Investigation of Electronic Effects in the Pyridine and Pyridine *N*-Oxide Rings. Part 2.[1] Reaction of Substituted Pyridine- and *N*-Oxylpyridine-carboxylic Acids with Diazodiphenylmethane †

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The reactivity of a series of substituted pyridine- and *N*-oxylpyridine-carboxylic acids with diazodiphenylmethane has been investigated and the empirical Hammett treatment applied to a study of substituent effects. In general, satisfactory additivity of substituent effects was obtained, and it was possible to correlate with the same regression line the rate constants for both investigated series. The calculated reaction constant (ρ 0·818) differs from that for substituted benzoic acids, reflecting the same attenuating effect observed in the hydrolysis of substituted pyridine carboxylates. A satisfactory correlation for the $\rho_{\mathrm{DDM}}-\rho_{\mathrm{hydr}}$ relationship was obtained with literature data for the hydrolysis of corresponding substituted methyl pyridinecarboxylates.

IN our previous investigation[1] the reaction of pyridine- and *N*-oxylpyridine carboxylic acids with diazodiphenylmethane (DDM) was used to study the structure–reactivity relationships in pyridine and pyridine *N*-oxide rings. This reaction has been thoroughly investigated[2a] and used extensively for quantitative structure–reactivity studies.[2b]

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[1] Part 1 is considered to be Dj. M. Dimitrijević, Ž. D. Tadić, M. Mišić-Vuković, and M. D. Muškatirović, *J.C.S. Perkin II*, 1974, 1051.

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Treating the pyridine aza-group and the *N*-oxyl group as substituents in a benzene nucleus,[3a] we applied the empirical Hammett treatment to the reaction of DDM with pyridine- and *N*-oxylpyridine-carboxylic acids. Using previously determined values for ρ and log k_0 for substituted benzoic acids,[4] we obtained σ values for the pyridine aza-group which were in fairly good agreement with the literature values for the alkaline hydrolysis of the corresponding esters.[2c,5] For the *N*-oxyl group, values for the 3- and 4-positions (σ_3 1.312, σ_4 1.140) indicated that the overall effect was electron withdrawing and the negative value for σ_2 (−0.395) was explained on the basis of intramolecular hydrogen bonding.[1]

Campbell *et al.*[5] studied the alkaline hydrolysis of substituted methyl pyridinecarboxylates of the three series where the additional substituent was *meta* or *para* to the ester and not adjacent to the ring nitrogen. It was reported that for this orientation of substituent and nitrogen, the effect of substituent on side-chain reactivity, as measured by ester hydrolysis, was normal, and that it could generally be correlated by Hammett σ values. For the other three possible series, where the substituent was *meta* or *para* to the ester, but adjacent to the ring nitrogen, the correlation was not completely general, particularly for those compounds where a donor–acceptor relationship between the substituent and nitrogen, respectively, was possible. This was attributed to the *ortho*-effect, which according to Charton[6] is primarily a field effect.

Satisfactory additivity of substituent effects in the pyridine system was also observed by Noyce *et al.*[7] who studied the solvolysis rates of the pyridine analogue of t-cumyl chlorides. Brown's σ^+ substituent constants obtained by extrapolation[7a] were used to predict the solvolysis rates of substituted 2-(2-pyridyl)- and 2-(3-pyridyl)-2-chloropropanes with substituents in positions 4 or 5, and 5 or 6, respectively.[7b] The prediction was quite accurate, and it was later shown that it was possible to correlate these data and the data for substituted t-cumyl chlorides with the same regression line.[8] The correlation was not satisfactory for 6-substituted 2-(2-pyridyl)-2-chloropropanes, and it was suggested that a new set of σ constants should be derived for this system.

Application of the Hammett equation to the reactivity of pyridine and pyridine *N*-oxide derivatives has previously been reported.[2c] In a recent review[8] an interesting presentation of the above results[5,7] was given, proving the previously derived relationships for the equality of reaction constants in the pyridine and benzene systems.[3]

In the present work, we have studied the substituent effects in both pyridine and pyridine *N*-oxide systems and determined the reaction constant ρ for the reaction of pyridine- and *N*-oxylpyridine-carboxylic acids with DDM, by examining the degree of correlation of the second-order rate constants with the additive substituent constants.

