Investigation of Electronic Effects in Diazine Rings. Linear Free Energy Relationships in the Reactivity of Diazine Mono- and Di-carboxylates†

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Rate constants for the reaction of six possible diazine monocarboxylates with diazodiphenylmethane (DDM) in ethanol, and also for the hydrolysis of the corresponding methyl carboxylate esters, have been determined at four selected temperatures. Correlations with sums of the Hammett σ constants for ring nitrogens treated as substituents, which are fairly satisfactory for the reaction with DDM at 30 °C ($\rho_{DDM} = 0.64$, $\log k_0 = -1.54$, $r = 0.92$, $s = 0.12$) and for ester hydrolysis ($\rho_{EH} = 2.28$, $\log k_0 = -3.36$, $r = 0.94$, $s = 0.36$) are, however, excellent for the intercorrelation of the two reaction series ($\rho_{DDM}/\rho_{EH} = 0.34$, $r = 0.99$, $s = 0.12$). The reactivity of *ortho*- and *para*-diazine dicarboxylates in the reaction with DDM, in ethanol and dimethylformamide, has been investigated and compared with the corresponding reactions of *ortho*- and *para*-benzene- and pyridine-dicarboxylates.

In our previous studies,[1–5] we used the reaction of diazodiphenylmethane (DDM) with heterocyclic carboxylic acids to investigate the electronic effects in the pyridine, pyridine *N*-oxide, and diazole rings. The rate constants obtained were interpreted by the use of linear free energy relationships, and were also compared with those for the hydrolysis of corresponding esters[2] and pK_a values[3] from the literature.[6,7] In the present paper we have studied the electronic effects operating in the diazine nuclei. As the probes, we used carboxy and methoxycarbonyl functions on pyridazine, pyrimidine, and pyrazine rings and employed well-established methods for this type of study: esterification with DDM (refs. 1–4 and literature therein) and alkaline hydrolysis of alkyl carboxylates.[6] We also investigated the reactivity of diazinedicarboxylic acids with DDM in ethanol and dimethylformamide (DMF). Linear free energy relationships were not extensively employed in the diazine heterocycles. We were able to find in the literature a Hammett treatment of substituted methyl pyrimidine,[8] an extensive study on the protonation of 2,4-diaminopyrimidines,[9] the determination of the basicities of some pyridazine derivatives,[10] and the correlation of proton shifts of pyrazines.[11] From the point of view of the present study, the most interesting is the very good correlation of the hydrolysis data for methyl diazinecarboxylates[12] and the remarkable agreement of these data with the effect of the ring nitrogen on the side chain reactivity of pyridine derivatives in the same reaction.[13]

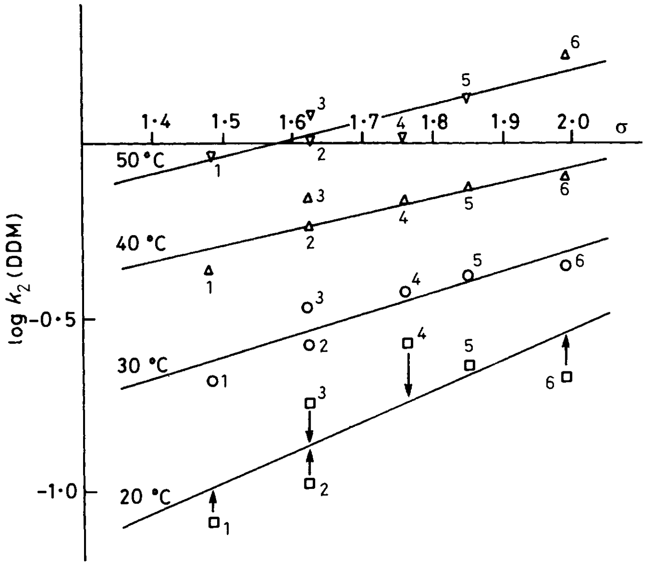

Figure 1. Relation between log k_2 of DDM with diazinecarboxylic acids and additive σ constants at temperatures 20–50 °C. Numerals as in Table 1.

