Kinetics of Ester Imidazolysis in Benzene

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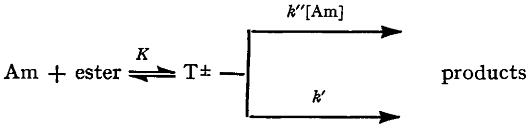
The reaction of imidazole (IM) and its 1-methyl (1-MIM) and 4-methyl (4-MIM) derivatives with *p*-nitrophenyl propionate has been investigated in benzene at 25°. Under pseudo-first-order conditions, the observed rate law is $k_\psi = k_2\,[\text{4-MIM}]^2$ and $k_\psi = k_2\,[\text{IM}]^2 + k_3\,[\text{IM}]^3$: 1-MIM is a catalyst of the reaction between 4-MIM or IM and the ester. The state of aggregation of IM and 4-MIM and the high kinetic order are taken as evidence of a main mechanism involving associated imidazole and ester to give a tetrahedral anion (paired to an imidazolium cation) as the intermediate whose breakdown is rate-limiting.

ESTER aminolysis in aprotic solvents has been the subject of several and often conflicting reports.[1-4] A unifying mechanistic theory proposed by Menger and his co-workers [2,3] suggests the operation of the mechanism shown in Scheme 1: a tetrahedral zwitterionic intermediate, T$^{\pm}$, is formed and its collapse to products with (k''[Am] route) or without (k' route) the aid of a second molecule of amine, Am, is generally the rate-limiting step. Scheme 1 accounts for the two-term rate law (1) usually observed for primary and secondary amines under pseudo-first-order conditions.



SCHEME 1

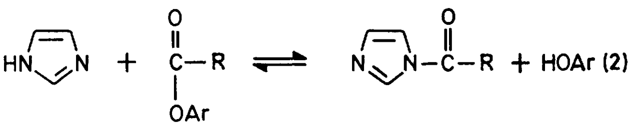
$$k_\psi = k_1[\text{Am}] + k_2[\text{Am}]^2 \qquad (1)$$

Imidazole, in spite of its enormous relevance in biochemical processes,[5] has not been investigated in much detail. Haake and his co-workers [4] have reported on the reactivity of imidazole with *p*-nitrophenyl acetate in moist ($[\text{H}_2\text{O}] = 1\text{M}$) acetonitrile where the reaction was found to obey the rate law (1), with k_1 3.1 × 10^{-3} l mol^{-1} s^{-1} and k_2 1.3 × 10^{-2} l^2 mol^{-2} s^{-1} at 30°. More recently, Menger and Vitale [3] have reported that imidazole reacts in toluene at 25° very slowly with *p*-nitrophenyl acetate and much faster (*ca.* 10^3 times for $[\text{IM}] = 1 \times 10^{-2}\text{M}$) with 2,4-dinitrophenyl acetate.

The present study, preliminary to an investigation [6] on the catalytic effects of added tetra-alkylammonium salts in the imidazolysis of esters, concerns the reactivity of imidazole (IM) and its 1-methyl (1-MIM) and 4-methyl (4-MIM) derivatives towards *p*-nitrophenyl propionate (PNPP) in benzene.

RESULTS AND DISCUSSION

The ^{1}H n.m.r. spectrum of an equimolar ($4.7 \times 10^{-2}\text{M}$) solution of IM and PNPP in deuteriobenzene after 14 days standing at 25° showed the signals of IM, PNPP, propionylimidazole (PIM), and *p*-nitrophenol present in equal amounts within the accuracy of measurement (estimated ±2—3%). No other product was detected and the spectrum remained unchanged after the solution was left at 25° for 20 more days. Thus, the reaction between IM and PNPP is described by equilibrium (2), the rate constants for the forward (aminolysis) and reverse (alcoholysis) reactions being the same under the conditions explored.



