. Ikenoue : This Bulletin, **12**, 514 (1964).

[*4] Taft7,11) reported that when $\delta_P^H = -0.41\,\sigma_I - 0.700\,\sigma_R$ or $\delta_P^H = -0.49\,\sigma_I - 1.04\,\sigma_R^0 - 0.02$ was used, a linear relation can be obtained.

1) H. S. Gutowsky, D. W. McCall, B. R. McGrarvey, L. H. Meyer : J. Am. Chem. Soc., **74**, 4809 (1952).
2) P. L. Cario, B. P. Daily : *Ibid.*, **78**, 3043 (1956).
3) A. A. Bothner-By, R. E. Glick : *Ibid.*, **78**, 1071 (1956); J. Chem. Phys., **26**, 1651 (1957).
4) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, R. E. Glick : *Ibid.*, **81**, 5352 (1959).
5) I. Yamaguchi, N. Nakagawa : Bull. Chem. Soc. Japan, **33**, 1128 (1960).
6) R. R. Fraser : Can. J. Chem., **38**, 2226 (1960).
7) R. W. Taft, Jr. : J. Phys. Chem., **64**, 1805 (1960).
8) H. Spiesecke, W. G. Schneider : J. Chem. Phys., **35**, 731 (1961).
9) P. Diehl : Helv. Chim. Acta, **44**, 829 (1961); *Ibid.*, **45**, 568 (1962).
10) B. P. Dailey, A. Gawer, W. C. Neikam : Discussions Faraday Soc., **34**, 18 (1962).

chemical shifts of ^{13}C of the benzene ring carbon show a good relativity with σ^+ parameters.8,12~14)

On the other hand, there are reports on the chemical shifts of aliphatic protons of benzene derivatives dealing with *meta*- and *para*- substituted acetophenones,15) *meta*- and *para*-substituted toluenes,15) *para*-substituted anisoles,16) aromatic aldehydes,17) *para*-substituted ethylbenzenes,18) *para*-substituted phenylhexachlorobicyclo[2,2,1]-heptenes,18) substituted phenylacetylenes,19,20) and *para*-substituted ethyl-2-nitrobenzenesulfate.21) All of these derivatives showed a reasonably good correlation between the original or modified δ values and the magnetic shieldings of the side chain protons. The chemical shift of ^{19}F which is used as alternative of side chain protons, has been correlated with the Hammett σ values.22)

All the foregoing reports proposed a relation between the chemical shifts of the aromatic proton (or F) in substituted benzenes or of the proton (or F) in the side chain and the corresponding Hammett σ values of substituents. However, the authors examined the relation between the chemical shifts of carboxylic proton in monosubstituted benzoic acids at infinite dilution in pyridine and the Hammett σ parameters, and it was found that the carboxylic proton in substituted benzoic acid undergoes an exchange with the lone pair electrons of pyridine and the concentration shift of carboxylic proton at infinite dilution depends on the electronegativity of a substituent in this compound. The consideration concerning the relation between the infinite dilution shifts in pyridine and the Hammett σ values will be described in this paper.

Experimental

Each of *o*-, *m*-, and *p*-methylbenzoic acids, *m*-, and *p*-cyanobenzoic acids, *o*-, *m*-, and *p*-nitrobenzoic acids, *o*-, *m*-, and *p*-chlorobenzoic acids, *o*-, *m*-, and *p*-bromobenzoic acids, *o*-, *m*-, and *p*-iodobenzoic acids, *o*- and *p*-fluorobenzoic acids, *o*-, *m*-, and *p*-methoxybenzoic acids, and benzoic acid which were all commercially available were recrystallized several times from appropriate solvents until its physical constants became consistent with those reported in the literature, dried under reduced pressure over P_2O_5 till a constant weight was obtained, and used after the purity and absence of crystal water were confirmed by elementary analysis.

Pridine used as the solvent was purified by the usual method and distilled with Widmer's fractionating column. The first ten fractions were discarded and the successive fifth 10 fractions were collected. The fractionation and dehydration were repeated in argon stream until its moisture content was below 10^{-4} molar %. The moisture content of pyridine was checked by measuring the shift of carboxylic proton in two-component system of pyridine-acetic acid.23)

Sampling was carried out in a vacuum apparatus ($10^{-5.3}\sim10^{-4.7}$ mm. Hg). The acid was first set in this vacuum apparatus, left as it was in vacuum for 0.5~1.0 hour to effect sufficient dehydration, then dissolved in pyridine, after degasing the acid again vacuum, and made to 3 molar % solution.[*5]

[*5] Because the δ_{OH} of the 3 molar % solution gave the same value as that of 1 molar % concentration within the range of experimental error, and the value at 3 molar % concentration was regarded as the infinite dilution value.

