# Kinetics of the Reaction of Imidazole with Benzoyl Fluoride in Acetonitrile: a Mixed Third and Fourth Order Reaction

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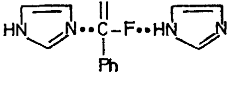
*Summary* The reaction of imidazole with benzoyl fluoride in acetonitrile to give *N*-benzoylimidazole is first-order in benzoyl fluoride and of mixed second and third order in imidazole.

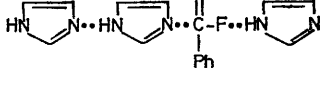
THE occurrence of histidine in the active site of serine esterases has led to extensive studies of reactions of imidazole with carboxylic acid derivatives.[1] These reactions in aqueous solution are generally first or second order in imidazole, representing a bimolecular nucleophilic displacement, general base assistance of the attack of water by imidazole, or general base catalysis of the attack of imidazole by imidazole. Similar studies in dipolar aprotic solvents are scarce, but it appears that aminolysis reactions in aprotic solvents are generally first or second order in amine.[2–5]

We report that the reaction of imidazole with benzoyl fluoride in acetonitrile, to give *N*-benzoylimidazole, is second and third order in imidazole (see Table). With imidazole in excess each run at a particular imidazole concentration showed good first-order kinetics. A plot of the observed first-order rate constant, $k_{\text{obs}}$, against imidazole concentration, [Im], is concave upwards as is a plot of $k_{\text{obs}}/[\text{Im}]$ *vs.* [Im]. A plot of $k_{\text{obs}}/[\text{Im}]^2$ *vs.* [Im] is linear, however, with a positive intercept. The rate law in acetonitrile is thus given by equation (1). A first-order

$$\text{Rate} = (k_3[\text{Im}]^2 + k_4[\text{Im}]^3)\ [\text{PhCOF}] \qquad (1)$$

term in imidazole is not experimentally detectable. Least squares treatment of $k_{\text{obs}}/[\text{Im}]^2$ *vs.* [Im] with the data in the Table gives $k_3 = 0{\cdot}208 \pm 0{\cdot}016$† $\text{l}^2\ \text{mol}^{-2}\ \text{s}^{-1}$ and $k_4 = 2{\cdot}23 \pm 0{\cdot}24\ \text{l}^3\ \text{mol}^{-3}\ \text{s}^{-1}$ ($r = 0{\cdot}992$) at 25 °C. Values at other temperatures are, for $k_3/(\text{l}^2\ \text{mol}^{-2}\ \text{s}^{-1})$: 0·117 (5 °C), 0·159 (15 °C), 0·244 (33 °C), and 0·317 (40 °C) which give an apparent $\Delta H^{\ddagger} = 4{\cdot}2 \pm 0{\cdot}5$ kcal mol$^{-1}$ and $\Delta S^{\ddagger} = -48$


(A)


(B)

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† All ± values represent 90% confidence intervals.

± 2 cal deg$^{-1}$ mol$^{-1}$ and for $k_4$/(l$^3$ mol$^{-3}$ s$^{-1}$): 1·74 (5 °C), 2·02 (15 °C), 2·25 (33 °C), and 2·94 (40 °C), which give an apparent $\Delta H^\ddagger = 1{\cdot}6 \pm 1{\cdot}1$ kcal mol$^{-1}$ and $\Delta S^\ddagger = -51 \pm 4$ cal deg$^{-1}$ mol$^{-1}$.

TABLE

Observed first-order rate constants[a] for the reaction of imidazole with benzoyl fluoride[b] in acetonitrile[c] at 25 °C.

| Imidazole/M | $10^3 k_{\mathrm{obs}}$/s$^{-1}$ |
|---|---|
| 0·0100 | 0·0221 |
| 0·0200 | 0·106 |
| 0·0427 | 0·540 |
| 0·0683 | 1·71 |
| 0·0853 | 2·86 |
| 0·0900 | 3·40 |
| 0·100 | 4·23 |

[a] Measured spectrophotometrically at 265 nm, estimated precision ±3%. [b] Concentration of PhCOF *ca.* $1 \times 10^{-4}$M. [c] Treated with CaH and fractionally distilled from $P_2O_5$.

The results show that benzoylation of imidazole by benzoyl fluoride in acetonitrile occurs by mechanisms where the rate-determining transition states contain the acid fluoride and two or three imidazole molecules. The term second-order in imidazole could represent general base catalysis of imidazole attack by imidazole or rate-determining imidazole-catalysed breakdown of a tetrahedral intermediate.[2] The third-order term could indicate a linear trimer of imidazole in the transition state since imidazole forms linear complexes in aprotic solvents,[6] or general base catalysis with a third imidazole molecule hydrogen-bonded either to fluorine or to the carbonyl oxygen. A rate determining breakdown of a tetrahedral intermediate with a transition state containing three imidazole molecules could also be envisaged.

Although imidazole forms linear complexes in carbon tetrachloride[6] this seems less likely in acetonitrile. Preliminary measurements[7] of heats of dilution also militate against any significant self-association of imidazole in acetonitrile at concentrations below 0·1M. On this basis, and the fact that solvolytic reactions of acid fluorides, but not chlorides, are acid-catalysed,[8] we prefer the transition-state structures (A) and (B), and come to no definite conclusion as to tetrahedral intermediate formation or the nature of the rate-determining step. The mechanism corresponding to the third-order term must have one or more equilibria before the rate-determining step. The apparent fourth-order constant $k_4$ (and probably $k_3$) is thus a composite quantity, which explains the low apparent $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values.

Finally, the third-order term in imidazole is absent in 95% MeCN–5% $H_2O$ and in propanol the reaction is only first-order in imidazole,[7] results which illustrate the importance of hydrogen bonding in the transition state for aminolysis reactions.[5,9]

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