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Reaction of imidazole with toluene-4-sulfonate salts of substituted phenyl *N*-methylpyridinium-4-carboxylate esters: special base catalysis by imidazole

Matthew J. Colthurst and Andrew Williams*
University Chemical Laboratory, Canterbury, Kent, UK CT2 7NH. E-mail: aw@ukc.ac.uk

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The reaction of imidazole in aqueous solution with toluene-4-sulfonate salts of substituted phenyl *N*-methylpyridinium-4-carboxylate esters obeys the rate law:

$$k_{obs} - k_{background} = k_2[\mathrm{Im}] + k_3[\mathrm{Im}]^2$$

where [Im] is the imidazole concentration present as free base. The parameters k_2 and k_3 fit Brønsted type free energy correlations against the pK_a of the leaving phenol with β_{Lg} values of −0.65 and −0.42 respectively. The imidazolysis is insensitive to catalysis by general bases and yet k_3 for the 3-cyanophenyl ester possesses a deuterium oxide solvent isotope effect of 4.43 consistent with rate limiting proton transfer. A special catalytic function is proposed for decomposition of the tetrahedral addition intermediate ($T^{\pm}$) *via* k_3 whereby the catalytic imidazole interacts electrophilically with the leaving phenolate ion and removes a proton from the nitrogen in the rate limiting step with subsequent non-rate limiting ArO–C bond fission. This is consistent with the change in effective charge on the leaving oxygen in the transition structure of k_3 which is more positive (−0.42) than that expected (−0.60) for the equilibrium formation of the zwitterion intermediate. The catalytic function at the leaving oxygen is likely to be an electrophilic role of the NH as a hydrogen bond donor. In the k_2 step the deuterium oxide solvent isotope effect of 1.51 for the 3-cyanophenyl ester and the β_{Lg} of −0.65 are consistent with rate limiting expulsion of the phenolate ion from the $T^{\pm}$ intermediate. The absence of general base catalysis of imidazolysis rules out the established mechanism for aminolysis of esters where $T^{\pm}$ is stabilised by a standard rate limiting proton transfer. The kinetically equivalent term for k_3 where T^- reacts with the imidazolium ion as an acid catalyst would require this step to be rate limiting and involve proton transfer not consistent with departure of the good aryl oxide leaving group.

Introduction

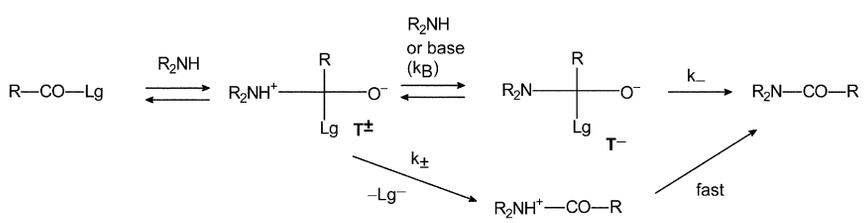
Rates of hydrolysis of phenyl esters catalysed by imidazole usually refer to the formation of an acyl-imidazole intermediate which hydrolyses to produce acid and imidazole in a subsequent slower step.[1,2] Caplow and Jencks observed that, for the reaction of imidazole with 4-nitrophenyl esters of benzoic acids, the plot of the pseudo first order rate constant against imidazole concentration has a slight upward curvature. This was interpreted as an additional term (k_3) involving a second imidazole molecule acting as a general base catalyst (Eqn. (1)).[3] The termolecular term, k_3, was observed by other workers[4,5] but the process:

$$\mathrm{Rate} = k_{background}[\mathrm{ester}] + k_2[\mathrm{imidazole}][\mathrm{ester}] + k_3[\mathrm{imidazole}]^2[\mathrm{ester}] \quad (1)$$

could not be studied in detail because the relative magnitude of k_3 and k_2 demanded concentrations of imidazole up to 1 M for the k_3 effect to be measured; the high imidazole concentration introduces the possibility that the curvature could be due to a non-specific solvent effect as well as making the measurements of k_3 less accurate than those of k_2.

Termolecular terms are well known in aminolysis reactions at acyl functions bearing relatively poor leaving groups,[6–12] where the catalytic function of the additional base is to trap, by proton transfer, the zwitterionic tetrahedral adduct from addition of primary or secondary amines; this circumvents the rapid return to reactants competing favourably with leaving group departure (Scheme 1).[6] The direct expulsion of the leaving group from $T^{\pm}$ leads to an unstable *N*-protonated amide as the initial product; unless the leaving group propensity is exceptional the general base catalysed route *via* T^- is generally favoured. Only highly activated esters such as 1-acyloxypyridines do not require trapping because their leaving groups are good enough to provide a favourable path direct from $T^{\pm}$ *via* R_2NH^+–CO–R to product.