11) R.W. Taft, Jr.: J. Am. Chem. Soc., **79**, 1045 (1957).
12) P.C. Lauterbur: Tetrahedron Letters, 274 (1961); J. Am. Chem. Soc., **83**, 1838 (1961); *Ibid.*, **83**, 1846 (1961); J. Ahem. Phys., 1406, 1415, 1432 (1963).
13) J.B. Stothers, P.C. Lauterbur: Can. J. Chem., **42**, 1563 (1964).
14) K.S. Dhami, J.B. Stothers: *Ibid.*, **43**, 510 (1965).
15) Y. Yukawa, M. Sakai, K. Kabazawa: Memoir Sci. & Ind. Research Osaka Uni., **17**, 185 (1960).
16) C. Heathcock: Can. J. Chem., **40**, 1865 (1962).
17) R.E. Klink, J.B. Stothers: *Ibid.*, **40**, 1071 (1962).
18) K.L. Williamson, N.C. Jacobus, K.T. Soucy: J. Am. Chem. Soc., **86**, 4021 (1964).
19) C.D. Cook, S.S. Danyluk: Tetrahedron, **19**, 177 (1963).
20) Y. Yukawa, H. Yamada: Nippon Kagaku Zasshi, **85**, 501 (1964).
21) C. Brown, D.R. Hogg: Chemical Communications, 150 (1965).
22) D.R. Eaton, W.A. Sheppard: J. Am. Chem. Soc., **85**, 1310 (1963).
23) T. Ikenoue: Abstr. Meeting of Chemical Structure Discussion in Japan, 1961, p. 39; T. Ikenoue, K. Kondo: Abstr. 15th Annual Meeting Chemical Society of Japan, 1962, p. 441.

Records of signal were all run through non-spinning measurement. Calibration of the spectra was based on the standard separation benzene and cyclohexane (1:1) having a space of 5.75_0 p.p.m., and caluculation of shifts was carried out by reading the separation between the shifts of β-proton in pyridine (Fig. 1) and that of carboxylic proton to which 5.95_6 p.p.m. was added to find the chemical shift based on cyclohexane. The line positions are the average of at least six measurements. The range of error was ±0.03 p.p.m.

All spectra were recorded with Varian V-4311 NMR Spectrometer. Temperature of measurement was 23°± 0.1° at frequency of 60 Mc./sec.

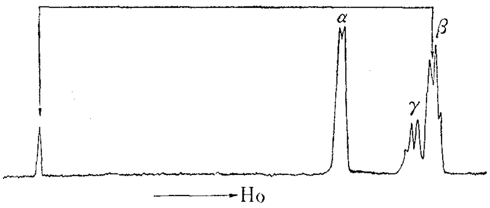


Fig. 1. Separation between β-Proton of Pyridine and Carboxylic Proton

Experimental Results and Discussions

In Table I are listed the infinite dilution shifts of carboxylic proton for the *meta*- and *para*-substituted benzoic acids dissolved to 3 molar % in pyridine solution.[*5]

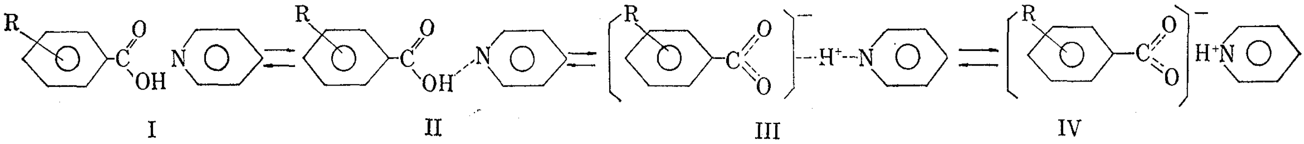
The chemical shift in NMR is essentially related to the ground state and is affected by the local electron density distribution of resonating nuclei. On the contrary, the Hammett σ value is related to the transition state complex and depends on the electrometric effect of an active center. Nevertheless, the relation between the Hammett σ values and chemical shifts, observed hitherto in many cases, suggests that there is a linearity between the two.

