The Kinetics of Hydrolysis of *N*-Trimethylammonioacetamide and of Substituted *N*-Trimethylammoniobenzamides in Concentrated Sulphuric Acid

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The hydrolysis of *N*-ammonioacetamide and a number of substituted *N*-ammoniobenzamides has been studied in sulphuric acid solutions of concentration greater than 75%, using ^{1}H n.m.r. and u.v. spectroscopic methods. Good first-order behaviour is found in all cases. The logarithms of the observed rate constants are linearly related to the H_0 (or H_+) acidity function, with slopes −1 to -1.2_8. This is consistent with a unimolecular mechanism of decomposition of the *N*-protonated substrates. Substituent effects on the observed rate constants are best correlated with Hammett substituent constants by a Yukawa–Tsuno equation, with ρ −3.9 ± 0.2 (r 0.986). The large negative value of this constant indicates the dominant effect of the rate-limiting unimolecular formation of the acyl cation intermediates upon the overall rate of the reaction.

N-TRIMETHYLAMMONIOAMIDATES (1), which become monoprotonated in dilute aqueous acid[1] to give acylhydrazinium ions (2) according to equation (1), are further

$$\underset{(1)}{\text{R-CO-}\bar{\text{N}}\text{-}\overset{+}{\text{N}}\text{Me}_3} + \text{H}_3\text{O}^+ = \underset{(2)}{\text{R-CO-NH-}\overset{+}{\text{N}}\text{Me}_3} + \text{H}_2\text{O} \qquad (1)$$

protonated in pure fluorosulphonic acid according to equation (2) to form dications (3), which have been

$$\underset{(2)}{\text{R-CO-NH-}\overset{+}{\text{N}}\text{Me}_3} + \text{HSO}_3\text{F} = \underset{(3)}{\text{R-CO-}\overset{+}{\text{N}}\text{H}_2\text{-}\overset{+}{\text{N}}\text{Me}_3} + \text{SO}_3\text{F}^- \qquad (2)$$

observed by n.m.r. spectroscopy.[1] In the more nucleophilic medium, concentrated sulphuric acid, these cations cannot be observed, because they undergo hydrolysis.

The hydrolysis in 98—100% sulphuric acid of amides, carrying electron-withdrawing substituents (nitro-substituted benzene rings) on the nitrogen, has been observed and followed previously by cryoscopy.[2] A limited study of substituent effects on rate led to the conclusion that this reaction occurred by rate-determining unimolecular breakdown of the *N*-protonated cations (the *A*-1 mechanism), with some assistance to the splitting of the amine by general acids.[2] The monocations (2) of the *N*-ammonioamidates are examples of amides carrying on the nitrogen the most electron-withdrawing substituent of all, a positive pole, and therefore undergo a similar reaction. The reaction was first discovered by a cryoscopic study of solutions of the *N*-ammonioamidates in 100% sulphuric acid.

The dissolution of *N*-trimethylammonioamidates in 100% sulphuric acid leads directly to solutions showing freezing point depressions with van't Hoff factors approaching 5 (i 4.52 for R = Me and 4.85 for R = Ph), corresponding to reaction (3) in which the medium becomes dilute oleum, owing to the abstraction of water by the hydrolysing species. Values of $i < 5$ are due to the suppression of the self-ionisation (4) of sulphuric acid by the HS_2O_7^- ion. The presence of protonated

$$\text{R-CO-}\bar{\text{N}}\text{-}\overset{+}{\text{N}}\text{Me}_3 + 4\text{H}_2\text{SO}_4 = \text{R-C(OH)}_2{}^+ + \text{H}_3\overset{+}{\text{N}}\text{-}\overset{+}{\text{N}}\text{Me}_3 + \text{HS}_2\text{O}_7{}^- + 2\text{HSO}_4{}^- \qquad (3)$$

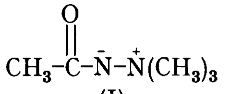
$$2\text{H}_2\text{SO}_4 \rightleftharpoons \text{H}_3\text{O}^+ + \text{HS}_2\text{O}_7{}^- \qquad (4)$$

carboxylic acids in the solutions was confirmed by n.m.r. spectroscopy.

