The Reversible Cyclisation of a Chalcone, 1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-ethoxyphenyl)prop-2-en-1-one: a Kinetic and Mechanistic Study

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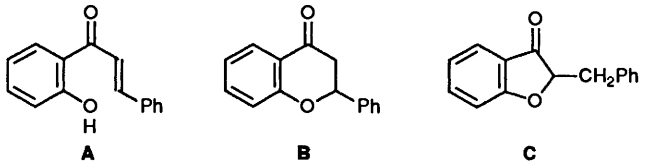
Cyclisation of the title 2'-hydroxychalcone **1** to the flavanone **2** in 30% v/v isopropyl alcohol is a reversible process with a complex rate–pH profile. In alkali, while the forward reaction goes through the anion of **1**, its reverse goes *via* hydroxide ion attack on **2**, so that k_f and k_r dominate under different conditions and can be separately studied and dissected. The hitherto unstudied reaction in acid shows a plateau at low pH which results from a change in rate-determining step. With the help of model rates and equilibria it has proved possible to assign values to every microscopic rate and equilibrium constant at both low and high pH. One result has been to assign a plausible value to log K_T for the keto–enol equilibrium present in **2**. Another has been the unequivocal assignment of reaction mechanism. In alkali, the reverse (β-elimination) reaction is neither E2 nor $(E1cb)_i$ but a rare example of the $(E1cb)_R$ mechanism with PhCO as activating group and PhO^- as nucleofuge; a value can be given to the hitherto unknown ranking order of PhO^- for this case. In acid, the mechanism of rate-limiting β-elimination is $(E1cb)_i$ but, in addition, loss of PhOH takes place at close to the encounter limit. The transition states for loss both of PhOH and of PhO^- involve minimal C–O bond fission. Some alternative reaction mechanisms are discussed and eliminated. In addition, the position of K_{eq} is discussed; it is concluded that ring closure probably involves EM ≈ 10^3.

The cyclisation of 2'-hydroxychalcones (**A**) to flavanones (**B**) is a well studied reaction[1] with several unusual features. As



A **B** **C**

pointed out by Johnson and co-workers,[2] preferential cyclisation to give a dihydroaurone (**C**) might have been anticipated since 5-*exo*-*trig* are generally favoured over 6-*endo*-*trig* ring closures,[3] yet this reaction has been detected only under atypical circumstances.[1,4] Secondly, the cyclisation is reversible; typically, the flavanone is favoured in acid and the chalcone in alkaline solution,[1] but the equilibrium tends to be quite finely balanced, as in the present case (*vide infra*). This reversibility has been traced[5] to the trapping of **A** as its phenoxide anion, so that, although this anion is the reactive species and generates **B**, it does so to a lesser extent the more the solution pH rises. Hence, with increasing alkalinity, the reaction proceeds faster and faster but with reversion to a higher and higher proportion of the original reactant; an intriguingly 'looking-glass' situation* which, however, can be employed to garner mechanistic information, as we shall demonstrate.

A number of workers[5,7–9] have investigated the kinetics and mechanism of this process; in addition, Pacheco and co-workers[10] have studied the position of equilibrium as a function of substitution in both rings. However, all have concentrated on the reaction in alkali, and only Tirouflet and Corvaisier[5] have studied the reaction in acid (*vide infra*). In addition, there is no agreement on mechanism: while Tirouflet and Corvaisier[5] and Main and co-workers[7,8] regard ketonisation of the enolate intermediate **9A** as the rate-limiting step, Furlong and Nudelman[9] prefer slow proton transfer to or from one ene carbon atom concerted with oxyanion addition to or from the other (*cf.* structure **13**). As Miles and Main[8b] point out, this is essentially the difference between E1cb and E2 processes, respectively, for the reverse (ring-opening) reaction. Moreover, despite the composite nature of the overall reaction rate [eqn. (1)], much mechanistic discussion has ignored this, especially with regard to solvent effects.[9b]

$$k_{obs} = k_f + k_r \quad (1)$$

The present investigation has given us the opportunity to fill in some of these lacunae. The title compound **1** is active against rhinovirus[11] and was considered as a candidate for development till this study put its stability *in vivo* in doubt. We concentrate here on a dissection of the reaction mechanism into its microscopic steps, using related but simpler reactions to supply model rate constants, and with further help from the reaction in acid, investigated in detail here for the first time. Since, for a reversible reaction, *every* step is either a pre-equilibrium or rate-limiting in one direction or the other, a potentially massive amount of information is there to be extracted.

Experimental

NMR spectra were taken on a Varian EM 390 90 MHz NMR spectrometer in $CDCl_3$ using tetramethylsilane as internal lock. UV spectra were run on a Unicam SP 1700 UV spectrometer equipped with a thermostatted 1 cm cell with facility for direct temperature measurement. pH values were measured on a Radiometer PHM 28 pH meter using Radiometer type B electrodes, which require a correction of only 0.03 pH units even at pH 13. In the kinetic and potentiometric experiments, water was glass distilled, while isopropyl alcohol and all inorganic reagents were of AnalaR grade. Temperatures were measured to ±0.1 °C.