In the case of imidazolysis the proton in $T^{\pm}$ does not reside on the nitrogen adjacent to the nascent carbonyl. Direct expulsion of the leaving group from $T^{\pm}$ does not therefore incur the heavy energy penalty suffered by $k_{\pm}$ in aminolysis because the product acyl-imidazolium ion has only a weak acidity



Scheme 1

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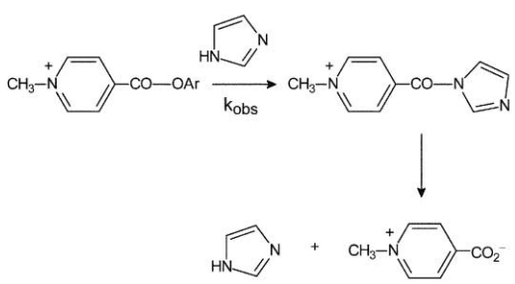
Table 1 Analytical data for the toluene-4-sulfonate salts of substituted phenyl *N*-methylpyridinium-4-carboxylate esters

Substituent	Mp/°C	Found			Formula	Calculated		
		N(%)	C(%)	H(%)		N(%)	C(%)	H(%)
4-CH_3CO–	198–200[dec]	3.13	61.46	4.76	$C_{22}H_{21}NO_6S$	3.28	61.81	4.95
Parent	153–155	3.50	61.01	4.93	$C_{20}H_{19}NO_5S$	3.63	62.3	4.97
3-Cl–	201–203	3.31	56.91	3.96	$C_{20}H_{18}ClNO_5S$	3.36	57.20	3.60
3-Cyano–	200–203[dec]	6.9	61.2	4.1	$C_{21}H_{18}N_2O_5S$	6.80	61.45	4.4

compared with that of acyl-ammonium ions ($RCO–NHR_2^+$). The advantage gained by general base trapping of the analogous $T^{\pm}$ from imidazole addition is unexpected on the basis of the mechanism for aminolysis by primary and secondary amines.

This study shows that the reaction of imidazole with substituted phenyl *N*-methylpyridinium-4-carboxylate esters has a much more substantial termolecular term relative to the bimolecular term, k_2, (Scheme 2) than the previously observed values for benzoate or acetate esters. The possession of a substantial termolecular effect means that k_3 values may be determined with good accuracy under conditions of relatively low imidazole concentration where non-specific solvent effects will be minor. Calculations from previous work show that at 0.1 M imidazole the percentage of total reaction flux passing through the termolecular pathway is only 8.06 and 2.86 for the imidazolysis of 4-nitrophenyl 4-nitrobenzoate[3] and 4-methoxyphenyl acetate respectively.[5] For this reason, the system of Scheme 2 is ideal as a vehicle to investigate the origins of the termolecular term of imidazolysis.



Scheme 2

Experimental

Materials

The toluene-4-sulfonate salts of substituted phenyl *N*-methylpyridinium-4-carboxylate esters were either already available or were prepared according to methods recorded in a previous investigation.[13] New esters were characterised by NMR and elemental analysis; melting points and analytical data are recorded in Table 1 and the ester salts with toluene-4-sulfonic acid were recrystallised from DMF. D_2O (99.9% D) and DCl in D_2O (20%, 99.5% D) were obtained from Goss Scientific.

Kinetics

All solutions were prepared with water that was doubly distilled from glass and degassed before use. Two solutions of identical buffer concentrations (HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid at 0.05 M), ionic strength (0.5 M), pH and solvent composition were prepared, only one of which contained imidazole. The sample solutions were prepared by dilution of the stock solution to give a series of solutions with different imidazole concentrations but with the other parameters remaining constant.

Reactions were initiated by the addition of an aliquot (0.01 to 0.05 mL) of a stock solution of the ester salt (in 50% v/v water–acetonitrile) on the tip of a glass or polypropylene rod into 2.5 mL of sample solution in a 1 cm path-length silica cell in the thermostatted cell-compartment of a UV/Visible spectrometer. A few vertical strokes of the rod effected mixing and the reaction was followed by monitoring the change in absorbance with time at the optimal wavelength, determined by repetitive scanning of the spectrum of a test solution undergoing reaction. The kinetics of the reactions in D_2O solvent were carried out as above using 1 mL capacity silica cells with 1 cm path-length.

The pH values of the solutions were measured before and after each kinetic run using a Radiometer PHM 62 meter fitted with a Russell CMAWL combined electrode, calibrated with BDH buffers. Measurements of pD were carried out with the hydrogen electrode using the formula $pD = pH_{meter\ reading} + 0.37$.[14] Data from experiments where the pH changed by more than 0.1 were discarded. Pseudo first order rate constants were obtained from the data by fitting the value A_t to the equation $A_t = A_\infty - (A_\infty - A_o)\exp(-kt)$.