At lower concentrations of sulphuric acid (75—97%) a region was found for each of the *N*-ammonioamidates (I)—(IV) over which the rate of the hydrolysis reaction (5) is conveniently measurable at 20—25 °C. The

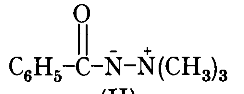
$$\text{R-CO-}\bar{\text{N}}\text{-}\overset{+}{\text{N}}\text{Me}_3 + \text{H}_2\text{O} + 2\text{H}_2\text{SO}_4 = \text{R-COOH} + \text{H}_3\overset{+}{\text{N}}\text{-}\overset{+}{\text{N}}\text{Me}_3 + 2\text{HSO}_4{}^- \qquad (5)$$

acidity dependence of the observed first-order rate constants is consistent with the *A*-1 mechanism. The wide range of substituted derivatives available (I)—(IV) has made possible a much more extensive study of substituent effects on this type of reaction than has been carried out so far for amides,[2] or indeed for esters which undergo analogous hydrolysis in concentrated sulphuric acid.[3]



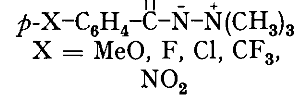
$\text{CH}_3\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-}\bar{\text{N}}\text{-}\overset{+}{\text{N}}(\text{CH}_3)_3$

(I)



$\text{C}_6\text{H}_5\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-}\bar{\text{N}}\text{-}\overset{+}{\text{N}}(\text{CH}_3)_3$

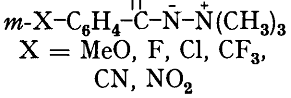
(II)



$p\text{-X-C}_6\text{H}_4\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-}\bar{\text{N}}\text{-}\overset{+}{\text{N}}(\text{CH}_3)_3$

X = MeO, F, Cl, CF_3, NO_2

(III)



$m\text{-X-C}_6\text{H}_4\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-}\bar{\text{N}}\text{-}\overset{+}{\text{N}}(\text{CH}_3)_3$

X = MeO, F, Cl, CF_3, CN, NO_2

(IV)

EXPERIMENTAL

Materials.—The *N*-trimethylammonioamidates were prepared and characterized by the methods already described.[4,5] Sulphuric acid solutions were prepared by dilution of the

98—99% B.D.H. AnalaR reagent. The concentrations were determined by titration with standard alkali.

Kinetic Measurements.—The rates of hydrolysis of *N*-trimethylammonioacetamide cation were followed by ^1H n.m.r. spectroscopy at 21 °C. The resonances of the products, acetic acid and the 1,1,1-trimethylhydrazinium ion, appear at lower field than those of the corresponding protons of the reactant. The rate constants obtained from peak height measurements on the resonance lines of either the reactants or the products were in agreement with each other to within 5%. The half-lives of the reaction were particularly easy to obtain from the resonances of the *N*-methyl protons, since the resonances of the reactant and the hydrazinium ion are close together and show the same linewidth.

The rates of the reactions of *N*-trimethylammoniobenzamides were followed at 25 °C by u.v. spectroscopy using a Cecil 202 u.v.–visible spectrophotometer with a thermostatted cell holder. The wavelengths used varied with the derivative, but were kept constant for each derivative with varying acid concentration, although the spectra at ' infinite ' time were dependent upon acid concentration. This is due to the fact that the carboxylic acid products of the reaction become progressively more protonated at higher acid concentrations in the concentration ranges used in kinetic measurements. The spectra of the reaction products, therefore, showed good isosbestic points, the maximum absorptions shifting towards longer wavelengths with increasing acid concentrations. The initial absorbance values were also dependent on acid concentration for each substrate and showed an increase with increasing acid concentration. Substrate concentrations were of the order of 5×10^{-5}M in the reaction mixtures. The substrate was introduced into sulphuric acid solutions as a 0.01M solution in water and the resulting dilution of sulphuric acid was taken into account in calculating sulphuric acid concentrations in the reaction mixtures.

The reactions were followed for at least two half-lives as a rule and the interval method was used to obtain the rate constants. Only some of the slowest runs were not followed for long enough to apply this method; ordinary plots of $\log(A_\infty - A_t)$ *versus* time were used to obtain the rate constants in such cases. Good first-order behaviour was found in all the experiments. The estimated error in the rate constants is ±5%.