(2)

Imidazole is known to form linear self-aggregates in aprotic solvents, the association taking place by means of intermolecular hydrogen bonds. The state of aggregation of IM has been defined for acetone [7] and carbon tetrachloride [8] solutions and found to be sensitive to the nature of the solvent.

The concentration dependence of the association of IM in benzene has been here examined with the aid of ^{1}H n.m.r. spectra. The relevant features observed concern the 1-H (N–H) signal which is not detectable for $[\text{IM}] < 1 \times 10^{-2}\text{M}$ because of line broadening induced by the nitrogen quadrupole moment and becomes narrower and narrower as the concentration approaches the saturation ([IM] *ca.* $6 \times 10^{-2}\text{M}$) limits. Moreover, the signal moves to lower field strengths with increasing concentration, the change being very large as shown in Figure 1A. Figure 1A also shows the small changes observed for the signals for 4- and 5-H, a two proton doublet, and for 2-H, a triplet. The changes observed for IM in benzene are similar to those described by Joop and Zimmermann [7] for the much more soluble 4-MIM in the same solvent and range of concentrations (see Figure 1B). Since the low-field shift of the N–H signal is a very sensitive parameter related to the state of association, as discussed by the

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[1] (*a*) F. M. Menger, *J. Amer. Chem. Soc.*, 1966, **88**, 3081; (*b*) A. Sami, A. S. Shawali, and S. S. Biechler, *ibid.*, 1967, **89**, 3020; (*c*) H. Anderson, C. Su, and J. W. Watson, *ibid.*, 1969, **91**, 6090; (*d*) F. M. Menger and J. H. Smith, *ibid.*, 1969, **91**, 5346; (*e*) D. P. N. Satchell and I. I. Secemski, *J. Chem. Soc.* (*B*), 1969, 130; 1970, 1013.

[2] F. M. Menger and J. H. Smith, *J. Amer. Chem. Soc.*, 1972, **94**, 3824.

[3] F. M. Menger and A. C. Vitale, *J. Amer. Chem. Soc.*, 1973, **95**, 4931.

[4] G. Wallenberg, J. Boger, and P. Haake, *J. Amer. Chem. Soc.*, 1971, **93**, 4938.

[5] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969.

[6] F. D'Andrea and U. Tonellato, *J.C.S. Chem. Comm.*, 1975, 859.

[7] N. Joop and H. Zimmermann, *Ber. Bunsengesellschaft Phys. Chem.*, 1962, **66**, 541.

[8] D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, *J. Chem. Soc.*, 1961, 2165.

above authors,[7,9] indications are that the increase of self-association of IM and 4-MIM with increasing concentration is approximately the same: this is illustrated by the diagram of Figure 2 from data by Joop and Zimmermann.[7]

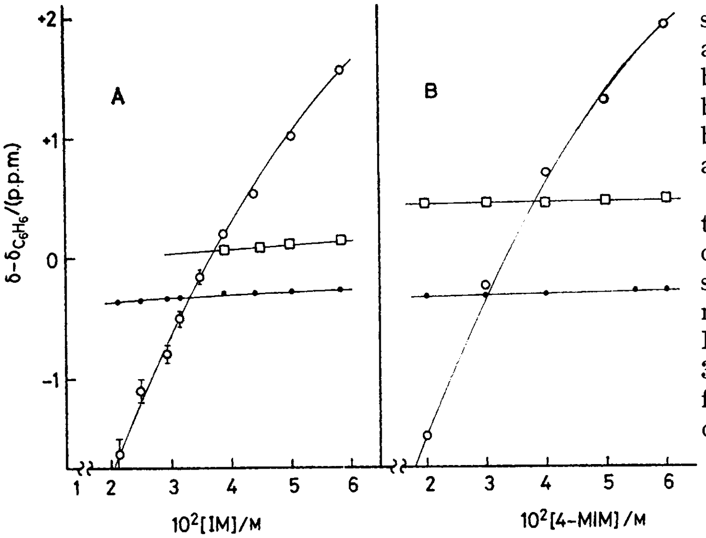

FIGURE 1 Chemical shifts of the protons of: A, imidazole (IM, 27°), and B, 4-methylimidazole (4-MIM, 23°), as a function of their concentration in deuteriobenzene: ○ H(1); □ H(2); and ● H(5) [4 (in the case of IM)]. Data for 4-MIM are taken from ref. 7 ($4-CH_3$ signals not shown)

