Intramolecular Nucleophilic Attack on a Carbamate System by the Ionized Carboxy-group

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Summary Hydrolysis of phenyl *N*-(*o*-carboxyphenyl)-carbamate is rapid and involves direct nucleophilic displacement by the CO_2^- group with the formation of an isatoic anhydride intermediate.

CARBAMATES with good leaving groups have recently been shown[1,2] to be hydrolysed by a base-catalysed elimination mechanism and the intermediate isocyanates formed have been trapped by suitable reagents both inter- and intramolecularly.[1] Hydrolysis by direct HO^- (or H_2O) attack on the carbamate, which occurs when the isocyanate pathway is blocked by *NN*-disubstitution, is far (up to 10^8-fold) less rapid.[1,3] We now report the first example of ready nucleophilic attack on this deactivated acyl system.

The hydrolysis of $PhNHCO_2Ph$ (**1**) in aqueous solution to aniline and phenol is rapid only at high pH; in this region the observed rate is proportional to $\{HO^-\}$ (Figure). At low pH (**1**) is essentially stable under these conditions. In contrast the *N*-(*o*-carboxyphenyl) analogue (**2**; R = Ph) reacts rapidly (as judged by the rate of phenol release) (Figure). The log k_{obs} *vs.* pH profile for this compound

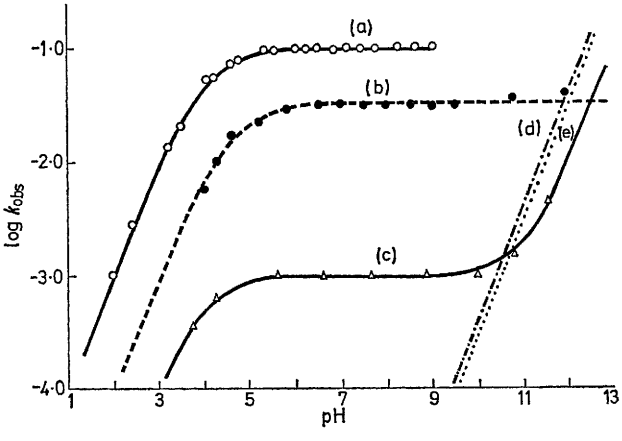
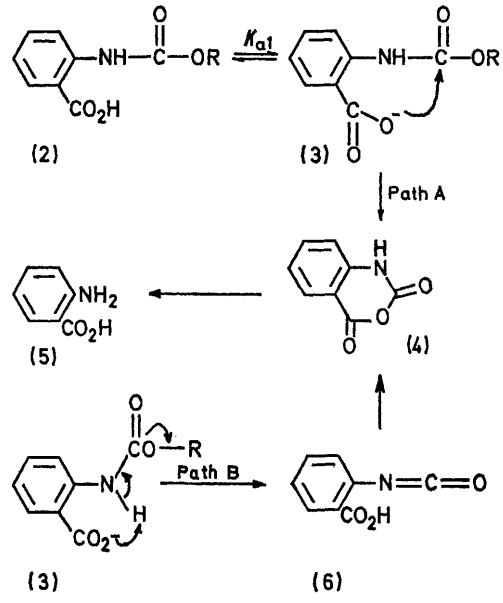


FIGURE. *Plot of log of observed rate constants* (s^{-1}) *measured in* 4:1 *water–dioxan at* 25° (μ = 1·0, KCl) vs. pH *for* (a) (**2**; R = p-$NO_2C_6H_4$), (b) *phenyl* N-*methyl*-N-(o-*carboxyphenyl*)*carbamate*, (c) (**2**; R = Ph), (d) *phenyl* N-*phenylcarbamate*, *and* (e) *phenyl* N-(p-*carboxyphenyl*)*carbamate*.

shows a large plateau region (*ca.* pH 4—10) where the observed rate is independent of pH. At pH 4 it can be calculated that the presence of the *o*-carboxy-group enhances phenol release *ca.* 10^6-fold.