RESULTS AND DISCUSSION

The results are given in Tables 1 and 2. Table 1 also lists acidity function values (H_0) for the sulphuric acid solutions [6] used in the kinetic runs and the relative chemical shift of the protons of the C–Me and the N–Me groups for the *N*-ammonioacetamide reactant, dissolved in sulphuric acid prior to reaction. It can be seen that the first-order rate constants increase with acid concentration. A plot of $\log k_{1,\text{obs}}$ *versus* $-H_0$ values is shown in Figure 1. The slope is 1.00, *i.e.* the reaction is acid catalysed. A hydrolysis reaction of an amide increasing in rate at these high sulphuric acid concentrations is likely to involve a protonated substrate, in this case a doubly protonated *N*-ammonioamidate, and *no* water molecules in the transition state, since the activity of water decreases sharply at these sulphuric acid concentrations (from *ca.* 0.1 in 65% sulphuric acid to *ca.* 10^{-6} in 100% sulphuric acid).[7] This is essentially the mechanism suggested by Duffy and Leinsten,[2] *i.e.* reactions (6) except that now R = NMe_3^+ and the reactive species in step (ii) is a dication. We do not need to assume the presence of a significant amount of the *O*-protonated amide tautomer, as was done by Duffy and Leisten,[2] since there is good n.m.r. evidence that *N*-ammonioacetamidate (like other *N*-ammonioamidates) is doubly protonated on the nitrogen in pure fluorosulphonic acid at low temperature.[1] The probability of similar protonation in sulphuric acid which contains some water is

TABLE 1

Rate constants for the hydrolysis of *N*-trimethylammonioacetamide and the relative chemical shift ($\delta_{NMe_3^+} - \delta_{CMe}$) in sulphuric acid at 21 °C

H_2SO_4 (%)	H_0 (25 °C)	$10^{-5}k_{1,\text{obs}}$/s^{-1}	($\delta_{NMe_3^+} - \delta_{CMe}$)/p.p.m.
75.24	−6.76	2.8	1.46
76.80	−7.02	5.2	1.46
79.10	−7.38	12.3	1.45
80.40	−7.58	19.5	1.43
81.83	−7.81	28.0	1.41
83.20	−8.02	52.0	1.40
85.37	−8.35	109.7	1.38

TABLE 2

Rate constants for the hydrolysis of substituted *N*-trimethylammoniobenzamides in sulphuric acid at 25 °C

Substituent	H_2SO_4 (%)	H_0	λ/nm	$k_{1,\text{obs}}$/s^{-1}	Slopes $\log k_{1,\text{obs}}$ *versus* H_0
H	75.60	−6.82	260	3.97×10^{-5}	−1.15
	79.07	−7.37		1.65×10^{-4}	
	82.52	−7.92		5.11×10^{-4}	
	84.97	−8.28		2.14×10^{-3}	
p-F	79.07	−7.37	260	1.10×10^{-4}	−1.04
	82.52	−7.92		1.95×10^{-4}	
	84.97	−8.28		6.84×10^{-4}	
	86.92	−8.57		1.43×10^{-3}	
p-Cl	82.52	−7.91	280	1.02×10^{-4}	−1.08
	84.97	−8.28		4.64×10^{-4}	
	86.92	−8.57		1.07×10^{-3}	
	90.21	−9.07		3.46×10^{-3}	
p-CF_3	90.21	−9.07	260	1.61×10^{-4}	−1.06
	91.99	−9.33		4.13×10^{-4}	
	93.93	−9.58		5.85×10^{-4}	
	96.02	−9.89		1.37×10^{-3}	
p-NO_2	96.15	−9.90	267	8.96×10^{-5}	−1.21
	97.02	−10.06		1.40×10^{-4}	
p-MeO	71.91	−6.22	300	2.39×10^{-4}	−1.17
	74.50	−6.64		8.21×10^{-4}	
	75.60	−6.82		1.26×10^{-3}	
	79.07	−7.37		6.14×10^{-3}	
m-MeO	82.52	−7.72	260	7.70×10^{-5}	−1.00
	84.97	−8.28		2.53×10^{-4}	
	86.92	−8.57		6.14×10^{-4}	
	90.21	−9.07		1.61×10^{-3}	
m-F	86.92	−8.57	260	1.60×10^{-4}	−1.00
	90.21	−9.07		5.90×10^{-4}	
	91.99	−9.33		1.02×10^{-3}	
	96.02	−9.89		3.49×10^{-3}	
m-Cl	86.92	−8.57	260	2.02×10^{-4}	−1.00
	90.21	−9.07		5.50×10^{-4}	
	91.99	−9.33		1.20×10^{-3}	
	93.93	−9.58		2.00×10^{-3}	
m-CF_3	91.99	−9.33	260	3.39×10^{-4}	−1.07
	96.94	−10.04		1.95×10^{-3}	
m-NO_2	96.02	−9.89	250	5.71×10^{-5}	−1.28
	96.89	−10.04		8.91×10^{-5}	
m-CN	96.02	−9.89	250	1.81×10^{-4}	−1.24
	96.89	−10.04		2.78×10^{-4}	

