Evidence Against Bifunctionality of Benzamidine

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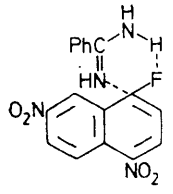
Summary Evidence is presented which is against the reported bifunctionality of benzamidine.

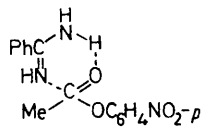
THE reactivity of benzamidine has recently aroused interest because of its assumed relevance to the mechanism of enzyme activity.[1-3] The structure of benzamidine is such

that cyclic transition states can be envisaged where the imino nitrogen acts as the nucleophilic atom, while the amino group catalyses the reaction electrophilically. Thus, benzamidine was believed to be bifunctional in its reactions with 4-fluoro-1,6-dinitronaphthalene[2] and *p*-nitrophenyl acetate[1] in aprotic solvents, as shown in (I) and (II) respectively.

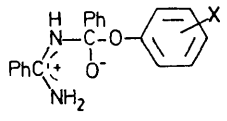
The concept of bifunctional reactivity assumes the formation of concerted transition states so that separation of charges is minimized. This would explain the much higher reactivity of benzamidine as compared to that of n-butylamine with the same substrates.[1,2] The reactions of benzamidine are normally first order[1,2,4] which is in accordance with the requirement of a concerted transition state.



(I)



(II)



(III)

We investigated the reactivity of benzamidine with a series of benzoate esters in MeCN. Analysis of the data (Table) indicates that benzamidine is probably not bifunctional. The order of reaction is higher than unity for the reactions with phenyl and *p*-methoxyphenyl benzoates. The rate law consists of two terms: rate/[substrate] $= k_1$[benzamidine] $+ k_2$[benzamidine]^2. The second term accounts for *ca.* 50% of the total rate of reaction at 0·1 M concentration of nucleophile for the *p*-methoxy derivative. Thus, a significant fraction of the reaction proceeds with the participation of two molecules of benzamidine in the transition state. This part of the reaction cannot be interpreted in terms of a single, concerted transition state and must be accounted for by a two-step mechanism.†

The first-order (in benzamidine) term in the rate equation might still be interpreted in terms of bifunctional catalysis. However, the low rate associated with the first-order term indicates that a non-concerted mechanism is much more likely and that both terms in the rate equation are much more easily explained by the usual addition–elimination mechanism which is well established for other aminolyses of esters in aprotic solvents.[5] The first term of the rate equation represents the uncatalysed expulsion of the leaving group from the intermediate, not a concerted reaction. In fact, assumption of a concerted reaction implies a high rate of reaction which would obscure any other catalysed, two-step mechanism.

TABLE. Rate constants for reactions of substituted phenyl benzoates, $PhCO_2C_6H_4X$, with benzamidine and n-butylamine.[a]

Reactant	X	k_1/l mol^{-1} s^{-1}	k_2/l^2 mol^{-2} s^{-1}
Benzamidine	*p*-NO_2	0·81	—
"	*m*-NO_2	0·31	—
"	*p*-Cl	$2·0 \times 10^{-2}$	—
"	*m*-Cl	$5·3 \times 10^{-2}$	—
"	None	$1·5 \times 10^{-3}$	$2·7 \times 10^{-3}$
"	*p*-MeO	$2·2 \times 10^{-4}$	$2·1 \times 10^{-3}$
n-Butylamine	*p*-NO_2	$6·7 \times 10^{-2}$	—
"	*p*-MeO	$2·8 \times 10^{-6}$	$5·1 \times 10^{-6}$

[a] In MeCN at 25°C, substrate 10^{-4} M.

The suggestion that a concerted mechanism might apply to other more reactive esters whose reactions do not lead to a term in the rate equation which is second order in benzamidine (see Table) must also be discounted. A Hammett plot of the second-order rate constant (k_2) is linear with $\rho = 3·3$. This indicates that all esters react with the same mechanism. Moreover, the relative reactivities of benzamidine and n-butylamine in MeCN are not very different. The reactivity ratio varies from *ca.* 10 for *p*-nitrophenyl benzoate to *ca.* 130 for *p*-methoxyphenyl benzoate at 0·1 M concentration of nucleophile.

Thus, the exceptional reactivity of benzamidine found in some cases cannot be ascribed to its bifunctionality but, as previously suggested,[4] to the delocalisation of the positive charge of the zwitterionic intermediate (III), which thus becomes more stable with a lower tendency to revert to reactants.

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† The second order in nucleophile cannot be explained with a pre-equilibrium formation of more reactive dimer, as has been suggested for other aminolyses. Benzamidine would in fact form an unreactive cyclic dimer.

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