Preparation of the Chalcone **1**.—2,4-Dimethoxy-6-hydroxy-

* 'Now, *here*, you see, it takes all the running *you* can do, to keep in the same place.'[6]

Table 1 Rate data at 49.6 °C in 30% v/v isopropyl alcohol[a]

pH[b,c]	Buffer (conc./mol dm^{-3})	λ_{anal}/nm[d]	$k_{obs}/10^{-4}$ s^{-1}	k/s.e. %
0.20	$HClO_4$ (1)	374	0.067 6	0.84
1.17	$HClO_4$ (10^{-1})	374	0.056 2	0.49
2.17 ± 0.03	$HClO_4$ (10^{-2})	374	0.033 9	0.57
3.10 ± 0.02	Formate (10^{-2})	374	0.009 33	0.51
3.64 ± 0.03	Formate (10^{-2})	374	0.002 57	0.46
6.92 ± 0.01	Phosphate (10^{-2})	374	0.010 0	0.62
7.28 ± 0.01	Phosphate (10^{-2})	374	0.019 1	0.49
7.47 ± 0.02	Phosphate (10^{-2})	374	0.030 2	0.50
7.69 ± 0.01	Phosphate (10^{-2})	374	0.051 3	0.83
8.23 ± 0.01	Phosphate (10^{-2})	374	0.129	0.33
8.40 ± 0.03	Borate (10^{-2})	374	0.209	0.66
8.77	Borate (10^{-2})	374	0.589	1.29
9.01 ± 0.01	Borate (10^{-2})	374	1.02	0.90
9.09	Borate (10^{-2})	336	1.17	0.53
9.46[e]	Carbonate (10^{-2})	336	2.45	0.47
9.78[e]	Carbonate (10^{-2})	336	4.79	0.22
10.24[e]	Carbonate (10^{-2})	336	10.7	0.49
10.59[e]	Carbonate (10^{-2})	336	16.6	1.00
10.62[e]	NaOH (10^{-3})	328	18.6	0.82
11.11	NaOH (2.5×10^{-3})	328	27.5	0.55
11.41	NaOH (5×10^{-3})	328	41.7	0.84
11.67[e]	NaOH (10^{-2})	328	70.8	0.63
11.94	NaOH (2.5×10^{-2})	328	145	1.78
12.20	NaOH (5×10^{-2})	328	302	4.23
12.55[e]	NaOH (10^{-1})	328	380	5.32
12.55	NaOH (10^{-1})	328	0.045 7[f]	1.33

[a] At I = 0.1 mol dm^{-3} (except for 1 mol dm^{-3} $HClO_4$), adjusted with $NaClO_4$ where necessary. [b] Mean of measurements at start and finish of reaction; absence of s.e. indicates no change. [c] Measured at 23 °C and shown here adjusted to 50 °C as described in Experimental section, except at pH < 4, where {H$^+$} has been assumed to be temperature-invariant (see text). [d] Analytical wavelength. [e] Measured at 50 °C. [f] Decomposition *via retro*-aldol reaction (see text).

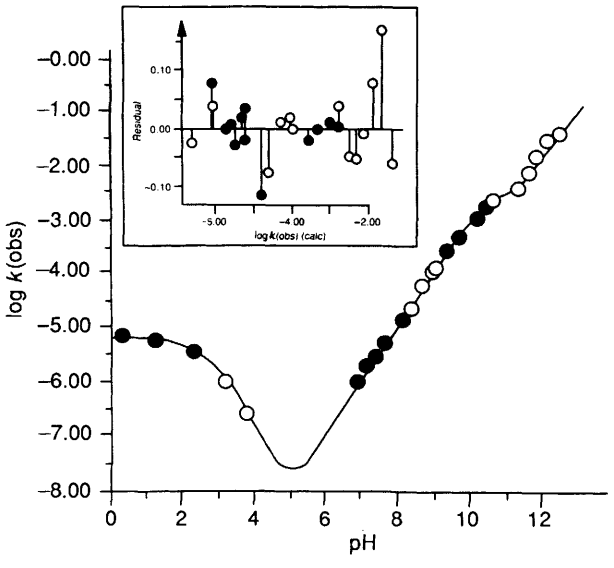


Fig. 1 Rate–pH profile in 30% v/v isopropyl alcohol at 49.6 °C for the reversible cyclisation of **1** to **2** (k_{obs} *vs.* pH). Alternating buffer regions are shown as filled and open circles (see the text). The line is drawn by ENZFITTER (ref. 17) and fitting constants are in Table 3.

acetophenone (3.0 g, 15.3 mmol) and 4-ethoxybenzaldehyde (2.76 g, 18.4 mmol) dissolved in warm ethanol (120 cm^3) were treated dropwise with 50% aqueous NaOH (12 cm^3) keeping the temperature below 40 °C. This solution was stirred at ambient temperature overnight and the resulting yellow precipitate was filtered, washed with dilute aqueous hydrochloric acid and then with water, and recrystallised from ethanol. The first crop of crystals was again recrystallised to yield the *product* (1.9 g, 38%), m.p. 137–138 °C (Found: C, 69.3; H, 6.0. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%); λ_{max}(EtOH)/nm 370; δ_H (90 MHz; $CDCl_3$) 1.40 (3 H, t, CH_2CH_3), 3.80 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.06 (2 H, q, CH_2CH_3), 5.92 and 6.06 (each 1 H, d, 3′-H and 5′-H), 6.82 (2 H, d, 3-H and 5-H), 7.55 (2 H, d, 2-H and 6-H), 7.77 (2 H, s, olefin CH), and 14.3 (1 H, s, OH).

