Investigation of Electronic Effects in the Pyridine and Pyridine *N*-Oxide Rings. Part 4.[1] Kinetics and Mechanism of the Reaction of Diazodiphenylmethane with Substituted Carboxypyridine and 2-Carboxypyridine *N*-Oxides in Dimethylformamide†

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Rate constants for the reactions of 15 substituted carboxypyridines and four substituted 2-carboxypyridine *N*-oxides with diazodiphenylmethane (DDM) in dimethylformamide (DMF) were determined at 30 °C, by the known spectrophotometric method. For comparison, rate constants for the reaction of 12 substituted benzoic acids were determined under the same conditions. Kinetic and thermodynamic parameters obtained, together with products analyses, essentially verify the previously proposed reaction mechanism in this solvent. The empirical Hammett treatment has been applied to the results, and it was shown that a scattered overall plot ($\rho = 1.019$, $\log k_0 = -2.98$, $r = 0.91$, $s = 0.22$, $n = 31$) was obtained with additive σ constants from the corresponding σ values for the pyridine aza-group and *N*-oxide group and Hammett σ constants for substituents. Fairly good separate correlations were obtained from the data for substituted benzoic acids ($\rho = 1.213$, $\log k_0 = -2.91$, $r = 0.985$, $s = 0.12$, $n = 12$), halogen- and nitro-substituted acids ($\rho = 1.07$, $\log k_0 = -2.99$, $r = 0.998$, $s = 0.02$, $n = 5$) and for the carboxypyridine *N*-oxides ($\rho = 1.18$, $\log k_0 = -3.35$, $r = 0.995$, $s = 0.04$, $n = 4$). A far less satisfactory correlation was obtained when it was applied to the substituted carboxypyridines, including the *N*-oxides ($\rho = 1.15$, $\log k_0 = -3.23$, $r = 0.91$, $s = 0.18$, $n = 19$). It was concluded that powerful solvent nucleophilic stabilisation of the reactant carboxylic acid in the initial state is greatly influenced by the type of substitution, substituent solvation, and probably also by the kind of electronic interaction of the particular substituent with the heteroaromatic nuclei.

As a continuation of our previous investigations of the reactivity of heterocyclic carboxylic acids with diazodiphenylmethane (DDM),[1-3] we considered that it would be interesting to study the diazole- and diazine-carboxylic acids because the corresponding heteroaromatic nuclei are related to important natural products. During this investigation[4] we encountered difficulty with the low solubility of these acids in absolute ethanol, which we used previously in the investigations of carboxypyridines, and also in other convenient solvents that have been suggested for this reaction.[5,6] It appeared that the carboxypyridines investigated are very soluble in dimethylformamide (DMF), and reacted with DDM although the reaction was very slow. However, we considered it necessary to investigate first the reactivity of DDM with substituted benzoic acids and carboxypyridines, previously studied in ethanol[1-3,7] in DMF, which has already been used as a solvent for the reaction of a limited number of monosubstituted benzoic acids with DDM.[8]

Results and Discussion

Investigations of electronic effects in the pyridine and pyridine *N*-oxide rings[1-3] have been extended to the study of the interrelation of solvent and substituent effects. Rate constants were determined for the reaction of substituted benzoic acids (Table 1) and carboxypyridines (Table 2) with DDM in DMF at 30 °C. Relevant thermodynamic parameters for two chosen carboxypyridines are also given in Table 2. Products analyses and the kinetic study showed that the only reaction product, both for the reaction of benzoic acids and carboxypyridines, is the corresponding benzhydryl ester.[9] It was previously determined that the reaction is strictly first order with respect to both reactants.[4,9] It was concluded, therefore, that the mechanism of the reaction and the structure of the transition state are essentially as have already been proposed for the reaction of carboxylic acids with DDM in non-hydroxylic solvents,[4-8] where the collapse of the reactive intermediate leads to the ester only, as there is no reaction with the solvent (Scheme). This mechanism is further corroborated by the results for the energy of activation and entropy of activation (Table 2), which are close to those previously determined for the reaction in ethanol.[2] (For 3-carboxypyridine, $E^{\neq} = 42.07$ kJ mol^{-1}, $\Delta S^{\neq} = -134.69$ J K^{-1} mol^{-1}.)

