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The base-catalysed cyclisation of phenyl *N*-(2-hydroxybenzyl)-*N*-methylcarbamates is concerted

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The kinetics of the cyclisation in aqueous solution of phenyl-(2-hydroxybenzyl)-*N*-methylcarbamates to 3-methyl-3,4-dihydrobenzo[*e*][1,3]oxazin-2-ones and phenolate ions fit the rate law:

$$k_{obs} = k_c/(1 + [H_3O^+]/K_a)$$

The values of k_c and pK_a fit Brønsted equations against the pK_a's of the corresponding free phenols but the system does not conform to the *reactivity–selectivity* hypothesis. The values of the Brønsted parameters β_Y and β_X vary as a function of Y and X according to the equations:

$$\beta_X = -0.179pK_a^{HY} + 0.87$$

$$\beta_Y = -0.179pK_a^{HX} + 2.30$$

The magnitude and sign of the Cordes–Thornton cross-interaction coefficient p_{XY} (−0.179) rule out a stepwise mechanism involving a tetrahedral intermediate and is consistent with a concerted displacement mechanism. A similar concerted mechanism is proposed for the base-catalysed cyclisation of phenyl-*N*-(2-hydroxyphenyl)-*N*-methylcarbamate esters to benzoxazol-2-ones.

Introduction

The study of intramolecular reactions provides a useful tool to investigate the mechanisms of fundamental reactions because the structure and geometry of the interaction between functional groups in intramolecular reactions can be defined more precisely than in the corresponding intermolecular processes. Intramolecular reactions, especially those involving nucleophilic displacements, are usually faster than the corresponding intermolecular ones by many orders of magnitude;[1] because of this it is possible to study bimolecular processes which would otherwise not be possible due to their poor reactivity.

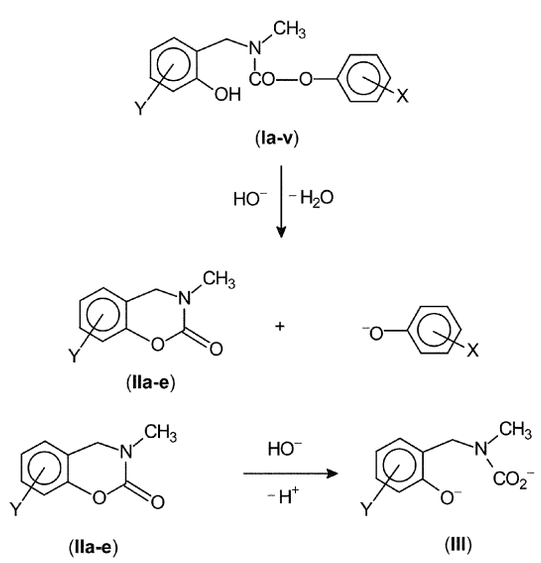
Carbamate esters possess acyl groups highly deactivated by resonance with the adjoining nitrogen; hydroxide ion reacts with 4-nitrophenyl-*N*-methyl-*N*-phenylcarbamate some 2×10^4 times more slowly than with 4-nitrophenyl acetate.[2,3] A fast intramolecular reaction is therefore an ideal vehicle for the study of the carbamoyl group transfer process.[4] The rapid intramolecular reaction would not be complicated by competitive intermolecular reaction with hydroxide ion. The present study exploits the cyclisation of X-(substituted)phenyl-*N*-[2-hydroxy-Y-(substituted)benzyl]-*N*-methylcarbamate esters (**Ia**–**v**) in alkaline solution followed by hydrolysis of the intermediate benzoxazinone (**II**) to give (**III**).

The cyclisation reaction has the advantage that the charge on both forming and breaking bonds can be studied by variation of Y or X respectively. The methylene group between benzene nucleus and the nitrogen reduces the influence of the substituents Y on the electrophilic reactivity of the carbamate group (*via* the nitrogen atom) which would otherwise complicate the interpretation of substituent effects on the displacement reaction.

Experimental

Materials

Buffer components were of analytical reagent grade and were used without further purification. Both NaOH and buffer solutions were prepared with water distilled from glass and free of CO_2. All solutions for kinetics were degassed before use. Compounds (**Ia**–**v**) and (**IIa**–**e**) (Table 1 and Scheme 1) were from previous studies.[5]



Scheme 1 (see Table 1 for the identities of the substrates).