Results and Discussion

Rate data for the reaction of the diazine monocarboxylates with DDM at four selected temperatures and the corresponding thermodynamic parameters are given in Table 1. In Figure 1, the logarithm of the rate constant is plotted against the additive σ_N values, obtained from those previously reported for the aza groups in *ortho-*, *meta-*, and *para*-positions in the pyridine nucleus.[1] The correlations for the acids investigated are only accurate for the following temperatures: 30 °C ($\rho = 0.62$, $\log k_0 = -1.54$, $r = 0.92$, $s = 0.12$); 40 °C ($\rho = 0.45$, $\log k_0 = -0.96$, $r = 0.87$, $s = 0.09$); and 50 °C ($\rho = 0.53$, $\log k_0 = -0.83$, $r = 0.90$, $s = 0.10$). The values at 20 °C failed to correlate at all, and a scattered plot was obtained ($\rho = 0.86$, $\log k_0 = 2.26$, $r = 0.78$, $s = 0.20$). The value for ρ at 50 °C is higher than predicted by the other three values in the plot of ρ *versus* T^{-1}. We believe that this is due to thermal decomposition of DDM. The lower accuracy of rate constants at 50 °C (Table 1) was also established in our previous investigations.[3]

The results of the hydrolysis of methyl diazinecarboxylates are given in Table 2, and Hammett-type correlation of the data is presented in Figure 2. The σ values used were as reported by Campbell and co-workers[6] from the study of the alkaline hydrolysis of substituted pyridinecarboxylates. We were encouraged to use the sums of these σ values for ring nitrogens because a high degree of accuracy, absence of steric effects, and accurate additivity of effects was established in a similar correlation.[13] The correlation obtained at 20 °C ($\rho = 2.39$, $\log k_0 = -3.82$, $r = 0.94$, $s = 0.38$), and 30 °C ($\rho = 2.28$, $\log k_0 = -3.36$, $r = 0.94$, $s = 0.36$) is again only moderate, and not nearly as good as that reported by Deady, Foskey, and

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Table 1. Rate constants for the reaction of diazinemonocarboxylates with DDM in ethanol.

No.	Acid	k_2/dm^3 mol^{-1} s$^{-1\,a}$ 20 °C	30 °C	40 °C	50 °C	$E^{\ddagger\,b}$/ kJ mol^{-1}	log A^c	$S^\ddagger$ (30 °C)/ J K^{-1} mol^{-1}
1	5-Carboxypyrimidine	0.082	0.179	0.393	0.802	65.1	10.55	−35.4
2	2-Carboxypyrazine	0.10	0.223	0.471	0.954	62.8	10.24	−40.6
3	3-Carboxypyridazine	0.173	0.368	0.744	1.431	53.4	8.73	−69.4
4	2-Carboxypyrimidine	0.188	0.396	0.790	1.509	39.8	6.43	−113.5
5	4-Carboxypyridazine	0.207	0.430	0.854	1.630	49.0	8.09	−82.2
6	4-Carboxypyrimidine	0.227	0.471	0.922	1.737	43.6	8.10	−99.5

[a] The rate constants are reproducible to ±2% (20–40 °C) and ±4% (50 °C) of the mean, from 4–6 runs. [b] Correlation coefficients 0.994–0.999, standard deviations s = 0.25–0.45. [c] Calculated from k_2 at 30 °C and $E^\ddagger$, as suggested by H. E. Avery, 'Basic Reaction Kinetics and Mechanism,' Macmillan, London, 1974, p. 53; although, except for 4-carboxypyridazine and 4-carboxypyrimidine, values of the intercept were almost identical.

Table 2. Rate constants for the reaction of alkaline hydrolysis of methyl diazinecarboxylates in 80% methanol.

No.	Methyl diazinecarboxylate	k_2/dm^3 mol^{-1} s$^{-1\,a}$ 20 °C	30 °C	40 °C	$E^{\ddagger\,b}$/ kJ mol^{-1}	log A^c	$S^\ddagger$ (30 °C)/ J K^{-1} mol^{-1}
1	Methyl Pyrimidine-5-carboxylate	0.150	0.310	0.615	58.5	9.58	−53.2
2	Methyl Pyrazine-2-carboxylate	0.257	0.519	1.003	56.5	9.46	−55.5
3	Methyl Pyrazine-3-carboxylate	0.525	1.021	1.926	53.9	9.29	−58.7
4	Methyl Pyrimidine-2-carboxylate	0.759	1.458	—	56.6	9.59	−53.0
5	Methyl Piridazine-4-carboxylate	1.155	2.183	—	53.7	9.60	−52.8
6	Methyl Pyrimidine-4-carboxylate	1.518	2.820	—	51.4	9.32	−58.1