Table I. Infinite Dilution Shifts of *meta*- and *para*-Substituted Benzoic Acids in Pyridine

Substituent in benzoic acid	σ	δ_0(p.p.m.)	Substituent in denzoic acid	σ	δ_0(p.p.m.)
p-NO_2	+0.778±0.02	15.72_4	*p*-I	+0.18±0.1	14.91_9
m-NO_2	+0.710±0.02	15.93_0	*m*-I	+0.352±0.02	15.16_7
p-CN	+0.660±0.02	15.56_5	*p*-F	−0.062−0.02	14.83_9
m-CN	+0.56±0.05	15.66_9	*p*-OCH_3	−0.268−0.02	14.29_4
p-Br	+0.232±0.02	14.90_8	*m*-OCH_3	−0.115−0.02	14.72_7
m-Br	+0.391±0.02	15.28_2	Nil	0	14.64_5
p-Cl	+0.227±0.02	15.01_8	*p*-CH_3	−0.170−0.02	14.40_8
m-Cl	+0.373±0.02	15.33_1	*m*-CH_3	−0.069−0.02	14.51_8

In p.p.m. relative to cyclohexane

Investigations hitherto carried out were related to chemical shifts of a ring proton (or ring ^{19}F), ^{13}C, and resonating proton of a side chain in substituted benzenes. Since each of them is a chemical shift in the ground state, the correlation was obtained by carring out various corrections on the original Hammett σ value. By the introduction of a polar group into benzenes, the ring current effect in these aromatic systems will be affected directly by changes in the local electron density distribution and, in addition, magnetic anisotropy effect of the substituent will overlap in a complicated manner, giving an effect on the chemical shifts of resonating proton that has no direct bearing on the chemical behavior of a molecule.



In the present work, the infinite dilution shifts of substituted benzoic acids in pyridine were measured and this shift is considered to depend on the time average of each chemical shift in the states shown by I, II, III, and IV. Since the shifts of a carboxylic proton at infinite dilution are approximately constant, regardless of the kind of carboxylic acids, the chemical shift in state I is constant. The chemical shift in state IV is based on pyridinium and, therefore, it is also constant, independent of the kind of carboxylic acid. Consequently, the infinite dilution shifts of substituted benzoic acids in pyridine should be determined by the time average of the chemical shifts in II and III states, and it can be considered that the shifts are controlled by the nature of a substituent.

From the above discussion, it may be anticipated that the infinite dilution shifts in pyridine would be related to the Hammett σ values because the Hammett σ parameters are the values determined from the dissociation constant of monosubstituted benzoic acids and the acids used in the present work are similar in that the total effect of substituents (sum of resonance effect, inductive effect, etc.) is concentrated into the state of electron density of carboxylic proton.

Infinite dilution shifts of *meta-* and *para*-substituted benzoic acids were plotted against the Hammett σ values and shown in Fig. 2.[*6] The σ values cited here were adopted from the thermodynamic dissociation constant of benzoic acid derivatives in an aqueous system at 25° measured by Brown and his co-workers.[24] It should be noted here that, although the electric effect of a substituent will vary according to the kind of a solvent used, most of its fluctuations are included in the variation of the ρ constant in practice and, consequently, the Hammett rule will be established within a permissible range by the use of the foregoing σ value. The σ values used here include in part the contribution of a σ^+ type resonance. Considering the nature of the infinite dilution shift, this σ valued seems to be closer to the actual state but a fairly good correlation is obtained by using Taft's δ^0 value, as will be seen from Fig. 3.

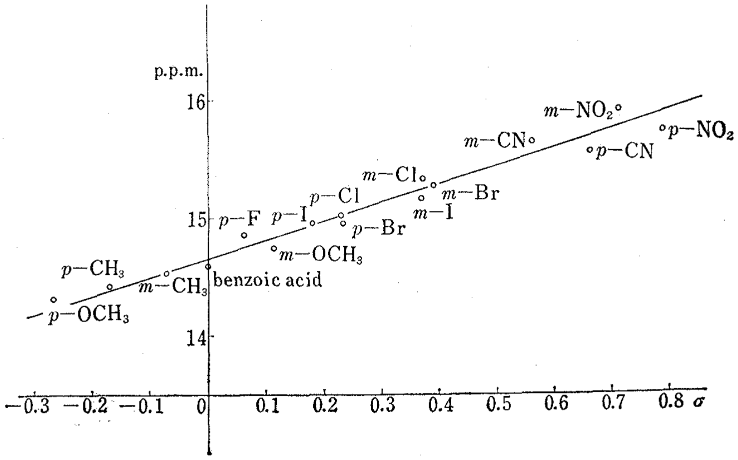


Fig. 2. Infinite Dilution Shifts in *meta-* and *para*-Substituted Benzoic Acids *vs* Hammett σ Constants