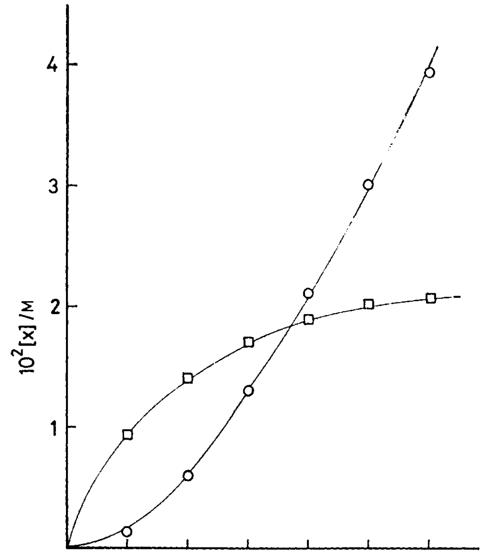

FIGURE 2 [X] = Concentration of □ monomeric and ○ associated 4-methylimidazole as a function of its total concentration $[4\text{-MIM}]_t$. Average degree of association: 2—5. Data from ref. 7

Imidazole associates with other species other than itself. This is the case of *p*-nitrophenol whose $\lambda_{max.}$ shifts from 305 to 320 nm by addition of excess of IM. The observation can be taken as an indication[10] of association through rather strong N · · · H–OAr bonds of the solute molecules. No significant spectral changes were observed for PNPP or PIM following addition of IM, although weak hydrogen bonds between this and carbonyl compounds are expected.[7] Water, although benzene and the reagents were carefully dried, cannot be disregarded as a component of the reacting system and, unfortunately, a variable one.

The rate of reaction has been measured by following the appearance of *p*-nitrophenol under pseudo-first-order conditions and the observed rate constants k_ψ were satisfactorily reproducible within a series of measurements involving a single batch of IM or 4-MIM (see Experimental section). Data are displayed in Figure 3A as a plot k_ψ/[im] *versus* [im]: a straight line is obtained for im = 4-MIM and a curved one for im = IM. In the case of 4-MIM the intercept is zero within the estimated error ($6 \pm 22 \times 10^{-5}$ s^{-1}) and the rate law (3) is obeyed. In the case of IM a plot $k_\psi/[\text{IM}]^2$ *versus* [IM] gives a reasonable straight line (see Figure 3B) and indicates that rate data fit the two-term rate law (4). The k_2 and k_3 values are in Table 1.

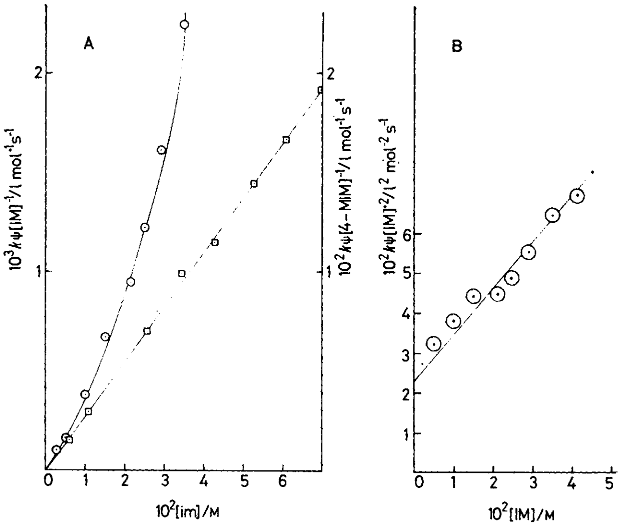

FIGURE 3 A, plot of k_ψ/[im] *vs.* [im]: im = ○ imidazole (IM), □ 4-methylimidazole (4-MIM). B, plot of $k_\psi/[\text{IM}]^2$ *versus* [IM]