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Table 1 Reactivity of **I** and **II** as a function of X and Y

	X	Y	$10^3 k/s^{-1}$	pK_a	$-\log k_{obs}$ [f]	pH [ag]	λ/nm [k]	N [h]	pK_a^X [i]	pK_a^Y [i]
Ia	H	H	1.26	9.98	2.82–3.92 [c]	8.49–13.30 [bd]	297	10	9.99	9.99
Ib	4-Cl	H	6.31	9.90	2.15–3.10	8.62–11.70	294	10	9.38	9.99
Ic	3-Cl	H	15.8	9.86	1.79–3.22	8.32–12.39 [b]	294	8	9.02	9.99
Id	3-NO_2	H	70.8	9.78	1.12–2.45	8.32–12.87 [b]	393	10	8.35	9.99
Ie	4-NO_2	H	275	9.70	0.53–2.47	7.53–12.87 [b]	400	9	7.14	9.99
If	H	5-Br	0.40	9.46	3.32–4.18	8.49–11.70	301	9	9.99	9.34
Ig	4-Cl	5-Br	1.26	9.40	2.93–3.77	8.32–11.70	303	10	9.38	9.34
Ih	3-Cl	5-Br	3.16	9.39	2.48–3.43	8.32–11.70	302	9	9.02	9.34
Ii	3-NO_2	5-Br	19.9	9.26	1.67–5.51	7.53–11.62	395	9	8.35	9.34
Ij	4-NO_2	5-Br	89.1	9.02	1.02–2.37	7.53–11.13	401	9	7.14	9.34
Ik	H	4-Cl	0.25	9.17	3.57–4.28	8.32–11.13	296	8	9.99	9.02
Il	3-Cl	4-Cl	1.26	9.05	2.87–3.37	8.32–11.13	275	8	9.02	9.02
Im	3-NO_2	4-Cl	7.94	8.91	2.08–2.53	8.32–11.13	244	8	8.35	9.02
In	4-NO_2	4-Cl	39.8	8.76	1.36–2.22	7.53–11.13	401	9	7.14	9.02
Io	H	4-NO_2	0.126	8.42	3.92–4.50	6.98–11.13	400	8	9.99	8.35
Ip	3-NO_2	4-NO_2	2.24	8.23	2.66–3.45	6.98–10.05	262	9	8.35	8.35
Iq	4-NO_2	4-NO_2	12.6	8.00	1.87–2.51	7.25–10.05	401	8	7.14	8.35
Ir	H	5-NO_2	0.063 [e]	7.36	4.23–4.63	6.70–10.05	414	8	9.99	7.14
Is	4-Cl	5-NO_2	0.080 [e]	7.31	4.08–4.46	6.70–10.05	412	8	9.38	7.14
It	3-Cl	5-NO_2	0.11 [e]	7.24	3.94–4.54	6.50–10.05	416	8	9.02	7.14
Iu	3-NO_2	5-NO_2	0.158	7.16	3.76–4.20	6.52–10.05	409	8	8.35	7.14
Iv	4-NO_2	5-NO_2	0.56	7.01	3.23–3.62	6.70–10.30	406	8	7.14	7.14
		$k_{OH}/M^{-1}\,s^{-1}$		pK_a^{ArOH} [j]						
IIa	H	0.033		9.99			290			
IIb	6-Br	0.055		9.34			301			
IIc	7-Cl	0.035		9.02			297			
IId	7-NO_2	0.125		8.35			392			
IIe	6-NO_2	0.235		7.14			400			

[a] Buffers employed in the pH-ranges were: 0.05 M HPO_4^{2-}, 0.025 M borate, 0.1 M 2-amino-2-(hydroxymethyl)propane-1,3-diol buffer and 0.05 M $H_2PO_4^-$. [b] NaOH solutions employed for the higher pH's. [c] Values of rate constants in NaOH solution were calculated from data using the consecutive two step equation. [d] Values of pH in NaOH were calculated from log[HO^-]. [e] Extrapolated from rate constants measured in the range 47–67 °C. [f] Range of observed rate constants. [g] Range of pH values employed in the kinetics. [h] Number of data points. [i] pK_a of the phenol corresponding to the substituent X or Y. [j] pK_a of the phenol corresponding to the leaving group in (**II**). [k] Wavelength for kinetic studies.

Methods

Ultraviolet-visible spectra were scanned with a Hewlett-Packard 8453 Diode Array Spectrometer. Buffer pH values were determined with an MV 870 Apparatus (VEB Pröcitronic) and a combined glass and silver electrode calibrated with standard aqueous buffers. The ionisation constants of esters (**I**) with reactivities less than 5×10^{-3} s^{-1} were determined spectroscopically[6] in phosphate, borate and carbonate buffers.

Kinetics were followed by injecting solutions of substrate (20 μL) in methanol into 2.5 mL buffer or NaOH solution in 1 cm silica cuvettes in the thermostatted cell compartment of the spectrometer. Initial substrate concentrations were between 2×10^{-5} M and 3×10^{-5} M in the cuvette . The spectrum was scanned repetitively to obtain the optimum wavelength for kinetic study. Absorbance at constant wavelength was measured as a function of time and was analysed according to a first order rate law ($A_t = A_\infty - (A_\infty - A_0)\exp(-kt)$). Data were fitted to theoretical equations by use of standard software.

Product analysis was carried out by comparing the UV spectra (after *ca.* 5–7 half lives) with the spectra of authentic samples (**II**) under the same conditions.

Results

Product analysis showed that the reaction involves formation of intermediate benzoxazinones (**II**) followed by their slow hydrolysis to (**III**) as in Scheme 1. In cases where the intermediate decomposes to final acid product at rates commensurate with its formation the rate of its decomposition was demonstrated to be the same as that of an authentic sample of the benzoxazinone (**II**) under the same conditions of pH.