$$RCO_2H + Ph_2CN_2 \xrightarrow{\text{slow}} RCO_2^- Ph_2CN_2H^+$$

$$RCO_2^- Ph_2CN_2H^+ \xrightarrow{\text{fast}} RCO_2^- Ph_2CH^+ + N_2$$

$$RCO_2^- Ph_2CH^+ \xrightarrow{\text{fast}} RCO_2CHPh_2$$

Scheme. Mechanism of the reaction of carboxylic acids with diazodiphenylmethane in aprotic solvents

A Hammett-type correlation of the data has been attempted, and the scattered overall plot (line A, $\rho = 1.019$, $r = 0.91$, $\log k_0 = -2.98$, $s = 0.22$, $n = 31$) given in the Figure was obtained. It was decided that the reasons for poor correlation were not experimental errors, as the reaction is fairly slow and easy to follow and, furthermore, there is very good agreement with the data for a certain number of the substituted benzoic acids determined by other investigators.[8]

However, a fairly good separate correlation for the benzoic acids (line B, $\rho = 1.213$, $r = 0.985$, $\log k_0 = -2.91$, $s = 0.12$, $n = 12$) was obtained and also very good correlations for halogen- and nitro-substituted carboxylic acids (line C, $\rho = 1.07$,

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Table 1. Rate constants for the reaction of DDM with substituted benzoic acids in DMF at 30 °C

Acid	Substituent	10^{-3} k_2/l mol^{-1} s^{-1}	log k_2	σ
1	4-Cl, 3,5-$(NO_2)_2$	4.00	−1.075	1.65
2	3,5-$(NO_2)_2$	67.20	−1.172	1.42
3	4-Cl, 3-NO_2	18.30	−1.735	0.94
4	3,5-$(Cl)_2$	15.80	−1.799	0.74
5	4-NO_2	10.90	−1.962	0.78
6	3-NO_2	10.00	−1.997	0.71
7	3-I	4.20	−2.376	0.35
8	3-Cl	3.60	−2.435	0.37
9	4-Cl	1.80	−2.744	0.23
10	4-Br	1.70	−2.765	0.23
11	H	0.85	−3.070	0
12	4-Bu^t	0.78	−3.106	−0.20

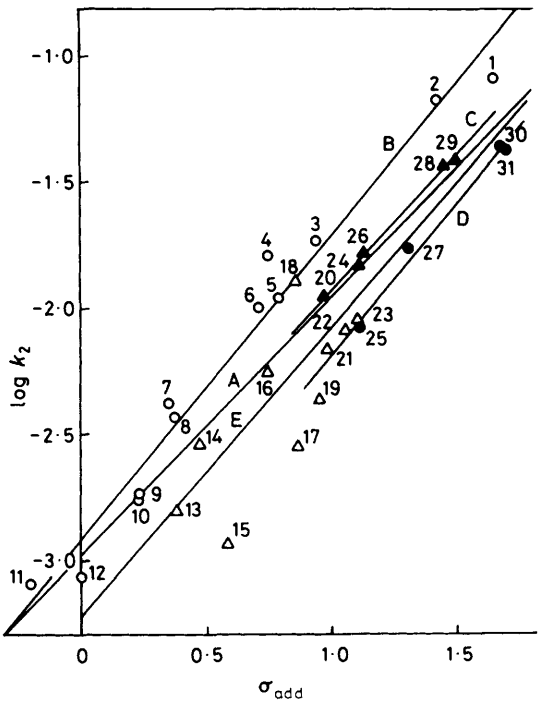

Figure. Plot of log k_2 for the reaction of DDM with investigated acids *versus* additive σ constants. ○ Benzoic acids, △ and ▲ carboxypyridines, and ● carboxypyridine *N*-oxides. See Tables 1 and 2 for identification of acids. Lines A—E are defined in the text.

log k_o = 2.99, r = 0.998, s = 0.02, n = 5) and for the carboxypyridine *N*-oxides (line D, ρ = 1.17, log k_o = 3.35, r = 0.995, s = 0.04, n = 4). This shows that acids with similar structure characteristics show a more accurate correlation with the Hammett parameters. However, this did not apply for the carboxypyridines, where correlation was as bad as the overall one (line E, ρ = 1.15, log k_o = −3.23, r = 0.91, s = 0.18, n = 19).

It should be noted, however, that the investigated series of substituted benzoic acids does not include those with electron-donor substituents. The reason is that these acids were not sufficiently soluble in DMF to provide a sufficiently large excess of acid, which would produce a measurable reaction rate.

