Transmission of Substituent Effects in Quinoline

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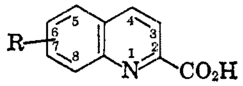
Dissociation constants of quinoline-2-carboxylic acids (25°), in 44.25% (w/w) aqueous ethanol, were found to satisfy the Hammett equation. These acids gave a ρ value of 1.782 with $s = 0.063$ and $r = 0.996$.

Whereas several workers have studied the effect of substituents on the basicity of the nitrogen in quinoline,[2,3] very little work has been reported on the transmission of substituent effects to other reaction sites in the quinoline nucleus. One such study was conducted by Illuminati, who, along with several coworkers,[3,4] investigated the rates of methoxy dechlorination of 2- and 4-chloroquinolines with substituents in various positions both in the heterocyclic ring and in the carbocyclic ring. Since this reaction involves nucleophilic attack directly on the ring, the Hammett substituent constants are σ^- values.

In order to evaluate the applicability of the Hammett equation to the transmission of substituent effects in quinoline using a reaction where normal σ values could be employed, we examined a series of substituted quinolinecarboxylic acids. Two sets of acids were studied, quinoline-2-carboxylic acids (I) substituted in the 4, 6, and 8 positions and quinoline-4-carboxylic acids (II) substituted in the 2 position.



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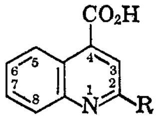

II

Results and Discussion

pK_a Values.—These values were determined by potentiometric titration. The solvent employed was 44.25% (w/w) aqueous ethanol. The values obtained are given in Table I. Corrections were made for the medium effect and the residual liquid-junction error.[5]

Data Used in Correlations.—A comprehensive theory for calculating substituent constants in aromatic systems was suggested by Dewar and Grisdale.[6] According to this theory, the σ constant for a substituent at position i when the reaction site is at position j is given by eq 1 where r_{ij} is the distance (in benzene C–C

$$\sigma_{ij} = F/r_{ij} + Mq_{ij} \qquad (1)$$

bond lengths) between positions i and j, and q_{ij} is the formal charge at position j produced by attaching the $-CH_2^-$ group at position i. F is a measure of the field effect caused by the electric dipole of the substituent–substrate bond, and M is a measure of the π-inductive resonance effect of the substituent. F and M, and ultimately, therefore, σ_{ij}, can be expressed in terms of σ_m and σ_p from the benzene series. This is convenient because there are well-established values of σ_m and σ_p.[7] The appropriate relationships for two fused six-membered rings were derived by Barlin and Perrin,[8] and it was these relationships, along with the σ_m and σ_p values of McDaniel and Brown, which we used to calculate substituent constants for use in our correlations. McDaniel and Brown do not give a σ_m value for the aza group; so the value used was that of Barlin and Perrin.[9] Table II gives the σ constants which we employed in our correlation studies.

TABLE I

pK_a VALUES OF QUINOLINECARBOXYLIC ACIDS IN 44.25% (w/w) AQUEOUS ETHANOL AT 25 ± 0.1°

Acid	No.	pK_a	n^a	Av dev^b
Quinoline-2-carboxylic	1	4.95	5	2.8
4-Aza	2	3.69	4	4.7
4-Chloro	3	4.28	5	3.7
4-Methoxy	4	6.29	4	2.4
6-Methyl	5	5.14	4	0.5
8-Nitro	6	4.15	4	2.4
Quinoline-3-carboxylic	7	4.59	4	1.1
Quinoline-4-carboxylic	8	4.42	5	3.2
2-Bromo	9	3.38	5	3.6
2-Chloro	10	3.37	7	11.9
2-Hydroxy	11	3.46	5	9.3

^{a} Number of determinations. ^{b} In parts per thousand.