The kinetics of cyclisation of carbamates (**Ia**–**v**) to (**II**) exhibited excellent pseudo-first-order kinetics over the ranges of pH shown in Table 1 except in the case where the leaving group is phenolate or 4-chlorophenolate ion (see later). The rate constants are independent of the nature and concentration of the buffer components (excepting the concentration of HO^-). The benzoxazinones (**IIa**–**e**) decompose slowly in NaOH solutions to give the carbamate salts (**III**) (Scheme 1). The hydrolysis of (**II**) did not interfere with the determination of the cyclisation rate constant except for X = H or 4-Cl when in some cases a biphasic progress curve was observed diagnostic of a two-step mechanism (Fig. 1). In those cases the rate constants for **I** ⟶ **II** and **II** ⟶ **III** were obtained from the biexponential equation:

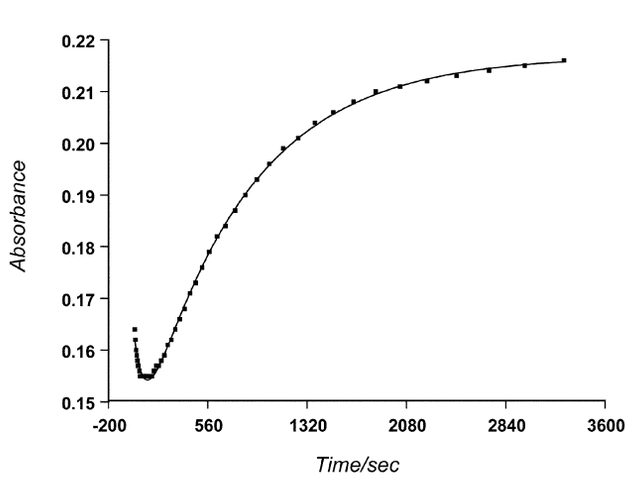


Fig. 1 Progress graph at single wavelength (297 nm) showing formation and decay of the intermediate (**IIa**) at pH 13.34 from **Ia**. (example shown is calculated from parameters in Table 1 and assuming A_0 is 0.146, A_∞ is 0.217, A_B is −0.0549, $k_1 = 0.00126$ s^{-1} and $k_2 = 0.0134$ s^{-1}).

Table 2 Brønsted and Leffler parameters for the cyclisation of **I**.[a]

$\beta_{X(Lg)}$	α_X[b]	$\log k_c^H$	r[c]	Y	pK_a^Y[d]
−0.82 ± 0.10	0.46	5.34 ± 0.84	0.9801	H	9.99
−0.85 ± 0.08	0.47	5.15 ± 0.69	0.9876	5-Br	9.34
−0.79 ± 0.07	0.44	4.32 ± 0.61	0.9923	4-Cl	9.02
−0.705 ± 0.040	0.39	3.17 ± 0.34	0.9984	4-NO_2	8.35
−0.34 ± 0.03	0.19	−0.908 ± 0.30	0.9850	5-NO_2	7.14
$\beta_{Y(Nuc)}$	α_Y[b]	$\log k_c^H$	r[c]	X	pK_a^Y[d]
0.44 ± 0.07	0.24	−7.46 ± 0.61	0.9645	H	9.99
0.635 ± 0.10	0.35	−8.67 ± 0.88	0.9882	4-Cl	9.38
0.723 ± 0.10	0.40	−9.21 ± 0.89	0.9816	3-Cl	9.02
0.932 ± 0.02	0.52	−10.45 ± 0.18	0.9993	3-NO_2	8.35
0.945 ± 0.05	0.53	−9.92 ± 0.42	0.9963	4-NO_2	7.14

[a] Parameters are for $\log k_c = \beta pK_a^{ArOH} + \log k_c^H$. [b] $\alpha = \beta/\beta_{eq}$ (see text). [c] r = correlation coefficient. [d] pK_a of the appropriately substituted phenol.

$$A_t = A_\infty + \{[(k_2 - k_1)A_0 + k_1(A_B - A_\infty)]/(k_2 - k_1)\}\exp(-k_1 t) - [k_1(A_B - A_\infty)/(k_2 - k_1)]\exp(-k_2 t).^7$$

The pH-dependence of the cyclisation reaction is illustrated in Fig. 2 for **1a**–**e**. The cyclisation rate constants fit a rate eqn. (1) and the values of k_c and pK_a for (**Ia**–**v**) are recorded in Table 1.

