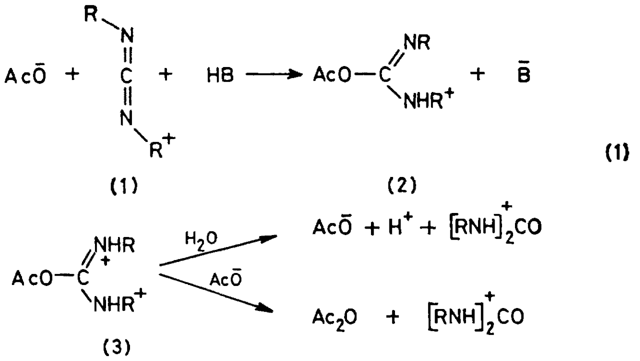
Concerted General Acid Catalysis in the Reaction of Acetate Ion with Water-soluble Carbodi-imide

By Ibrahim T Ibrahim and Andrew Williams*
(*University Chemical Laboratories, Canterbury, Kent* CT2 7NH)

Summary An intermediate, identified as an *O*-acetylisourea, is observed spectroscopically in the reaction of a water-soluble carbodi-imide with acetate buffers, a stepwise mechanism for intermediate formation as currently accepted is excluded by the observation of general acid catalysis, while acetate ion attack on carbodi-imide is concerted with proton transfer, and monoanions of dicarboxylic acids react with carbodi-imide with intramolecular concerted proton transfer

Carbodi-imides have been used for over two decades in dehydration and peptide coupling reactions,[1a] it is now well established that an *O*-acylisourea intermediate is formed and then reacts with further acid to yield anhydride, the major acylating species [1b,c] Previous work on the analogous isocyanate, isothiocyanate, carbon disulphide, and carbon dioxide species in water indicates a stepwise addition of nucleophile followed by proton transfer [2]

We demonstrate here the formation of an intermediate with properties consistent with an *O*-acetylisourea (**2**) which is formed by concerted attack of acetate ion and a general acid on the carbodi-imide (**1**) This finding is contrary to previous postulates of protonation prior to attack of the carboxylate [1c,3] This communication reports the first observation of an intermediate in carbodi-imide mediated dehydrations and the novel concerted mechanism of addition



