Reactions of carbonyl compounds in basic solutions. Part 32.[1] The Perkin rearrangement

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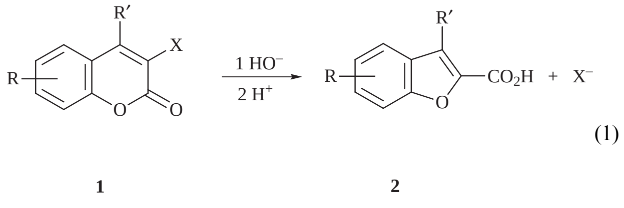
The Perkin rearrangement of 3-halocoumarins to benzofuran-2-carboxylic acids, catalysed by base, proceeds in two separate stages. The first stage is a relatively rapid base-catalysed ring fission of the 3-halocoumarins to give (*E*)-2-halo-3-(2-hydroxyphenyl)acrylic acids. Rate coefficients have been measured for the base-catalysed ring fission of 6-substituted and 4-methyl-3-bromocoumarins and of 3-chlorocoumarin in 70% (v/v) dioxane–water at various temperatures. The second stage is a relatively slow cyclisation process. Rate coefficients have been measured for the cyclisation of the same series of substrates in 70% (v/v) dimethyl sulfoxide–water at various temperatures. The enthalpies and entropies of activation have been evaluated. The Hammett reaction constant for the ring fission at 30.0 °C is 2.34 and for the cyclisation at 60.0 °C is −3.54. The ring fission appears to occur by rate-determining addition of hydroxide anion to the carbonyl group, followed by a relatively rapid ring opening process; while the cyclisation probably proceeds by rate-determining fission of the carbon–halogen bond, following formation of a relatively unstable carbanion intermediate formed by intramolecular nucleophilic attack on the vinyl group by the phenoxide anion.

In 1871, Perkin[2] reported the formation of benzofuran-2-carboxylic acid (coumarilic acid) by the action of alkali on 3-bromocoumarin. This rearrangement was shown to be general for 3-halocoumarins, **1**,[3,4] with a 4-substituted coumarin giving a 3-substituted benzofuran-2-carboxylic acid, **2**, as shown in eqn. (1). The pathway for this rearrangement has been considered to involve the base-catalysed ring fission of the 3-halocoumarin, **1**, to form the corresponding dianion of the (*E*)-2-halo-3-(2-hydroxyphenyl)acrylic acid, followed by an intramolecular nucleophilic attack by the phenoxide anion on the vinyl halide to give the anion of **2** as the final product.[4] However, there is no obvious activation of the S_N reaction of the vinyl halide. A study[5] of the closely related rearrangement of 3-chlorocoumarin by methoxide anion to give methyl benzofuran-2-carboxylate (methyl coumarilate) led Newman and Dalton to prefer, following ring fission, a Michael addition of methanol to the alkene, followed by an intramolecular S_N cyclisation of the alkyl halide and subsequent elimination of methanol.



(1)

1 **2**

X = Br or Cl

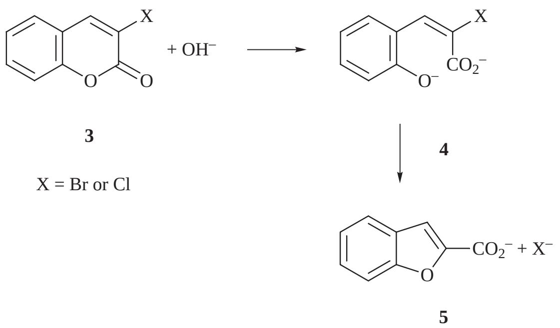
The mechanism of the base-catalysed ring fission of coumarins has been studied in some detail.[6–8] The rate-determining step appears to be the addition of hydroxide anion to the coumarin carbonyl group, followed by relatively rapid ring fission. However, nucleophilic substitution of vinyl halides can proceed by a number of mechanistic pathways, particularly those involving addition–elimination.[9]

We describe here the Perkin rearrangement of a series of substituted 3-bromocoumarins and 3-chlorocoumarin. The kinetics of reaction, intermediates, effects of substitution, solvent composition and activation parameters are discussed in terms of a detailed mechanism.