The formation and decay of the intermediate *N*-acylimidazole was followed by trapping it with hydroxylamine to give the hydroxamic acid which was detected as its complex with Fe(III) ions using the absorption at 540 nm.[15] Solutions of 3.5 M NaOH and 4 M $HONH_3Cl$ were prepared and mixed in the ratio 2 vol. NaOH to 1 vol. $HONH_3Cl$ to give a stock hydroxylamine solution. A solution of $FeCl_3 \cdot 6H_2O$ was prepared in 0.7 M HCl to use as the developing agent. A kinetic run was initiated by mixing 1.25 mL, 51.6 mM ester (50% v/v $CH_3CN–H_2O$) with 1.25 mL, 0.2 M imidazole stock at pH 7. Aliquots of 0.05 mL were taken at intervals and added to 0.5 mL of the stock hydroxylamine solution. Each sample was then diluted, after 3 min, with 2 mL $FeCl_3$ solution and the absorbance read at 540 nm. An experiment to determine the molar absorption coefficient at 540 nm had water replacing the imidazole to obtain an absorbance corresponding to a known amount of ester; the molar absorption coefficient, ε_{540}, under the conditions of these experiments is 1002. A further control experiment under the same conditions measured the release of the 4-nitrophenolate ion by following its absorbance at 400 nm.

Results

The change in UV/Visible absorbance in the reactions of the esters in buffers containing imidazole obeyed excellent pseudo first order kinetics over at least 90% of the total reaction, except for the kinetics with the 3-cyanophenyl ester with HPO_4^{2-} followed at 275 nm. The total absorbance changes at the wavelengths used for the kinetic measurements were compared with the expected changes and this indicated complete release of phenol from the phenyl esters; there is no evidence for substitution in the phenolic aromatic nucleus or in the pyridinium ring.

The experiments using the hydroxamic acid assay technique (Fig. 1) show that an activated acyl function is still present after all the 4-nitrophenolate ion has been expelled from the 4-nitrophenyl *N*-methylpyridinium-4-carboxylate esters in imidazole buffers. The release of 4-nitrophenolate ion measured at 400 nm was found to be substantially complete after about 20 s. Fig. 1 illustrates the time dependence of the hydroxamic acid assay on an identical solution. The decay of the active acyl function is

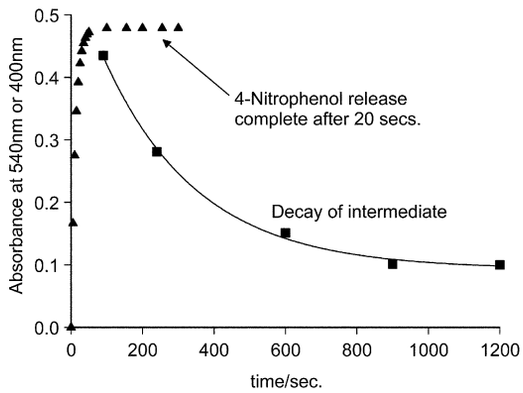


Fig. 1 Assay of active ester in imidazolysis of 4-nitrophenyl ester (■); ▲ show the absorbance at 400 nm of the release of 4-nitrophenolate ion.

much slower than the release of the 4-nitrophenolate ion and this is judged to be consistent with the formation of the *N*-(*N*′-methylpyridinium-4-carbonyl)imidazole intermediate followed by its gradual decay.

Imidazolysis of 3-cyanophenyl *N*-methylpyridinium-4-carboxylate was followed at 275 nm in the presence of increasing concentrations of phosphate at pH 7.00 and an intermediate was detected. The kinetics were analysed according to the biexponential equation (2) for the consecutive two step process (A ⟶ B ⟶ C) where L_1, L_2 and L_3 are functions of k_a, k_b, molar absorption coefficients of A, B and C and the initial concentration of A.

$$Abs_t = L_1\exp(-k_a t) + L_2\exp(-k_b t) + L_3 \qquad (2)$$

The value k_a corresponds to formation of the acyl-imidazole and k_b to its decomposition.

The pseudo first order rate constants measured spectrophotometrically for the reactions of the esters with imidazole fit a rate law involving a squared term in total imidazole concentration (Eqn. (3)).

$$k_{obs} = k_{background} + k_2'[\text{total imidazole}] + k_3'[\text{total imidazole}]^2 \qquad (3)$$

The parameter $k_{background}$ is essentially due to the reaction of hydroxide ion with the ester. The fit to Eqn. (3) is illustrated in Fig. 2 for the 4-nitrophenyl ester. The k_2' term for the 3-cyanophenyl ester is demonstrated to be due to reaction of the base form (free imidazole) as k_2' is proportional to the fraction of free base (FB); this result is expected from previous work with other phenyl esters.[1–5] The k_3' term for the 3-cyanophenyl ester is proportional to (FB × FB) as illustrated in Fig. 3. Eqn. (1) therefore governs the reaction of imidazole with the 3-cyanophenyl ester and it is assumed to hold for the other esters studied here. Bruice and Benkovic demonstrated this rate law for the imidazole-catalysed imidazolysis of 4-methylphenyl and 4-methoxyphenyl acetates.[5]