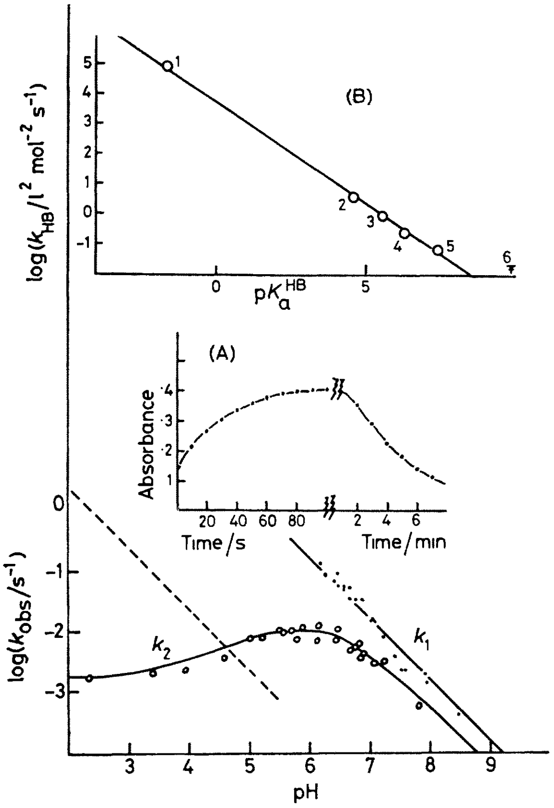


FIGURE. Dependence on pH of the reaction of (**1**) with aqueous acetate buffers at 1 M. Conditions: 25 °C, ionic strength made up to 1 M with KCl. Formation of intermediate: k_1; decomposition of intermediate: k_2. The lines are theoretical from the equations in the text and the parameters: pK_a, 6·8; $k(H_2O)$, $0{\cdot}00176\ s^{-1}$; k_{AcO^-}, $0{\cdot}00794\ l\ mol^{-1}\ s^{-1}$; k_{HOAc}, $3{\cdot}5\ l^2\ mol^{-2}\ s^{-1}$; k_H, $8{\cdot}16 \times 10^4\ l^2\ mol^{-2}\ s^{-1}$; the dashed line is theoretical for the hydrolysis of the carbodi-imide (1) in the absence of buffers, ref. 7. Calculations from the above parameters show that at pH 6·86 in the absence of added general acid (HB) and at AcO^- at 1 M the third order term (k_{HOAc}) takes some 60% of the total reaction flux.
Inset A: Time course of the absorbance (250 nm) for the reaction of (**1**) at 0·004 M in 1 M sodium acetate at pH 6·86; the base line represents the absorbance at infinite time; the absorbance has been 'backed-off' by 0·4 units. The line is theoretical from data for k_1 and k_2.
Inset B: The Brønsted relationship of k_{HB} versus pK_a^{HB}; the line is theoretical with slope −0·67. **1**, H^+; **2**, AcOH; **3**, *N*-propargylmorpholine hydrochloride; **4**, *N*-chloroethylmorpholine hydrochloride; **5**, *N*-methylmorpholine hydrochloride; **6**, trimethylamine hydrochloride (upper limit).

We followed the reaction of (**1**) ($R = Et$, $R^+ = CH_2CH_2CH_2\overset{+}{N}Me_3$) with aqueous buffers using a spectrophotometer set at 250 nm; an intermediate is observed (Figure inset A) and we dissected the consecutive reactions to give formation (k_1) and decay (k_2) pseudo first order rate constants. Buffering of the reaction medium at pH values outside the capacity of the acetic acid–acetate buffer was effected using a machine† which delivered acid or base to a stirred reacting mixture in the 2·5 ml u.v.-cell in the cell compartment of the spectrometer. The products of the reaction are urea and acetic anhydride which decomposes to acetic acid rapidly under the prevailing conditions. The O→N acyl group shift to yield *N*-acetylurea is shown by titration studies on the product to constitute < *ca.* 2·5% of the total reaction.

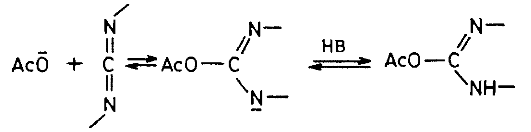
We interpret the kinetics to indicate that the unstable intermediate is the *O*-acetylisourea; the pH-dependence of k_2 and its dependence on total acetic acid buffer concentration may be fitted to a reaction scheme (equation 1) where

$$k_2 = (k_{H_2O} + k_{AcO^-}[AcO^-])/(1 + K_a/a_H) \qquad (2)$$

$$k_1 = k_{HB}[HB][AcO^-] \qquad (3)$$

water and acetate ion act on the proposed *O*-acetylisouronium cation (equation 2). The kinetically determined pK_a value from equation 2 (6·8) is in the region expected for ionisation of an *O*-acetylisouronium dication (**3**). It is possible to estimate the pK_a of a model of (**3**) namely $PhCO\text{-}O\text{-}C(NH_2)_2^+$ using Charton's equation ($pK_a = 11{\cdot}01\ \sigma_I + 13{\cdot}17$);[4a] the value σ_I for PhCO-O- (0·43) is estimated from the pK_a of benzoylglycolic acid[4b] using Charton's method.[4c] The correlation is not very reliable ($r = 0{\cdot}815$)[4c] and the estimated pK_a (8·43) is judged to possess an error which may encompass the kinetically determined value (6·8). The lower observed value is also partly due to the electrostatic effect of the positively charged side chain in (**3**) which is not allowed for in the Charton type calculations. Pratt and Bruice[4d] find a pK_a value of 8—9 for the *S*-benzoylisothiouronium salts. Since *S*-methylisothiouronium and *O*-methylisouronium salts have similar pK_a's (Charton)[4a] a monocationic *O*-acetylisouronium species would be expected to have a pK_a in the 8—9 region confirming the above predictions. The *O*-benzoylisouronium salt isolated by Hegarty and co-workers[4e] has a structure which does not allow comparisons to be made on pK_a values.