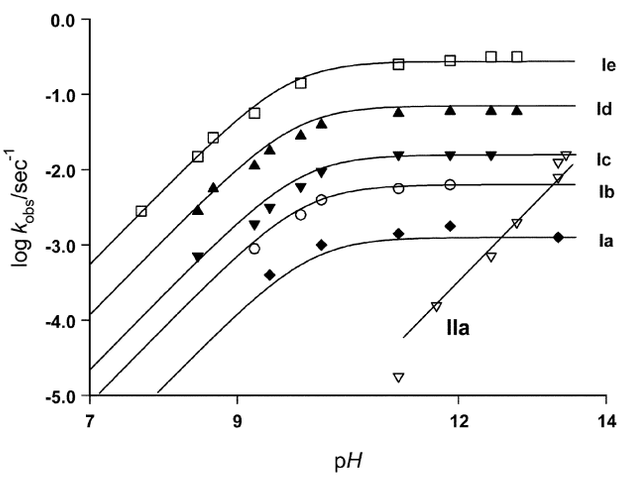


Fig. 2 pH-Dependence of the rate constants of cyclisation **Ia**–**e** and of hydrolysis of **IIa**. Lines are theoretical from parameters in Table 1 and eqn. (1) for **Ia**–**e** and a bimolecular equation for **IIa**. (Example shown is calculated from parameters in Table 1 and assuming A_0 is 0.146, A_∞ is 0.217, A_B is −0.0549, $k_1 = 0.00126$ s^{-1} and $k_2 = 0.0134$ sec^{-1}).

$$k_{obs} = k_c/(1 + [H_3O^+]/K_a) \quad (1)$$

The kinetics of hydrolysis of benzoxazinones (**II**) has pseudo-first-order rate constants linear up to 0.5M concentrations of HO^- (see Fig. 2) and the corresponding k_{OH} values, evaluated from the linear relationship, are recorded in Table 1. The rate constants, k_c, fit Brønsted relationships illustrated in Fig. 3.

The values of the Brønsted parameters, β_X and β_Y recorded in Table 2, are dependent on Y and X respectively (Fig. 4) according to the eqns. (2) and (3). The Cordes–Thornton coefficient (p_{XY}),[8] is −0.179 ± 0.03.

$$\beta_X = p_{XY} pK_a^Y + 0.87 \pm 0.25 \quad (2)$$

$$\beta_Y = p_{XY} pK_a^X + 2.30 \pm 0.26 \quad (3)$$

$$\log k_{OH} = -0.318 \pm 0.072 pK_a^{ArOH} + 1.64 \pm 0.62 \ (r = 0.9316) \quad (4)$$

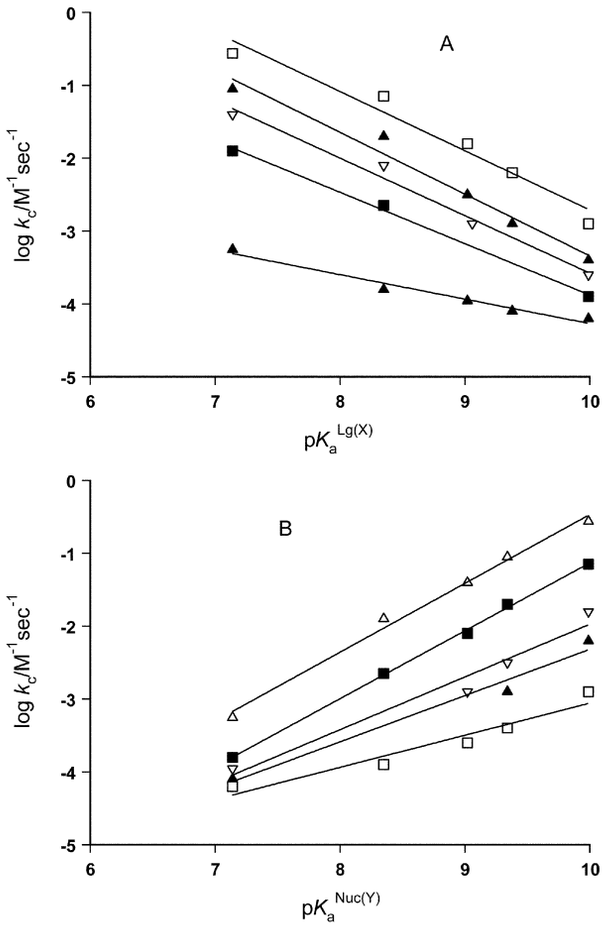


Fig. 3 Brønsted dependences of k_c on the pK_a of (A) X-substituted phenols (Y = constant) and (B) Y-substituted phenols (X = constant); data points are from Table 1 and lines are calculated from parameters in Table 2.

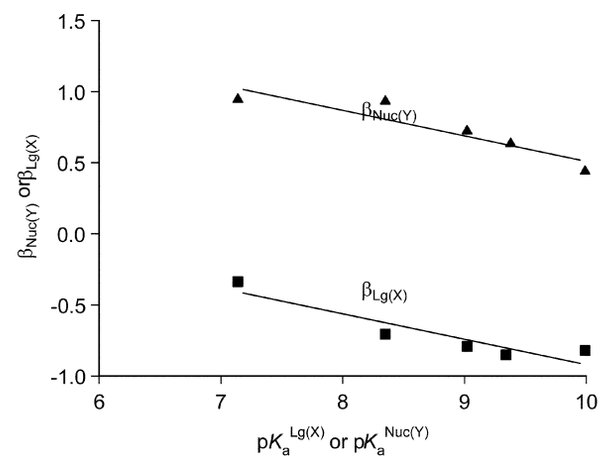


Fig. 4 Dependence of β_X and β_Y on pK_a^{Nuc} and pK_a^{Lg} respectively; data are from Table 2 and the lines are calculated from eqns. (2) and (3).

