Isocyanate Intermediates in *Elcb* Mechanism of Carbamate Hydrolysis

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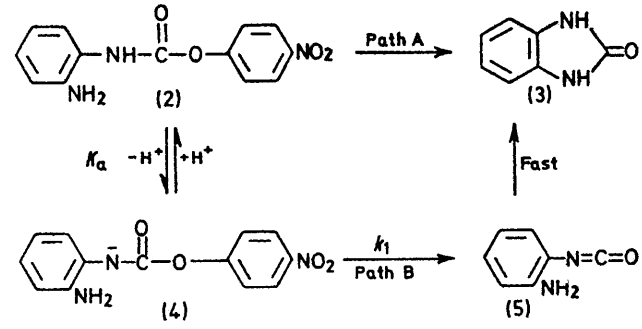
Summary Both the use of external and internal traps and the substituent effects support the formation of an isocyanate intermediate in carbamate hydrolysis.

THE mechanisms of both hydrolytic cleavage and nucleophilic attack on simple *N*-monosubstituted carbamates ($R^1NHCO_2R^2$, **1**) have been controversial, direct attack ($B_{Ac}2$) and prior elimination followed by addition of the nucleophile being suggested.[1] The presence or absence of an isocyanate intermediate ($R^1{-}N{=}C{=}O$) is the feature which distinguishes these mechanisms.

As part of a study of amino-group reactions with deactivated acyl systems, we have examined the role of the amino-group in the carbamate (**2**). In this case the nucleophile and the carboxy-group are close, thus facilitating (relative to the bimolecular case) direct attack by the amine.

The hydrolytic product obtained from (**2**) over a wide pH range was the cyclic urea (**3**). Unexpectedly, however, the rate of formation of the urea (**3**) was, even at low pH, first-order in [HO^-]. Thus a plot of log k_{obs} *vs.* pH [over the pH range 5—8 in 4:1 water–dioxan at 25°, μ = 1·0 (KCl)] is linear with unit slope. This kinetic behaviour is inconsistent with the direct involvement of the amino-group



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as a nucleophile (Path A, Scheme) since in this pH region the amino-group is unprotonated and the carbamate is present almost entirely as the neutral species (**2**).

Of the two mechanisms† consistent with the observed kinetic data, Path B, (Scheme) which involves the intermediate formation of a reactive isocyanate (**5**) is favoured. Direct S_N2 displacement of p-$NO_2C_6H_4O^-$ by HO^- (or *via* a tetrahedral intermediate) would lead to the formation of a different product, 1,2-diaminobenzene. The latter compound would be formed on ready decarboxylation of the unsubstituted carbamate, o-$NH_2C_6H_4NHCO_2H$.

The cyclisation of (**2**) to (**3**) is *ca.* eight times more rapid than the rate of hydrolysis of the p-amino-isomer (**1**; $R^1 = p$-$NH_2C_6H_4$, $R^2 = p$-$NO_2C_6H_4$). This is not a specific effect for (**2**) since all *ortho*-substituted carbamates show this pattern, being more readily hydrolysed than the unsubstituted parent compound (independent of whether the o-substituent is electron-withdrawing or donating). Thus the pH–rate profiles for the o-substituted carbamates (**1**; $R^1 = o$-XC_6H_4, $R^2 = p$-$NO_2C_6H_4$) are similar to that for (**2**) with $10^3 k_{obs}$ (s^{-1}) = 3·98 (X = H), 13·8 (MeO), 31·6 (Me), 41·0 (NH_2), 178 (Br) (at pH 6·5 in 4:1 dioxan–water at 25°, μ = 1·0).

The isocyanate intermediate may also be effectively trapped by an external nucleophile. The presence of p-chloroaniline at pH 7 does not cause (within experimental error) an increase in the rate of reaction of the carbamate (**1**; R^1 = Ph, $R^2 = p$-$NO_2C_6H_4$). Yet the product isolated from the reaction was shown to be *ca.* 98% *N*-phenyl-*N'*-(p-chlorophenyl)urea. The absence of a rate enhancement demonstrates that the reaction of the aniline did not occur with the carbamate substrate and supports the involvement a reactive isocyanate intermediate (PhNCO in this case) on the reaction pathway.

The effect of substituents in R^1 and R^2 on hydrolysis are also consistent with the elimination (*Elcb*) mechanism (Path *B*, Scheme), showing a close similarity to those reported for ester hydrolysis *via* keten intermediates.[2] Hydrolysis is very sensitive to the nature of the leaving group in the carbamates (**1**; R^1 = Ph, $R^2 = XC_6H_4$); thus the Hammett ρ +3·17 (r 0·989) for 6 *m*- and *p*-substituents (using a σ^- value for X = p-NO_2). Even allowing for the fact that k_{obs} (at a given pH) is a composite constant involving K_a and k_1 (Scheme) this value represents considerable acyl oxygen bond cleavage in the transition state. On the other hand, substitutents attached to nitrogen (**1**; $R^1 = XC_6H_4$, R^2 = Ph) have a small effect, ρ +0·64 (r 0·990) for **5** substituents. Apparently a substituent in this case which increases K_a causes a decrease in k_1 with little resultant effect on k_{obs}.

NN-Disubstituted carbamates (which cannot form isocyanate intermediates) are far less reactive (up to 10^8-fold in k_{obs}, dependent on substituents present) than their *N*-monosubstituted analogues. Substituent effects confirm that in this case an alternative mechanism (presumably direct HO^- attack) is operative. Thus, sensitivity to the leaving group (in $PhNMeCO_2C_6H_4X$ hydrolysis) is small (ρ *ca.* +1·3). It is interesting that a change in sensitivity to the nature of the leaving group of similar magnitude also accompanies the change in ester hydrolysis mechanism from *Elcb* to nucleophilic attack.[2]

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† Other possible mechanisms, *e.g.* HO^- catalysis of NH_2 attack, will be dealt with in the final report.

[1] See D. A. Woodcock, *Chem. Comm.*, 1968, 267; P. Adams and F. A. Baron, *Chem. Rev.*, 1965, **65**, 567, and references therein.
[2] R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5957; L. R. Fedor and W. R. Glave, *ibid.*, 1971, **93**, 985.