It was concluded that the reason for the above behaviour must be the solvent itself. Dimethylformamide as a solvent

Table 2. (a) Rate constants for the reaction of DDM with substituted carboxypyridines and carboxypyridine *N*-oxides in DMF at 30 °C

No.	[Acid]		10^{-3} k_2/ mol^{-1} s^{-1}	log k_2	σ_{add}
13	3-CO_2H,	6-OH	1.63	−2.80	0.38
14	3-CO_2H,	6-OMe	3.71	−2.43	0.47
15	3-CO_2H,	5-NH_2	1.14	−2.94	0.58
16	3-CO_2H,	H	5.38	−2.27	0.74
17	3-CO_2H,	5-OH	3.12	−2.50	0.86
18	3-CO_2H,	5-OMe	1.26	−1.90	0.86
19	3-CO_2H,	5-NHAc	4.34	−2.36	0.95
20	3-CO_2H,	6-Cl	11.30	−1.94	0.97
21	4-CO_2H,	6-NHAc	6.70	−2.17	0.98
22	3-CO_2H,	5-CO_2Me	8.21	−2.08	1.05
23	4-CO_2H,	H	9.00	−2.04	1.10
24	3-CO_2H,	5-Cl	14.70	−1.83	1.11
25	4-CO_2H(NO),	H	8.29	−2.08	1.11
26	3-CO_2H,	5-Br	16.40	−1.78	1.13
27	3-CO_2H(NO),	H	17.30	−1.76	1.31
28	3-CO_2H,	5-NO_2	37.50	−1.42	1.45
29	4-CO_2H,	6-Br	39.00	−1.41	1.49
30	3-CO_2H(NO),	5-Cl	44.80	−1.34	1.68
31	3-CO_2H(NO),	5-Br	44.50	−1.36	1.70

(b) Thermodynamic parameters at three different temperatures

		20 °C	40 °C	50 °C	E^*/kJ mol^{-1}	ΔS^*/ J K^{-1} mol^{-1}
16	3-CO_2H, H	1.96	9.09	18.1	61.46	−95.94
26	3-CO_2H, 5-Br	9.34	31.3	66.4	54.76	−106.78

shows both nucleophilic and electrophilic solvation effects.[10] Specifically, for the reaction with diazodiphenylmethane, powerful nucleophilic stabilisation of the carboxylic acid is balanced by relatively weak electrophilic stabilisation of the transition state.[11] A probable explanation for the poor correlation in the present study, resulting in the scattered plot (Figure, line A), is the simultaneous solvent interaction with the substituent, which could be subject to either nucleophilic or electrophilic solvation both in the initial and in the transition state. As suggested by a referee, it seems very likely that there are specific interactions between the solvent and the N or N–O centres of the pyridine compounds and these lower the overall reactivity of pyridine and, more especially, the *N*-oxide acids, and are affected by the substituents to extents not related to the constants of these substituents. This can also be seen from the plots in the Figure. The final result, the magnitude of the reaction constant, is therefore a sum of several effects. Solvent dependence of values has been previously mentioned[10] and it is possible that a method proposed for the dissection of substituent and solvent effects could also be applied to this problem, provided that the rate data for investigated acids are known in other solvents.[12]

The deviations from the overall plot are so large that it is difficult to discuss the reasons for the non-applicability of ordinary σ constants to describe the reactivity of particular acids with DDM in DMF. However, it is interesting to note that the majority of points that deviate considerably from the overall plot belong to the carboxypyridines with electron-donor substituents, whose reactivity is lower than predicted by additive Hammett values. Although only a few substituents are in the *p*-position where direct conjugation with the reaction centre is possible, a degree of donor–acceptor interaction with the highly electron-attractive pyridine nucleus is possible. Therefore, DMF by its powerful nucleophilic solvation ability

stabilises the positive charge on the substituent, and a consequent negative charge on the nucleus could affect the reaction rate *via* the field effect. The difference between the correlation for benzoic acids and carboxypyridines both in ρ (slight) and $\log k_o$ (fairly large) is obviously due to the difference in electron effect succeptibility of the corresponding nuclei, and their different ability to interact with the substituent, causing the difference in the charge on the substituent.

However, in the molecules where interaction with the electron-acceptor nucleus is less probable, as for the halogen-[13] and nitro-substituted acids, the correlation is very good, as the solvation effect by DMF could not introduce a marked electron perturbation.