$$pK_a^{Y,NO2} = 0.948 \pm 0.034 pK_a^{ArOH(Y)} + 0.19 \pm 0.30 \ (r = 0.9981) \quad (5)$$

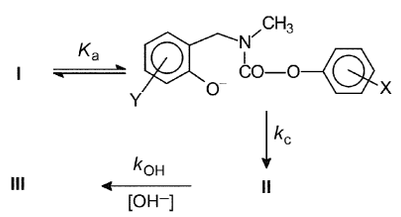
The rate constants for the alkaline hydrolysis of the benzoxazinones (**II**) obey a Brønsted eqn. (4) as do the pK_a values for the ionisation of the carbamate esters (**I**) (**Ia**–**e**, Eqn. 5) and (**Ie**, **Ij**, **In**, **Iq and Iv**, Eqn. 6). The superscripts Y and X refer to the substituents in the two rings as indicated in Scheme 1.

$$pK_a^{H,X} = 0.098 \pm 0.009 pK_a^{ArOH(X)} + 8.985 \pm 0.078 \ (r = 0.9879) \quad (6)$$

The Brønsted β value for the effect of changing Y on $pK_a^{Y,NO2}$ is 0.948 close to unity as expected for substituents directly attached to the nucleus nucleus of the ionising phenol. The value of β (0.098) for the effect of changing X on $pK_a^{H,X}$ is consistent with the substituent change being insulated from the ionising phenol hydroxyl group. It is possible that the residual effect of X is due to some sort of field interaction because inductive transmission from the X-substituted phenyl through six atoms is likely to be vanishingly small even though there is a possibility of π-electron polarisation *via* the benzene and carbamate ester functions.

Discussion

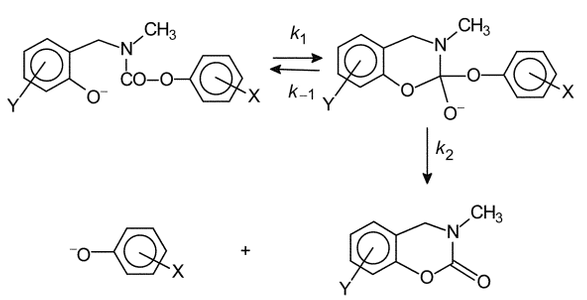
The pH-dependence and the observation of an intermediate in the hydrolysis of the carbamate esters (**I**) are consistent with a mechanism involving ionisation to the conjugate base followed by its rate limiting breakdown (k_c) to benzoxazinone (**II**) and a slower decomposition of **II** to **III** (Scheme 2).



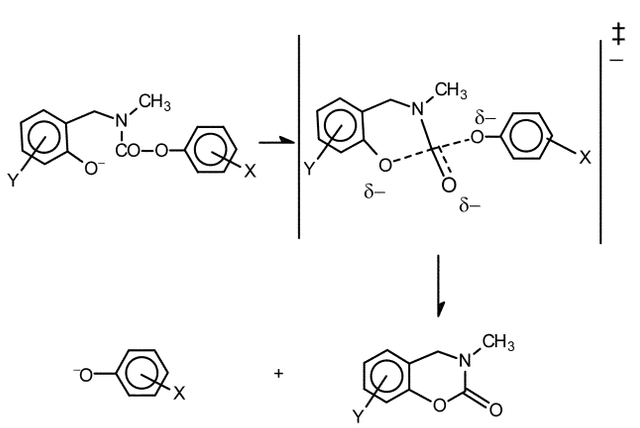
Scheme 2

Cross-interaction effects

The formation of benzoxazinone from the conjugate base of **I** could be either stepwise (Scheme 3) or concerted (Scheme 4).



Scheme 3 Stepwise mechanism for the k_c step.



Scheme 4 Concerted mechanism for the k_c step.

The substituent effect β_Y or β_X is a measure of the extent of bond formation or fission respectively in the transition structure of the rate limiting step.[9] Thus the effect of Y on the cyclisation rate constant refers to bond formation between oxyanion and carbamyl carbon. The effect of changing X refers to bond fission between leaving oxygen and the carbamyl carbon.

In addition to reporting the extent of bond change the effect of substituents Y and X can also monitor the interaction between these bond changes. This property is termed the cross-interaction effect and is alternately the effect of X on β_Y or Y on β_X. The parameter $p_{XY} = \partial\beta_Y/\partial pK_a^X = \partial\beta_X/\partial pK_a^Y$ where pK_a^X and pK_a^Y refer to the phenols corresponding to X and Y. The existence of a substantial cross-interaction effect in a displacement reaction is evidence of a concerted process.[9]