high, since the presence of water encourages acylammonium ion formation.[8] The unimolecular mechanism of the acid-catalysed hydrolysis of amides requires that such a cation be the reactive species. Increasing amounts of the dication (3) formed with increasing acid concentration should lead to increasing rates of hydrolysis, as observed. Evidence for the presence in solution of

$$\left.\begin{array}{ll}\text{(i)} & R'CONHR + H_3O^+ \rightleftharpoons R'CO\overset{+}{N}H_2R + H_2O \\ \text{(ii)} & R'CONH_2R^+ \xrightarrow[\text{Slow}]{k_1} R'CO^+ + RNH_2 \\ \text{(iii)} & RNH_2 + H^+ \xrightarrow[\text{Fast}]{} RNH_3^+ \\ \text{(iv)} & R'CO^+ + H_2O \xrightarrow[\text{Fast}]{} R'CO_2H_2^+ \end{array}\right\} \quad (6)$$

these unstable dications comes also from the relative chemical shift of the C–Me and N–Me protons of *N*-trimethylammonioacetamide cation: The resonance of the C–Me protons shifts downfield rather more with increasing acid concentration than the resonance of the N–Me protons, because the chemical shift of the latter is dominated by the positive charge on the ammonio nitrogen ($\overset{+}{N}Me_3$) and is less dependent on the extent of protonation. If the relative chemical shift of the two resonances for the fully formed dication were known, it would be possible to estimate the degrees of preprotonation (i) in the reacting mixtures, using a known method.[9] Unfortunately, this shift is not obtainable, because of the rapid reaction at higher acid concentrations. However, the fact that the logarithms of the observed rate constants vary linearly with the acidity function H_0 is an indication that the extent of preprotonation (i) is small ($\alpha < 0.5$) at sulphuric acid concentrations used in the kinetic runs. Since the substrates in the present study are in fact monocations, the *N*-ammonioamides, the acidity function relevant to the preprotonation is H_+, and not H_0, but the two acidity scales are known to be parallel functions of acid concentration.[10] The unit slope would thus be found equally in a plot of log $k_{1,\text{obs}}$ *versus* $-H_+$. The H_0 function was used here, because more extensive and more reliable data are available for it.[6]

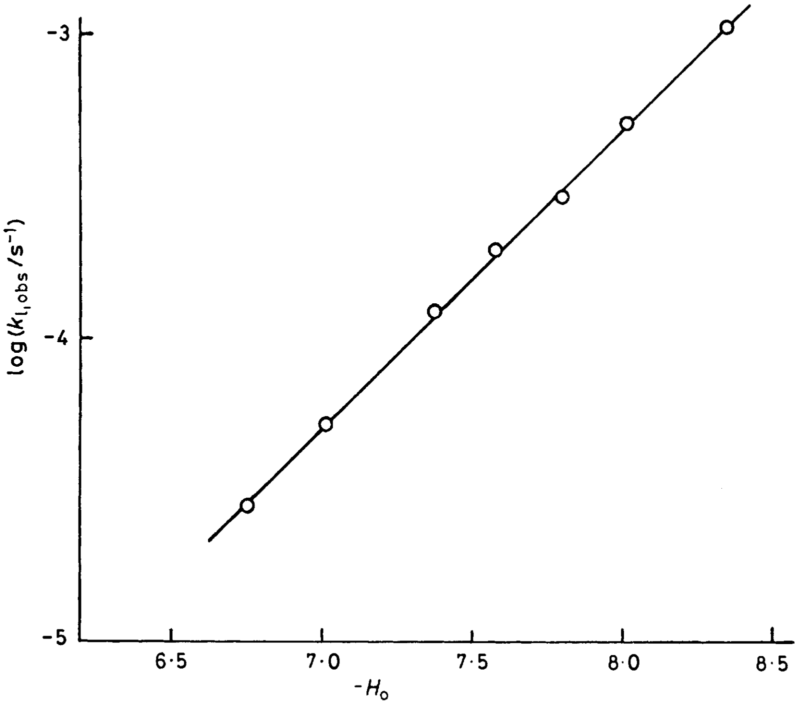


FIGURE 1 A plot of the logarithms of the observed first-order rate constants for the hydrolysis of *N*-trimethylammonioacetamide at 21 °C *versus* the acidity function H_0