Results and discussion

General

The reaction has been found to be a two-stage process, as shown in Scheme 1. The first stage is a relatively rapid reaction which is first-order both in the 3-halocoumarin substrate **3** and in the hydroxide anion. The product of the first stage appears to be the anion of the (*E*)-2-halo-3-(2-hydroxyphenyl)acrylic acid. The second stage is a relatively slow reaction, which is first-order in the dianion, **4**, giving as the final product the anion of the benzofuran-2-carboxylic acid, **5**. The UV spectra of the three species are distinctive, *i.e.* in 70% aqueous dioxane **3**, **4** and **5** have λ_{max} at 275, 325 and 330 nm, respectively. However, the ^{1}H NMR spectra, in D_2O–$(CD_3)_2SO$ without or with DO^-, are diagnostic for the structures with 4-H of **3**, 3-H of **4** and 3-H of **5** giving signals at 8.51, 6.90 and 7.65 ppm, respectively. Coumarin and its hydrolysis product, under the same conditions, had signals for the 4-H of coumarin at 7.93 ppm (1H, d, *J* 9.6 Hz) and for the 3-H of the hydrolysis product at 6.45 ppm (1H, d, *J* 13.2 Hz). No other stable intermediate in the reactions of **3** and **4** has been observed. Furthermore, reaction in D_2O–$(CD_3)_2SO$ containing DO^- gave a final product **5** in which the



Scheme 1

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Table 1 Rate coefficients (k_2) for the alkaline ring fission of the 6-substituted and 4-methyl-3-bromocoumarins and of 3-chlorocoumarin 70% (v/v) dioxane–water at several temperatures[a]

3-Bromocoumarin 6-substituent	k_2/dm^3 mol^{-1} s^{-1}				λ/nm[b]
H	69.0 (30.0 °C)	149 (40.8 °C)	258 (49.0 °C)	544 (61.0 °C)	290
CH_3	35.0 (30.3 °C)	71.4 (39.8 °C)	148 (50.0 °C)	305 (60.3 °C)	277
OCH_3	13.0 (30.0 °C)	30.2 (40.0 °C)	74.8 (51.4 °C)	124 (60.0 °C)	288
Cl	356 (30.0 °C)	601 (40.0 °C)	961 (50.0 °C)	1500 (60.0 °C)	280
Br	306 (30.0 °C)	548 (40.5 °C)	911 (50.0 °C)	1450 (60.0 °C)	285
NO_2	4040 (30.0 °C)	6050 (40.0 °C)	8830 (50.0 °C)		290
3-Bromo-4-methylcoumarin	14.3 (30.0 °C)	29.6 (40.0 °C)	59.1 (50.0 °C)	112 (60.0 °C)	272
3-Chlorocoumarin	95.9 (30.0 °C)	184 (40.0 °C)	354 (50.2 °C)	613 (60.0 °C)	280

[a] The rate coefficients were reproducible to ±3%. [b] Wavelength used to monitor the fission.

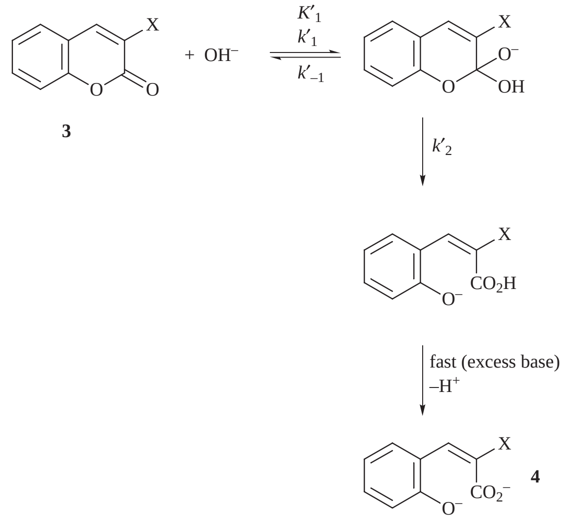
integration of the ^{1}H NMR spectral signal for the 3-H indicated *no* exchange with deuterium.

Ring fission

A detailed reaction pathway for the base-catalysed ring fission of the coumarins is shown in Scheme 2.[6] The rate coefficients at several temperatures for the reaction in 70% (v/v) dioxane–water are shown in Table 1. Comparison of the rates of ring fission for 3-bromo- and 3-chlorocoumarin with that of the unsubstituted coumarin[6] at 30 °C in the same medium indicates that the 3-halo groups cause significant rate enhancement, *i.e.* by a factor of 175 (3-Br) and 243 (3-Cl). This appears to arise from the combination of a powerful electron-withdrawing effect facilitating reaction and a more modest 'bulk' steric effect inhibiting reaction[10] arising from the proximate halo group. The significant rate decrease caused by the 4-methyl group of a factor of 0.21 compares closely with the effect of a *trans*-3-methyl substituent on the alkaline hydrolysis of methyl acrylates.[11] The Hammett equation [eqn. (2)] can be applied to the