Predictably, 1-MIM was inert toward PNPP in the range of concentrations used for IM, the appearance of *p*-nitrophenol from ester being measurable for solutions with [1-MIM] > 0.2M.

$$k_\psi = k_2[4\text{-MIM}]^2 \qquad (3)$$

$$k_\psi = k_2[\text{IM}]^2 + k_3[\text{IM}]^3 \qquad (4)$$

Addition of 1-MIM to either IM and 4-MIM increases the observed rate of aminolysis as shown by data of Table 2. The increase is linear with [1-MIM] at any concentration of IM or 4-MIM and the data seemingly fit the rate expressions (3) and (4) when an additional term $\{k_2'[4\text{-MIM}][1\text{-MIM}]$ to (3) and $k_2'[\text{IM}][1\text{-MIM}]$ to

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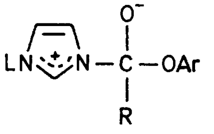
[9] N. Joop and H. Zimmermann, *Ber. Bunsengesellschaft Phys. Chem.*, 1962, **66**, 441; A. Mannschreck, W. Seitz, and H. A. Staab, *ibid.*, 1963, **67**, 470.

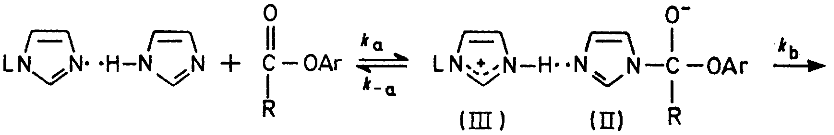
[10] J. Steigman and P. M. Lorenz, *J. Amer. Chem. Soc.*, 1966, **88**, 2083 and references therein.

(4)} is added. The k_2' values thus evaluated are in Table 1.

The absence in each case of a first-order kinetic term in the rate expression for k_ψ indicates that a tetrahedral zwitterionic intermediate (I), if formed, yields very few products: a neutral imidazole molecule would be an exceedingly better leaving group than a *p*-nitrophenolate anion in the absence of solvation. A second molecule of imidazole is required to remove the proton of (I; L = H) in a base catalysis mode consistent with the effect of 1-MIM. The life-time of the doubly charged intermediate (I) is very short in water [11,12] and, very likely, too short in benzene for a second molecule of amine to place itself in the correct position for proton transfer to take place. In view of the state of self-association of IM and 4-MIM analysed above, it is surmised that the reaction proceeds only between associated imidazole and ester and that the significant intermediate is anion (II) paired to imidazolium ion (III) (Scheme 2). It is assumed that the base catalyst is hydrogen bonded to the reactant and the intermediate and transition state are not at equilibrium with respect to proton transfer to or from other components of the solution.[13] The rate-limiting step is the collapse of (II) to amide and *p*-nitrophenolate anion as required by the huge phenol leaving group effect observed by Menger and Vitale.[3] The fact that the k_2' term for both IM and 4-MIM is approximately one-half of k_2, contrary to the observation that unhindered tertiary amines [1c,2] are just as effective as secondary amines although of different basicity, may be due to a statistical factor applied to associated 1-MIM ··· IM relative to IM ··· IM.



