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]

(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.

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.

(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

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]

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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

(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).

are collected in Table I. The available data which will be utilized in the next section are thus the bimolecular rate constants at 75° for the methoxy-dechlorination of 6- and 7-substituted 4-chloro-quinolines given in Part II,[1b] and the pK_a values for the 6-substituted compounds given in Part I[1a] and for the 7-substituted compounds herein reported. To these we have added the pK_a value for 7-methyl-4-chloroquinoline as calculated from the dissociation constants of 7-methylquinoline[2] and of 4-chloroquinoline on the basis of the ascertained additivity[1a] of the substituent effects.

TABLE I

DISSOCIATION CONSTANTS OF SOME 7-SUBSTITUTED 4-CHLOROQUINOLINES AT 25°[a]

Substituent	λ, mμ	pK_a (app.)[b]	pK_a (thermod.)
OCH_3	306	4.37	4.32
F	312	3.09	3.04
Cl	316	2.85	2.80
Br	255	2.88	2.83

[a] Determined in 7.7% (by weight) aq. ethanol. [b] Means from two independent determinations.

Conventional numbering of the azanaphthalene system may be misleading if used to indicate, from time to time, the actual position of a substituent *relative to varying reaction centers;* for this reason Erdmann's nomenclature for naphthalene[3] was found more convenient in our case. For example, a 6-substituent is *cata* to the seat of chlorine displacement and *epi* to the seat of nitrogen protonation; the reverse is true for a 7-substituent. The situation is illustrated by formulas I and II in

I   II
Dissociation   Nucleophilic substn.
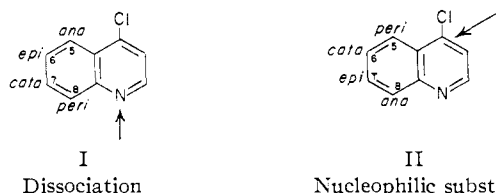
which the arrows indicate the reaction centers. Accordingly, all the above mentioned data on 6- and 7-substituted 4-chloroquinolines are found properly rearranged as *epi* and *cata* data in the first two columns of Table II.

Linear Free Energy Relationships.—A plot of log k_2 *vs.* log K_a is reported in Fig. 1 and shows that a linear relationship exists between the two examined reactions. By least square methods the equation of the straight line was found to be log $k_2 = 1.02$ log $K_a + 0.12$ with a correlation coefficient $r = 0.982$. In Part I we have shown that the dissociation of 4-chloroquinolines obeys the Hammett equation and that the reaction constant, ρ_{diss} at 25°, has practically the same value, 5.71, as that determined by Jaffé and Doak[4] for the dissociation of substituted pyridines. Thus the rate data for the methoxydechlorination reaction are just as good as the dissociation data in the application of the Hammett equation, and the validity of this conclusion is especially supported by the

(2) W. A. Felsing and B. S. Biggs, THIS JOURNAL, **55**, 3624 (1933).
(3) See footnote 5 in Part II (ref. 1b).
(4) H. H. Jaffé and G. O. Doak, THIS JOURNAL, **77**, 4441 (1955).

TABLE II

epi AND *cata* SUBSTITUENT CONSTANTS FROM METHOXIDE-CHLORINATION AND DISSOCIATION DATA ON 1-AZA-4-CHLORONAPHTHALENES

Substituent	pK_a,[a] at 25°	10^4k_2,[a] at 75.2°	σ_{epi} and σ_{cata} (SN reaction) (dissocn.)	(SN reaction)	(mean)
cata-$N(CH_3)_2$		0.0721		−0.264	−0.264
epi-OCH_3	3.93	1.440	−0.037	− .040	− .038
cata-OCH_3	4.32	0.529	− .105	− .115	− .110
epi-OC_2H_5	3.82		− .017		− .017
cata-OC_2H_5		0.472		− .123	− .123
cata-SCH_3		3.048		.016	.016
epi-CH_3	3.96		− .042		− .042
cata-CH_3	4.00	0.957	− .049	− .071	− .060
H	3.72	2.47	0	0	0
epi-F	2.95	12.36	0.135	0.120	0.128
cata-F	3.04	5.25	.119	.056	.088
epi-Cl	2.81	21.44	.159	.161	.160
cata-Cl	2.80	16.80	.161	.143	.152
epi-Br	2.83	21.77	.156	.162	.159
cata-Br	2.83	21.41	.156	.161	.158
cata-NO_2		1058		.452	.452

[a] For the probable errors and the reliability of these data the preceding papers[1] should be consulted. ADDED IN PROOF.—In the course of further studies the k_2 value for the *cata*-$N(CH_3)_2$ derivative, as obtained with a more highly purified sample, was essentially confirmed.

markedly different nature of the nuclear reactions under comparison.