$$\log (k/k_o) = \rho\sigma \qquad (2)$$

effects of substitution on the reactivity.[12] The previous study[6] of the effects of 6- and 7-substituents on the base-catalysed ring fission of coumarin in 70% aqueous dioxane required the employment of the modified Hammett equation by Jaffé,[13] giving a combined ρ value of *ca.* 2.35 at 30 °C. An excellent correlation was obtained using *para*-σ values alone for the base-catalysed ring fission of 6-substituted 3-bromocoumarins in 70% aqueous dioxane as shown in Table 2. The ρ value of *ca.* 2.33, closely comparable to that described above for coumarins, confirms the rate-determining step to be k'_1 in Scheme 2. The enthalpies and entropies of activation for the ring fission, shown in Table 3, confirm the bimolecular nature of the rate-determining step. The entropies of activation are somewhat less negative for 3-bromocoumarins than for the coumarins,[6] presumably arising from facilitation of solvation by the 3-bromo substituent. A decrease in the enthalpy of activation is observed for electron-withdrawing substituents and the converse for electron-releasing substituents, as expected.



Scheme 2

Table 2 Hammett reaction constants (ρ) for the alkaline ring fission and for the cyclisation reactions of the 6-substituted 3-bromocoumarins[a]

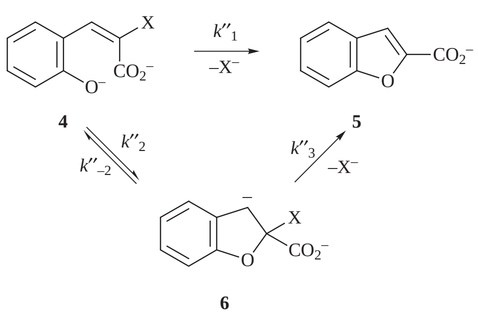
	T/°C	ρ	$\log k_o$	r	s	n
Ring fission in 70% (v/v) dioxane–water	30	2.340	1.838	0.993	0.140	6
Cyclisation in 70% (v/v) DMSO–water	60	−3.536	−3.536	0.991	0.198	6

[a] s is the standard deviation, r the correlation coefficient and n the number of substituents studied.

Cyclisation

The cyclisation reaction has been found to be first-order in the dianion **4**. The rate coefficients at several temperatures for the reaction in 70% (v/v) dimethyl sulfoxide (DMSO)–water are shown in Table 4. The rates of reaction were *too* slow to be conveniently measured in 70% (v/v) dioxane–water at these temperatures.

Possible pathways for this reaction are elimination–addition [*via* dianionic 3-(2-hydroxyphenyl)propiolic acids], Michael addition of water–substitution–elimination,[5] addition–elimination (*via* dianionic carbanions) and direct intramolecular nucleophilic substitution.[9] Elimination–addition is not possible for 3-bromo-4-methylcoumarin and, in any case, would have resulted in quantitative deuteration in DO^-–D_2O at the 4-position for all other substrates (which is *not* observed). Thus this pathway can be discounted. Michael addition of water would result in saturated intermediates, which are not observed, and, in the absence of base catalysis, both addition and elimination would be expected to be very slow.[9] Addition–elimination and the intramolecular S_N pathway are shown in Scheme 3. Rappoport[9] has reviewed nucleophilic vinylic substi-



Scheme 3

Table 3 Activation parameters for the alkaline ring fission and for the cyclisation reactions at 30.0 °C[a]

	Ring fission 70% (v/v) dioxane–water		Cyclisation 70% (v/v) DMSO–water	
3-Bromocoumarin 6-substituent	$\Delta H^\ddagger$/kcal mol^{-1}	$\Delta S^\ddagger$/cal mol^{-1} K^{-1}	$\Delta H^\ddagger$/kcal mol^{-1}	$\Delta S^\ddagger$/cal mol^{-1} K^{-1}
H	12.8	−8	27.8	8
			[29.6	13][b]
			[26.0	5][c]
			[24.0	2][d]
CH_3	13.9	−6	27.3	7
OCH_3	14.7	−5	24.9	1
Cl	9.0	−17	29.1	10
Br	9.8	−15	31.3	16
NO_2	7.0	−19	27.3	1
3-Bromo-4-methylcoumarin	13.2	−10	18.8	−24
3-Chlorocoumarin	12.0	−10	15.2	−37

[a] Values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are considered accurate to within ±400 cal mol^{-1} and ±2 cal mol^{-1} K^{-1}, respectively. [b] In 60% (v/v) DMSO–water. [c] In 80% (v/v) DMSO–water. [d] In 90% (v/v) DMSO–water.