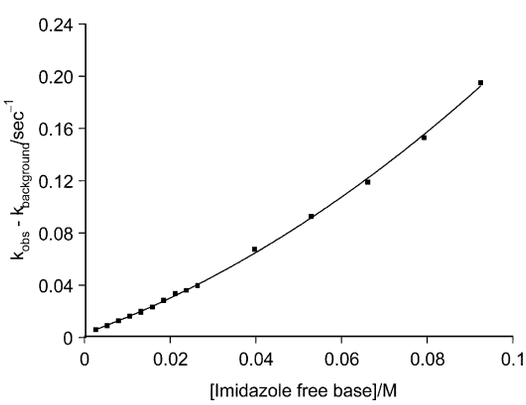


Fig. 2 Reaction of 4-nitrophenyl *N*-methylpyridinium-4-carboxylate in buffers containing increasing concentrations of imidazole. Conditions as in Table 2.

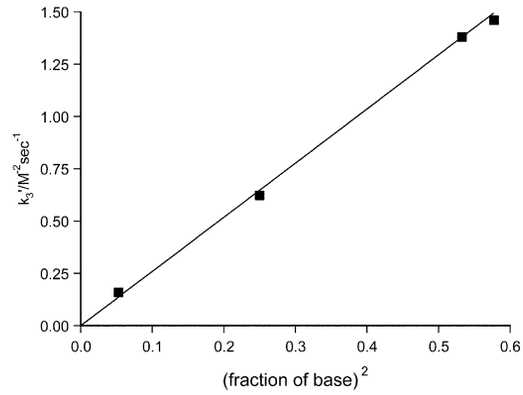


Fig. 3 Values of k_3' as a function of FB^2 for the reaction of 3-cyanophenyl *N*-methylpyridinium-4-carboxylate in imidazole-containing buffers. Conditions as in Table 2.

The effect of general bases on the reaction of imidazole with *N*-methylpyridinium-4-carboxylate esters was tested by the use of 2,6-lutidine. This base was chosen as it is relatively non-nucleophilic[13] and therefore does not compete with imidazole for attack at the ester function. Changing the concentration of 2,6-lutidine did not affect the observed rate constant for the 3-cyanophenyl ester (measured at 300 nm) in the presence of 0.1 M free imidazole base (Fig. 4). Assuming that the k_3 term for 2,6-lutidine acting as a general base is the same as that for imidazole, the calculated rate constant at pH 7.00 for 0.126 M free 2,6-lutidine (calculated from the pK_a = 6.77 and total 2,6-lutidine of 0.2 M) should be 1.7-fold that without the base. This calculated change is well outside the error limits of the experiments. A similar insensitivity was obtained in the case of imidazolysis of the 4-nitrophenyl ester with 2,6-lutidine as the potential base catalyst. The rate constants for formation of acyl-imidazole in the presence of increasing concentrations of phosphate buffer (k_a, see Eqn. (2)) are 0.055, 0.050 and 0.051 s^{-1} for 0.04, 0.1 and 0.2 M respectively in total phosphate at pH 7.00 (at a fraction of free base at 0.381 based on a pK_a of 7.21 for phosphate). The argument used for the 2,6-lutidine experiments indicates that 0.2 M in total phosphate should raise the observed rate constant by 1.4-fold if there were general base catalysis. The reaction is thus insensitive to the free base, HPO_4^{2-}, within the error limits of the measurements.

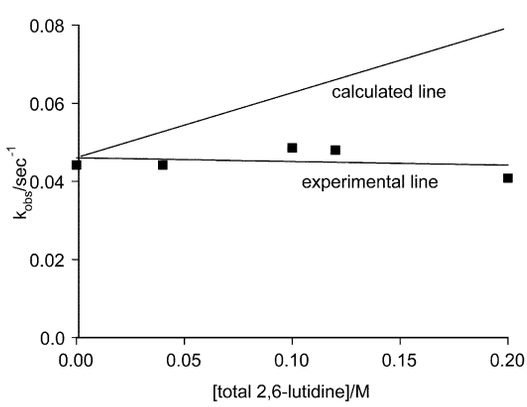


Fig. 4 Effect of increasing concentration of 2,6-lutidine on the rate of reaction of imidazole with 3-cyanophenyl *N*-methylpyridinium-4-carboxylate ester. Conditions as in the text.