From the slope of the straight line we readily can calculate the reaction constant, ρ_{SN} at 75°, for the nucleophilic substitution

$$\rho_{SN} = \text{slope} \times \rho_{diss} = 1.02 \times 5.71 = 5.82$$

The value thus found is one of the highest known so far in aromatic nucleophilic substitutions.[5] This confirms that a study of reactions at ring carbon or nitrogen is particularly favorable to establishing the rather weak effects of heteronuclear substituents. High reaction constants such as ρ_{SN} and ρ_{diss} should therefore lead to reliable estimates of substituent constants.

Some comments on the observed ρ-values are necessary at this point. The reaction constant for the dissociation of substituted quinolines was obtained by use of literature values, taken from various sources; it was, however, encouraging to note that these data fitted satisfactorily into the well established Hammett line for the substituted pyridines.[1a] Also, since the synthesis of 7-substituted 4-chloroquinoline is in principle less reliable (because of the possible formation of isomeric mixtures) than that of the 6-isomerides, we have limited in the present study our consideration of 7-isomerides to some of the best known compounds. The result has been a comparison of the two reactions examined here (Fig. 1) within rather a limited reactivity range; this disadvantage is however compensated by a good correlation coefficient from a fair number of experimental points. We hope to give an independent estimate of the ρ_{SN} value and to extend the above correlation to a wider range of substituent types in due course.

Although we do not pretend to draw conclusions on the detailed mechanism of the methoxydechlor-

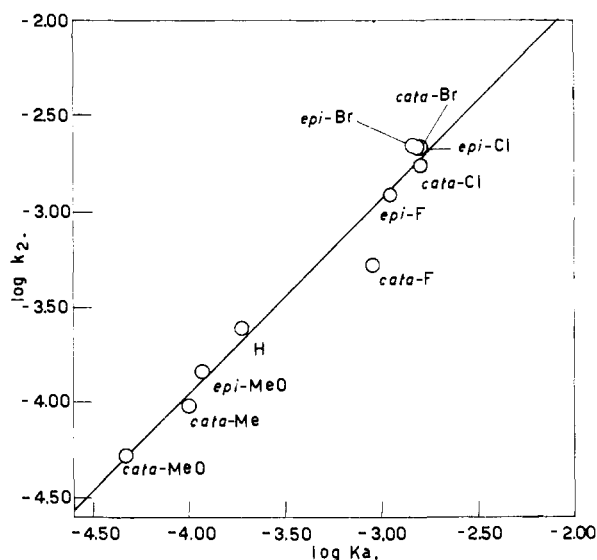(5) See J. Miller, *Austr. J. Chem.*, **9**, 61 (1956), and refs. thereof.

Fig. 1.—Correlation of rate data (log k_2) for methoxydechlorination with basicity data (log K_a) on some substituted 4-chloroquinolines.

ination reaction until sufficiently thorough extensions of this study are available, from the convergence of the substituent effects in the two different phenomena under consideration, one might speculate on what is the common basis for the observed correlation (see, especially, the methoxy group). The most obvious answer would be the initial state condensed-ring system. Apart from the fact that the initial state in the "thermodynamic" activation process leading to the transition state of the methoxydechlorination reaction may be as important as the (corresponding) initial state in the equilibrium of the nitrogen protonation, one tempting implication of the observed correlation on the transition state model for the rate-determining step is that the C_{Ar}–Cl bond-breaking and the C_{Ar}–OCH$_3$ bond-making have both made little progress. Now, not only evidence of transition states with no or little progress in the C_{Ar}–X bond-breaking (X = leaving group),[6] but also evidence of transition states with little progress in the C_{Ar}–Y bond-making (Y = incoming group)[7] has been given in recent years. In the latter case, Hammond and his co-workers have expressed the view that the transition states in displacements by negatively charged nucleophiles are located much closer along the reaction coördinate than in displacements by amines. Also, the location along the reaction coördinate would depend largely on the specific reaction and, we may add, on whether the substrate is a nitro- or an aza-activated system.

epi and *cata* **Sigma Constants.**—Application of the Hammett equation in its conventional form[8]

$$\log(k/k_0) \text{ or } \log(K/K_0) = \rho\sigma$$

(6) G. S. Hammond and L. R. Parks, This Journal, **77**, 340 (1955); J. F. Bunnett, E. W. Garbisch and K. M. Pruitt, *ibid.*, **79**, 385 (1957).