Table 2 lists also the wavelengths used in obtaining kinetic data for each derivative and the slopes of the log $k_{1,\text{obs}}$ *versus* $-H_0$ plots. The slopes can be seen to fall within the range -1.0 to -1.2_8 for all the substituted derivatives. The same conclusions may, therefore, be drawn about the reactions of these substrates as about the reaction of *N*-ammonioacetamide cations. The deviations from unit slopes may partly be due to experimental error and it may be unjustified to read any mechanistic significance into them, although it is possible that the general acid catalysis of the removal of the amine, suggested by Duffy and Leisten[2] in order to explain the inhibiting effect of dilution of sulphuric acid on the rate of hydrolysis of otherwise fully protonated amides, may account for the tendency of the slopes to be greater than unity.

The difference in the rates of hydrolysis of the *N*-trimethylammonioamide cations and the nitro-substituted acetanilides and benzanilides, studied by Duffy and Leisten,[2] is striking: our substrates are fully hydrolysed in 100% sulphuric acid immediately upon dissolution at 10 °C (cryoscopic experiments referred to in the introduction), whereas the substrates of Duffy and Leisten hydrolyse only at higher temperatures (50—65 °C) with quite long half-lives (50—70 min), even though they are fully protonated in 100% sulphuric acid. The extent of the second protonation of our substrates in 100% sulphuric acid is not known, but chemical shifts of resonance lines (Table 1) and the variation in the absorbance at zero time of the substrates in Table 2 with acid concentration suggest that measurable amounts are diprotonated in sulphuric acid solutions used in the kinetic runs. Since these are of considerably lower acidity than 100% sulphuric acid, it is likely that the protonation of most of our substrates is virtually complete in that medium. The much faster hydrolysis of these substrates in that medium, even at 10 °C, as compared with the substrates of Duffy and Leisten, is due to the much greater instability of the dication (3) with respect to the unimolecular decomposition (ii) which is the rate-limiting step in the reaction. The greater instability can be ascribed to the much more strongly electron-withdrawing character of the NMe_3^+ pole, compared with that of nitro-substituted benzene rings.

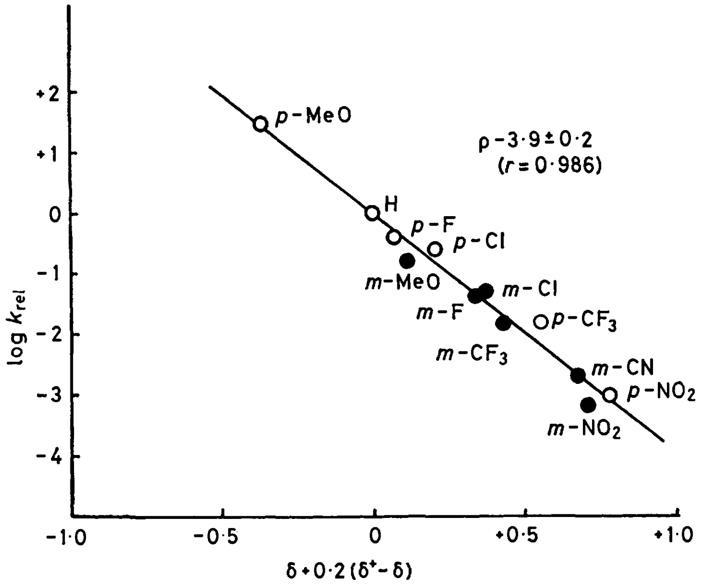


FIGURE 2 The Yukawa–Tsuno plot of the relative rate constants for the hydrolysis of substituted *N*-trimethylammoniobenzamides at 25 °C: ○, *para*-derivatives; ●, *meta*-derivatives

The mechanism (6) leads to the rate equation (7)

$$\text{Rate} = k_1[\text{SH}^+] \qquad (7)$$

$$[\text{SH}^+] = \frac{1}{K_{\text{SH}^+}}[\text{S}][\text{H}^+]\frac{y_\text{S}y_{\text{H}^+}}{y_{\text{SH}^+}} = \frac{1}{K_{\text{SH}^+}}[\text{S}]h_0 \qquad (8)$$