It is surprising that the correlation for the *N*-oxide acids is good. However, there are only four acids, and they are either non-substituted or halogen-substituted acids, where no substantial resonance interaction of the substituent and pyridine *N*-oxide nucleus could be expected.[13] Also, the *N*-oxide group itself is not liable to nucleophilic solvation, as its most exposed atom is either neutral or negatively charged.

Experimental

Rate Measurements.—Rate constants for the reaction of diazodiphenylmethane (DDM) with a series of substituted benzoic acids, carboxypyridines, and carboxypyridine *N*-oxides were determined by the spectroscopic method proposed by Roberts and his co-workers.[7,14] Absorbance measurements were performed at 525 nm with 1 cm cells in dimethylformamide (DMF) solution at 30 °C. A Varian Superscan 3 spectrophotometer was used. All the acids were sufficiently soluble in DMF, so the reactions were 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. These values are given in Tables 1 and 2.

Materials.—DDM was prepared by the method of reference 15, and recrystallized from absolute methanol. Stock solutions (*ca.* 0.06M) were stored in a refrigerator and diluted for use.

Solvent. NN-Dimethylformamide for ultraviolet spectroscopy (Fluka).

Benzoic acids. 3-Nitrobenzoic, 3-bromobenzoic, 4-bromobenzoic, 4-methylbenzoic, 4-hydroxybenzoic, 4-aminobenzoic, 4-nitrobenzoic, 3-iodobenzoic, 3-chlorobenzoic, 4-chlorobenzoic, 3,5-dichlorobenzoic, 4-chloro-3-nitrobenzoic, 3,5-dinitrobenzoic, 4-chloro-3,5-dinitrobenzoic, 4-t-butylbenzoic, and benzoic acids were commerical grade samples from Fluka, also 3-carboxypyridine, 4-carboxypyridine, and 3-carboxy-6-hydroxypyridine were commercial samples from Fluka, and after recrystallization from suitable solvents had melting points in agreement with those in the literature.

Carboxypyridines. 3-Carboxy-5-bromopyridine, m.p. 183 °C,[16] 3-carboxy-5-nitropyridine, m.p. 171—172 °C,[17] 3-carboxy-5-aminopyridine, m.p. 292 °C,[16] 3-carboxy-5-hydroxypyridine, m.p. 292—293 °C,[17] 4-carboxy-6-acetylaminopyridine, m.p. 286—287 °C,[18] 3-carboxy-6-methoxypyridine, m.p. 237—238 °C,[19] 3-carboxy-6-chloropyridine, m.p. 192—193 °C,[20] 4-carboxy-6-chloropyridine, m.p. 199 °C,[20] 4-carboxypyridine *N*-oxide, m.p. 266 °C,[21] 3-carboxy-5-bromopyridine *N*-oxide, m.p. 268 °C,[22] 3-carboxy-5-chloropyridine *N*-oxide, m.p. 260 °C,[22] 3-carboxypyridine *N*-oxide, m.p. 249 °C,[23] 3-carboxy-5-methoxycarbonylpyridine *N*-oxide, m.p. 207—210 °C,[24] were prepared by known methods and had m.p.s in agreement with those in the literature.

3-Carboxy-5-acetylaminopyridine. This was prepared by refluxing 3-carboxy-5-aminopyridine (4 g), NaOAc (2 g), and Ac_2O (20 ml) for 1 h, distilling off the solution *in vacuo*, and treating the residue with H_2O. This gave 4.2 g of 3-carboxy-5-acetylaminopyridine, m.p. 289—290 °C; the melting point given in the literature (161—162 °C) is not correct[17] (Found: C, 53.4; H, 4.4; N, 15.5. $C_8H_8N_2O_3$ requires C, 53.3; H, 4.4; N, 15.55%).

Diphenylmethyl ester of 3-carboxy-5-bromopyridine N-oxide. The reaction of equimolecular amounts of 3-carboxy-5-bromopyridine *N*-oxide and diazodiphenylmethane yielded one product, a solid substance whose analysis corresponded to the expected ester, m.p. is 160 °C, test for *N*-oxide group positive[25] $\nu_{max.}$(KBr) 1 295 (N→O)[26] and 1 720 cm^{-1} (C=O).[27] The carboxy band (3 000—3 250 cm^{-1}), noticeable in the spectrum of the acid, was completely absent (Found: C, 59.4; H, 3.6; N, 3.6. $C_{19}H_{14}BrNO_3$ requires C, 59.4; H, 3.6, N, 3.6%).

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