The plots of Fig. 3 are not unusual in that reactions known to proceed by general base catalysis yield separate Brönsted equations for radically different types of bases.[9] It is generally found that all bases characterized by $-O^-$ as the attacking nucleophile fall into a single line and this may be noted to be so for the phenols and CH_3COO^-. The divergence of HPO_4^{--} from this line is due to the fact that the pK_a' is not truly a measure of its proton affinity. A suitable statistical correction places this point much closer to the plot for other $-O^-$ bases. It may also be noted that the value of log k_2 for H_2O falls above that which would be predicted from plots for $-O^-$ and $\geqslant N:$ species, but the value of log k_2 for OH^- is considerably lower than expected. It is usual to have the value of k_c for H_2O near to that expected from the Brönsted plot, but k_c for OH^- is generally lower. Probably of greatest interest is the magnitude of the essentially parallel displacement of the lines connecting the points for bases of similar type from the Brönsted plot (log $k_2 = 0.8pK_a' - 4.3$) for the imidazoles and the decidedly greater nucleophilicity of the nitrogen as compared to the negative oxygen (and CN^-) bases when the affinity for the proton is used as standard.

The inability to correlate displacement reactions on carbon to pK_a' has been treated by Swain and Scott[10] who suggest the equation log $k/k_0 = sn$ for non-solvolytic nucleophilic displacement reactions on carbon. According to Swain, plots of the log k_2 relative to water (*i.e.*, log k/k_0) *vs.* derived nucleophilic constants (n) afford linear plots with slope s. When the equation of Swain is applied to the bases studied herein for which values of n are available (CH_3COO^-, pyridine, HPO_4^{--}, OH^- aniline and CN^-) a value of $s = 1.16$ is obtained and the median deviation is 0.6 n unit. The major deviant is OH^- (3.4 n units). Swain noted a large deviation for OH^- (3.74 n units) in its reaction with β-propiolactone and suggested this to be due to the particularly relative effectiveness of OH^- as a nucleophile in displacement reactions on the ester carbonyl group. A derived value of $n = 8.0$ for OH^- from the β-propiolactone rate data brings the point for the reaction of OH^- with p-NPA into line with the other nucleophiles studied. The application of the more recent dual basicity equation of Edwards[11] corrects for the large deviation of OH^- by allowing suitable weighting of pK_a' values in comparison with the nucleophilic constant, but the plot then acquires the same characteristics as the Brönsted plot (Fig. 3).

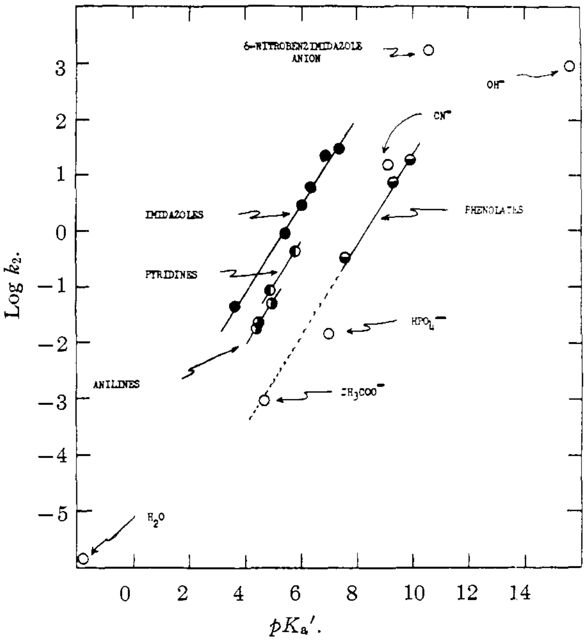

Fig. 3.—A Brönsted type plot of log k_2 *vs.* pK_a' for the reaction of general bases with p-nitrophenyl acetate.

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[9] R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, Chapt. V.

[10] C. G. Swain and C. B. Scott, This Journal, **75**, 141 (1953).