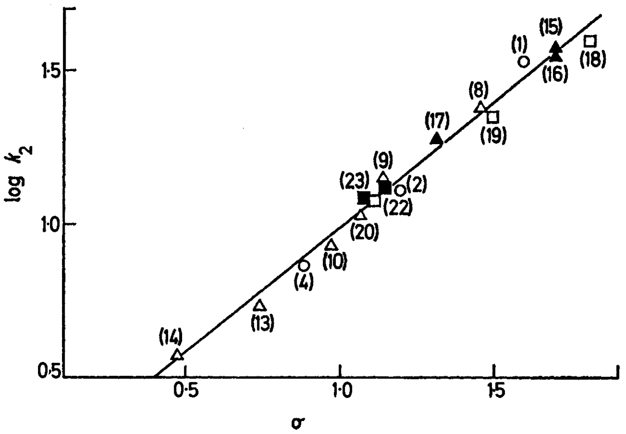

FIGURE 1 Relation between log k_2 of DDM with substituted carboxy-pyridines and -pyridine *N*-oxides and additive σ constants. Open symbols, pyridines; full symbols, *N*-oxides; circles, 2-carboxy; triangles, 3-carboxy; squares, 4-carboxy

Rate constants (k_2/l mol^{-1} min^{-1}) for the reaction of DDM with substituted pyridine- and *N*-oxylpyridine-carboxylic acids

		X	k_2	log k_2
2-Carboxy-X-pyridine	(1)	4-NO_2	33.2	1.521
	(2)	4-CO_2Me	12.8	1.107
	(3)	5-CO_2Me	12.5	1.096
	(4)	H	7.3	0.863
	(5)	6-CO_2Me	6.3	0.799
	(6)	4-OMe	5.8	0.760
	(7)	6-Me	4.7	0.675
3-Carboxy-X-pyridine	(8)	5-NO_2	24.5	1.389
	(9)	5-Br	14.3	1.155
	(10)	5-CO_2Me	10.4	1.017
	(11)	6-CO_2Me	8.8	0.944
	(12)	6-Cl	8.6	0.934
	(13)	H	5.4	0.732
	(14)	6-OMe	3.7	0.570
3-Carboxy-X-pyridine *N*-oxide	(15)	5-Br	38.8	1.580
	(16)	6-CO_2Me	35.6	1.550
	(17)	H	19.1	1.281
4-Carboxy-X-pyridine	(18)	6-NO_2	38.9	1.589
	(19)	6-Br	22.0	1.342
	(20)	H	11.9	1.075
	(21)	6-NHAc	9.4	0.970
4-Carboxy-X-pyridine *N*-oxide	(22)	H	12.9	1.110
	(23)	6-Me	11.9	1.075

A series of substituted pyridine- and *N*-oxylpyridine-carboxylic acids were synthesized, with substituents *meta* and *para* to the reaction centre, but *ortho*, *meta*, and *para* to nitrogen and the *N*-oxyl group. Rate constants were determined as previously reported[1] for the compounds which were soluble in absolute ethanol under

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[3] C. D. Johnson, 'The Hammett Equation,' Cambridge University Press, Cambridge, 1973, (*a*) p. 103; (*b*) p. 33.

[4] J. D. Roberts, E. A. McElhill, and R. Armstrong, *J. Amer. Chem. Soc.*, 1949, **71**, 2923.

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[7] (*a*) D. S. Noyce, J. A. Virgilio, and B. Bartman, *J. Org. Chem.*, 1973, **38**, 2657; (*b*) D. S. Noyce and J. A. Virgilio, *ibid.*, p. 2660.

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reaction conditions. The rate constants (k_2; 30°; EtOH) are given in the Table, and the corresponding log rate constants are plotted against the additive σ values in Figure 1. Substituent constants used are ordinary σ_m and σ_p values as calculated by McDaniel and Brown,[9] although for the *m*-OCMe group in acid (6) and the *m*-NO_2 group in acid (1), $\sigma_m^{+\,3b}$ values give a better correlation. σ_N and σ_{NO} constants are as previously reported.[1] The σ_m and σ_p values for the methoxycarbonyl group are taken from the work of van Bekkum *et al.*[9]

The interesting feature of the plot presented in Figure 1 is that it was possible to correlate with the same regression line the log rate constants for the reaction of both pyridine- and *N*-oxylpyridine-carboxylic acids with DDM with additive σ constants. However, the points for 2-carboxy-5-methoxycarbonyl- (3), 2-carboxy-4-methoxy- (6), 2-carboxy-6-methyl- (7), 2-carboxy-6-methoxycarbonyl- (5), 3-carboxy-6-methoxycarbonyl- (11), and 4-carboxy-6-acetylamino-pyridine (21) deviate considerably from the regression line. The substituted 2-carboxypyridine *N*-oxides failed to correlate at all in this manner [10] and will be the subject of a separate study.

