Esterolytic Reactivity of Carboxylate Ion–Imidazole Pairs in Benzene

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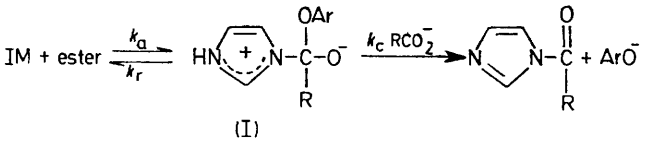
Summary Cetyltrimethylammonium propionate greatly accelerates the imidazolysis of *p*-nitrophenyl propionate in benzene; carboxylate ion–imidazole pairs are indicated as the effective catalytic species.

WE report kinetic evidence of the effective role of propionate ion–imidazole pairs in the esterolysis of *p*-nitrophenyl propionate (PNP) in benzene. The catalytic mode of co-operation is analogous to that proposed[1] for the Asp-102 carboxylate and the His-75 imidazole residues, in a region inaccessible to water (solvent) molecules, in the 'charge-relay' mechanism of α-chimotrypsin and related enzymes.[2]



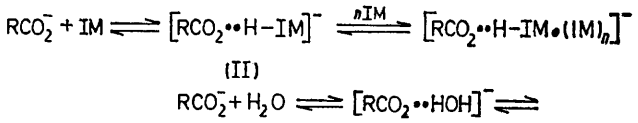
(I)

SCHEME 1

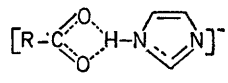
Our results confirm recent reports that the benzoate anion of tetralkylammonium salts is a very effective catalyst in the reaction between imidazole (IM) and *p*-nitrophenyl acetate in acetonitrile[3] and toluene.[4] The observed effect has been explained[4] as shown in Scheme 1 where the anion, by removing the proton from the cationic component of (I) favours the partitioning of the intermediate to products. The corresponding rate (equation 1) was obeyed in toluene, at least under the conditions $[RCO^-_2] > [IM]$.

$$k_{obs} = k_a[IM]k_c[RCO_2^-]/(k_r + k_c[RCO_2^-]) \quad (1)$$

Our data indicate that the above Scheme is inadequate in some significant respects. We have investigated the effects of cetyltrimethylammonium propionate $Me_3(C_{16}H_{33})N^+ EtCO_2^-$ (CTAP) on the reaction between IM and PNP in benzene at 25 °C. In the absence of CTAP the reaction is very slow: the observed rate constants measured by following the appearance of *p*-nitrophenol are in the range $0{\cdot}28—3{\cdot}8 \times 10^{-6}$ s^{-1} for $[IM] = 0{\cdot}25—1{\cdot}0 \times 10^{-2}$M. Addition of CTAP to solutions of IM up to [CTAP] = *ca.*[IM] causes a rate increase which is linearly dependent only on [CTAP]. The effect is smaller when a measured amount of



(II)

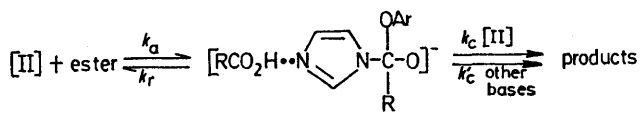


(II)

SCHEME 2

water is added to the solvent as shown in the Figure. Addition of IM to solutions of constant [CTAP] increases the observed rate up to [IM] = *ca.* [CTAP]; further addition is no longer effective or causes a decrease in the reactivity of the system as shown in the Figure (conditions C and D).

These and other results can be reasonably explained in terms of strongly hydrogen bonded ion–molecule aggregates.[5] Carboxylate anions can hardly be viewed as 'bare' ions in a hydrocarbon solvent containing hydrogen bonding agents, *e.g.* imidazole or water and, besides ion-pair aggregations, equilibria of the type shown in Scheme 2 must be considered. The ion–molecule (II) is apparently the most effective nucleophilic or basic species in the system probably owing to the partial anionic character of the external nitrogen. Scheme 3, although only approximate, may account for the major observed effects.



SCHEME 3

The approximate steady state rate expression, under the conditions [CTAP] < [IM] are given by equation (2) which, assuming k_c[II] > k_r, becomes $k_{obs} = k_a$[II], independent

$$k_{obs} = k_a k_c [II]^2/(k_r + k_c[II]) \quad (2)$$

of the excess of ([IM] − [CTAP]) imidazole concentrations.

Scheme 3, while avoiding unlikely charge separation during the k_a step, emphasizes the co-operation between the unsolvated carboxylate anion and imidazole in the absence of other factors such as binding, orientation, and proximity effects important in determining the activity of enzymes.

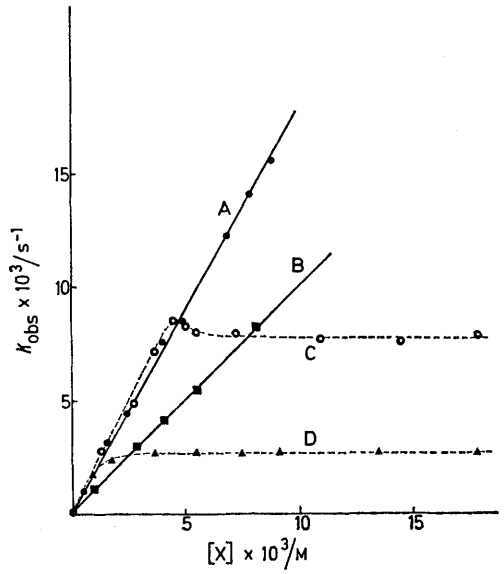


FIGURE. ● A:X = CTAP, [IM] = 1·95 × 10^{-2}M, [H_2O] = *ca.* 2—3 × 10^{-3}M. ■ B:X = CTAP, [IM] = 1·95 × 10^{-2}M, [H_2O] = *ca.* 12 × 10^{-3}M. ○ C:X = IM, [CTAP] = 4·5 × 10^{-3}M, [H_2O] = *ca.* 2—3 × 10^{-3}M. ▲ D:X = IM, [CTAP] = 1·0 × 10^{-3}M, [H_2O] = *ca.* 2—3 × 10^{-3}M. [PNP] = 5·4 × 10^{-5}M in all cases. Kinetics were measured by following the appearance of *p*-nitrophenol at 410 nm (325 nm when [CTAP] < 0·6 × 10^{-3}M) and, occasionally, from the disappearance of PNP at 290 nm a few seconds after mixing of the reagents to completion.

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