The kinetic parameters of Eqn. (1) fitting the observed rate constants of the esters are collected in Table 2 together with the conditions of pH, buffer, ranges of imidazole concentrations and observed rate constants.

Table 2 Kinetic parameters and conditions for the reaction of imidazole with substituted phenyl *N*-methylpyridinium-4-carboxylate esters in aqueous solution[d,e]

Substituent	pK_a^{ArOH}	$k_3/M^{-2}\ s^{-1}$	$k_2/M^{-1}\ s^{-1}$	pH	$10^4\ k_{OH}/M^{-1}\ s^{-1}$[g]	*N*	[Imidazole][f]	$k_{obs} \times 10^3/s^{-1}$	λ/nm
H	9.95	0.641 ± 0.068	0.0161 ± 0.0066	8.00[a]	0.309 ± 0.034	27	9–92	3.4–10.3	285
4-Ac	8.05	5.13 ± 0.46	0.32 ± 0.038	7.99[a]	1.21 ± 0.17	12	16–80	13–70	325
3-Cl	9.02	2.33 ± 0.24	0.115 ± 0.021	7.99[a]	0.872 ± 0.035	21	4–90	8.6–38	290
3-CN(H_2O)	8.61	3.32 ± 0.47	0.172 ± 0.035	6.47–7.50[a,c]	1.45 ± 0.07	43	3–80	6.5–44.8	275
3-CN(D_2O)		0.749 ± 0.203	0.114 ± 0.038	7.00 (pD)	—	17	40–120	1.7–8.95	275
3-NO_2	8.35	8.29 ± 0.68	0.409 ± 0.059	8.00[a]	1.68 ± 0.09	21	6–90	20–120	330
4-NO_2	7.14	9.44 ± 0.65	1.18 ± 0.060	7.00[b]	3.24 ± 0.48	15	2.6–92	6.0–190	350

[a] 0.05 M HEPES. [b] No added buffer. [c] Fractions of base (data points): 0.23 (6), 0.5 (14), 0.73 (7) and 0.76 (22); k_3' : 0.159, 0.623, 1.38 and 1.46 $M^{-2}\ s^{-1}$ respectively. [d] Solvent composition was between 1 and 2% v/v CH_3CN–water. [e] Temperature 25 °C, ionic strength adjusted to 0.5 M with KCl. [f] Total imidazole concentration/mM. [g] k_{OH} for 4-cyano ester is 2.30 ± 0.04 × 10^4 $M^{-1}\ s^{-1}$.

The parameters k_2 and k_3 fit Brønsted type equations (4) and (5) respectively and these are illustrated in Fig. 5. The second order rate constants for alkaline hydrolysis of the esters were obtained from the values of $k_{background}$ and are recorded in Table 2; they fit the Brønsted equation (6) which has a β_{Lg} similar to that for alkaline hydrolysis of substituted phenyl esters of other acids.

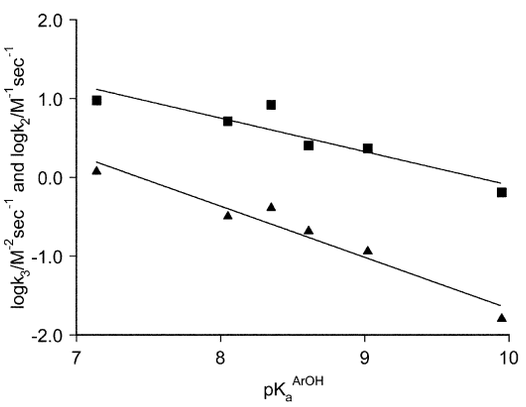


Fig. 5 Brønsted lines for the parameters k_2 (▲) and k_3 (■) for the reaction of substituted phenyl *N*-methylpyridinium-4-carboxylate esters in imidazole containing buffers. Lines are calculated from Eqns. (4) and (5).

$$\log k_2 = -0.65 \pm 0.077 pK_a^{ArOH} + 4.83 \pm 0.66\ (r = 0.9729) \quad (4)$$

$$\log k_3 = -0.42 \pm 0.090 pK_a^{ArOH} + 4.16 \pm 0.77\ (r = 0.9208) \quad (5)$$

$$\log k_{OH} = -0.352 \pm 0.053 pK_a^{ArOH} + 7.08 \pm 0.15\ (r = 0.9486) \quad (6)$$

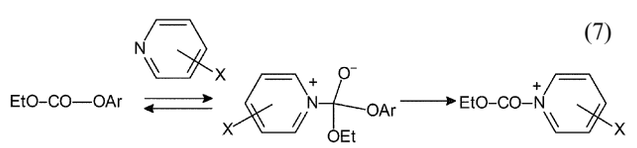
The proportion of reaction flux taken by the k_3 term relative to that *via* the k_2 term in the reaction of imidazole with the *N*-methylpyridinium-4-carboxylate ester of 4-nitrophenol is much greater than that for the other published systems. Calculations from the data from Table 2 show that at 0.1 M imidazole, the percentage reaction flux taken through the k_3 term by the 4-nitrophenyl *N*-methylpyridinium-4-carboxylate ester is 44% and at 1 M imidazole it is 89%.

