Neighbouring Carboxylate Group Participation in Ester Aminolysis in Non-hydroxylic Solvents. The n-Butylaminolysis of Aspirin in Acetonitrile

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Summary In acetonitrile the carboxylate group of aspirin anion has been found to assist the n-butylaminolysis of the neighbouring ester function with a mechanism changing from nucleophilic to concomitant nucleophilic and probably general base catalysis as the amine concentration is increased.

THE problem of neighbouring group participation in acyl transfer processes is of primary importance for it is relevant to an understanding of the mechanism of enzyme catalysis.[1] However, while detailed studies have been carried out in hydroxylic solvents, apparently less attention has been devoted to non-hydroxylic solvents, although these appear to be suitable media for enzyme model studies.[1,2]

As a part of our investigation on the role played by a neighbouring carboxy-group in the aminolysis of an ester function in a non-hydroxylic solvent,[3] we report here results for the n-butylaminolysis of aspirin and its corresponding methyl ester (*o*-CPAM) in acetonitrile at 25 °C. Kinetic data are reported in the Figure. Decrease in the

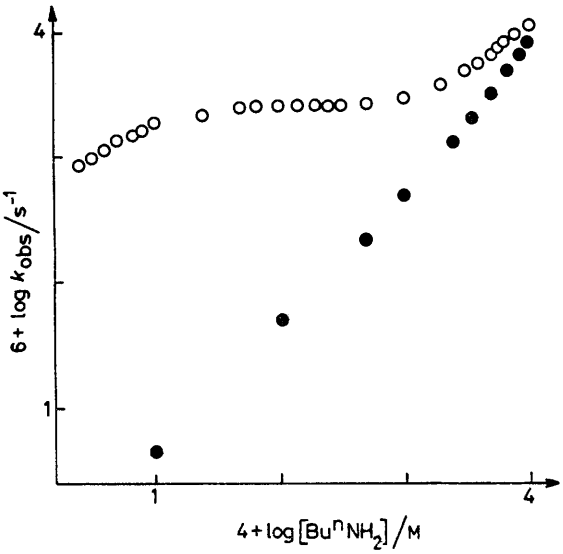
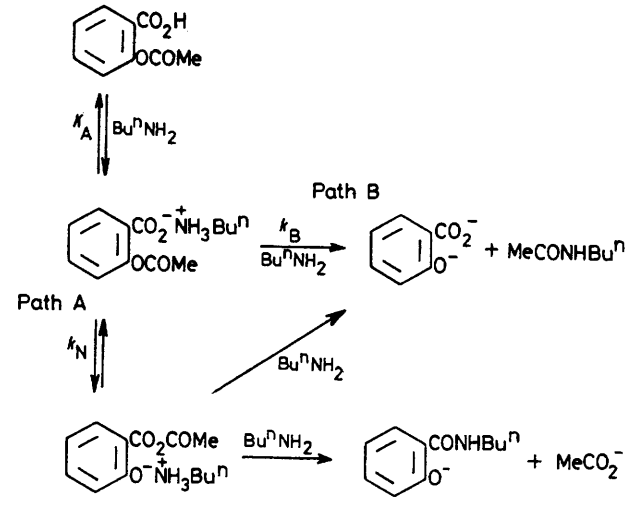


FIGURE. Plot of log k_{obs} *vs.* log [Bu^nNH_2] for the n-butylaminolysis of aspirin (open circles) and *o*-CPAM (filled circles) in acetonitrile at 25 °C. k_{obs} is the pseudo-first-order rate constant determined by following spectrophotometrically (u.v.) phenol release (at 296 nm for aspirin and at 305 nm for *o*-CPAM).