[a] The rate constants are reproducible to ±1.0% (20 °C) and ±0.5% (30–40 °C) of the mean, 3–4 runs. [b] Correlation coefficients 0.999–1, standard deviations s = 0.19–0.30. [c] Values calculated from k_2 at 30 °C and $E^\ddagger$, and the intercepts are practically identical.

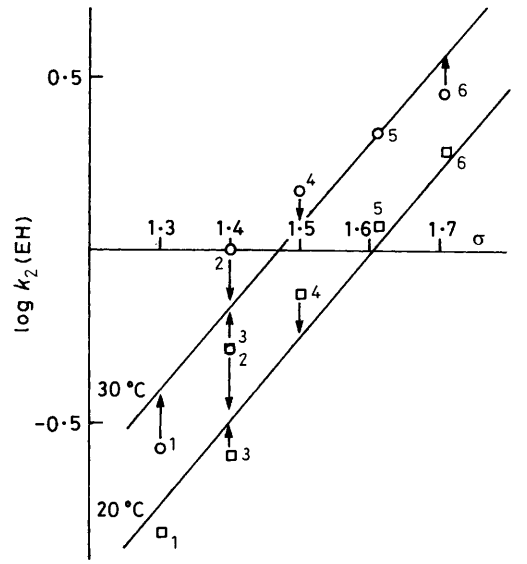

Figure 2. Relation between log k_2 of alkaline hydrolysis of methyl diazinecarboxylates and additive σ constants at temperatures 20 °C and 30 °C. Numerals as in Table 2.

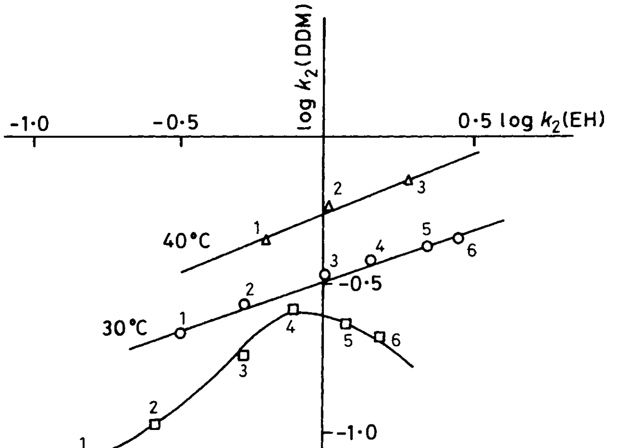

Figure 3. Relation between log k_2 of DDM with diazinecarboxylates and log k_2 of alkaline hydrolysis of methyl diazinecarboxylates at temperatures 20–40 °C. Numerals as in Tables 1 and 2.

Shanks, for the same set of compounds but under different experimental conditions.[12] However, very interesting conclusions could be drawn from the relation of log k_2 for the reaction with DDM with log k_2 for the hydrolysis of the corresponding esters. Extremely good correlations were obtained for data at temperatures 30 °C (regression constant 0.330, r = 0.994, s = 0.12, n = 6) and 40 °C (regression constant 0.40, r = 0.98, s = 0.10, n = 3), while the data at 20 °C failed to correlate at all (Figure 3). The good correlation at 30 °C and 40 °C shows that under these experimental conditions both reactions are satisfactory for the study of the interactions in diazine rings, but that the additive σ constants from both reaction series do not satisfactorily explain the electronic effects operating in the corresponding nuclei.

The reason for the failure of the same relationship at 20 °C is probably the same as that for the poor correlation for the reaction with DDM at the same temperature as presented in Figure 1. The influence of the *ortho*-effect on the reactivity of methyl diazinecarboxylates has already been suggested.[12] Given that the *ortho*- or proximity effect studies (ref. 2 and refs. therein) indicate that the *ortho*-effect is largely a field effect, it is reasonable to expect that the reaction with DDM, considering the structure of its transition state[14,15,16] should be more susceptible to interactions of this type. In connection with this, it is interesting to note that 2-carboxypyrimidine is fairly reactive,

Table 3. Rate constants (k_2/dm^3 mol^{-1} s^{-1}) for the reaction of DDM with *ortho-* and *para*-benzene-, pyridine-, and diazine-dicarboxylates in DMF and ethanol at 30 °C.