In the present case the variations of β_Y and β_X with X and Y respectively predict a substantial cross-interaction effect (−0.179) which is *prima facie* evidence of a concerted process (Scheme 4). By considering the direction of the observed changes in β_X and β (Table 2) as a function of cross-substituent X or Y it is possible to exclude the stepwise process of Scheme 3. According to Scheme 3 increasing the value of pK_a^Y will decrease k_{-1} while leaving k_2 relatively unchanged. This should alter the rate limiting step from k_2 to k_1 so that k_2 (which is X-dependent) becomes less predominant in k_c. Thus β_X should become numerically smaller in contrast to the experimentally observed *increase* in its numerical magnitude (−0.34 ⟶ −0.82, see Table 2). When pK_a^X increases, the rate constant k_2 should decrease, whereas k_{-1} should be relatively unchanged under these conditions; in this case the rate limiting step should change from k_1 to k_2 so that bond formation (which is monitored by β_Y) is fully complete in the transition structure of the rate limiting step. Thus β_Y should increase towards unity contrary to the experimentally observed *decrease* (0.945 ⟶ 0.44, see Table 2).

The changes in β_Y as a function of change in X are not consistent with the More O'Ferrall–Jencks map for the stepwise mechanism. The k_1 step would be rate limiting in the putative stepwise mechanism because k_2 is likely to be fast due to the stability of the cyclic intermediate (**II**). Thus an increase in pK_a^X should increase β_Y and shift the position of the transition structure South to North in Fig. 5 (ie according to the Hammond

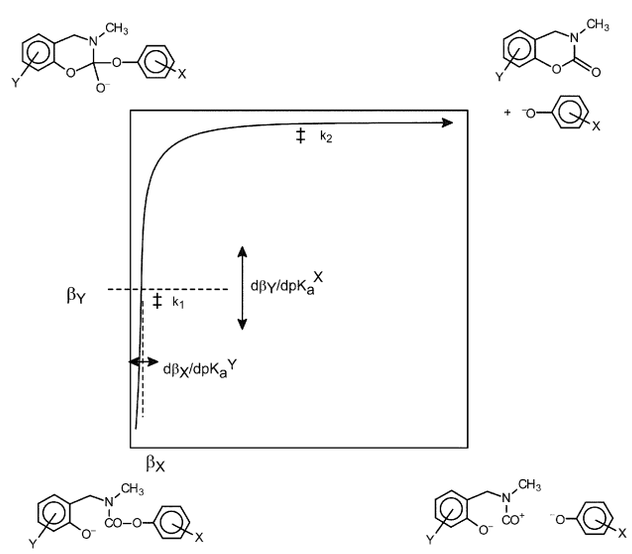
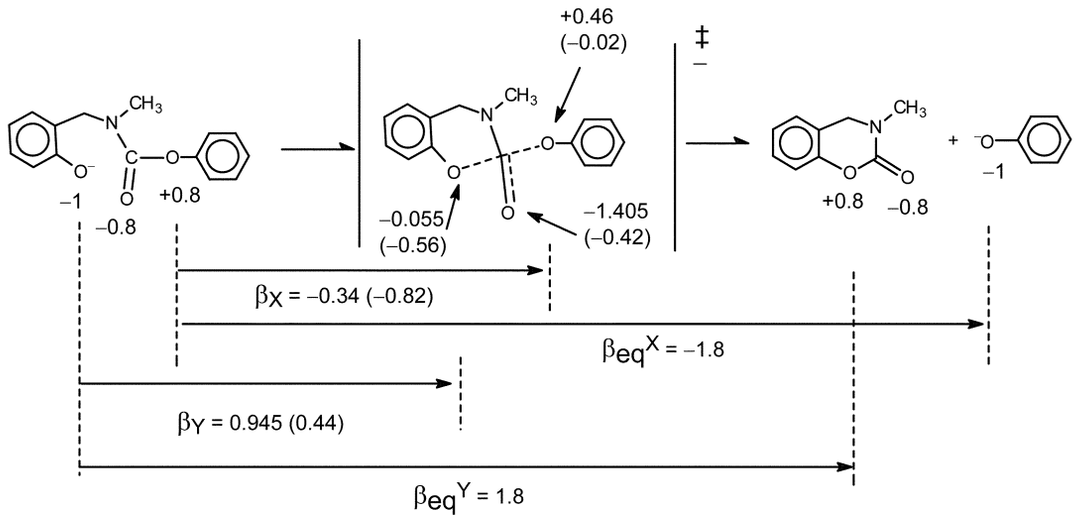


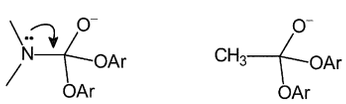
Fig. 5 More O'Ferrall–Jencks diagram for the putative stepwise cyclisation mechanism (Scheme 3).

postulate). An increase in pK_a^Y should not substantially change bond fission so that β_X should remain constant (and relatively small); the position of the transition structure would only suffer a small West–East change as illustrated in Fig. 5. Another way of expressing this argument is as follows: when the k_1 step is rate limiting and the transition structure is close to the western edge of the diagram the shape of the surface will constrain any movement of the transition structure largely in a North–South direction and be essentially controlled by Hammond's postulate.[10]



Scheme 5 Effective charge map for concerted cyclisation of **Iv** (NO_2,NO_2) and **Ia**. (H,H). Numbers in brackets are values of effective charge for **Ia**. Numbers on reactants and products refer to both **Iv** and **Ia**.