(written here for an uncharged substrate, S, for simplicity) where equation (8) applies if the protonation of the substrate follows the acidity h_0. Furthermore, if the degree of preprotonation is small, $[\text{S}] \cong c_\text{S}$, where c_S is the stoicheiometric concentration of the substrate. Upon substitution of this approximation into equation (8), we have (9) and further substitution into equation (7) leads to equation (10) for the rate of the reaction whence it can be seen that one obtains (11) for the

$$[\text{SH}^+] \cong \frac{1}{K_{\text{SH}^+}} c_\text{S}h_0 \qquad (9)$$

observed first-order rate constant. This is in accord with the finding that log $k_{1,\text{obs}}$ values are linear functions of $-H_0$, with slopes of 1.

$$\text{Rate} = -\frac{\text{d}c_\text{S}}{\text{d}t} \cong k_1\frac{1}{K_{\text{SH}^+}} c_\text{S}h_0 \qquad (10)$$

Equation (11) may also be used to account for substituent effects on rate. If we attach a subscript 0 to

$$k_{1,\text{obs}} = k_1\frac{1}{K_{\text{SH}^+}} h_0 \qquad (11)$$

the quantities referring to the parent compound, then relative rate constants, obtained at a fixed acidity function value, will be given by equations (12) and (13). Equation (13) is, in fact, a four parameter Hammett equation, which may be written as (14) where ρ_1 refers

$$k_\text{rel} = \frac{k_1/k_{1,0}}{K_{\text{SH}^+}/K_{\text{SH}^+,0}} \qquad (12)$$

$$\log k_\text{rel} = \log(k_1/k_{1,0}) - \log(K_{\text{SH}^+}/K_{\text{SH}^+,0}) \qquad (13)$$

to the rate-limiting step and ρ_e to the pre-equilibrium. It is assumed here that the pre-equilibrium would be governed by the σ constants, since the protonation of

$$\log k_\text{rel} = \rho_1\sigma^+ - \rho_\text{e}\sigma \qquad (14)$$

benzamides is governed by these constants,[11] and the cations of benzamides, formed in dilute acid, have an *N*-protonated structure[8,11] like the one found for the present substrates.[1] The rate-limiting step is assumed to be governed by the σ^+ constants, since it involves the formation of a carboxonium ion, in which through-resonance with *para*-substituents is possible. The substituent effects on rate should thus be complex, and it has been found that neither a plot of log k_{rel} *versus* σ nor *versus* σ^+ is linear. The *p*-MeO-substituted derivative shows particularly large deviations in both plots. It proved possible to obtain a good linear plot using the Yukawa–Tsuno equation (15) which involves both kinds

$$\log k_{rel} = \rho[\sigma + r(\sigma^+ - \sigma)] \qquad (15)$$

of substituent constant. The plot is shown in Figure 2. The values of the parameters are ρ −3.9 ± 0.2 (correlation coefficient *r* 0.986) and *r* 0.2.

The ρ value is quite reasonable. Earlier estimates of $\rho_1 = -3.1$ and -3.4 (based on two substituents only)[2] for the slow step, coupled with $\rho_e \cong 1$ for the preprotonation (this is an estimate close to the value found for the protonation of substituted benzamides[11]), lead to an estimate of an overall ρ of *ca.* −4, very close to the observed value.

The low value of *r* implies a low weighting of σ^+ constants, contrary to what might have been expected from a comparison of equation (15) with (14), bearing in mind the above estimates of the values of ρ_1 and ρ_e (a value of *r* *ca.* 0.75 would have been consistent with these estimates). The observed value of *r* largely depends upon the k_{rel} value for the *p*-MeO derivative (because of the large $\sigma^+ - \sigma$ difference for this substituent) and it seems possible that the low value of *r* may be due to an overestimate of the importance of through-resonance between this substituent and the emerging acyl cation centre in the transition state. The use of the normal value of σ^+ for this substituent (−0.778)[12] implies full operation of this through-resonance. If the through-resonance were reduced, *e.g.* on account of the hydrogen-bonding interaction of the solvent sulphuric acid with the *p*-MeO group, then the use of a correspondingly smaller σ^+ value for this substituent would be justified and would result in a higher value of *r*. In view of the nature of the medium, this kind of interaction seems highly likely. The *p*-MeO group is certainly not protonated in the reaction mixtures, because its effect would then be electron-withdrawing and not electron-releasing, as found, but hydrogen-bonding to sulphuric acid would be expected and would reduce this electron-releasing effect.

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