Deuterium oxide solvent isotope effects of $k_2^{H/D}$ = 1.51 and $k_3^{H/D}$ = 4.43 for the 3-cyanophenyl ester are well within the ranges expected for reactions involving no rate limiting proton transfer (for k_2) and proton transfer (for k_3).[16] However, both isotope effects are larger than those reported by Caplow and Jencks for the imidazolysis of 4-nitrophenyl 4-nitrobenzoate.[3]

Discussion

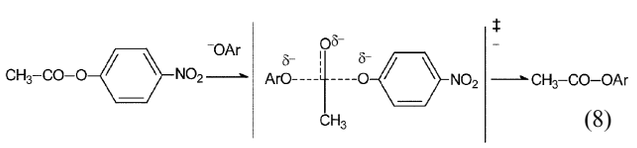
The reaction between substituted phenyl *N*-methylpyridinium-4-carboxylate esters and imidazole in aqueous buffers involves nucleophilic substitution at the ester followed by hydrolysis of the *N*-(*N*′-methylpyridinium-4-carbonyl)imidazole intermediate. Fig. 1 shows that a hydroxylamine-active species (the acyl-imidazole) persists after all the 4-nitrophenolate ion has been expelled from the ester. The reactivity of 2,6-lutidine with the 4-nitrophenyl ester (< 0.08 $M^{-1}\ s^{-1}$)[13] is significantly less than that of k_2 for imidazole attack (1.19 $M^{-1}\ s^{-1}$). General base catalysed hydrolysis by imidazole is therefore of minor importance because the hindered 2,6-lutidine, which has a similar basicity (pK_a = 6.77) to that of imidazole (pK_a = 7.05), should have approximately the same reactivity. Kinetics of the reaction of 3-cyanophenyl *N*-methylpyridinium-4-carboxylate ester in imidazole buffers in the presence of phosphate dianion exhibit an intermediate when followed at 275 nm (Eqn. (2)). The intermediate is assumed reasonably to be the acyl-imidazole and decays due to its reaction with phosphate dianion.

Substitution reactions between heterocyclic bases (such as pyridines) and aryl esters and other unsaturated centres can be stepwise[17] involving an addition intermediate which breaks down to give the product (see for example Eqn. (7)). The stability of the zwitterionic intermediate



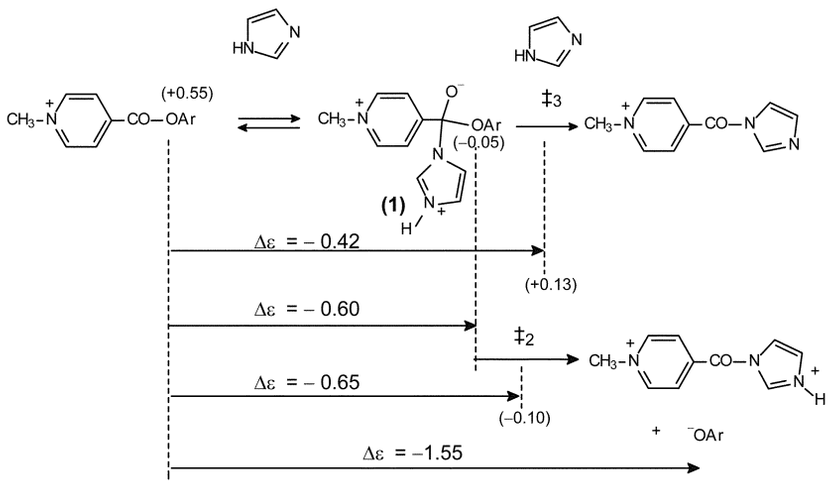
(7)

is thought to be the cause of the reaction taking a stepwise pathway[18] rather than the *concerted* route often taken by substitution reactions of phenolate ions at unsaturated centres (Eqn. (8)).[19] Guthrie and Pike calculated that the energies of the putative tetrahedral and acylium ion