Table 4 Rate coefficients (k_1) for the cyclisation of products of fission of the 6-substituted and 3-bromo-4-methylcoumarins and of 3-chlorocoumarin in 70% (v/v) DMSO–water at several temperatures[a]

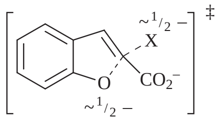
3-Bromocoumarin 6-substituent	$k_1/10^{-5}$ s^{-1}				λ/nm[b]
H	29.2 (60.0 °C)	57.5 (65.3 °C)	104 (70.2 °C)	185 (75.0 °C)	340
	[18.0 (60.0 °C)	37.9 (65.5 °C)	66.5 (69.8 °C)	132 (75.2 °C)][c]	
	[66.5 (60.0 °C)	129 (65.5 °C)	233 (70.0 °C)	377 (75.0 °C)][d]	
	[374 (60.0 °C)	633 (65.0 °C)	1090 (70.0 °C)	1860 (75.0 °C)][e]	
CH_3	31.3 (60.0 °C)	112 (70.4 °C)	185 (74.6 °C)	348 (80.2 °C)	345
OCH_3	60.8 (60.0 °C)	99.5 (64.4 °C)	202 (70.7 °C)	330 (75.0 °C)	348
Cl	9.01 (60.0 °C)	20.1 (65.0 °C)	35.0 (70.0 °C)	68.9 (75.0 °C)	350
Br	8.29 (60.4 °C)	27.7 (69.0 °C)	69.2 (75.8 °C)	121 (80.1 °C)	355
NO_2	1.20 (60.0 °C)	2.00 (64.2 °C)	4.03 (70.0 °C)	15.5 (81.0 °C)	340, 440
3-Bromo-4-methylcoumarin	2.01 (60.0 °C)	3.13 (65.0 °C)	4.71 (70.0 °C)	8.50 (77.2 °C)	340
3-Chlorocoumarin	0.543 (60.0 °C)	1.11 (70.3 °C)	1.46 (75.0 °C)	2.10 (80.0 °C)	347

[a] The rate coefficients were reproducible to ±4%. [b] Wavelength used to monitor the cyclisation. [c] In 60% (v/v) DMSO–water. [d] In 80% (v/v) DMSO–water. [e] In 90% (v/v) DMSO–water.

tution, $\mathrm{S_N}$V, in detail. The addition–elimination pathway can be a two-stage process in which, usually, the nucleofuge is intramolecularly expelled from the carbanion faster than protonation occurs. An alternative is the single-stage process in which nucleophilic attack and nucleofuge expulsion occur *via* a single transition state. A detailed analysis indicated that poor nucleofuges and strongly electron-withdrawing β-substituents favour the two-stage process. In this study, the nucleofuges Br or Cl are relatively good and no strong electron-withdrawing β-substituents are present. The element effect, k_{Br}/k_{Cl} here, has been considered good evidence of the nature of the rate-determining step.[9] In this study k_{Br}/k_{Cl} at 60.0 °C equals *ca.* 54 (see Table 4), indicating that carbon–halogen bond breaking occurs in the rate-determining step. The Hammett ρ value for cyclisation of the 6-substituted 3-bromocoumarins at 60.0 °C equals *ca.* −3.5, as shown in Table 2, clearly indicating nucleophilic attack of the phenoxide anion on the vinyl group. The ρ values for the ionisation of phenols in water and in DMSO at 25 °C equal *ca.* 2.3 and 5.3,[14] respectively. An estimate of the latter ρ value in 70% aqueous DMSO at 60.0 °C would be *ca.* 3.4.[15] Using an approach similar to that of Williams,[16] it can be estimated that the transition state for the nucleophilic attack process is relatively complete. The increase in rate by a factor of *ca.* 21 at 60 °C with increasing DMSO content of the solvent from 60 to 90% (v/v), as shown in Table 4, confirms the importance of the nucleophilic attack process. In the latter the progressive decrease in the availability of protic solvation stabilises the transition state relative to the initial state. The effect of the 4-methyl group is to sharply decrease the rate by a factor of *ca.* 0.069 at 60.0 °C, as shown in Table 4. This appears to arise, mainly, from a 'bulk' steric effect in forming the more crowded transition state from the initial state,[9] together with a minor electron-releasing effect.