pH Measurement.—In mixed aqueous solvents there is no ambiguity concerning [H$^+$] and [OH$^-$] when only strong acids and alkalis are used, but acute problems arise when, as here, buffers have to be employed across most of the pH range. We calibrated our electrodes at 25 °C using aqueous buffers of known pH,[12] and then used these to measure the apparent pH of buffer solutions of known composition in 30% v/v isopropyl alcohol, adjusted with sodium perchlorate to I = 0.1 mol dm^{-3}. This process, using the identical buffer solutions, was repeated at 50 °C, and at other temperatures where appropriate (*vide infra*). From these readings, calibration graphs of buffer pH at 25 °C *vs.* 50 °C could be constructed. In the kinetic measurements, buffer pH values were measured at 25 °C for each solution before and after each kinetic run, and the mean pH was then converted to 50 °C using these calibration graphs. These values, for the rate–pH profile at 49.6 °C, appear in Table 1. Since hydrogencarbonate will slowly decompose at elevated temperatures, this procedure was not used for carbonate buffers, which were measured directly at 50 °C. Perchloric acid and formate buffer solutions were measured only at 25 °C, since [H$^+$] is by necessity temperature-invariant in the former case, while formate buffers are known[12] to possess very small temperature coefficients. The smoothness of the rate–pH profile at 49.6 °C (Fig. 1), with no sign of any discontinuity between the various buffer regions, is evidence that this procedure was successful.

These apparent pH values are subject to an unknown liquid junction potential, and additionally require correction for any departure of f_{H^+} from unity. The first three pH readings of Table 1 suggest, however, that the combined effect of these two corrections cannot exceed 0.2 pH units; this is consistent with the known[13] very small liquid junction correction required for aqueous methanol in the water-rich region. We believe, therefore, that no important difficulty arises from either source when comparing these pH values with those in water.

In order to interpret the microscopic rate constants (*vide infra*) it is necessary to know pK_a for **1** and also pK_s, the autoprotolysis constant for 30% v/v isopropyl alcohol, both as a function of temperature. Because of the rate of reaction at elevated temperatures, pK_a was measured at a number of lower temperatures to obtain eqn. (2) from which the values of Table 4

$$pK_a = 8.30(36) + 698(109)/T\,K \quad (2)$$
$$(n = 5 \quad r^2 = 0.932 \quad s = 0.04 \quad F = 41)$$

have been derived. pK_s was obtained, at 23 and 50 °C, by assuming the relation K_s = {H$^+$} [OH$^-$] where [OH$^-$] represents the known concentration of NaOH and {H$^+$} is obtained from the pH meter reading. Both derivations make the same assumptions as the pH scale itself (*vide supra*) so that self-consistency is maintained. The temperature-dependence of pK_s was assumed to obey an equation of type (2), as is known[14] for pK_w itself. In fact, $\Delta pK_s = -0.87$ between 23 and 50 °C is closely similar to the known[14] value of −0.81 for ΔpK_w. The greater value of pK_s than pK_w at a given [H$^+$] demonstrates the greater f_{OH^-} expected[14] for a solvent of lower relative permittivity than water.

Rate Measurements.—Buffer solutions (50 or 100 cm^3) were prepared as described above (for details see Table 1) and kept in a thermostat bath at the reaction temperature. To start the

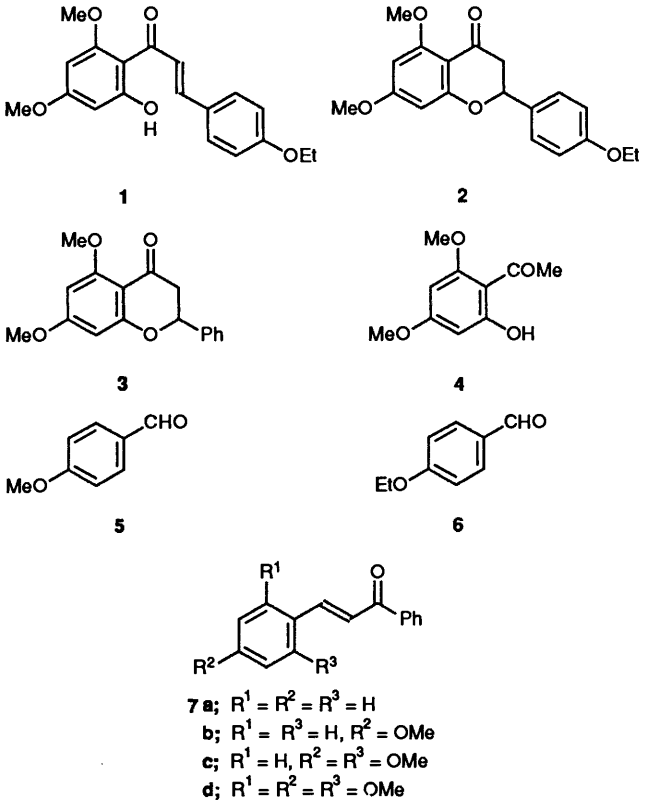
Table 2 UV data for **1** and model compounds

