Pyridinolysis of Methyl Chloroformate and the Interpretation of Curved Brönsted Plots in Nucleophilic Reactions

By ENRIQUE A. CASTRO and ROY B. MOODIE*
(*Department of Chemistry, The University of Exeter, Exeter* EX4 4QD)

Summary The curvature of the Brönsted plot obtained for the pyridinolysis of methyl chloroformate is examined in the light of two equations which attribute the effect either solely to a change in rate-determining step or solely to variable transition-state geometry in a one-step reaction; the former is found to be more acceptable.

SATISFACTORY correlations of nucleophilic reactivity and basicity usually require a series of bases of closely similar structural type. Recently many interesting examples of curved Brönsted plots for acyl transfer have appeared[1,2] but the significance of these is diminished by the need to include for instance anilines with aliphatic amines[2] or carboxylate ions with phenolate and alcoholate ions,[1] in order to achieve a sufficiently wide range of basicities.

Substituted pyridines offer the advantages of quite a wide range of pK_a's within the pH region, with the minimum of significant structural change, and the use of tertiary nitrogen bases avoids complications due to general base catalysis.[3] The curvature referred to above has been observed with highly reactive acetyl compounds and it seemed desirable to study a compound with an even better leaving group, such as chloride ion. The methoxy-group of methyl chloroformate afforded sufficient acyl deactivation for these reactions to be conveniently studied.

The Figure shows a Brönsted plot for the reaction of substituted pyridines with methyl chloroformate. The second-order rate constants k_n for the reaction of the free bases of pyridine and of 3- and 4-methylpyridine with methyl chloroformate to give the 1-methoxycarbonylpyridinium ion were obtained by spectroscopic observation of the appearance and disappearance of the latter, the hydrolysis of which occurred at a similar rate to its formation, and which typically achieved its maximum concentration in 0·5—3 min. With the other pyridines a 'pH-stat' method was used, hydrolysis of the 1-methoxycarbonylpyridinium ion being either much faster (3-CN, 4-CN, 3-Cl, 2-aza) or much slower (4-NH_2, 4-NMe_2) than its formation, so that k_n was readily obtained from the observed first order rate constant.

Reactions were studied at several concentrations of nucleophile at more than one pH value, but only in the cases of 4-amino- and 4-dimethylamino-pyridine was a kinetic term other than that for nucleophilic attack of the free base pyridine revealed. These two bases gave a minor additional term which was solely first order in the concentration of the conjugate acid.[4] This will not be further discussed here. Pyridine concentrations were always low and free base association was not a complication.[1b]

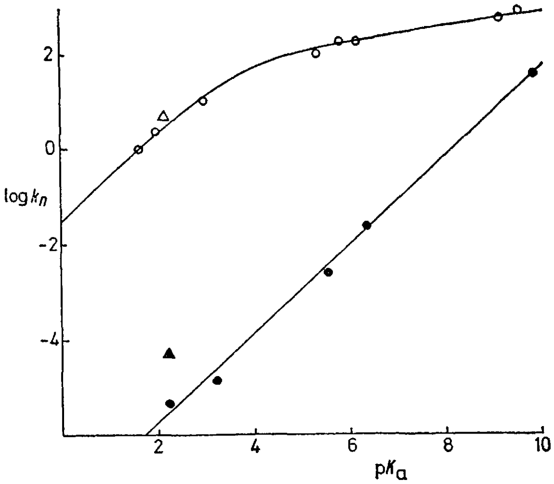

FIGURE. Plots of log (k_n/M^{-1} s^{-1}) against pK_a for the reaction of methyl chloroformate (open circle, I = 0·2M, full line calculated from equation (2) with β_1 = 0·17, β_2 = 0·93, pK_0 = 3·58; log k_n = 1·55) and p-nitrophenyl acetate (full circle, I = 1·0M, full line is best least-squares line through the experimental points). The points for pyridazine (triangles) are statistically corrected.[10]

Also shown is a Brönsted plot for reaction of the pyridines with p-nitrophenyl acetate, for which our rate constants supplement literature values[1a,8] and greatly extend the range of observed linearity (Figure). The slope (β) is 0·93. In contrast the Brönsted plot for methyl chloroformate is non-linear.

The curvature can be described in terms of a change in rate-determining step in a two step mechanism, or a change in transition state geometry (a "Hammond Postulate" effect[5]) in a one-step mechanism.

With the two-step mechanism (1), in which A is the

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} D \qquad (1)$$

constant electrophile (for instance methyl chloroformate), B is the series of nucleophiles (such as the substituted pyridines studied here), C is a reactive intermediate, and D is the product (in this case the methoxycarbonylpyridinium ion) then:

$$k_n = k_1k_2/(k_{-1} + k_2)$$

If the plot of log k_n against pK_a has a constant slope β_1 when the step with rate constant k_1 is rate determining, and a constant slope β_2 when the step with rate constant k_2 is rate determining, then we can show that the plot can be described by equation (2), where k_n° and pK_0 refer to the

$$\log(k_n/k_n^{\circ}) = \beta_2(pK - \mathrm{p}K_0) - \log\left[\frac{1 + 10^{(\beta_2-\beta_1)(\mathrm{p}K-\mathrm{p}K_0)}}{2}\right] \qquad (2)$$

(hypothetical) nucleophile for which $k_2 = k_{-1}$.

Alternatively with a one-step process, a treatment similar to that of Murdoch's for proton transfer,[6] making the same assumption about the variation of transition state geometry with ΔG^0 for the equilibrium, leads us to equation (3).

$$\log(k_n/k_n^{s}) = 0{\cdot}5\beta\,(\mathrm{p}K - \mathrm{p}K_s) + \frac{\beta^{2}(\mathrm{p}K-\mathrm{p}K_s)^2}{16\log(hk_s/k_BT\mathrm{M}^{-1})} \qquad (3)$$

Here k_n^s and pK_S refer to the nucleophile which gives a symmetrical energy barrier , and β' is the Brönsted slope for the equilibrium (here reasonably ascribed a value of *ca.* 1·6 by analogy with pyridine acetylation[1b]), k_BT/h is the familiar term of transition-state theory and M = mol dm^{-3}.

Equation (2) can give a good description of the observations (see the solid line in the Figure; β_2 has been chosen as the same as for *p*-nitrophenyl acetate to avoid too many adjustable constants and because it is not expected to vary greatly with reactivity[6]) but equation (3) predicts far less curvature at this level of reactivity. Clearly this could change with different assumptions about transition-state geometry, as is found with proton transfer,[7] but at present the two-step reaction mechanism seems the better description of our results. We tentatively identify C as the tetrahedral intermediate despite the problems this raises,[1a] which will be discussed elsewhere. This identification accounts for the fact that in the pyridinolysis of two compounds of similar absolute reactivity but with poorer leaving groups, namely acetic anhydride[1b] and the 1-acetoxy-4-methoxypyridinium ion,[1a] the limited data available show that any break in the Brönsted plot must occur at higher pK's than observed here.

Pyridazine shows a pronounced α-effect with *p*-nitrophenyl acetate (ref. 8 and this work) but with methyl chloroformate the enhancement of reactivity is not significant, which is surprising in view of the similarity of the Brönsted slopes in this region.[9]

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