		DMF[a]		Ethanol[b]	
No.	Dicarboxylate	k_2 ($\times 10^{-2}$)	log k_2	k_2	log k_2
1	Benzene-2,3-	0.6	−2.176	0.26	−0.582
2	Pyridine-2,3-	2.2	−1.654	0.703	−0.152
3	Pyridine-3,4-	5.5	−1.257	0.883	−0.053
4	Pyrazine-2,3-	4.2	−1.375	1.39	0.143
5	Pyrimidine-4,5-	4.5	−1.343	1.48	0.171
6	Pyridazine-4,5-	7.3	−1.132	1.98	0.297
7	Benzene-1,4-	0.15	−2.823	0.07	−0.167
8	Pyridine-2,5-	0.9	−2.014	0.56	−0.249
9	Pyrazine-2,5-	2.1	−1.670	0.825	−0.083
10	Pyrimidine-2,5-	3.6	−1.441	0.903	−0.044

[a] The rate constants are reproducible to ±4–5%, correlation coefficients 0.98–0.99, standard deviations 0.05–0.20. [b] Calculated by the graphical method from the initial rates;[18] the rate constants are reproducible to ±5%.

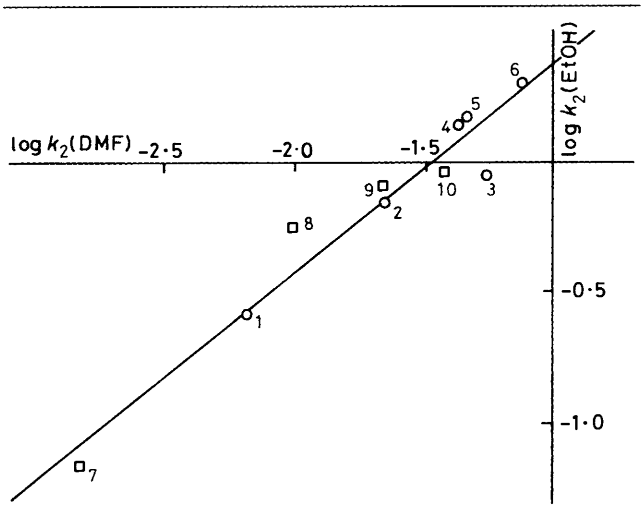

Figure 4. Relation between log k_2 of DDM with benzene-, pyridine-, and diazine-dicarboxylates in DMF and log k_2 of the same reaction in ethanol. Numerals as in Table 3; ○, *ortho*-dicarboxylates; □, *para*-dicarboxylates.

requiring the lowest energy of activation of the series investigated (due to the strong inductive effect of the two *ortho* nitrogens) but the high negative entropy change (Table 1) indicates that a specific orientation of the reacting molecules is necessary in the transition state, probably due to the strong field effect.

It is also possible that some sort of association, more important at lower temperatures, *i.e.* intermolecular hydrogen bonding, affects the values of the rate constants and the proportionality of ΔH and ΔS in the reaction with DDM, causing poorer correlation.[17]

Further investigation concerns the study of the applicability of the principles of the linear free energy correlations to the reactivity of the *ortho-* and *para*-dicarboxylates in the benzene, pyridine and diazine series. We did not find in the literature any criteria for the use of linear correlation to the bifunctional compounds, except for dissociations.[18] We therefore decided to treat the aromatic nuclei as a whole and to examine the electronic effects operative on both reaction centres, on the basis of the data presented in Table 3, for the reactions in ethanol and DMF. However, we were not able to find satisfactory correlation with any form of additive σ constants, which would, as we expected, reflect the reactivity of the difunctional acid molecule. That a certain sort of linear correlation for this type of compounds does exist could be seen from the diagram given in Figure 4, where the logarithm of the rate constant for the reaction investigated (dicarboxylic acids with DDM in ethanol) is plotted against the logarithm of the rate constant for the same acids in DMF. Even this correlation is not particularly good ($\rho_{\mathrm{EtOH}}/\rho_{\mathrm{DMF}} = 0.796$, $r = 0.97$, $s = 0.42$, $n = 10$), which is understandable, bearing in mind the differences in the reactivity and type of correlations previously established for the reaction of substituted pyridine carboxylic acids in ethanol and DMF.[4]