Correlations.—The unmodified Hammett equation was applied to these two sets of acids (see eq 2). The

$$pK = -\rho\sigma + pK^\circ \qquad (2)$$

reaction constant (ρ), the standard deviation (s), the correlation coefficient (r), and the regression intercept (pK° calcd) were calculated using the formulae given by Jaffé.[10] We applied eq 2 to the data for 4-aza-, 4-chloro-, 6-methyl-, 8-nitro-, and unsubstituted quinoline-2-carboxylic acids and found $\rho = 1.782$, $s = 0.063$, and $r = 0.996$. Thus, the confidence level is greater than 99%.

The regression intercept (pK° calcd) was 5.00. This compares favorably with the observed value of 4.95 for the pK_a of quinoline-2-carboxylic acid.

The data for 4-methoxyquinoline-2-carboxylic acid were not included in the correlation because the pK_a for this acid was much higher than expected. The methoxy group has a positive σ_m value (electron withdrawing) and so this acid would be expected to be stronger than the unsubstituted acid. On the other

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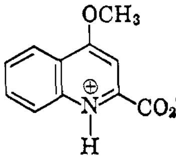
TABLE II

SUBSTITUENT CONSTANTS USED IN CORRELATIONS

Substituent	COOH position	j[a]	*a*	Relationship for calculating σ_{ij} [b]	σ_m [c]	σ_p [c]	σ_{ij}
H	2 or 4				0.00	0.00	0.00
4-Aza	2	2	4	σ_m	0.73		0.73
4-Chloro	2	2	4	σ_m	0.373		0.373
4-Methoxy	2	2	4	σ_m	0.115		0.115
6-Methyl	2	2	6	$0.58\ \sigma_m$	−0.069		−0.040
8-Nitro	2	2	8	$0.35\ \sigma_m + 0.35\ \sigma_p$	0.710	0.778	0.521
2-Bromo	4	1	3	σ_m	0.391		0.391
2-Chloro	4	1	3	σ_m	0.373		0.373
2-Hydroxy	4	1	3	σ_m	0.121		0.121

[a] In order to use the available relationships for calculating σ_{ij}, the reaction center (j) has been designated the 1 position or the 2 position. Thus, the carboxyl group in quinoline-4-carboxylic acids is said to be at the 1 position, and the position of a substituent (i) is designated accordingly. [b] Reference 8. [c] Reference 7, except for the value of σ_m for the aza group which is from ref 9.

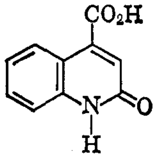
hand, its σ_p value is negative (electron donating). When its σ_{ij} value is calculated for transmission from the 4 position to the heteroatom in quinoline, it is found to be −0.415, indicating a very strong electron donor. It is possible, therefore, that the 4-methoxy group increases the basicity of the nitrogen to such an extent that the acid exists in the zwitterionic form (III), and



III

the pK_a value determined in our study would represent loss of a proton from nitrogen rather than from the carboxyl group. This conclusion is confirmed by the fact that, when the infrared spectra of all the acids were studied in the solid state in KBr, only this acid did not show an absorption band in the 1725–1680-cm^{-1} region. Further evidence for form III may be obtained by comparing the pK_a of the acid with that of 4-methoxyquinoline which is reported to be 6.65, in water, at 25°.[11] This compares well with the value obtained for the acid (6.29) since the electron-withdrawing 2-carboxylate group would be expected to lower the pK_a. When the data for 4-methoxyquinoline-2-carboxylic acid were included in the correlation, it was found that $\rho = 2.308$, $s = 0.656$, and $r = 0.772$. These values indicate a poor correlation.

The data for quinoline-4-carboxylic acids were insufficient for a statistical study. The pK_a of 2-hydroxyquinoline-4-carboxylic acid was not included in the correlation because of the probability that this acid exists in the keto form (IV). Evidence that this is the



IV

case is provided by the infrared spectrum of the solid acid in KBr. The spectrum has a very strong amide band at 1658 cm^{-1}. Only three acids were available, therefore, in the quinoline-4-carboxylic acid series. Two of these had closely related chloro and bromo groups, and a statistical study of these data would not have much meaning. A reaction constant was calculated, however, by substituting the appropriate data for 2-bromoquinoline-4-carboxylic acid in eq 2. By this means, it was found that $\rho = 2.7$. More data are necessary before an adequate conclusion can be drawn.