[11] J. O. Edwards, *ibid.*, **76**, 1540 (1954); **78**, 1819 (1956).

[Contribution from the Faculty of Engineering, Kyoto University]

Electronic Structure and Auxin Activity of Benzoic Acid Derivatives

By Kenichi Fukui, Chikayoshi Nagata and Teijiro Yonezawa

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The π-electron distribution of various benzoic acid derivatives has been calculated by a molecular orbital method. A distinct parallelism is found between the electronic structure and the auxin activity of these compounds. A discussion of the mechanism of plant growth action is given. A strong resemblance is pointed out between the plant growth action of these compounds and the carcinogenic action of aromatic compounds.

Since the discovery of the natural plant growth substance, indole-3-acetic acid, numerous active substances have been synthesized, and in order to elucidate the mechanism of hormonal action of these compounds, many studies[1-9] have been made. The mechanism of the action of these plant growth hormones nevertheless has remained elusive.

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[1] R. M. Muir, C. Hansch and A. H. Gallup, *Plant Physiol.*, **24**, 359 (1949); C. H. Hansch and R. M. Muir, *ibid.*, **25**, 389 (1950); R. M. Muir and C. Hansch, *ibid.*, **28**, 218 (1953).

[2] R. L. Wain, *J. Sci. Food Agr.*, 101 (1951).

[3] R. M. Muir and C. Hansch, *Plant Physiol.*, **26**, 369 (1951).

[4] C. Hansch, R. M. Muir and R. L. Metzenberg, *ibid.*, **26**, 812 (1951).

[5] J. M. F. Leaper and J. R. Bishop, *Bot. Gaz.*, **112**, 250 (1951).

[6] J. Bonner and R. S. Bandurski, *Ann. Rev. Plant Physiol.*, **3**, 59 (1952).

[7] A. Rhodes and R. de B. Ashworth, *Nature*, **169**, 76 (1952).

[8] H. Veldstra, *Ann. Rev. Plant Physiol.*, **4**, 151 (1953).

[9] C. J. Schoot and K. H. Klassens, *Rec. trav. chim.*, **75**, 271 (1956).

Hansch and Muir, *et al.*,[1,3,4] assumed that plant growth substances would interact with plant substrates and the interaction would be the first step of plant growth action. They investigated the effects of various analogs of indoleacetic acid, phenoxyacetic acid, phenylacetic acid and benzoic acid on the elongation of sections of *Avena coleoptiles*, and suggested that the carboxyl group and a position in the ring *ortho* to the carboxyl group would be two sites of reaction. That is, they assumed that the reaction would take place by a displacement of the electronegative atom or group at the *ortho* position by the nucleophilic plant substrate and, at the same time, the carboxyl group would become attached to the other site of the plant substrate by salt formation of amide linkage.

This assumption is not unreasonable from either the chemical or the biological points of view and was generally formulated by Foster, McRae and Bonner[10] as a two point attachment hypothesis and was supported by their kinetic investigations, and still more was confirmed by the experiment of Hansch, Muir and Metzenberg.[4] They detected Cl^- ion in experiments on elongation of *coleoptile* sections by benzoic acid derivatives and showed that the amount of Cl^- ion detected was parallel to plant growth activity.

The present authors have previously presented the frontier electron theory[11-14] and have found a distinct parallelism between the frontier electron distributions and the experimental chemical reactivity of π-electron systems. In the present paper, the theory is applied to a number of benzoic acid derivatives and an intimate correlation is found between the frontier electron distribution at the *ortho* position and the plant growth activity of these compounds.

Theoretical Index for Activity.—In this paper, we do not refer to the details of the frontier electron theory but briefly describe the theoretical indices which are used in that theory as a measure of chemical reactivity of conjugated molecules. These are the frontier electron density, the superdelocalizability (S_r) and the approximate superdelocalizability (S_r').