Compound	Solvent	λ_{max}/nm	log (ε/dm^3 mol^{-1} cm^{-1})
1	Hexane	354	
	MeCN	366	
	30% v/v Pr^{i}OH	372	4.51
1 anion	30% v/v Pr^{i}OH	328	4.38
2[a]	30% v/v Pr^{i}OH–1 mol dm^{-3} $HClO_4$	289	4.24
3[b]	EtOH	284, 315s	4.26, 3.65
5[c]	EtOH	277	4.17
4[d]	48% EtOH–0.05 mol dm^{-3} NaOH	288, 338	3.82, 3.62
4 + **6**[e]	30% v/v Pr^{i}OH–1 mol dm^{-3} NaOH	290, 333	4.18, *ca.* 4.0

[a] Estimated for cyclisation product after 4 half-lives, after correction for concentration of **1**. [b] C. Enebank and J. Gripenberg, *Acta Chem. Scand.*, 1957, **11**, 866. [c] N. J. Leonard, R. T. Rapala, H. L. Herzog and E. R. Blout, *J. Am. Chem. Soc.*, 1949, **71**, 2997. [d] As anion: C. Enebank, *Acta Chem. Scand.*, 1957, **11**, 895. [e] Final product spectrum after 10 half-lives at 49.6 °C (see Table 1 and text).

reaction, 3 cm^3 of buffer solution was placed in a 1 cm UV cuvette held in a thermostatted cell block, and 30 mm^3 of a stock solution of **1** was injected once the required temperature had been attained. This stock solution consisted of *ca.* 2 × 10^{-3} mol dm^{-3} **1** dissolved in isopropyl alcohol–dimethyl sulfoxide (90:10 by volume), in which it is indefinitely stable at ambient temperature. Reaction rate was monitored by the fall in absorbance at 374 nm (pH < pK_a) or 328 nm (pH > pK_a) or otherwise as given. The solution pH was monitored as detailed above.

Pseudo-first-order rate constants (k_{obs}) were obtained by a least-squares procedure according to Swain's method,[15] which is particularly well suited to reactions for which the infinity point is not known. Rate constants for the pH profile at 49.6 °C (Fig. 1), with their standard errors (s.e.), appear in Table 1. The latter are in general small, but increase markedly at pH > 12, where the conversion to flavanone is only a few per cent (see below).



7a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^3 = H$, $R^2 = OMe$
c; $R^1 = H$, $R^2 = R^3 = OMe$
d; $R^1 = R^2 = R^3 = OMe$

Results

Identification of Reaction Products.—No attempt was made to isolate these. The product peak is at λ_{max} 289 nm and at pH < 9, where conversion is *ca.* 90%, its approximate intensity may be calculated. The flavanone **2** has not been reported but its UV characteristics, obtained this way, are satisfactorily close to those of **3** (Table 2).

At high pH a further, irreversible reaction takes place which is presumably the reverse of the aldol condensation that generates **1** (see Experimental section). Again, the product UV spectrum is satisfactorily close to the sum of **4**, and **5** as a model for **6** (Table 2). Its rate (Table 1) is *ca.* 10^{-4} that of the isomerisation process so is unlikely to have affected the study of this in any way. It has not been further investigated. In 95% ethanol at 45 °C, Noyce and co-workers[16] find k_{OH} = 2 × 10^{-4} dm^3 mol^{-1} s^{-1} for fission of the chalcone **7a** to benzaldehyde and acetophenone, which is about four times that of **1** but reasonable since the latter will probably be deactivated by its substituents.

The Rate–pH Profile at 49.6 °C.—This is shown as Fig. 1, on which the line has been generated by the non-linear least-squares program ENZFITTER,[17] using the empirical eqn. (3);

$$k_{obs} = k_H[H^+]/(K_A + [H^+]) + k_fK_C/(K_C + [H^+]) + k_rK_s/[H^+] \quad (3)$$

values of the fitting constants k_H, k_f, k_r, K_A and K_C are given in Table 3. Here k_H is the overall plateau rate at low pH whereas k_f and k_r, respectively, represent the forward and reverse reaction processes catalysed in some sense by alkali. This equation is similar to those used by Main and co-workers,[7,8] with two important differences. Firstly, the term in k_H is not linear in [H$^+$] but takes into account the plateau at low pH, so that K_A is an apparent ionisation constant (*vide infra*). Secondly, there appears to be no need for an uncatalysed term; if one exists, it must possess k < 10^{-7} s^{-1} at 50 °C. Values of up to 10^{-5} s^{-1} at 30 °C have been reported by Miles and Main,[8] but this is for water in which the reaction is considerably faster, and involves 2′,6′-dihydroxychalcones for which its mechanism may be subtly different. It is possible that these two differences are connected.