Tautomerism.—It is recognized that there is a possibility that all of these acids can exist to some extent in zwitterionic forms such as III. Two groups of workers have examined the problems involved in applying the Hammett equation to tautomeric systems.[12,13] Kabachnik[13] showed that the dissociation constants of tautomeric acids follow the Hammett equation only when the tautomeric equilibrium is strongly shifted toward one of the forms. Our results indicate that this equilibrium is shifted toward the neutral form. As a further test of the predominance of this form, a correlation study was attempted using our pK_a values for the set of 2-acids, and substituent constants for transmission to the 1 position rather than the 2 position of the quinoline ring. It was found that $\rho = 1.742$, $s = 0.371$, and $r = 0.933$. Thus, the correlation is poor, confirming our conclusion concerning the neutral nature of the acids.

The values of ρ for 4-substituted quinolines in 50% aqueous ethanol and in water were reported to be 6.15 and 5.72, respectively.[14] In the quinoline-2-carboxylic acids, if ionization were occurring at the nitrogen atom, the value of ρ should be comparable with the values obtained for the 4-substituted quinolines. The fact that ρ is much lower (1.7) indicates that this is not the reaction which is taking place.[15]

Experimental Section

Preparation of Acids.—Quinoline-2-carboxylic acid, quinoline-4-carboxylic acid, and 2-hydroxyquinoline-4-carboxylic acid were obtained from commercial sources, recrystallized to constant melting point, dried under reduced pressure, and analyzed. All the other acids were prepared according to reported methods and similarly purified and analyzed. 4-Azaquinoline-2-carboxylic acid (quinoxaline-2-carboxylic acid) was prepared by the method of Maurer and Boettger,[16] 4-chloroquinoline-2-carboxylic acid by the method of Spath,[17] and 8-nitroquinoline-2-carboxylic

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acid by the method of Roth and Erlenmeyer.[18] 6-Methylquinoline-2-carboxylic acid[19] was prepared by a method similar to that described by Kaslow and Stayner[20] for the synthesis of 4-methylquinoline-2-carboxylic acid. 4-Methoxyquinoline-2-carboxylic acid[21] was prepared by the methylation of kynurenic acid with diazomethane. 2-Bromoquinoline-4-carboxylic acid[22] and 2-chloroquinoline-4-carboxylic acid[23] were prepared by the action of phosphorus halides on the 2-hydroxy acid.

pK_a Values.—The pK_a values were determined by potentiometric titration. pH Values were measured between 30 and 70% neutralization using a Beckman Expandomatic pH meter. The electrodes were standardized before each determination in aqueous buffers, and the standardization was checked following completion of the titration. A correction was applied to the pH values for the medium effect and the residual liquid-junction error. The value for this correction (0.18 pH unit) was obtained for 44.25% ethanol by interpolation using values given by Bates[5] for other aqueous ethanol solvents. A correction was also made for hydrogen ion activity. The temperature of the solutions was maintained at 25.0 + 0.1° by measuring the pH of the solutions in a jacketed beaker through which was pumped water from a constant-temperature bath. The average of values for six to nine points in one titration constituted one determination.

Registry No.—1, 93-10-7; 2, 879-65-2; 3, 15733-82-1; 4, 15733-83-2; 5, 15733-84-3; 6, 15733-85-4; 7, 6480-68-8; 8, 486-74-8; 9, 15733-87-6; 10, 5467-57-2; 11, 15733-89-8; quinoline, 91-22-5.