Frontier electron density[11,12] has been shown to be a good index for discussing intramolecularly the chemical reactivity of aromatic compounds. The position which is the most susceptible to attack is that of the highest frontier electron density, not only in the case of substitution but also in the case of addition. Frontier electrons are defined as the two electrons occupying the highest molecular orbital in the ground state in the case of reaction with an electrophilic reagent. In the case of reaction with a nucleophilic reagent, the frontier orbital is the lowest vacant orbital of the ground state: and, in the case of reaction with a radical reagent, both the two orbitals mentioned above.[12]

Superdelocalizability was defined according to the type of reaction as[13,14]

(a) for an electrophilic reaction

$$S_r^{(E)} = 2 \sum_{j=1}^{m} \frac{C_r^{(j)2}}{\lambda_j}$$

(b) for a radical reaction

$$S_r^{(R)} = \sum_{j=1}^{m} \frac{C_r^{(j)2}}{\lambda_j} + \sum_{= m+1}^{N} \frac{C_r^{(j)2}}{(-\lambda_j)}$$

(c) for a nucleophilic reaction

$$S_r^{(N)} = 2 \sum_{j=m+1}^{N} \frac{C_r^{(j)2}}{(-\lambda_j)}$$

where N is the total number of π-orbitals in the molecule; the occupied levels are denoted by $1, 2, \ldots, m$ and the unoccupied levels by $m + 1, m + 2, \ldots, N$; $C_r^{(j)}$ is the coefficient of the r th atomic π-orbital in the j th molecular orbital; and λ_j is the coefficient of the resonance integral, when the energy of a molecular orbital is expressed in the form $\alpha + \lambda_j\beta$.

α and β are the coulomb and the resonance integral of a carbon atom and C–C bond in benzene, respectively. It is easily understood that the contribution of the frontier level to S_r is the largest in almost all cases because the $|\lambda|$ value of the frontier level is the smallest. Hence, the S_r may be approximated by taking into account only the contribution of the frontier level. This "approximate" superdelocalizability is defined as

$$S_r'^{(E)} = 2 \frac{C_r^{(m)2}}{\lambda^m}$$

$$S_r'^{(R)} = \frac{C_r^{(m)2}}{\lambda_m} + \frac{C_r^{(m+1)2}}{-\lambda_{m+1}}$$

$$S_r'^{(N)} = 2 \frac{C_r^{(m+1)2}}{-\lambda_{m-1}}$$

It is stressed that S_r' is not a mere approximation to S_r, but serves as a better index than S_r in some special reactions. For example, the carcinogenic activity of polycondensed aromatic hydrocarbons has been interpreted successfully by the values of S_r' at the principal carcinogenophore (phenanthrene double bond) and subsidiary carcinogenophore (anthracene *meso*-position).[15]

Parameters Used in Calculation.—The calculation of S_r' is carried out by using the simple LCAO–MO (linear-combination-of-atomic-orbitals molecular orbital) treatment, solving the secular equation. The coulomb integral of the two equivalent oxygen atoms in the $-COO^-$ group is taken as $\alpha + 2\beta$. The coulomb integral of the substituent X, that of the carbon atom attached to X, and the resonance integral between that carbon

Table I

Parameters Used in the Calculation

Substituent X	a_X	a_r	
F	2	0.5	1.3
Cl	2	.5	.8
Br	1.8	.4	.7
I	1.5	.3	.5
OH	0.3	0	.4
NH_2	0	0	.2
CH_3	2	0	1
NO_2	$\alpha_N = 1$ $\alpha_O = 1$	0.2	1

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(10) R. J. Foster, D. H. McRae and J. Bonner, *Proc. Natl. Acad. Sci.*, **38**, 1014 (1952).

(11) K. Fukui, T. Yonezawa and H. Shingu, *J. Chem. Phys.*, **20**, 722 (1952).

(12) K. Fukui, T. Yonezawa, C. Nagata and H. Shingu, *ibid.*, **22**, 1433 (1954).

(13) K. Fukui, T. Yonezawa and C. Nagata, *Bull. Chem. Soc. Japan*, **27**, 423 (1954).

(14) K. Fukui, T. Yonezawa and C. Nagata, *J. Chem. Phys.*, **26**, 831 (1957).