$$k_{obs} = k_fK_C/[H^+] + k_rK_s/[H^+] \quad (4)$$

At $K_A \gg [H^+] \gg K_C$, eqn. (3) simplifies to eqn. (4), from which $K_{eq} = k_fK_C/k_rK_s$ = 7.54, or 88% conversion to flavanone. Since this relation defines the conditions under which chalcone and flavanone are present as substantially the neutral species, K_{eq} = 7.54 *necessarily* reflects the position of equilibrium at all pH ≪ pK_a. This value is roughly confirmed by comparison of

Table 3 Fitting constants and activation parameters for the reaction at 49.6 °C in 30% v/v isopropyl alcohol[a,b]

Constant	Value	$\Delta H^{\ddagger}$/cal mol^{-1}	$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}
k_H/s^{-1}	6.35 (±0.48) × 10^{-6}		
k_f/s^{-1}	1.80 (±0.26) × 10^{-3}	16 190 ± 410	−21.1 ± 1.4
k_f'/dm^3 mol^{-1} s^{-1}	3.40	5 170 ± 440	−41.0 ± 1.5
k_r/dm^3 mol^{-1} s^{-1}	0.466 (±0.037)	9 340 ± 410	−31.7 ± 1.4
pK_A	2.29 (±0.05)		
pK_C	10.31 (±0.07)		
k_f/s^{-1}[c]	5.8 (±0.5) × 10^{-2}	12 750 ± 880	−25.2 ± 3.0

[a] 1 cal. = 4.184 J. [b] See eqn. (3) for definition of rate constants (for k_f' see following text). [c] For 10% v/v isopropyl alcohol in which $k_{obs} \equiv k_f$ (see the text).

Table 4 Equilibrium data for 30% v/v isopropyl alcohol[a]

	25 °C	49.6 °C
ΔH_{eq}/cal mol^{-1}	−4170	
ΔS_{eq}/cal K^{-1} mol^{-1}	−9.3	
ΔG_{eq}/cal mol^{-1}	−1400	
K_{eq}	10.6	7.3
pK_s[b]	14.47 ± 0.04[c]	13.60 ± 0.05
pK_a (**1**)[d]	10.66 ± 0.04	10.46 ± 0.04
pK_a (2-hydroxyacetophenone)	10.24 ± 0.02[e]	
pK_a (4-hydroxyacetophenone)	7.98 ± 0.08[e]	
pK_a (2-cyanophenol)	6.86[e]	
pK_a (4-cyanophenol)	7.97[e]	

[a] 1 cal = 4.184 J. [b] Based on replication (n = 3) at these two temperatures only. [c] At 23 °C. [d] Interpolated from eqn. (2). [e] Mean of published values in water (ref. 20).

A_{374} at the beginning and end of the reaction over the pH range 0–9, given that UV absorption by the flavanone product at this wavelength is insubstantial. Eqn. (3) may also be used to calculate the conversion to flavanone at [OH$^-$] = 0.1 mol dm^{-3} as only 4%, so that k_{obs} under these conditions is substantially k_r.

Temperature Coefficients.—Since the reaction rate at [OH$^-$] = 0.1 mol dm^{-3} is overwhelmingly that for the reverse reaction, the temperature coefficient of k_r was measured in [NaOH] = 0.1 mol dm^{-3}, at six temperatures over the range 11–40 °C, using the formula $k_r = 0.96\, k_{obs}[H^+]/K_s$. (The point for 49.6 °C was found to fit the regression line). The forward reaction however is pseudo-unimolecular and here the required formula is $k_f = 0.88\, k_{obs}[H^+]/K_a$ at pH ≪ pK_a, where [H$^+$] and K_a are known as a function of temperature and the temperature range, 37–65 °C (n = 5), was so chosen that the factor of 0.88 is appropriate at the centre of it.

The latter data can also be used to estimate a quantity $k_f' = 0.88\, k_{obs}[H^+]/K_s$ which represents the hypothetical second-order rate constant for attack of hydroxide ion on **1**, and from which $K_{eq} = k_f'/k_r$ follows directly. The activation parameters for all three rate constants, calculated from the Eyring equation,[18] are in Table 3, and the resultant terms for K_{eq} are in Table 4. Calculated this way, K_{eq} at 49.6 °C is 7.3, which compares satisfactorily with 7.54 from the pH profile as given above.

The Effect of Solvent.—Furlong and Nudelman[9b] have studied the cyclisation of some hydroxychalcones in several mixed aqueous solvents which appear to show that the reaction rate goes through a maximum as co-solvent is added; for aqueous isopropyl alcohol, this maximum appears to correspond to *ca.* 20% co-solvent. We have studied k_{obs} at 49.6 °C over the range 10–30% isopropyl alcohol and find the relation of eqn. (5) with no sign of any departure from linearity.† Furthermore,

$$\log[k_{obs}/s^{-1}] = -2.30(0.05) - 15.8(0.7)\, x_{(Pr^iOH)} \quad (5)$$
$$(n = 5\ r^2 = 0.994\ s = 0.05\ f = 502)$$