Experimental

Rate Measurements.—Reaction with diazodiphenylmethane (DDM). Rate constants for mono- and di-carboxydiazines, dicarboxypyridines, and dicarboxybenzenes were determined as previously reported,[1–4] in absolute ethanol[1–3] and dimethylformamide (DMF),[4] by the spectrophotometric method proposed by Roberts and co-workers.[16] Absorbance measurements were performed at 525 nm with 1 cm cells at 30 °C, and for diazinemonocarboxylic acids also at 20, 40, and 50 °C. A Varian Superscan 3 spectrophotometer was used. In ethanol, rate measurements were performed under second-order conditions and the results interpreted as before,[1–4] for the diazinemonocarboxylates. The rate data for the diazinedicarboxylates determined at 30 °C failed to conform to the variation of the Guggenheim procedure devised for this reaction,[14] and the method of initial rates was used.[19] In DMF, reactions of investigated dicarboxylates were studied as first-order processes and the second-order rate constants were calculated from the observed first-order rate coefficients.[4] The corresponding values are given in Table 3.

Hydrolysis of Methyl Diazinecarboxylates.—The hydrolysis of methyl esters of diazine monocarboxylic acids was followed under second-order conditions in 80% methanol (v/v) at 20, 30, and 40 °C. The reactions were performed in carbon dioxide free atmosphere, and the method used was the procedure of Evans and co-workers,[20] slightly modified.[21] The corresponding rate data are given in Table 2.

Materials.—DDM was prepared by the method of Smith and Howard,[22] and recrystallized from absolute methanol. Stock solutions in solvents used (*ca.* 0.06 mol dm^{-3}) were stored in a refrigerator and diluted before use.

Solvents.—Good commercial grade ethanol (Merck) was further treated by the Smith method.[23] *N,N*-Dimethylformamide was the grade used for uv spectroscopy (Fluka).

The diazinecarboxylic acids were prepared according to methods from the literature and had the following m.p.s (°C): pyridazine-3-carboxylic acid 200–201 (lit.,[24] 200–201); pyridazine-4-carboxylic acid 239–240 (lit.,[24] 235–239); pyrimidine-2-carboxylic acid 199–200 (lit.,[25] 200); pyrimidine-4-carboxylic acid 240–241 (lit.,[26,27] 238–239); pyrimidine-5-carboxylic acid 270–271 (lit.,[28] 270–271); pyridazine-4,5-dicarboxylic acid 213 (lit.,[24] 213); pyrazine-2,3-dicarboxylic acid 183–185 (lit.,[29] 183–185);[29] pyrazine-2,5-dicarboxylic acid 282 [lit.,[30] 270 (subl.); 282 (decarboxylation)]; and pyrimidine-4,5-dicarboxylic acid 265 (lit.,[30] 265). Pyrimidine-2,5-dicarboxylic acid, m.p. 278–280 °C was synthesized from 2-methylquinazoline.[32] Its preparation and identification is reported.[33]

Pyrazinecarboxylic acid and pyridine monocarboxylic- and pyridine dicarboxylic acids were commercial samples from 'Light' and 'Fluka,' and after recrystallization from suitable solvents had the m.p.s stated in the literature.

Methyl diazinecarboxylates (mono) were synthesized by esterification with diazomethane,[34] except for the methylpyrazinedicarboxylate, which was obtained by a methanol–HCl method. The esters were chromatographically pure (GLC) and had m.p.s (°C) in very good agreement with those stated in the literature:[12] methyl pyridazine-3-carboxylate 139–140 (137–138); methyl pyridazine-4-carboxylate 63–64 (63); methyl pyrimidine-2-carboxylate 104–105 (104–106); methyl pyrimidine-4-carboxylate 70–71 (69–70); methyl pyrimidine-5-carboxylate 84–85 (80–81); and methyl pyrazinecarboxylate 60–61 (61–62).

Acknowledgements

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