(15) C. Nagata, K. Fukui, T. Yonezawa and Y. Tagashira, *Cancer Research*, **15**, 233 (1955).

TABLE II

RELATION BETWEEN REACTIVITY INDICES AND AUXIN ACTIVITY OF BENZOIC ACID DERIVATIVES

Benzoic acid derivatives	$S_r'^{(N)}$	$S_r'^{(E)}$	$S_r'^{(R)}$	Net charge at the oxygen atom in carboxyl group, Q_{oxy}[b]	Auxin[c] activity
2,5-Dichloro-	0.7771(2)[a]	0.2985(6)[a]	0.5239(2)[a]	......	++
2,4-Dichloro-	.7186(2)	.2894(6)	.4911(2)	......	−
2,3,6-Trichloro-	.7108(6)	.2753(2)	.4848(6)	......	++++
2-Chloro-	.7093(2)	.3043(6)	.5012(2)	−0.8140	+
2,3,5-Trichloro-	.7074(2)	.2503(6)	.4773(2)	......	++++
2,4,6-Trichloro-	.6918(2,6)	.3137(2,6)	.5028(2,6)	......	−
2-Bromo-	.6825(2)	.3014(6)	.4885(2)	− .8150	+
2-Iodo-	.6810(2)	.2942(6)	.4807(2)	− .8145	±
2-Bromo-6-chloro-	.6777(6)	.2819(2)	.4781(6)	......	+
3-Methyl-	.6705(2)	.4873(2)	.5789(2)	− .8157	−
2,6-Dichloro-	.6693(2,6)	.2593(2,6)	.4644(2,6)	......	+
2,6-Dibromo-	.6501(2,6)	.2706(2,6)	.4604(2,6)	......	−
2-Methyl-	.6483(6)	.3384(2)	.4783(6)	−0.8201	−
3-Chloro-	.6430(6)	.3202(2)	.4691(6)	− .8157	−
3-Fluoro-	.6364(2)	.4680(2)	.5522(2)	− .8157	−
3-Hydroxy-	.6351(2)	.3188(2)	.4770(2)	− .8157	−
3-Bromo-	.6327(6)	.3267(2)	.4662(6)	− .8157	−
3-Iodo-	.6312(6)	.3173(2)	.4574(6)	− .8157	−
4-Chloro-	.6199(2,6)	.2982(2,6)	.4590(2,6)	− .8141	−
4-Iodo-	.6160(2,6)	.2874(2,6)	.4517(2,6)	− .8144	−
4-Bromo-	.6142(2,6)	.2888(2,6)	.4515(2,6)	− .8150	−
2-Hydroxy	.6133(6)	.0591(6)	.3362(6)	− .8227	−
2-Fluoro-	.6096(6)	.3127(2)	.4526(6)	− .8170	−
3,4,5-Triiodo-	.6079(2,6)	.2487(2,6)	.4283(2,6)	......	−
Benzoic acid	.6020(2,6)	.3289(2,6)	.4655(2,6)	− .8157	−
2-Amino-	.6010(6)	.4555(2)	.4088(6)	− .8201	−
4-Amino-	.5733(2,6)	.4756(2,6)	.5245(2,6)	− .8199	−
4-Nitro-	.5567(2,6)	.3407(2,6)	.4487(2,6)	......	−
4-Fluoro-	.5564(2,6)	.2432(2,6)	.3998(2,6)	− .8169	−
4-Hydroxy-	.5538(2,6)	.0823(2,6)	.3181(2,6)	− .8220	−
4-Methyl-	.5427(2,6)	.2488(2,6)	.3958(2,6)	− .8195	−
2-Nitro-	.3764(6)	.3068(6)	.3416(6)	......	−