the slope in water-rich conditions is the *opposite* of that claimed by Furlong and Nudelman, increasing rapidly as the solvent becomes more aqueous and extrapolating to an overall rate 60 times faster in water than in 30% v/v isopropyl alcohol. Our results were obtained at a constant pH 9.00 for each mixed solvent, so that k_{obs} in each case was dominated by the forward reaction. [We do not know pK_a (**1**) except in 30% isopropyl alcohol; its likely pK_a in water is discussed below]. Furlong and Nudelman state that 'kinetics were measured for the pH-independent region' but no such region exists for 2′-hydroxychalcone itself[7] on which most of their work was carried out (*cf.* Fig. 1).§ We are forced to regard their results as artefactual, probably the complex resultant of changing pH and pK_a values. Nevertheless it should be noted that their data for *pure* solvents, which show the reaction in water to be much the fastest, are entirely consistent with the trend of eqn. (5). We consider the probable interpretation of this relation below; meanwhile, it may be noted that the content of chalcone at equilibrium drops from 12% in 30% isopropyl alcohol to <3% at 10% isopropyl alcohol content, so evidently k_f accelerates much more rapidly than k_r as the conditions approach pure water.

Discussion

Ideally, work of this type is best carried out in water at or near 25 °C, to avoid problems in the interpretation of pH and related thermodynamic quantities, and this has been achieved in most previous studies,[7–9] but the low aqueous solubility of **1** precluded it here. We chose 30% v/v isopropyl alcohol for its UV-transparency and also for its lower acidity (pK_a 17.1), and much lower nucleophilicity, than water.[19] Hence the lyate anion in this mixed solvent is overwhelmingly OH$^-$, the more so since the mole fraction of water is still almost 0.89, and this will be responsible for any alkaline catalysis detected. In fact, we have no evidence for the intervention of lyate ion except as a proton transfer agent; similarly, the smoothness of the pH profile points to no or very slight buffer catalysis at the concentrations employed here.

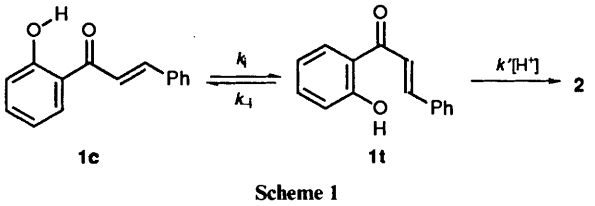
In order to compare our rates with those for model reactions, we need some estimate of the difference between this reaction at 49.6 °C in 30% v/v isopropyl alcohol and those in water near 25 °C. We proceed as follows. Old and Main[7] find pK_a = 9.55

† For solubility reasons, the results for 10% isopropyl alcohol were obtained by extrapolation from higher temperatures.

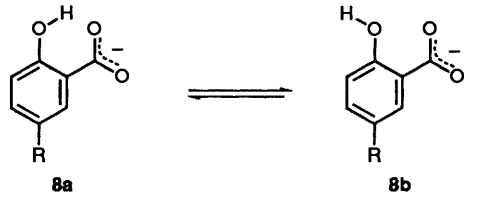
§ 2′,6′-Dihydroxychalcones show a plateau at high pH due to intervention of the second chalcone ionisation step.[8a] However, since this results from the interaction of two independent reaction processes it does not have the simple significance of k_f in the present case, so that, as for k_{obs} here, its variation, *e.g.* with temperature or solvent,[9] cannot be interpreted unless the balance of these is known. In addition, special catalytic pathways are available to 2′,6′-dihydroxychalcones, due to the second OH group,[8a] which may profoundly alter the balance of the microscopic reaction steps. For that reason, they will not be considered further in this paper.

for 2′-hydroxychalcone itself, unchanged for the 4′-methoxy but down to 8.95 in the 6′-methoxy derivative. Hence substitution of OR has little effect on phenol pK_a except where it can affect planarity, as in the latter case, a conclusion confirmed by the results for simpler phenols,[20] and accordingly we estimate $pK_a \approx 9.0$ for **1** in water. So, at pH 9.0 where we studied the effect of solvent (see above), the concentration of chalcone anion **1A** will have increased *ca.* 10-fold in going from 30% isopropyl alcohol to water. Since this is the reactive species for k_f, which dominates k_{obs}, the *ca.* 60-fold increase in k_{obs} must contain a *ca.* 6-fold rise in rate due to intrinsic reactivity. However, the calculated drop in k_{obs} between 49.6 and 25 °C is just about of this order (see activation parameters of Table 3). Hence these factors roughly cancel and a direct comparison can be made. Concerning equilibria, pK_a values of cationic acids are rather insensitive to solvent,[21] and all low pK_a values to temperature;[12] we consider phenols as acids later. However, isomeric and tautomeric equilibria are expected to show considerable solvent effects, which we discuss below.