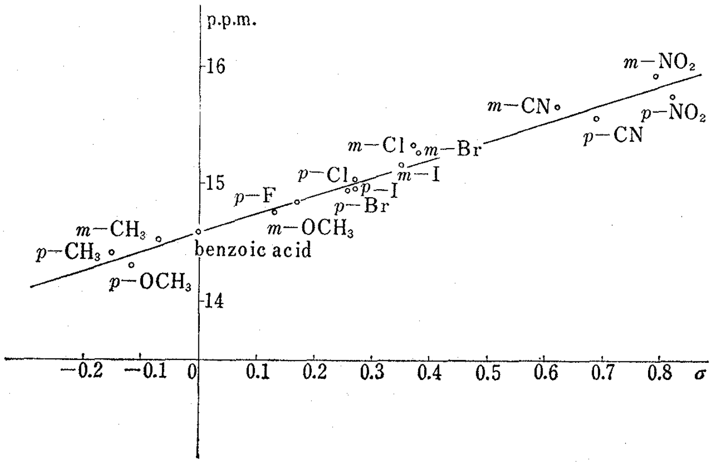


Fig. 3. Infinite Dilution Shifts in *meta-* and *para*-Substituted Benzoic Acids *vs* Taft's σ^0 Parameters

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[*6] The infinite dilution shifts of benzoic acid derivatives possessing a substituent with a large resonance effect in *para*-position, such as *p*-nitro- and *p*-cyano-benzoic acids, make a high field shift beyond the limit of experimental error and its reason has not been clarified yet.

24) D.H. McDaniel, H.C. Brown: J. Org. Chem., **23**, 420 (1958).

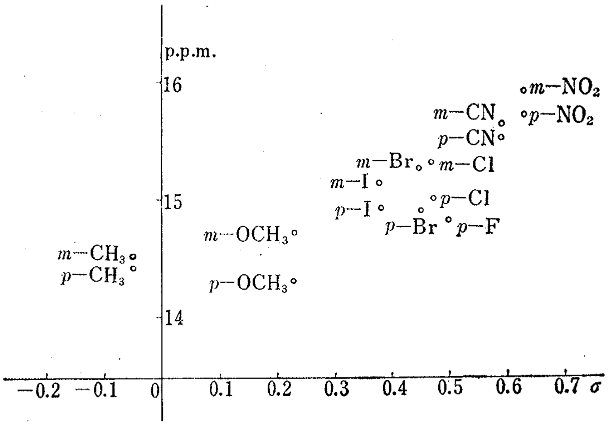

Fig. 4. Infinite Dilution shifts in *meta-* and *para-* Substituted Benzoic Acids *vs* σ_I Parameters

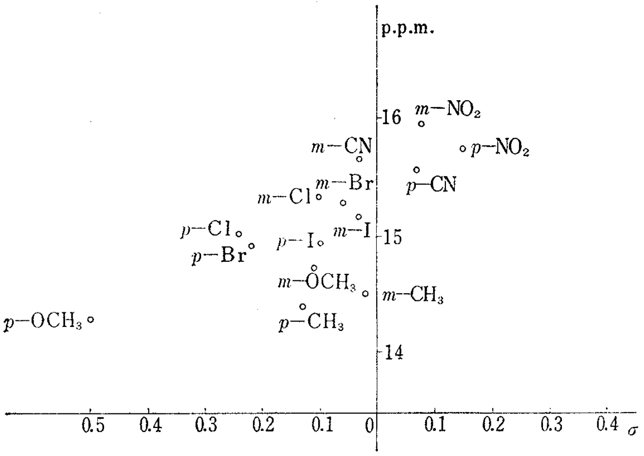

Fig. 5. Infinite Dilution Shifts in *meta-* and *para-* Substituted Benzoic Acids *vs* σ_R Parameters

Fig. 4 illustrates the relationship between σ_I values and infinite dilution shifts. It may be seen from this graph that the deviation is larger than the σ values in Fig. 2 and that the infinite dilution shifts are not dependent solely on the polar effect. Fig. 5 shows the plot between the infinite dilution shifts and σ_R parameters. This indicates that there is entirely no correlation, which may be a matter of course.

Up to the present, relationship between the chemical shifts and the Hammett σ values in *ortho*-substituted benzoic acids has scarcely been investigated. Plotting of the infinite dilution shifts for *ortho*-substituted benzoic acids against σ_P gave a good linearity, as shown in Fig. 6, and the values obtained are listed in Table II.