[a] Figures in parentheses indicate the position of attack. The position of attack is assumed to be *ortho* with respect to the carboxyl group. If there are two non-equivalent *ortho* positions in a molecule, the one with the greater S_r' is chosen. [b] Calculation of Q_{oxy} for di- and tri-substituted compounds as well as nitro compounds has not been carried out, because of its tediousness. [c] The signs, + and −, indicate the degree of auxin activity. The larger the number of + signs, the greater is the activity. The sign ± indicates that the compound is very feebly active. The sign − indicates that the compound has been reported to be inactive.

atom and X, are written as $\alpha + a_x\beta$, $\alpha + a_r\beta$, and $l\beta$, respectively. The numerical values of a_x, a_r and l adopted by us are shown in Table I. These values do not complicate the calculation so much and yet do not differ much from those of the other authors[16,17]; also they lead to a reasonable result in some other problems.

Results and Discussion

The results of the calculation of approximate superdelocalizability are indicated in Table II. As is clearly seen, the values of $S_r'^{(N)}$ at the position *ortho* with respect to the carboxyl group show a distinct parallelism with the magnitude of auxin activity. The larger value of $S_r'^{(N)}$ a compound has, the more active it is. On the contrary, the values of $S_r'^{(E)}$ as well as $S_r'^{(R)}$, turn out to have no such relation to the auxin activity. Since $S_r'^{(N)}$ is a good index for discussing the reactivity in nucleophilic substitution, as is described in the previous section, it may be said that the chemical reaction of benzoic acid derivatives at the *ortho* position with a nucleophilic group of the plant substrate is the most important factor determining its plant growth activity. Almost all the compounds whose $S_r'^{(N)}$ are above the threshold value (about 0.65) are active and the compounds whose $S_r'^{(N)}$ are less than this value are inactive.

As stated in the introductory section, Hansch and Muir[1,3,4] considered the plant growth action of these compounds in a qualitative fashion and concluded that at an early stage of *in vivo* reaction, the electronegative atom or group at the *ortho* position of these compounds would be displaced by the nucleophilic plant substrate and this would be the cause of hormonal action. It is of the greatest interest to see that the conclusion from the molecular orbital treatment and that of Hansch and Muir are entirely the same.

It is, of course, unwise to say that plant growth activity will be determined by the values of $S_r'^{(N)}$ alone. In addition to the chemical reactivity, there are a few other factors such as permeability, diffusibility and solubility of the plant growth substance into the tissues and cells. Moreover, re-

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(16) H. H. Jaffé, *J. Chem. Phys.*, **20**, 279 (1952).

(17) C. Sandorfy, *Bull. soc. chim. France*, 615 (1949).

sults of tests may be influenced by the procedures as well as the kind of plants used in the test. It may be permissible, therefore, to allow a few exceptions to our theory. The value of $S_r'^{(N)}$ of 2,4-dichlorobenzoic acid and 2,4,6-trichlorobenzoic acid are above the threshold, but they have been reported experimentally inactive. This is probably due to steric circumstances,[18] or, otherwise, to some factors other than chemical reactivity described above.

The discussion so far relates only to the reactivity of the position *ortho* with respect to the carboxyl group. According to the two point attachment hypothesis of Hansch and Muir, *et al.*,[1,3,4] we cannot consider the discussion complete without paying attention to another reaction center, the carboxyl group. The interaction of the carboxyl group with a site of the plant substrate is supposed to be electrostatic in nature, at least in the earliest stage of the interaction. Hence, the magnitude of the net charge at the carboxyl oxygen comes into question. In order to determine the value, it is necessary to know the inductive and mesomeric displacement of the π-electrons. The former is obtained easily according to the method by Coulson and Longuet-Higgins[19] and the latter is obtained by an equation developed by the present authors.[20]

The result of the calculation is indicated in the fifth column of Table II. As is seen there, the net charge of the carboxyl oxygen atom, Q_{oxy}, does not change remarkably in its value and, moreover, it has no evident correlation with the auxin activity. It may be concluded from this result that the net charge of carboxyl oxygen does not participate in the plant growth action in such a way that a slight difference in its magnitude exercises a serious influence upon the activity. Of course, it is not the opinion of the present authors that the carboxyl group plays no role in the plant growth action. The presence of a carboxyl group in a molecule seems to be a necessary condition to the occurrence of activity from the experimental fact that the molecules with no carboxyl group or group convertible to carboxyl have no activity.