(7) L. R. Parks, G. S. Hammond and M. F. Hawthorne, *ibid.*, **77**, 2903 (1955).

(8) For a different approach to the application of the Hammett relationship to condensed-ring systems see H. H. Jaffé, *ibid.*, **76**, 4261 (1954).

and insertion of the appropriate numerical values yielded a set of 15 new σ-values for *epi* and *cata* positions. The values obtained from the dissociation and methoxydechlorination reactions and their means are reported in Table II. In eight cases in which the σ-constant was evaluated for both reactions the agreement was found to be good with the exception of a somewhat too high *cata-F* value derived from the dissociation reaction. With less certainty the values given for the dimethylamino and nitro groups, as obtained from the nucleophilic substitution data alone, can be at present considered valid for the dissociation reaction because of the strong resonance interaction expected for the former group in the (electron-demanding) ionization equilibrium and for the latter in the transition state of the (electron-repelling) substitution. It may be noted, however, that since Jaffé and Doak[4] have successfully used the side-chain σ-constants in the ionization of pyridines even in the case of the *p*-amino group, the *cata*-dimethylamino value is likely to apply to both reactions. Further investigations are needed to show the limits of applicability of the heteronuclear σ-values evaluated by the method reported in this work.[9] Comparison with previous investigations will be treated in the next section.

In view of some analogy between the pair *cata*, *epi* and the pair *para*, *meta*[1b] and for the sake of clarity in the following discussion, a comparison of *cata* to *para* and *epi* to *meta* substituent constants is given in Table III. The main features concerning the electronic transmission from the positions *cata* and *epi* to the seat of reaction can be summarized as follows.

(1) The intensity of the effects, even though reduced as compared with that related to homonuclear substituents, is still markedly large. In most cases the heteronuclear over-all effects as expressed by the magnitudes are between one-half and one-third as large as the homonuclear over-all effects.

(2) Although reduced, the main effects (inductive and conjugative) appear to be equally well transmitted. This point is best illustrated with groups having opposing electronic effects of the $-I+T$ type. Thus, the conjugative effect is responsible for the negative values of the *cata*-dimethylamino and alkoxy groups, and the inductive effect for the positive values of the *cata*- and *epi*-halogens, in essentially the same order as that observed at homonuclear corresponding positions.

(3) The parallel between the pair *cata*, *epi* and the pair *para*, *meta* is illustrated by the difference in the σ-values of pairs of isomerides for the methoxy and ethoxy groups and for fluorine (Table III). More negative or less positive values for the *cata* and *para* substituents as compared with *epi* and *meta* substituents, respectively, are due to a greater resonance interaction with the ring of the former than of the latter types of substituents. The parallel is not, however, exact since *epi*-methoxy and ethoxy groups have negative values

(9) For this reason we have used the σ symbol in a generic sense. Apart from likelihood of application of most such values to a side-chain reaction, it would seem unwise to assign any special subscript to the symbol at this stage of our knowledge.

TABLE III

COMPARISON OF HETERONUCLEAR WITH HOMONUCLEAR CONSTANTS[a]

Substituent	cata	epi	para	meta	$\sigma_{cata} - \sigma_{ep}$	$\sigma_p - \sigma_m$
N(CH$_3$)$_2$	-0.264		-0.600	-0.211		-0.389
OCH$_3$	$-.110$	-0.038	$-.268$	.115	-0.072	$-.383$
OC$_2$H$_5$	$-.123$	$-.017$	$-.250$	.150	$-.106$	$-.400$
SCH$_3$	.016		$-.047$	.144		$-.191$
CH$_3$	$-.060$	$-.042$	$-.170$	$-.069$	$-.018$	$-.101$
F	.088	.128	.062	.337	$-.040$	$-.275$
Cl	.152	.160	.227	.373	$-.008$	$-.146$
Br	.158	.159	.232	.391	$-.001$	$-.159$
NO$_2$	.452		1.270[b]	.710		.560

[a] The homonuclear σ constants are from ref. 12.　[b] For the use of this value see, for example, refs. 5 and 12.