The anionic species (**3**) is the major one present in the plateau region and the decrease in rate in acid solution coincides with its conversion into the unreactive protonated form (**2**). This can be deduced from the empirical equation used to correlate the observed rate constants, $k_{obs} = k_1[K_a/(K_a + a_H)] + k_2\{HO^-\}$, where for (**2**; R = Ph), $k_1 = 1{\cdot}0 \times 10^{-3}$ s^{-1}, $k_2 = 1{\cdot}0$ l mol^{-1} s^{-1}, and $K_a = 1{\cdot}06 \times 10^{-4}$. Since the p$K_a$ of methyl *N*-(*o*-carboxyphenyl) carbamate is 4·26 then clearly it is not unreasonable that K_{a1} (see Scheme) = K_a. In basic solution (**3**; R = Ph) is



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hydrolysed by the normal *E*1*cB* mechanism, the *o*-CO_2 group slowing the overall rate three-fold (presumably by destabilizing anion formation on the adjacent nitrogen).

The enhanced reactivity shown by (**3**) is only apparent when the carboxy-group is adjacent to the carbamate linkage. Thus the *p*-CO_2H analogue of (**2**) [phenyl *N*-(*p*-carboxyphenyl)carbamate] is hydrolysed in a manner exactly analogous to (**1**) (see Figure); no rapid phenol release is observed at low pH. The pH independent plateau observed for (**3**) cannot therefore be due merely to an electronic effect (assuming that transmission of these effects from the *o*- and *p*-positions would be similar). Also phenyl *N*-(*o*-ethoxycarbonylphenyl)carbamate shows only *E*1*cB* reactivity.

Of the three most likely modes of carboxy-group involvement in hydrolysis of (**3**), intramolecular general base catalysis of H_2O attack can be ruled out. The solvent deuterium isotope effect, $k(H_2O)/k(D_2O) = 1{\cdot}2$, is inconsistent with the involvement of water in the transition state[4] and moreover isatoic anhydride (**4**) is an intermediate in the reaction pathway. The anhydride (**4**) is itself further hydrolysed to anthranilic acid (**5**) in basic solution[5] but its presence can be detected by isolation and/or spectrophotometric determination over the entire pH range studied.

A mechanism involving direct intramolecular nucleophilic attack by the ionized carboxy-group (Path A, Scheme) is favoured rather than Path B, general base catalysis of proton removal from the neighbouring NH group involving formation of an isocyanate intermediate (**6**), which would rapidly cyclize to (**4**). The *N*-methyl analogue of (**2**) [(**7**)] is also hydrolysed rapidly at pH > 4 ($k_1 = 3{\cdot}3 \times 10^{-2}$; $k_2 \sim 0$; $K_a = 2{\cdot}18 \times 10^{-5}$) (Figure). In this compound reaction *via* Path B is blocked and since *N*-methylisatoic anhydride is formed as an intermediate in this case it is thus likely that both materials, (**2**; R = Ph) and (**7**), react *via* the same pathway, *i.e.* A.

Replacement of phenoxide by the better leaving group *p*-nitrophenoxide (**2**; R = *p*-$NO_2C_6H_4$) causes a 10^2-fold rate enhancement in the conversion of (**3**) into (**4**) (Figure). Similarly, introduction of a poorer leaving group (**2**; R = Me) causes a large rate depression. This suggests that the rate-determining step in the plateau region may be loss of the leaving group from a tetrahedral intermediate. The sensitivity to leaving group variation observed for cyclization of (**3**) is however markedly less than in the *E*1*cB*-type elimination.[1]

Several examples exist of enzymatically-catalysed biological reactions in which nucleophilic attack at the carbamoyl group apparently occurs.[6] The present work demonstrating the rapid cyclization of (**3**) to (**4**) provides a model for these reactions.

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