The Reaction in Acid.—This is sigmoidal in form with an inflection at pH 2.29 which takes the form of an apparent pK_a (pK_C, Table 3). However, no UV change accompanies this inflection, and protonation of **1** is not expected till pH $\ll 0$.[22] Accordingly, a change in rate-limiting step is implicated. One possibility involves isomerisation in a pre-equilibrium step (Scheme 1).* Furlong and Nudelman,[9a] following Pacheco *et al.*,[10] show the hydroxychalcones they have studied to exist overwhelmingly as the *s-cis* form **1c** which contains an intramolecular hydrogen bond, a conclusion strongly supported in the present case by $\delta_{OH} = 14.3$. This form must isomerise to the *s-trans* conformer **1t** before reaction can take place. However, this is for non-aqueous solvents; we have to enquire as to rates and equilibria in aqueous or near-aqueous solution. Something is known concerning such rates and equilibria,[23] though not precisely for the present case. The nearest analogue is probably the salicylate anion **8**,[23,24] for which making and

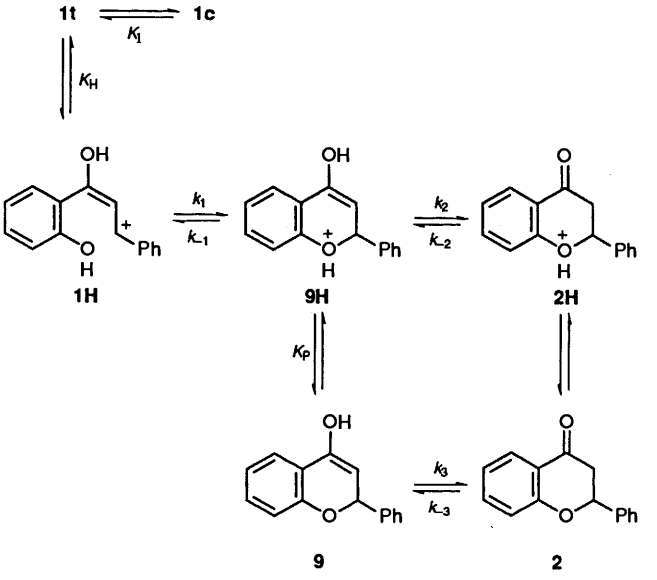


Scheme 1



breaking the intramolecular hydrogen bond involves rates of $>6 \times 10^7$ s^{-1} and $>6 \times 10^4$ s^{-1}, respectively. In fact, the latter rate appears remarkably constant for a variety of structural types.[23-25] Since this step is required to be rate-determining at pH < 2 [*cf.* eqn. (3)], Scheme 1 can be rejected. Of course, Scheme 1 collates two stages, the other being rotation about both single bonds to carbonyl, but since the rate of this process in acrylates has been calculated (STO-3G)[26] as *ca.* 10^{11} s^{-1}, the entire process must be considered a pre-equilibrium in any plausible reaction mechanism. The above calculation,[26] incidentally, supports the *s-cis* conformer as that likely to be dominant[9a] for unsaturated ketones generally.

Our preferred reaction mechanism is shown as Scheme 2.



Scheme 2

Here the above isomerisation appears as a pre-equilibrium, and we need first to estimate K_1. We proceed as follows. In general, pK_a is lower for 2-X-substituted than for 4-X-substituted phenols when X is a polar substituent, such as CN, incapable of forming an intramolecular hydrogen bond; when this happens however the situation reverses, as for the hydroxyacetophenones (for both see Table 4). Given near-identical pK_a values for the two *para*-isomers, we may estimate $pK_a \approx 7$ for 2-hydroxyacetophenone in the absence of such bonding.† Hence, following Hibbert,[23] we have $K \approx 10^{3.3}$ for hydrogen bond formation in that case. The lower pK_a for **1** in water, estimated above as *ca.* 9, most probably results from some twisting as a result of 2,6-disubstitution, leading to a weaker internal bond with substantially no change in 'intrinsic' acidity; hence $K_1 \approx 10^{-2}$ for **1** in water. Since this bond should be stronger in the less polar solvent 30% isopropyl alcohol, we assign most of the rise in pK_a for **1** to that factor, with K_1 now close to 10^{-3} and k_i and k_{-i}, as defined by Scheme 1, probably very close to the values found for **8**.[23]

Two protonic acid pK_a values need to be considered. The chalcones **7a–d** possess[22] pK_a values of −5.17, −4.25, −4.04 and −3.25, respectively, rising that is as alkoxy-substitution increases. The chalcone **1** contains four electron donors three of which are in the same ring as carbonyl, so might be more basic than **7d**. On the other hand, vinylogous conjugation as for **7** is often more effective than contiguous conjugation as for **1**; for example, aminoenones are much stronger bases than simple amides.[28] In view of these uncertainties we adopt $pK_a \approx -4$ for **1H** as a reasonable compromise. This choice of value affects those for k_1 and K_1 only. There is less doubt concerning **9H**, for which pK_a −6.51 for anisole[29] seems a good model.

$$k_f = \left\{\frac{[H^+]}{[H^+] + K_H}\right\}\left\{\frac{k_1K_1(k_2[H^+] + k_3K_P)}{(k_{-1} + k_2)[H^+] + k_3K_P}\right\} \quad (6)$$

* Note that substituents other than OH are omitted from the Schemes in the interests of clarity.