The enthalpies and entropies of activation for the cyclisation process shown in Table 3 parallel those found by Illuminati *et al.*[17] for the cyclisation of the anion of 2-(2-bromoethyl)phenol. Thus $\Delta S^\ddagger$ for the 3-bromocoumarin substrates are relatively small and positive, as would be expected for an intramolecular and unimolecular process. The reduced enthalpy of activation for the 3-bromo-4-methylcoumarin substrate and large negative entropy of activation for the 3-chlorocoumarin substrate are not those expected, but could arise from solvation effects.

The cyclisation reaction studied here can be classified as 5-*endo-trig* and, according to the Baldwin rules, would not be favoured.[18] These rules are based on the assumption of ring formation by addition of the nucleophile to the carbon–carbon double bond with a stereochemical trajectory having a subtended angle between the three interacting atoms of *ca.* 109°. Here, this reaction pathway would result in formation of the carbanion **6** which, if coplanar, would have *ca.* 39° of ring angle strain. However, the alternative intramolecular $\mathrm{S_N}$ process would have a transition state **7**, with a linear nucleophile-carbon-leaving group and a trajectory having a subtended angle between nucleophile and carbon–carbon double bond of *ca.* 90°. Similarly, this would result in *ca.* 20° of ring angle strain. A study[19] of the cyclisation of nucleophilic addition of phenolate anions to unactivated double bonds indicated a two-step process with rate-determining formation of the carbanion.



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The evidence relating to the cyclisation process appears to favour a mechanistic pathway involving the formation of a very unstable carbanion, followed by rate-determining fission of the carbon–halogen bond, as shown as k''_3 in Scheme 3. This implies that loss of halide anion from **6** is more difficult than ring fission to the phenoxide anion **4**, which is surprising. It is possible that there is a mechanistic switch between the 3-bromo and 3-chloro substrates. A concerted intramolecular S_N process, as shown as k''_1 in Scheme 3, cannot be ruled out. More studies are required of systems that potentially involve high energy carbanion intermediates.

Experimental

Materials

Coumarin was obtained commercially and the 6-substituted coumarins were prepared as previously described.[6] 4-Methylcoumarin was prepared by the reaction of phenol with ethyl acetoacetate catalysed by aluminium chloride.[20] Bromination of the 6-substituted coumarins and 4-methylcoumarin by bromine in chloroform gave the 3-bromo derivatives.[21] Chlorination of coumarin by chlorine in carbon tetrachloride gave 3-chlorocoumarin.[22] The substituted benzofuran-2-carboxylic acids were synthesised by the action of base on the corresponding 3-halocoumarins.[4,21,23] The mps of the coumarins, after repeated recrystallisation and drying under reduced pressure (P_2O_5), were in good agreement with the reported[1,21,22,24–26] values. The following previously unreported coumarins gave satisfactory elemental analysis. 6-Methoxy-3-bromocoumarin had mp 153–154 °C and 6-chloro-3-bromocoumarin had mp 209–210 °C, both being recrystallised from ethanol. The structures and purity of the coumarins and rearranged products were monitored by ^1H and ^{13}C NMR, IR spectroscopy and mass spectrometry. Solvents were purified as described previously.[6,27]

Measurements

Rate coefficients for the alkaline ring fission of the coumarins and cyclisation of the products of fission were determined spectrophotometrically by use of a Perkin-Elmer lambda 16 UV–VIS spectrometer. The cell temperature was controlled to within ±0.05 °C by means of a Haake DC3 circulator. The procedure used was that described previously.[28] The reactions were followed at the wavelengths stated in Tables 1 and 4. The substrate concentrations were *ca.* 5×10^{-5} mol dm^{-3} and the base concentrations 1 to 4×10^{-4} mol dm^{-3} for the ring fission and 1×10^{-4} to 8×10^{-3} mol dm^{-3} for the cyclisation. For the ring fission, the second-order rate coefficients were checked by the method devised by Corbett,[29] which can be applied if the excess used is only two-fold. Good, simple isosbestic points were observed for all substrates in *both* reactions by judicious choice of the reaction conditions, *i.e.* the *much* faster alkaline fission reaction is first-order in base and relatively slow in aqueous dioxane, compared to aqueous DMSO; whereas the *much* slower cyclisation is zero-order in base and relatively fast in aqueous DMSO, compared to aqueous dioxane.

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