Excluding those acids which obviously did not fit the correlation, a ρ value of 0.818 (r 0.993, s 0.04, n 17, log k_0 0.167) was calculated, from a regression analysis of the results. The reduction in the susceptibility of the reaction to substituent effects compared with that of the corresponding substituted benzoic acids (ρ_{pyr}/ρ_{benz} 0.87), is nearly the same as that for the hydrolysis of substituted pyridine carboxylates [5] which was explained as due to the attenuating effect of the electronegative nitrogen.

In an effort to explain the deviations (slower rates than expected) of the results for acids (3), (5)—(7), (11), and (21), and considering that in four cases out of six [(5), (7), (11), (21)] the substituent was vicinal to nitrogen, log rate constants for all available acids with this particular relation of substituent and nitrogen or *N*-oxyl group are plotted in Figure 2. Points corresponding to the rate factors for ten acids [(12)—(14), (16)—(20), (22), (23)] show excellent correlation (r 0.997, s 0.03, n 10) with the corresponding additive σ values, giving ρ 0.747 and log k_0 0.242. However, acids (5), (7), (11), and (21) deviate considerably from the plot. With the exception of acid (7) the three others have fairly large substituents, methoxycarbonyl [(5), (11)] and acetylamino [(21)], all adjacent to nitrogen. The large number of results from the alkaline hydrolysis of substituted ethyl benzoates [6] and ethyl pyridinecarboxylates [5c] as well as the data from other *ortho*- or proximity-effect studies [11] indicate that the *ortho*-effect is primarily a field effect. This could explain the deviation of the results for acids (5), (11), and (21), but the true nature of this perturbation remains unexplained. However, it should be noted that the log rate constant for 3-carboxy-6-methoxycarbonylpyridine *N*-oxide correlated satisfactorily with the corresponding σ_p value. It seems that the *o*-methoxycarbonyl group does not interact appreciably with the N^+–O^- group, although it might be expected for conformational reasons.

The deviation of the points for 2-carboxy-6-methylpyridine (7) from both plots (Figures 1 and 2) and for 2-carboxy-4-methoxypyridine (6) from the overall plot (Figure 1) are most probably due to substituent–nitrogen interactions, considering that in both cases a donor–acceptor pair of substituents are present in the *ortho*- and *para*-positions, respectively. Dipole moment [12] and i.r. studies [13] indicate that this type of conjugation occurs if nitrogen and strong electron-donating substituents are *para* to each other, but the data on ester hydrolysis [5b] indicate that such interactions are not transmitted to the *ortho*-position in 4-substituted 2-methylpyridinecarboxylates and that the correlation was normal. However, a rate lowering effect was reported [5c] for strong donor substituents adjacent to nitrogen in the 3-carboxy-series, and the log rate constant for the hydrolysis of methyl 6-methoxypyridine-4-carboxylate was half that calculated assuming additive substituent effects.[14] A similar interaction, which seems to include other substituents as well, was observed in 4-substituted 2-carboxypyridine *N*-oxides.[10] In our investigation, the deviation of 2-carboxy-5-methoxycarbonylpyridine remains unexplained.

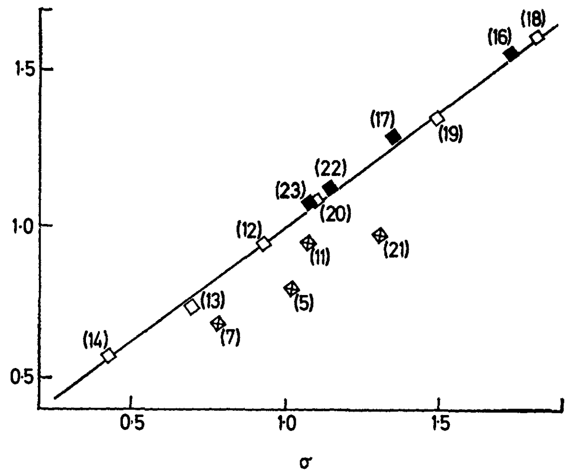

FIGURE 2 Relation between log k_2 of DDM with substituted carboxy-pyridines and -pyridine *N*-oxides with adjacent substituents, and additive σ constants. Open symbols, pyridines; full symbols, *N*-oxides

