Intramolecular Catalysis in the Acylation of Amidoximes

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Summary Amidoximes are highly reactive towards *p*-nitrophenyl acetate, benzoyl fluoride, and ethyl chloroformate in the pH range 6—9, the catalytic action increasing with the lability of the leaving group.

ALTHOUGH the concept of bifunctional catalysis was established[1] by the strong catalytic action of 2-pyridone on the mutarotation of glucose, surprisingly few examples of a similar nature are known, particularly of reactions in aqueous solution. According to a recent investigation,[2] several reports of this type of action in the literature are incorrect.

We report the remarkable reactivity of amidoximes in the pH range 6—9 towards *p*-nitrophenyl acetate, benzoyl fluoride, and ethyl chloroformate (Table). Oximes and hydroxamic acids are known to be very reactive in the anionic form towards carbonyl and phosphoryl compounds. Amidoximes, which have similar reactivities to oximes at high pH, are highly reactive in the neutral form, the overall pseudo-unimolecular rate constants k being given by the expression

$$k = k_a[\mathrm{AO}]\left[\frac{K_H}{K_H + [\mathrm{H^+}]} - \frac{K_A}{K_A + [\mathrm{H^+}]}\right] + k_b[\mathrm{AO}]\left[\frac{K_A}{K_A + [\mathrm{H^+}]}\right]$$

where k_a and k_b are the rate constants for the reaction of the neutral form and ionic form, respectively, K_H is the equilibrium constant for the protonation of the amidoxime of total concentration [AO], and K_A is its ionisation constant. The pH–rate profiles for the reaction of several amidoximes with *p*-nitrophenyl acetate are compared with that of benzaldoxime in Figure 1. Rate constants (in terms of total nucleophile concentration) are given as $l.mole^{-1}min.^{-1}$.

By analogy with amidines,[3] the imino-nitrogen atom of the amidoxime is probably the more basic than the amino-group, and since the catalytic action leading to the high

reactivity in neutral solution involves proton migration, two alternative reaction mechanisms can be envisaged.

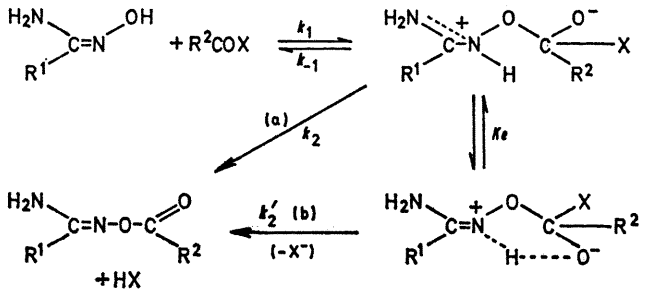

TABLE 1

Comparison of the rates of acylation of benzamidoxime and benzaldoxime at pH 7·0

Reactant	EtOCOCl[a]	PhCOF[b]	$MeCO_2 \cdot C_6H_4 \cdot NO_2$-*p*[c]
Benzaldoxime	2·42	1·22	1·59
Benzamidoxime	2,100	903	5·28
Relative reactivity	870	740	3·3

[a] Water at 5°; [b] 55% H_2O—45% acetone (v/v) at 5°; [c] water at 25°.

Rate constants (in terms of total nucleophile concentration) are given as l. $mole^{-1}$ $min.^{-1}$.

The present results do not differentiate between an intramolecular general base catalysis involving concomitant nucleophilic attack of oxygen on carbonyl [path (a)] which has been suggested in several reactions, *e.g.* the catalytic action of Tris buffer,[6] and hydrogen bonding to the carbonyl oxygen atom (path b) as in the reaction of fluorophosphates with catecholate ions.[5]

The reactions of amidoximes are similar to the rapid *O*-acylations of hydroxylamine,[4] which Jencks and Carriuolo[6] originally explained by intramolecular general base catalysis [*cf.* mechanism (a)]. More recently Jencks[7] has suggested the alternative mechanism [type (b)].

We find that the rate constants for the reactions of several amidoximes and hydroxylamines are related logarithmically to the basicity of the neutral reagents (Figure 2). The large slope ($\alpha = 0{\cdot}85$) suggests that the proton is almost completely transferred from the OH group to the nitrogen atom in the transition state.†

The relative reactivity of amidoxime and oxime varies with the structure of the acylating agent (Table). Although these differences may be due in part to the different reaction conditions unavoidably used, the large difference in the catalysis of the reaction of the chloroformate and *p*-nitrophenyl ester cannot be attributed to this factor. We explain the change in relative reactivity by the lability of the leaving group[8] X, which is expected to increase with acidity of X. Thus according to the above reaction scheme

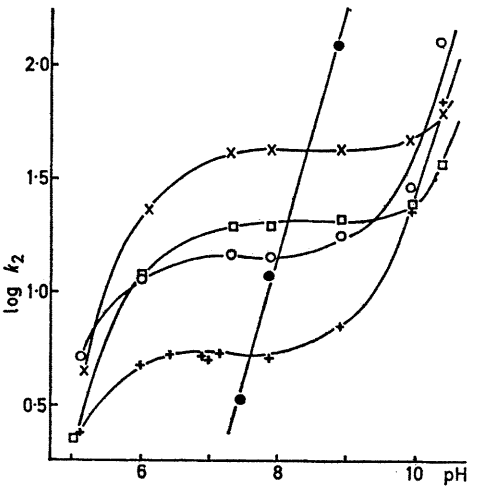

FIGURE 1. *The* pH*–rate profile for the reactions of* p*-nitrophenyl acetate in water at* 25° *with benzamidoxime*(+); *acetamidoxime* (×); *formamidoxime* (○); *NN-diethylbenzamidoxime* (□); *and benzaldoxime* (●).

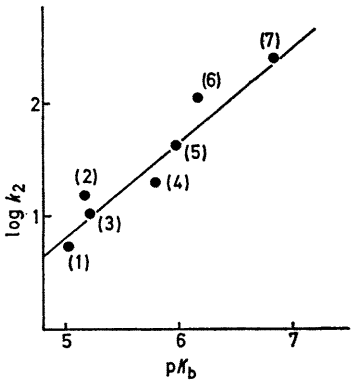

FIGURE 2. *Relationship between log* k_2 *and* pK_b *for protonation on the following reactants*: (1) *benzamidoxime*; (2) *formamidoxime* (3) N-*dimethylhydroxylamine*; (4) N-*diethylbenzamidoxime*; (5) *acetamidoxime*; (6) *hydroxylamine*; (7) N-*diethylacetamidoxime*.

assuming mechanism (a), for the halides $k_2 > k_{-1}$, but for the esters $k_2 < k_{-1}$. Since the catalysis influences both forward and backward reactions, partitioning in a tetrahedral intermediate will reduce the overall catalytic effect, and for this reason the observed catalysis may be very small for molecules with poor leaving groups.

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† This may explain the low deuterium isotope effect observed by Jencks (ref. 6) in the reaction between hydroxylamine and *p*-nitrophenyl acetate.

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