The sign and magnitude of the observed changes in β_X and β_Y as a function of pK_a^Y and pK_a^X respectively (p_{XY})[8] can be accomodated by a concerted mechanism (Scheme 4).[11] This conclusion is in agreement with concerted displacement mechanisms discovered for other acyl group transfer reactions[12,13] where the concerted mechanism of acyl group transfer is favoured by weakly basic nucleophiles and leaving groups such as phenolate ions or pyridines.[14] Decreased stability of the tetrahedral intermediate of the putative stepwise mechanism is also important in favouring a concerted process.[13] In the carbamate case the greater electron donating power of the nitrogen would destabilise the putative tetrahedral adduct (**IV**) compared to that of the methyl group (**V**). Since the reaction of phenolate ions with phenyl acetates is concerted it follows that the phenolate ion displacements at the carbamoyl function should also be concerted because the structural factors are even more favourable for a concerted process.



(**IV**) (**V**)

The consequences of variation of X and Y on the position of the transition structure in the More O'Ferrall–Jencks diagram[13,15] are illustrated in Fig. 6. It is convenient at this stage to use normalised β values (Leffler parameters $\alpha_X = \beta_X/\beta_{eq}^X$ and $\alpha_Y = \beta_Y/\beta_{eq}^Y$) as these are used conventionally as x and y coordinates for the diagrams (Fig. 6). We make the reasonable assumption that the parameters β_{eq}^X (−1.8) and β_{eq}^Y (+1.8) are the same as that for transfer of the NH_2CO– group between phenolate ion nucleophiles.[16] The derived values of α_X and α_Y are recorded in Table 2.

Expressed in terms of Leffler α parameters the x,y coordinates of the transition structure for **1v** are (0.19,0.53) and for **1a** are (0.46,0.24). These coordinates represent two extremes of structure and the transition structures for all the esters (**1a**–**v**) studied here lie within the envelope bounded by the two reaction coordinates illustrated in Fig. 6. Changing the Y-substituent in **I** (for example **Ir** ⟶ **Ie**) alters the coordinates in a West–East direction (with no North–South movement) whereas change in the X-substituent (for example **Iv** ⟶ **Ir**) moves the transition structure in a North–South direction with no West–East movement.

Since the putative stepwise mechanism has been ruled out the large changes in transition structure can only be due to changes on an energy surface corresponding to a concerted mechanism.

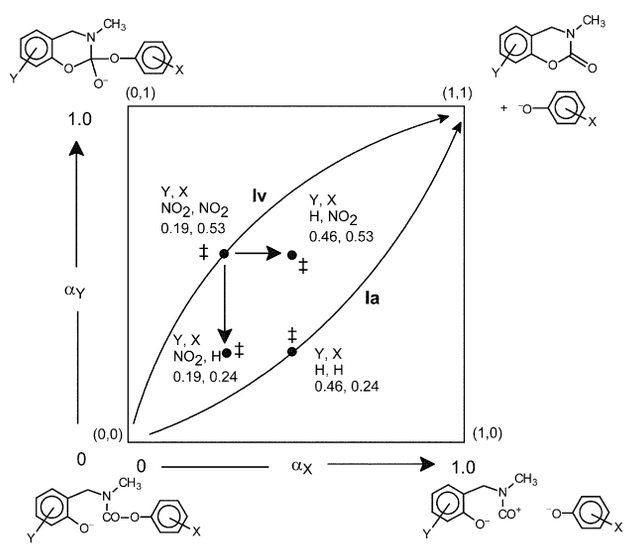


Fig. 6 More O'Ferrall–Jencks diagram for the concerted cyclisation reaction **I** ⟶ **II** illustrating the movement of the position of the transition structure as a function of increasing electron donating power of X and Y.

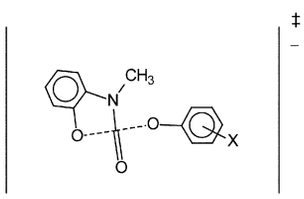
An effective charge map[17] can be constructed for the cyclisation **I** ⟶ **II** and the effective charge distribution in the transition structure will vary according to the identity of the substituents X and Y. The map is illustrated for the cyclisation of **Iv** (4-NO_2, 5-NO_2) and **Ia** (H,H) in Scheme 5.

In the case of **Iv** the change in effective charge on the carbonyl oxygen, obtained by difference assuming additivity of effective charge, is (−1.405 − −0.8 = −0.605); together with the changes in charge on nucleophilic and leaving oxygen (+0.945) and (−0.34) respectively it is deduced that the transition structure has some of the character of a tetrahedral adduct. In the case of **Ia** the slight increase in positive effective charge on the carbonyl oxygen (−0.42 − −0.8 = +0.38) is consistent with a transition structure with some acylium ion character.