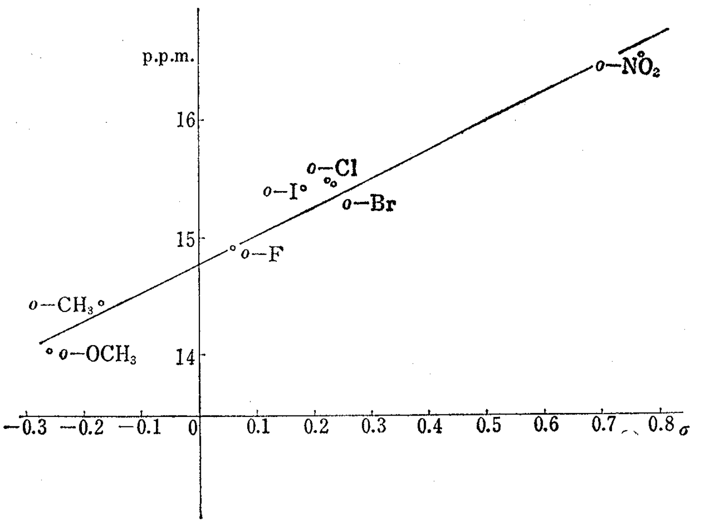

Fig. 6. Infinite Dilution Shifts in *ortho*-Substituted Benzoic Acids *vs* σ_p Parameters

Generally, *ortho*-substituents do not follow the Hammett rule due to the so-called *ortho*-effect. This *ortho*-effect includes steric hindrance and deviation caused by resonnance inhibition and intramolecular hydrogen bonding. In the case of NMR, further when the magnetic anisotropy effect of the *ortho*-substituent produces an effect upon the proton being observed, it will create a problem. When the *ortho*-substituent is a polar group, its effect can't be disregarded. In fact, in the case of *ortho*-substituted phenols in which exchangeable proton receives interference of the *ortho*-substituent, a large variation has been observed between the infinite dilution shifts and pKa.[25) When the exchange of *ortho*-substituted benzoic acid with pyridine is carried out, the exchangeable proton (carboxylic proton) is in a far enough distance from the *ortho*-substituent that it does not receive any effect of steric hindrance. Consequently, it can be considered that the so-called *ortho*-effect will not be seen in such a case. Also, deviation due to intramolecular hydrogen bond between *ortho*-substituent and

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25) T. Ikenoue: Abstr. Meeting of Molecular Structure Discussion in Japan, 1963, IV, p. 13.

Table II. Infinite Dilution Shifts of *ortho*-Substituted Benzoic Acids

Substituent in benzoic acid	σ_p	δ_0(p.p.m.)	Substituent in benzoic acid	σ_0	δ_0(p.p.m.)
o-NO_2	$+0.778 \pm 0.02$	16.61_8	*o*-F	$+0.062-0.02$	14.84_8
o-I	$+0.18 \pm 0.1$	15.39_3	*o*-CH_3	$-0.170-0.02$	14.40_7
o-Br	$+0.232 \pm 0.02$	15.46_9	*o*-OCH_3	$-0.268-0.02$	14.09_1
o-Cl	$+0.227-0.02$	15.48_7	Nil	0	14.64_5

In p.p.m. relative to cyclohexane

carboxylic proton should be included in the *ortho*-effect. When this intramolecular hydrogen bond becomes strong, the infinite dilution shift should shift to s higher magnetic field. However, the observed results suggest that this intramolecular hydrogen bond may be negligibly small or perphaps weakened in protophilic solvent like pyridine. The other factor that may be considered is the effect of an electric field caused by the *ortho*-substituent. In the substituent of a small Van der Waals radius, as in the case of steric hindrance, its effect on the shift will be small if the distance to exchangeable proton is taken into consideration. Even if a group with small magnetic anisotropy effect is out of the question, effect of nitro group should be fully considered.[26] Magnetic anisotrpy effect of a nitro group on the resonance of the methyl group has been determined for several of polymethyl-nitronaphthalenes[27] and methyl-nitronaphthalenes.[28] According to this result, effect of a nitro group on the methyl proton is quite small (average shift, -0.07 p.p.m.).[28] There is still some question in applying such a result directly to the substituted benzoic acid derivatives of the present study but the influence on exchangeable proton may be regarded as almost negligible.

Summary

The relation between the chemical shifts (δ_0) of *ortho*-, *meta*-, and *para*-substituted benzoic acids at infinite dilution in pyridine and the Hammett σ values was investigated. A good linear correlation against σ constants was observed for any of *ortho*-, *meta*-, and *para*-substituted benzoic acids. No correlation has been found up to the present for *ortho*-substituted benzoic acids by direct method such as the one based upon physical chemistry or NMR, but a good linearity was obtained by the above method.

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26) P. Diehl, G. Svegliado: Helv. Chim. Acta, **46**, 461 (1963).
27) I. Yamaguchi: Mol. Phys., **6**, 105 (1963).
28) P.R. Wells: Aust. J. Chem., **17**, 967 (1964).