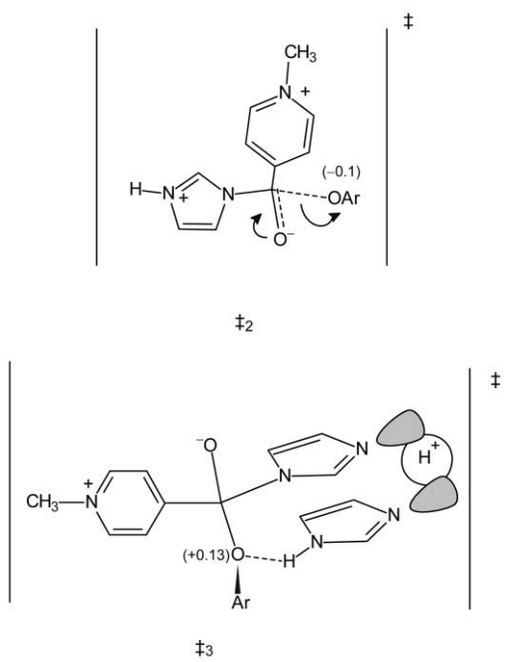
(8)

intermediates are such that the displacement of 4-nitrophenolate ion from the acetate ester by imidazole involves a transition structure close to that of the tetrahedral intermediate.[20] The present results for the *N*-methylpyridinium-4-carboxylate esters can be explained on the basis of the stepwise mechanism (Scheme 3) where the k_3 term arises from the transition state $\ddagger_3$ for proton transfer to the second imidazole with subsequent non-rate limiting ArO–C bond fission; the k_2 term corresponds to $\ddagger_2$. The effective charge map[17,21,22] of the system (derived from the Brønsted exponents, Scheme 3) shows that the leaving oxygen is more negatively charged in the transition structure $\ddagger_2$ (−0.10) than in $\ddagger_3$ (+0.13).



Scheme 3

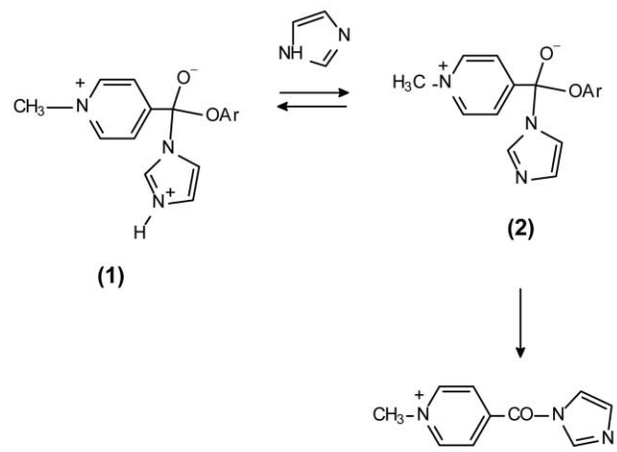
The D_2O solvent isotope effect on k_2 ($k_2^{H/D}$ = 1.51) is consistent with ‡$_2$ in Scheme 4; such values of the isotope effect (1.0–1.8) have been observed for other imidazolysis reactions where no proton transfer step is rate limiting.[5]



Scheme 4

General bases do not catalyse the imidazolysis reaction and this excludes the mechanism shown in Scheme 5 analogous to that for aminolysis by primary and secondary amines. Nevertheless, the k_3 term involves rate limiting proton transfer as evidenced by the D_2O solvent isotope effect ($k_3^{H/D}$) of 4.43. Satterthwait and Jencks[6] estimated that the change in effective charge on the ether oxygen of an aryl ester from the ester reactant to an addition intermediate (**1**) is −0.6 (Δε), indicating a build-up of charge more negative than that observed in the transition structure of the rate limiting step (Δε = −0.42). The mechanism of Scheme 5 with a rate limiting transition state *after* formation of (**1**) would *not* be expected to have a smaller build-up of negative effective charge on the aryl oxygen than that in the addition intermediate (**1**). Moreover, the mechanism for k_3 represented by Scheme 5 predicts catalysis by general bases at a level not observed for the present system.

The effective charge on the leaving oxygen in ‡$_3$ (more positive than expected in the intermediate (**1**)[6]) is consistent with a mechanism where the catalyst interacts electrophilically with



Scheme 5

the anionic leaving group. This is possible in a transition structure ‡$_3$ shown in Scheme 4 where the catalytic imidazole can remove a proton from the imidazolium NH of (**1**) as well as interacting (for example by H-bonding or proton transfer) with the phenolic oxygen. Model-building demonstrates that the stereochemistry is possible and catalysis should occur when the planes of the two imidazolyl nuclei are roughly parallel. It is possible that some advantage is achieved by a stacking interaction[23] between the two imidazolyl functions.