(I)



SCHEME 2

TABLE 1

Rate parameters, k_2, k_2', and k_3, for the imidazolysis of PNPP in benzene at 25°

	k_2/l² mol⁻¹ s⁻¹	k_2'/l² mol⁻² s⁻¹	k_3/l³ mol⁻³ s⁻¹
IM	0.022	0.011	1.15
4-MIM	0.27	0.092	

Microscopic reversibility requires that the rate-limiting step of the reverse process, *i.e.*, the reaction of *p*-nitrophenol with PIM in the presence of imidazole, is the formation of (II) paired to (III) from *p*-nitrophenolate anion and the amide with a protonated imidazolium ion as acid catalyst located at the IM end of (II). The positioning of IMH⁺ could occur, as indicated in Scheme 3, through rotation within complex (IV) before or early in the k_{-b} slow step. The transition state of the reaction following the mechanism of Schemes 2 and 3 is analogous to one suggested by Jencks and his co-workers [13,14] for the reaction of hydroxylic nucleophiles or thiols with acetylimidazole in water; it is more likely here in view of the inertness of the solvent.

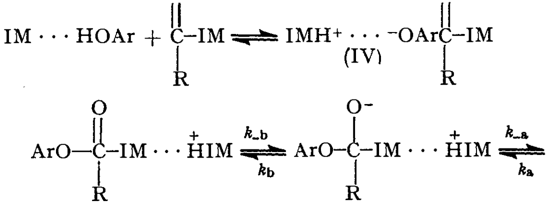
TABLE 2

Rate constants, $10^5\,k_\psi/\mathrm{s^{-1}}$, for the reaction between IM or 4-MIM and PNPP [a] in the presence of 1-MIM

10²[1-MIM]/M	10²[IM]/M		10²[4-MIM]/M	
	2.12	2.91	1.04	2.59
	2.01	4.65	2.75	18.6
1.37	2.25	5.10	3.85	21.8
2.75	2.75		5.45	23.2
5.50	3.38	6.60	8.27	31.5
6.85	3.70	7.05		33.2

[a] $[\mathrm{PNPP}]_0 = 3.75 \times 10^{-5}$M.

Schemes 2 and 3 would account for the k_2 and k'_2 kinetic terms. The k_3 term for IM indicates a process involving three molecules of imidazole in the transition state. Although there is little basis for speculation, the role of the third molecule could be that of support catalyst in the process responsible for the second-order kinetic terms. It could, as a part of a higher aggregate reacting with the ester, help in removing the proton in the k_a–k_{-a} pre-equilibrium or in switching the proton from the IM nitrogen end to the OAr oxygen of (II) in the k_b slow step. The latter hypothesis is made unlikely, again, by the leaving group effect.[3]



$$\mathrm{IM\cdots HOAr} + \mathrm{R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}IM} \rightleftharpoons \underset{\text{(IV)}}{\mathrm{IMH^{+}\cdots{}^{-}OAr\overset{\displaystyle O}{\overset{\|}{C}}{-}IM}}$$

$$\underset{\text{(IV)}}{\mathrm{ArO{-}\overset{\displaystyle O}{\overset{\|}{C}}(R){-}IM\cdots \overset{+}{H}IM}} \underset{k_b}{\overset{k_{-b}}{\rightleftharpoons}} \underset{\text{(II)}}{\mathrm{ArO{-}\overset{\displaystyle O^-}{\overset{|}{C}}(R){-}IM}}\cdots\underset{\text{(III)}}{\mathrm{\overset{+}{H}IM}} \underset{k_a}{\overset{k_{-a}}{\rightleftharpoons}}$$

SCHEME 3

The absence of a detectable third-order term in the case of 4-MIM is then to be explained. Admittedly, solutions of 4-MIM could contain more water than those of IM since the former is a highly hygroscopic substance. It

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[11] A. C. Satterthwait and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 7018 and references therein.

[12] W. P. Jencks, *Chem. Rev.*, 1972, **72**, 705.

[13] W. P. Jencks and K. Salvesen, *J. Amer. Chem. Soc.*, 1971, **93**, 1419.