amine concentration causes a gradual decrease in the reactivity of *o*-CPAM, according to the two-term rate-law in equation (1). In contrast, the reactivity of aspirin

$$k_{obs} = 4{\cdot}33 \times 10^{-3}[Bu^nNH_2] + 3{\cdot}07 \times 10^{-3}[Bu^nNH_2]^2 \quad (1)$$

decreases gradually in the range 1—0·1 M and below 5×10^{-3} M, and is independent of amine concentration in the range 5×10^{-3}—0·1 M (plateau region). In the light of these results, the aminolysis of *o*-CPAM seems to occur through the stepwise mechanism proposed by Menger and his co-workers[4] for ester aminolysis in aprotic solvents,† whereas the reaction of aspirin seems to proceed *via* a completely different mechanism. We suggest that the first step in the aminolysis of aspirin involves a fast acid–base reaction followed by intramolecular attack by the carboxylate group on the neighbouring ester function to give salicylic acetic anhydride (Scheme; path A); this, following further fast attack of a second amine molecule, would lead to the products. At [Bu^nNH_2] < 0·1 M this is the only mechanism operating. At [Bu^nNH_2] > 0·1 M the intramolecular nucleophilic pathway competes with a new process involving direct attack of the amine on the ester function assisted by the neighbouring carboxylate group probably acting as general base (Scheme; path B).



SCHEME

The following evidence supports the anhydride mechanism with rate-determining anhydride formation. (a) The presence of a plateau in the rate profile can be reasonably explained only in terms of a complete displacement to the right of the first equilibrium (at amine concentration > 5×10^{-3} M) and rate-determining intramolecular attack of carboxylate on the ester function. (b) If salicylic acetic anhydride is formed during the reaction, *N*-n-butylsalicylamide would be expected to be one of the products.‡ In fact, control experiments, carried out with [aspirin] = $5{\cdot}3 \times 10^{-4}$ M and [Bu^nNH_2] = 0·01 M, showed that *N*-n-butylsalicylamide is formed in *ca.* 6% yield (high-pressure liquid chromatography).[5] (c) Given the low acidity of the phenol group[6] of the mixed anhydride, only a limited amount of anhydride should exist in unprotonated form. This supports the hypothesis of rate-determining anhydride formation, which requires that the intermediate anhydride should react more rapidly with Bu^nNH_2 than it reacts intramolecularly with the phenolic oxygen atom to regenerate starting material. It is also likely that at low amine concentration the slow step is anhydride formation and that the rate decrease observed below 5×10^{-3} M depends on a decrease in the concentration of the ionized form of aspirin rather than on a change in the rate-determining step (*i.e.* attack of amine upon the anhydride). A rapid change in the u.v. spectrum when Bu^nNH_2 is added to aspirin prior to the measured reaction supports this hypothesis.§

At [Bu^nNH_2] > 0·1 M, the following considerations suggest a direct attack of amine upon the ester function with probable base catalysis by the neighbouring carboxylate group.

† Cyclic mechanisms leading directly to products have been proposed alternatively by other authors [D. P. N. Satchell and I. I Secemski, *J. Chem. Soc.* (*B*), 1969, 130] to account for some experimental results in the aminolysis of esters in non-hydroxylic solvents

‡ Theoretically, the anhydride and then the salicylamide could also be formed by direct attack of salicylic acid (in the ionized form) upon *N*-n-butylacetamide, but this hypothesis was ruled out by a control experiment carried out under conditions similar to those for the kinetic ones.

§ At 270·5 nm (isosbestic point of the aminolysis reaction) a 12% decrease in absorbance occurs when an equimolar amount of n-butylamine is added to aspirin.

(a) The reaction is first order in amine. (b) The value of the second order rate constant ($k = 9 \times 10^{-3}$ l mol^{-1} s^{-1}) is about twice that for aminolysis of *o*-CPAM, despite the unfavourable σ-values of substituent in the leaving group.[4,7¶]

A comparison of these results with those obtained in water[7,8] illustrates the striking difference in the mechanism of aminolysis of aspirin between a non-hydroxylic and a hydroxylic solvent.[9] One of the main reasons responsible for this different behaviour might be the increased nucleophilicity of the carboxylate group compared to amine due to the dramatic change of the relative acidity of the two groups on going from water to acetonitrile solvent.[6]

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¶ Actually, these facts furnish direct evidence of base catalysis only if free ions are involved in the reaction mechanisms; if ion pairs are formed in the first equilibrium other types of catalysis (ref. 4) cannot be discounted at present.

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