The action of the plant growth compound has been considered in connection with the problem of cancer metabolism by Nickell.[21] We have also taken a warm interest in the strong resemblance between the hormonal action of plant growth compounds and the carcinogenic action of aromatic compounds. The details of this point will be discussed elsewhere.

Besides the benzoic acid derivatives, numerous compounds such as phenylacetic acid derivatives, and phenoxyacetic acid derivatives,[1,4] thioglycolic acid derivatives,[22] and N-phenylglycine derivatives, have been tested for their activities. The results of calculations for these compounds will be reported in the future.

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[18] From the standpoint of chemical reactivity, 2,4-dichloro derivative will far more easily be attacked than 2,6-derivatives by a nucleophilic reagent, as was pointed out by Hansch, Muir and Metzenberg (ref. 4). Regarding plant growth action, nevertheless, the 2,6-derivative is active while the 2,4-derivative is inactive. An assumption could improve the situation—that *para*-substituted benzoic acid derivatives, in general, would be inactive due to their increased molecular size which prevents their reaching the site of reaction. In Table II, it is observed that the other *para*-derivative is inactive.

[19] C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* (*London*), **A191**, 39 (1947).

[20] The equation was derived using the perturbation theory. The derivation is rather tedious, and will be published elsewhere.

[21] C. P. Rhoads, "Antimetabolites and Cancer," Amer. Assoc. Adv. Sci., Washington, 1955, pp. 129–151.

[22] *E.g.*, J. Kato, *Memor. Coll. Sci. Univ. Kyoto*, **B21**, 77 (1954).

[23] *E.g.*, A. Takeda and J. Senda, *Nogaku Kenkyu*, **42**, 19 (1954); **43**, 178 (1956).

KYOTO, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF GENERAL CHEMISTRY OF THE UNIVERSITY OF ROME]

Electronic Transmission Through Condensed Ring Systems. III. The Evaluation of *epi* and *cata* Sigma Constants from Dissociation and Methoxydechlorination Data on Substituted 1-Aza-4-chloronaphthalenes[1]

BY ENRICO BACIOCCHI, GABRIELLO ILLUMINATI AND GIANLORENZO MARINO

RECEIVED SEPTEMBER 24, 1957

Kinetic and equilibrium data on 6- and 7-substituted 4-chloroquinolines have been conveniently compared with each other in terms of *epi* and *cata* substituent data. There is found a linear free energy correlation which has enabled the evaluation of the ρ-constant for the methoxydechlorination reaction and of 15 new heteronuclear substituent constants. Both inductive and primary conjugative effects seem to be equally well transmitted through the fused ring system. The over-all effects on heteronuclear σ-constants result in an intensity of transmission of one-half to one-third as large as that observed for homonuclear σ-constants. The analogy between *cata*, *epi* and *para*, *meta* effects is discussed. The $\sigma_{cata}-\sigma_{epi}$ differences are found to be poorer measures of conjugative effects than the $\sigma_p-\sigma_m$ differences.

In the preceding papers of this series[1] we have been concerned primarily with the determination of the substituent effects on the dissociation and nucleophilic displacement reactions of 4-chloroquinoline. We now wish to compare the two sets of reactions, show the applicability of the Hammett equation and give estimates of a number of new heteronuclear substituent constants. The fulfillment of this part of our program required the determination of the dissociation constants of some additional compounds in the series of 7-substituted 4-chloroquinolines.

Results and Treatment of Numerical Data.—The results from the spectrophotometric determination of the 7-substituted 4-chloroquinolines

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[1] (a) Part I, E. Baciocchi and G. Illuminati, *Gazz. chim. ital.*, **87**, 981 (1957); (b) Part II, G. Illuminati and G. Marino, THIS JOURNAL, **80**, 1421 (1958).