[14] D. G. Oakenfull, K. Salvesen, and W. P. Jencks, *J. Amer. Chem. Soc.*, 1971, **93**, 188.

has been verified that for 4-MIM not carefully dried and handled there is a decrease in reactivity and mixed first- and second-order kinetics [equation (1)]. Thus, water diminishes both the over-all rate and the order in imidazole and this is probably one factor responsible for the low order in IM [equation (1)] observed by Haake and his co-workers[4] in moist acetonitrile. On the other hand, it has been generally observed[13,15] that the relative importance of catalysed and uncatalysed reactions of carbonyl compounds decreases with increased nucleophile basicity and this could be the case for 4-MIM (pK_1 7.45[16]) relative to IM (pK_1 6.95[17]). A third-order term of the magnitude of that observed for IM (Table 2) would be barely detectable in the case of 4-MIM since it is masked by a 12-fold k_2 term.

The closer (than any amine) analogues to imidazole investigated in ester aminolysis in aprotic solvents are benzamidine[1a] and THP (1,4,5,6-tetrahydropyrimidine)[1c] in terms of the structural and steric implications discussed by Ciuffarin *et al.*[18] Both imidines react smoothly with *p*-nitrophenyl acetate in chlorobenzene by a first-order rate law, $k_\psi = k_1$[imidine], at least in dilute solution (THP in the 10^{-4}M range[1c]) where association is probably unimportant (see Figure 2). Stronger bases (by at least 3 pK units) than IM, they seemingly react by way of rate-limiting formation of a tetrahedral intermediate.[18] These facts point to the large variety of kinetic manifestations, as a result of the mechanistic flexibility, expected for ester aminolysis in aprotic solvents.

EXPERIMENTAL

Reagent grade benzene and [$^2H_6$]benzene (99.5% isotopic purity) were refluxed over and distilled from calcium hydride onto Linde type 5A sieve and stored under nitrogen. Imidazole (IM) was crystallized from benzene, 4-methylimidazole (4-MIM) purified by triple sublimation, and 1-methylimidazole (1-MIM) by fractional distillation under reduced pressure; their purity was ascertained by standard criteria and they were dried over P_2O_5 *in vacuo* or under reduced pressure for at least one day before use. 4-MIM was transferred when needed in a glove bag.

p-Nitrophenyl propionate, m.p. 61—62° (lit.,[19] 62°) τ (C_6D_6) 2.18, 2.33, 3.16, and 3.42 (4 H, ArH), 7.95 (2 H, q, *J* 7.8 Hz), and 9.11 (3 H, t), and propionylimidazole, m.p. 38—39° (lit.,[20] 38°), τ (C_6D_6) 2.43 (1 H), 3.03 (1 H), 3.06 (1 H), 8.34 (2 H, q, *J* 7.3 Hz), and 9.25 (3 H, t), were prepared by described procedures.

^{1}H N.m.r. spectra were recorded on a Bruker FT-WP 60 MHz instrument at 27°.

Kinetics.—Typically, 2.00 ml of a solution of imidazole (or its derivatives) were equilibrated at 25° for 20 min in the thermostatted cell compartment of a Gilford 2400 spectrophotometer. A benzene solution (20 μl) of ester was then added ([PNPP]$_0$ 1—3 × 10^{-5}M) and the increase in absorbance at 320 nm recorded until the reaction was over. The k_ψ constants were obtained by applying the integrated first-order kinetic law which was well obeyed up to at least 80% reaction. For dilute solutions of IM and 4MIM (<0.01M) the rate constants were determined by the initial rate method following a careful determination of the extinction coefficient of *p*-nitrophenol in the kinetic solution. Data in Figure 3 are the average values of at least a duplicate measurement.

Rate constants were reproducible to ±3% within a series of measurements involving a single batch of IM or 4-MIM and to ±10% when two different batches of IM were used.

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[6/1521 *Received, 3rd August,* 1976]

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[18] E. Ciuffarin, L. Senatore, and L. Sagramora, *J.C.S. Perkin II*, 1973, 534.

[19] S. Kreisky, *Acta Chem. Scand.*, 1957, **11**, 913.

[20] K. Kindler, *Chem. Ber.*, 1956, **89**, 1938.