TABLE IV

DIFFERENTIAL EFFECTS OF HETERONUCLEAR SUBSTITUENTS ON REACTIVITY IN THE ISOMERIC PAIRS cata, epi AND amphi, pros

		$\Delta \log k$	
Reaction	cata–epi, α[a]	cata–epi, β[b]	amphi–pros[c]
Basicity of naphthylamines (NO$_2$-substituted)[d]	0.32	0.30	0.23
Basicity of naphthylamines (SO$_3$$^-$-substituted)[e]	.14	.07	.21
Piperidinodebromination of nitrobromonaphthalenes[f]	..	1.22	1.24

[a] Log k for a 1,7-disubstituted derivative minus log k for a 1,6-disubstituted derivative (reaction center α).　[b] Log k for a 2,8-disubstituted derivative minus log k for a 2,5-disubstituted derivative (reaction center β).　[c] Log k for a 2,6-disubstituted derivative minus log k for a 2,7-disubstituted derivative.　[d] Data from A. Bryson, Trans. Faraday Soc., **45**, 257 (1949).　[e] Data from A. Bryson, ibid., **47**, 522 (1951).　[f] Data from P. Van Berk, P. E. Verkade and B. M. Wepster, Rec. trav. chim., **76**, 286 (1957).

in contrast with the corresponding meta values. This effect stands for the predominance of a primary conjugative over a primary inductive effect, whatever the detailed mechanism of the transmission may be, in the case of alkoxy groups which have large and negative σ_p-values and relatively small and negative σ_m-values. On the contrary, the methylthio group, which has a small and negative σ_p-value and a larger and positive σ_m-value, shows a slightly but definitely positive σ_{cata}-value, thus showing that the two types of effects are nearly at balance here, with some predominance of the inductive effect even at a heteronuclear position of the higher resonance interaction type.

In the light of the above observations, the flattening out of the $\sigma_{cata}-\sigma_{epi}$ differences with respect to the $\sigma_p-\sigma_m$ differences, as it appears from the values listed in Table III, is not only accounted for by the reduced intensity of electronic transmission through the fused ring, but also by a greater mixing, in the separate heteronuclear σ-values, of the contributions of the inductive and conjugative effects, as compared with the σ_p- and σ_m-values, which are themselves not completely differentiated with respect to such effects.[10] In other words, the hetero-

(10) See ref. 12, p. 194; see, also, R. W. Taft in Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 578.

nuclear $\sigma_{cata}-\sigma_{epi}$ differences are a poorer still measure of resonance effects than the homonuclear $\sigma_p-\sigma_m$ differences.

Comparison with Other Investigations.—In principle, there are two different pairs of adjacent positions of the type cata, epi, depending on whether the reaction center occupies a position α or β of the naphthalene system. These and the amphi, pros pair[3] are most suitable to a discussion of electronic effects of heteronuclear substituents in the absence of steric disturbances, apart from possible peri-hydrogen effects in the cata, epi isomerides with the reaction center in the β-position. Experimental data from previous investigations indicate that the reactivity differences arising from the effects of a given substituent (NO$_2$ and SO$_3$$^-$) are substantially similar among the three different pairs (Table IV). These observations justify a comparison of our results with some of Price and Michel's σ-values obtained from a side-chain reaction.[11,12] It is interesting to note, e.g., that our cata and epi σ-values for the methoxy group, -0.110 and -0.038, correspond reasonably well to the amphi and pros values, -0.164 and -0.044, respectively, in accordance to the fact that in the latter pair the amphi position allows the higher resonance interaction. Also, in agreement with the recognized anomaly[11] of Price and Michel's cata value for the nitro group, 0.322, our cata value, 0.452, is higher than their epi value, 0.407. Mainly because of the above-mentioned peri-hydrogen effects, which are not however firmly established and may be negligible in many cases, further work will tell in which cases a formal distinction of the cata, epi pair in the two α- and β-varieties (see Table IV) is required. Higher still heteronuclear σ-values for the nitro group have been calculated from the dissociation of naphthylamines.[12]

Experimental

Dissociation Constants of 7-Substituted 4-Chloroquinolines.—Data on the preparation and properties of the samples used for the measurements were recorded in Part II. The pK_a determinations were carried out by the same procedure and under the same conditions described for the 6-substituted derivatives in Part I.

ROME, ITALY

(11) C. C. Price and R. H. Michel, THIS JOURNAL, **74**, 3652 (1952).
(12) H. H. Jaffé, Chem. Revs., **53**, 191 (1953), see p. 245.