Finally, to check the validity of our experimental

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data by comparison with results for a different reaction series, we plotted the log rate constants for the acids which were the subject of this study against the log rate constants for the hydrolysis of the corresponding methyl pyridinecarboxylates.[5] A fairly good plot was obtained and is presented in Figure 3. The results from both

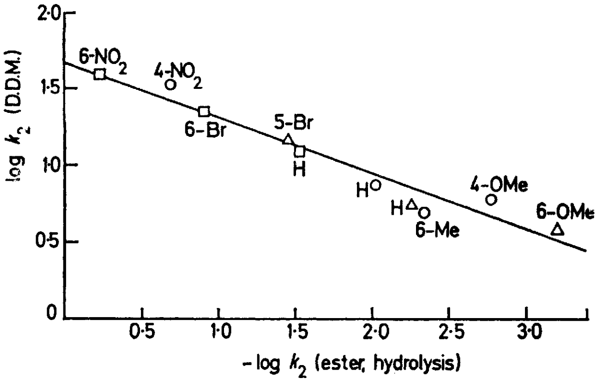

FIGURE 3 Relation between log k_2 of DDM with substituted carboxypyridines and $-$log k_2 of alkaline hydrolysis of substituted pyridinecarboxylates (5). Circles, 2-carboxy; triangles, 3-carboxy; squares, 4-carboxy

reactions correlated satisfactorily with a regression constant of 0.373 (r 0.973, s 0.08, n 10), which is very close to the ratio of the reaction constants obtained by the correlation of log rate constants with additive σ constants in each individual series, $\rho_{\mathrm{DDM}}/\rho_{\mathrm{hydr}} = 0.818/2.00 = 0.409$. This is very encouraging, as it verifies the validity of both reactions for the study of substituent effects and interactions in the pyridine series, as sufficient data for pyridine *N*-oxides were not available for this analysis. This also proves that the Hammett treatment is basically valid for the study of structure–reactivity relationships in the pyridine nucleus. It should be noted that two of the methoxy-substituted model compounds, 2-carboxy-4-methoxypyridine in the present study and the 3-carboxy-6-methoxypyridine in the study of the hydrolysis of substituted pyridinecarboxylates,[5c] did not fit the individual plots and were excluded from the correlation, but correlated fairly well in the last analysis. It appears that the kinetic procedures and the reactions chosen are basically sound, but more information about substituent–substituent and substituent–probe interactions is necessary for a more general prediction of reaction rates in the pyridine system.

EXPERIMENTAL

Rate Measurements.—Second-order rate constants k_2 for the reaction of substituted pyridine- and *N*-oxylpyridinecarboxylic acids with DDM were determined as previously reported,[1] by the spectroscopic method of Roberts and his co-workers.[4] Optical density measurements were performed at 525 nm with 1 cm cells in absolute ethanol at 30 °C. The spectrophotometer used was a Unicam SP 600. For the acids which were sufficiently soluble in absolute ethanol and whose reactions were not too fast, the reaction was initially studied as a first-order process, the concentration of acid being 0.06M and of DDM 0.006M, and the second-order rate constants were calculated from the observed first-order rate coefficients. However as some of the acids were not sufficiently soluble, or their reaction with DDM was inconveniently fast, for the sake of uniformity, rate measurements for all investigated compounds were performed under second-order conditions, *i.e.* at concentrations of 0.006M for both acid and DDM, and the results interpreted in the sense of well documented kinetic and mechanistic studies.[15,16] These values are given in the Table. In the present study, as previously reported,[15] second-order rate constants, calculated from the first-order values, were lower than those determined from direct measurements, although not to the same extent.

Materials.—Diazodiphenylmethane was prepared by the method of ref. 17, and was recrystallized from absolute methanol. Stock solutions of *ca.* 0.06M were stored in a refrigerator and diluted for use. Absolute ethanol was prepared by known procedures. 3-Carboxy-5-bromopyridine, m.p. 183 °C,[18] 3-carboxy-5-nitropyridine, m.p. 172 °C,[19] 3-carboxy-6-chloropyridine, m.p. 199 °C,[20] 3-carboxy-6-methoxypyridine, m.p. 237—238 °C,[21] 4-carboxy-6-nitropyridine m.p. 174—175 °C,[22] and 4-carboxy-6-acetylaminopyridine, m.p. 286—287 °C,[23] were prepared by known methods and had m.p.s in agreement with those in the literature. 2-Carboxy-5-methoxycarbonylpyridine, m.p. 183—185 °C,[24] and 3-carboxy-6-methoxycarbonylpyridine, m.p. 226—228 °C,[24] were prepared by literature methods.