The formation step (k_1) is catalysed by general acids and follows the rate law of equation (3) where HB = AcOH, H^+, or HB. The observation of a Brønsted relationship (inset B) with slope considerably less than unity and covering a large pK_a range is consistent with proton transfer concerted with nucleophilic attack of the acetate ion on the carbodi-imide. Further evidence for this conclusion is the observation of a solvent D_2O isotope effect of $k_{HB}/k_{DB} = 2{\cdot}33$ when the acid *N*-methylmorpholine hydrochloride is employed. The kinetically equivalent mechanisms represented by $k[B][AcOH]$ may be excluded because the only function of the base could be to remove the proton from acetic acid; at the pH's in question this is not necessary.



(4)

(**4**) (**2**)

If the initially formed intermediate (**2**) had a $pK_a < pK_w$ and a stepwise mechanism were operating (equation 4) then general acid catalysis would be observable but the Brønsted plot would conform to the classical 'Eigen' type.[5] Since

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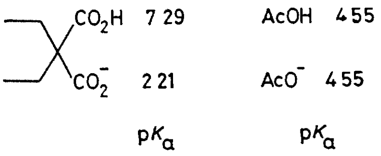
† Details of this device will be presented in a forthcoming paper.

the pK_a of (**2**) → (**4**)‡ is expected to be greater than pK_w, acid catalysis should not be observed if equation (4) were the pathway taken Even if proton transfer from water was not predominant equation (4) would yield a Brønsted α-value of zero Pre-equilibrium protonation of the carbodi-imide followed by rate limiting acetate ion attack as previously proposed[1c,3] is not consistent with general acid catalysis, the mechanism with rate-limiting proton transfer to the carbodi-imide followed by acetate ion attack predicts kinetics which would be zeroth order in acetate ion concentration.

The pK_a of (**2**) → (**4**) is estimated to be well in excess of the pK_a's of the catalytic acids which are larger than that of the conjugate acid of the carbodi-imide;§ thus Jencks' rule[6] indicates that a concerted mechanism is possible which, in this case, provides a less energetic pathway than the stepwise one Stepwise proton transfer occurs in the reaction of anilines with the water-soluble carbodi-imide (no catalysis is observed) because the stability of the addition complex analogous with (**4**) is increased by its zwitterionic character Acid catalysis is not observed owing to the pK_a of the zwitterion being greater than pK_w whereas in the attack on isocyanate 'Eigen' type acid catalysis is seen [2b]

A corollary of the observation of the third order term (k_{HB}) is that intramolecular catalysis should be observed with carboxylate nucleophiles bearing acid functions 2,2-Diethylmalonic acid monoanion reacts with carbodi-imide (**1**) with a second order rate constant $8{\cdot}0 \times 10^{-2}$ l mol^{-1} s^{-1}; unlike the acetate reaction, that of the malonate is insensitive to added acids Comparison with the termolecular rate constant for acetate (k_{HOAc} in equation 3)[7] and allowing for the different reactivity of the malonate, nucleophile and internal acid leads to an effective molarity of 23 M, this value is well within the range expected for comparison of inter- and intramolecular proton transfers [8]

A direct comparison of the rate constant for malonate and acetate is not possible because the nucleophiles and acids have different pK_a's and hence different electronic reactivities We may calculate the expected difference due to



ΔpK_a^{HB} using $\alpha = -0{\cdot}67$, the reaction of a series of carboxylates with (**1**) using *N*-propargylmorpholine as HB has a $\beta_{Nuc} = +0{\cdot}50$ and this is used to estimate the effect of $\Delta pK_a^{RCO_2H}$ For a bifunctional species with nucleophile and acid possessing pK_a 4·55 the bimolecular rate constant is calculated to be 81 l mol^{-1} s^{-1} compared with the termolecular term 3·5 l^2 mol^{-2} s^{-1}.

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‡ The pK_a's of neutral amidines are resonably expected to be in excess of pK_w because those for the corresponding amidinium ions are in the range 9·7—13 9, (ref 4b).

§ There are no precise estimates of the pK_a of protonated carbodi-imides but our kinetic work on the hydrolysis indicates a value less than zero

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[7] I T Ibrahim and A Williams, *J Amer Chem Soc* , 1978, **100** 7420, an important error is noted in this paper attack of acetate (1 M) buffer on the soluble carbodi imide (**1**) at pH 5 4 has a rate constant of 0 63 s^{-1} instead of the quoted 1 6 $\times$ 10^{-3} s^{-1}

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