The hydrolysis of the conjugate base of phenyl-*N*-(2-hydroxyphenyl)-*N*-methylcarbamate (**VI**), which involves cyclisation to 3-methyl-2,3-dihydrobenzo[1,3]oxazol-2-one (**VII**) (Scheme 6), is analogous to that of the present study.[18] The cyclisation rate constant is almost three orders of magnitude larger than that of **Ia** in agreement with the observation that cyclisation by intramolecular reaction of oxygen nucleophiles with a carbonyl group to five-membered rings is invariably faster than the formation of six-membered rings.[1,19–23] The

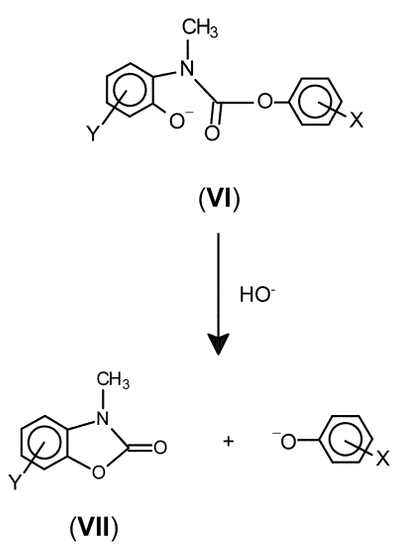
hydrolysis of the oxazolone (**VII**) (k_{OH} = 4.8.10^{-3}M^{-1}sec^{-1}) is ten times smaller than that of **Ia**. The cyclisation reactions of HO–$CH_2CH_2NPhCO_2Ph$ and of HO–$CH_2CH_2NCH_3CO_2Ph$[24] are equally reactive indicating that the replacement of N–CH_2– by NPh is unlikely to be the cause of the enhanced rate of cyclisation to benzoxalone (**VII**) compared with that to benzoxazinones (**II**).

The effective molarity for the reaction of Scheme 6 (Y = X = H) is *ca.* 10^8 M compared with the effective molarity for the cyclisation to benzoxazinone (**IIa** from **Ia**) of 2.10^{5}M using the calculated intermolecular rate constant of Hutchins and Fife.[18] The substantial value of the Hammett ρ obtained for Scheme 6 when Y = H[3] translates to a β_{Lg} of −0.9 and α_{Lg} = 0.53 consistent with advanced fission of the ArO–C bond in the transition structure of the rate limiting step. Moreover Hegarty *et al.*[25] showed that bond *formation* is substantially advanced in the transition structure. The results fit both stepwise and concerted processes. We propose a concerted displacement mechanism for the formation of the benzoxazolone (**VIII**) on the basis of the present data for the benzoxazinone formation.



VIII

The kinetics of hydrolysis of esters (**I**),[26] where a nitro group is substituted *para* to an hydroxyl function, show enhanced resonance interaction due to extensive bond formation and fission in the transition structure. The data indicate that rehybridisation and bond formation or fission are not synchronous.[27] Studies with more than one group capable of undergoing resonance interactions will be necessary before further comment is possible on the relative progress of delocalisation and bond formation in this reaction.



Scheme 6

Reactivity–selectivity hypothesis

The increase in reactivity as a function of X or Y is associated with an *increase* in selectivity (Fig. 3) and this is manifested in the sign of the Cordes–Thornton coefficient, −0.179).[8,11,28] The variation of reactivity with structure does not conform with the *reactivity–selectivity* hypothesis.[10,29] In contrast the intermolecular displacement reaction between substituted phenolate ions and substituted phenyl acetate esters has a positive p_{XY} coefficient (+0.17) and the structure reactivity variation conforms with the *reactivity–selectivity* hypothesis. There is no cogent reason why the reactivity–selectivity hypothesis should be adhered to except in a reaction where only one bond is undergoing a major change and there are no concurrent changes such as solvation or resonance interactions.[10] The results for the benzoxazinone formation contrast with that for the phenolysis of phenylacetate esters where increasing the nucleophilicity of nucleophile and leaving group moves the transition structure towards that of the putative *tetrahedral* structure (0,1); the same change in nucleophilicity for the cyclisation **I** ⟶ **II** shifts the structure towards the putative *acylium ion* structure (1,0).[30]

It is interesting to speculate on the reason why electron donating substituents cause the motion of the transition structure towards the acylium ion structure (1,0). In this case the acylium ion structure is more stable than that of the acetylium ion (CH_3CO^+) in phenolysis of phenyl acetate esters due to the adjacent nitrogen. The More O'Ferrall–Jencks map is therefore more skewed towards the (1,0) coordinate in the benzoxazinone formation. It is unlikely that the acylium ion structure would be stabilised by electron donating substituents X or Y. However, these substituents would decrease the stability of the putative adduct at (0,1) and thus move the transition structure in a South–East direction.

Conclusions

This study shows that the base-catalysed cyclisation (Scheme 1) does not conform to the reactivity–selectivity hypothesis and involves a concerted displacement reaction at the carbamoyl centre. Arguments show that a similar concerted mechanism probably operates for the formation of the benzoxazolone (Scheme 6). The results add to the substantial body of evidence that a concerted displacement mechanism is possible at a carbonyl centre under certain conditions of nucleophile, leaving group and acyl function.

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