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The Reactions of β-Dicarbonyl Compounds with Tetrakis(dimethylamino)titanium

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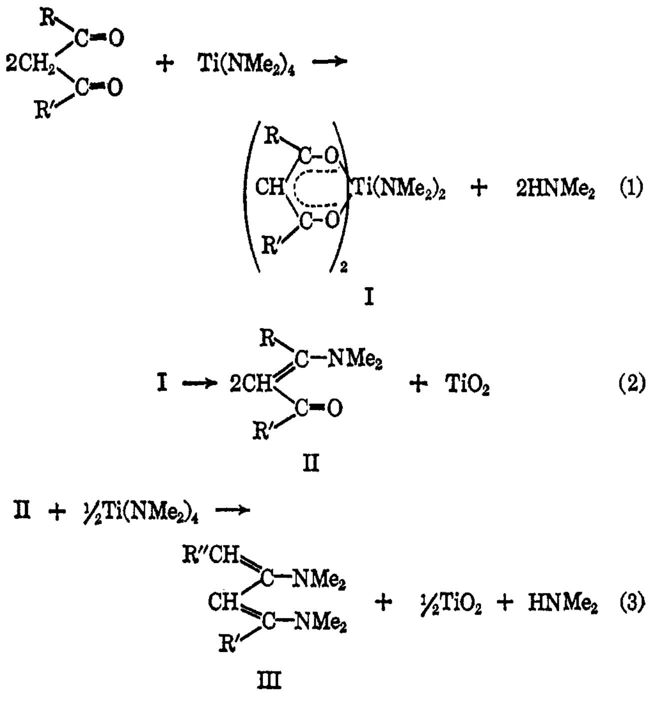
β-Dicarbonyl compounds ($RCOCH_2COR'$) have been found to react with tetrakis(dimethylamino)titanium to give complexes, enamine amides, enamine esters, ketenamines, and the previously unknown dienediamines and dienetriamines depending on the nature of the R and R′ groups.

The amination of carbonyl containing organic compounds by $B(NR_2)_3$, $P(NR_2)_3$, $As(NR_2)_3$, and $Ti(NR_2)_4$ has recently been the subject of several papers.[1-6] In the reactions with aldehydes, ketones, and carboxylic acids, the relative order of reactivity has been found to be $Ti(NR_2)_4 \gg As(NR_2)_3 > P(NR_2)_3$. $B(NR_2)_3$ and $P(NR_2)_3$ react with β-diketones and β-keto esters yielding enamino ketones and β-enamino esters or amides, respectively.[1,6] This paper presents the results of a study of the reactions of the much more reactive $Ti(NR_2)_4$ with some representative β-diamides, β-diesters, β-ketamides, β-keto esters, and β-diketones.

Results and Discussion

Tetrakis(dimethylamino)titanium reacts with β-dicarbonyl compounds according to eq 1, 2, and 3, where the nature of the products obtained depends upon the substituents R and R′ and the ratio of $Ti(NMe_2)_4$ to carbonyl compound. Reactions of all other aminating agents studied with β-dicarbonyl compounds stop at the enamine (II). However, with $Ti(NMe_2)_4$, two new classes of compounds, 1,3-diene-1,3-diamines (III) and 1,3-diene-1,1,3-triamines (III, R′ = NMe_2), can be formed.

N,N,N′,N′-Tetramethylmalonamide and dimethyl malonate both react with $Ti(NMe_2)_4$ to yield deep red complexes (I, R = R′ = NMe_2 and R = R′ = OMe, respectively). These are analogous to the dihalo- and dialkoxybis(β-diketonato)titanium compounds,[7-11] and their structure and properties will presently be the subject of another paper.



Methyl acetoacetate and N,N-dimethylacetoacetamide react with $Ti[N(CH_3)_2]_4$ to yield methyl 3-(dimethylamino)crotonate (II, R = CH_3 and R′ = OCH_3)[12] and 3-(dimethylamino)-N,N-dimethylcroton-

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