6-*Bromo*-4-*carboxypyridine* was prepared from 2-bromo-4-methylpyridine[25] (3.5 g) treated with $KMnO_4$ (7.5 g), the filtrate being neutralized by H_2SO_4 and evaporated to a volume of 50 ml. Crystalline K_2SO_4 was filtered off, and the filtrate made acid to pH 4 with HCl. 4-Carboxy-6-bromopyridine crystallized out, m.p. 245—246 °C (lit.,[26] 229 °C for a substance obtained in a different manner) (Found: C, 35.7; H, 2.0; N, 6.95. $C_6H_4BrNO_2$ requires C, 35.85; H, 2.0; N, 7.0%).

2-*Carboxy*-4-*methoxycarbonylpyridine*. This was prepared by partial hydrolysis[24] (0.1N-KOH in methanol; heating for 15 min) of 2,4-bismethoxycarbonylpyridine. Work-up gave crystals (from ethanol), m.p. 227—229 °C (Found: C, 53.0; H, 3.9; N, 7.7. $C_8H_7NO_4$ requires C, 53.05; H, 3.85; N, 7.75%).

2-*Carboxy*-6-*methoxycarbonylpyridine*. This was prepared

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as above by partial hydrolysis of 2,6-bismethoxycarbonylpyridine (0.1N-KOH, heating for 1 h). Recrystallization from benzene gave crystals, m.p. 149—150 °C, in agreement with the value from ref. 27 (Found: C, 52.7; H, 3.85; N, 7.7%).

3-*Carboxy*-5-*methoxycarbonylpyridine*. This was prepared as above [24] by partial hydrolysis of 3,5-bismethoxycarbonylpyridine, except that the hydrolysis was performed without heating but the mixture was left for 12 h at room temperature. Recrystallization gave crystals, m.p. 207—210 °C (Found: C, 53.0; H, 3.9; N, 7.9%).

3-*Carboxy*-6-*methoxycarbonylpyridine* N-*oxide*. This was synthesized by a modification of the method of Ochiai.[28] A mixture of acetic anhydride (2 ml), acetic acid (2 ml), and 80% H_2O_2 (2 ml, stabilized) was heated for 1/2 h at 50 °C, cooled to room temperature, and 3-carboxy-6-methoxycarbonylpyridine (0.5 g) was added. The mixture was kept for 4 h at 50—60 °C. On cooling, a solid (0.27 g) crystallized out, m.p. 186—188 °C. Recrystallization from methanol yielded fine crystals, m.p. 188 °C; test for *N*-oxyl group positive [29] (Found: C, 49.05; H, 3.65; N, 7.25. $C_8H_7NO_5$ requires C, 48.7; H, 3.55; N, 7.15%).

5-*Bromo*-3-*carboxypyridine* N-*oxide*. This was prepared by the method of Ochiai [28] from the pyridine derivative [18] except that the heating was prolonged for 10 h. Recrystallization from water and then ethanol gave pale yellow needles, m.p. 270 °C (Found: C, 33.05; H, 1.95; N, 6.65. $C_6H_4BrO_3N$ requires C, 33.05; H, 1.85; N, 6.4%).

4-*Carboxy*-6-*methylpyridine* N-*oxide*. This was obtained as a side-product in the oxidation of 2,4-dimethylpyridine *N*-oxide by the modification of the usual $KMnO_4$ method.[30] 2,4-Dimethylpyridine *N*-oxide (7 g; Fluka) was treated by the amount of $KMnO_4$ necessary for the oxidation of both methyl groups. After neutralization of the reaction mixture, light brown crystals were obtained which recrystallized from ethanol yielding needles, m.p. 260 °C (Found: C, 54.9; H, 4.45; N, 8.8. $C_7H_7NO_3$ requires C, 54.9; H, 4,55; N, 9.15%); i.r. and n.m.r. data showed that only one methyl group was oxidised and that the relative position of the methyl and carboxy-groups was as indicated.

2-Carboxy-4-nitropyridine, m.p. 152 °C, 2-carboxy-4-methoxypyridine, m.p. 210 °C, and 2-carboxy-6-methylpyridine, m.p. 126 °C, were obtained by the reduction of corresponding pyridine *N*-oxide derivatives. The preparation of these was reported [31] and will be published elsewhere.

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