The proton transfer from **1** to the catalytic imidazole in ‡$_3$ cannot occur with linear geometry. The transfer involves overlap of the lone pair HOMO on the catalytic imidazole with the LUMO of the N^+–H bond in $T^{\pm}$. The diagram, ‡$_3$, in Scheme 4 illustrates a notional MO configuration for the transition structure (filled orbitals shaded and the empty orbital on the proton unshaded). Although this geometry appears to be unprecedented it is analogous to known hydrogen-bond systems where the donor–H–acceptor bonding is non-linear.[24–26] The transition structure, ‡$_3$, would involve a relatively symmetrical arrangement of the hydrogen between the nucleophilic nitrogen atoms as described in the structure in Scheme 4 and this could be considered qualitatively as an interaction between the empty σ orbital of the proton and the filled sp-orbitals comprising the lone pairs on the imidazolyl nitrogens. The proton transfer, and A_ND_N process, is analogous to the front-side nucleophilic aliphatic substitution mechanisms (S_NF) of contemporary interest.[27]

A mechanism for k_3 where the imidazole base owes its reactivity solely to stacking with the imidazolium group in (**1**) would explain the absence of catalysis by the phosphate dianion which is unable to complex by stacking. Although the preferred

model includes a stacking process the effective charge results indicate that a significant component of $\ddagger_3$ comes from an electrophilic interaction at the phenolic oxygen atom. The mechanism involving $\ddagger_3$ in Scheme 4 explains why 2,6-lutidine is not a catalyst because, although it can stack with **1** and has its lone pair available for the proton transfer, there is no electrophilic component available for interaction at the phenolic oxygen. Proton transfer at the leaving oxygen is not a reasonable activation process because consideration of the microscopic reverse mechanism reveals that attack by phenol would involve general base catalysis, an unlikely requirement under the prevailing conditions of pH.

A process where the proton transfer from **1** to catalytic imidazole is "linear" would not allow any interaction with the leaving aryl oxygen and would therefore not explain why the effective charge on the oxygen in the transition structure is more positive than that in the transition structure for the uncatalysed process ($\ddagger_2$).

Although the mechanism involving rate limiting proton transfer from $T^{\pm}$ is excluded, rate limiting attack by the imidazolium ion on $T^{\pm}$ (k_- step in Scheme 1) would give the observed rate law (k_3). The proton transfer step $T^{\pm} \longrightarrow T^{-}$ would not give rise to a substantial solvent deuterium oxide effect because it would be an equilibrium step. Thus, the observed isotope effect of 4.43 would come from k_- and indicate rate limiting proton transfer to the departing aryl oxygen leaving group. However a good leaving group such as an aryl oxide ion should not require assistance from proton transfer as indicated above.

The decomposition of **1** *via* $\ddagger_3$ does not necessarily involve concerted ArO–C bond fission and proton transfer steps. The simplest explanation is that the decomposition involves proton transfer to the catalytic imidazole in the rate limiting step and the ArO–C fission occurs in a subsequent non-rate limiting step. The effective charge on the aryl oxygen is more positive than that in k_2 due to an electrophilic interaction rather than to a bond fission process.

The termolecular term is not seen with 4-nitrophenyl esters of aliphatic acids nor with those of 4-methoxy- or 4-methylbenzoic acids and increasing the reactivity of the acyl function promotes its observation. The termolecular term provides an alternative route to direct expulsion of the phenolate anion (the k_2 term). As the acyl group becomes more reactive (electron withdrawing) the decomposition of the intermediate **1** *via* k_2 becomes less efficient (relative to k_3) because the product acylimidazolium ion becomes less stable. The proton transfer step (k_3) provides a more efficient pathway than that represented by k_2 because the initial product is the more stable acyl-imidazole (rather than acyl-imidazolium ion) product.

Bruice and Mayahi[10] showed that the ammonolysis reaction of substituted phenyl acetates has terms corresponding to general base catalysis by ammonia (k_3) and direct expulsion (k_2). The Brønsted slopes are -0.25 and -0.84 respectively; the value of -0.84 measures the change in charge from reactant to the transition structure of the $k_{\pm}$ step. The β_{Lg} of -0.25 measures the change in charge to $T^{\pm}$ although this value is very uncertain due to the paucity of data and the small spread of pK_a values. Kirsch and Kline[11] studied the ammonolysis of 4-nitrophenyl esters of substituted benzoic acids and found a value of ρ_2 (rate *via* $k_{\pm}$) (see Scheme 1) of 1.08 whereas that for k_3 (ammonia catalysed ammonolysis) is 1.84. The value of 1.84 corresponds to the formation of the $T^{\pm}$ intermediate as the proton transfer step should not depend on σ. The lower value of ρ_2 is due to the $k_{\pm}$ step being rate limiting having a transition structure with substantial carbonyl bond formation bringing the structure back closer to that of the reactant than $T^{\pm}$. The value of 1.84 is similar to that observed for the addition of nucleophiles to substituted benzoyl groups such as benzaldehydes.[28] The existence of catalysis in a termolecular term by tertiary amines precludes the mechanism described here for the ammonolysis reactions of esters.

On the basis of the arguments for the special base catalytic function of imidazole in imidazolysis of *N*-methylpyridinium-4-carboxylate esters it is reasonable to postulate a similar mechanism for the k_3 term of the acetate[5] and benzoate[3] esters.

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