† No help is to be had from *ortho* σ-values, whose σ_I/σ_R balance varies with the system so that no universal scale is possible.[27]

Steady-state treatment of Scheme 2 leads to eqn. (6). Given $K_H = 10^4$, $K_P = 10^{6.5}$ and $[H^+] \leqslant 1$, the first bracket collapses to $[H^+]/K_H$ while the k_2 term in the numerator disappears from the second. The rationale behind Scheme 2 is that k_1 cannot be rate-limiting since expulsion of OH (k_{-1}) is likely to be very much faster than the ketonisation step k_2; deprotonation of **9H** to **9** is necessary for the reaction to go forward. Application of this and the above conditions leads to the simplified eqn. (7).

$$k_f = k_1k_3K_1K_P[H^+]/K_H(k_{-1}[H^+] + k_3K_P) \quad (7)$$

The contribution of k_f to the plateau rate k_H is then given by $k_3K_1K_1K_P/K_H = 10^{-5.3}$ s^{-1}. For the spontaneous or water-catalysed ketonisation of PhC(OH)=CH$_2$, Kresge and co-workers[30a] give $k = 1.9$ s^{-1} at 25 °C in water from which $k_3 = 10^{0.3}$, leading to $K_1 = 10^{-5.1}$. Furthermore, at the point of inflection $[H^+] = K_A$, we have $k_{-1}K_A = k_3K_P$; substituting for k_3, K_A and K_P as above gives $k_{-1} = 10^{9.1}$ s^{-1}. Hence $k_1 = k_{-1}K_1 = 10^{4.0}$ s^{-1} may also be deduced.†

$$k_r = k_{-1}k_{-3}[H^+]/(k_{-1}[H^+] + k_3K_P) \quad (8)$$

On the same assumptions as for eqn. (7), eqn. (8) represents the steady-state equation for k_r. On the plateau this simplifies to $k_r = k_{-3}$. Given that $k_r = 10^{-0.9}k_H$ (because $K_{eq} = 7.54$), we have $k_{-3} = 10^{-6.1}$ s^{-1}: *i.e.* the reversion of **2** to **1** at low pH *directly measures* its spontaneous enolisation rate.

From $k_3 = 10^{0.3}$ and $k_{-3} = 10^{-6.1}$ there follows $K_3 = 10^{6.4}$, the tautomeric ratio K_T = **[2]**/**[9]**. We have next to enquire whether this value is reasonable. The known log K_T values for acetophenone, acetone, cyclopentanone and cyclohexanone, are 7.90[30a] (or 8.15),[32] 8.22[30b] (or 8.46),[32] 8.00,[32] and 6.39[33] (or 6.54),[32] respectively. Hence cyclohexanone is somewhat out of line with the remainder. One possible reason lies in compression of the CCC bond angle in ketones as is both known to occur, and supported at every level of *ab initio* calculation;[34] this probably originates in the same lone pair–bonding pair electron repulsion that has been shown[35] to produce similar effects at tetrahedral carbon in species such as H_3CO^-. This could act to destabilise the keto-form in six-membered rings relative to open-chain structures. There could also be a solvent effect. Mills and Beak[36] have examined a number of tautomeric ketones over a range of solvents from which we choose **10** since this is the only one not complicated by other sorts of interaction.

10a **10b**

For **10** they find the linear solvation energy relation (LSER) of eqn. (9), where α and β are the solvent proton donor and

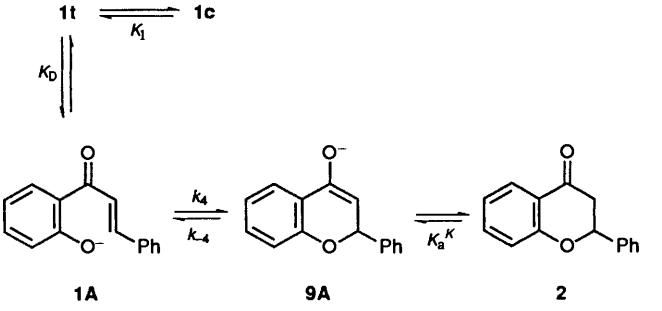
$$\Delta G_s = 4.0 + 1.87\alpha - 5.5\beta \quad (9)$$

acceptor terms of Kamlet *et al.*[37] We may use their values to calculate, for **10**, $\Delta\log K_T = -2.55$ as the predicted effect of substituting isopropyl alcohol for water. On a mole fraction basis as appears valid for log k (see above), a further change in Δ log K_T of *ca.* −0.3 might be expected from this source. We conclude that log K_T = 6.4 for **[2]**/**[9]** is eminently reasonable.

† It is not of course pretended that these microscopic constants can be estimated to an accuracy of 0.1 log units. However, we take heed of the warning[31] that premature rounding-off can needlessly coarsen even very approximate estimates.

Alternative reaction pathway. Johnson and co-workers[38] have studied the cyclisation of some 4-substituted 2′-hydroxychalcones in trifluoroacetic acid (TFA) and, from the variation in rate with substituent, postulate protonation at C-α rather than on carbonyl, so generating a carbocation at the point of attack. Part of their argument is based on a substantial solvent kinetic isotope effect (SKIE) which is taken as evidence for a proton in flight during the rate-limiting step. There is no necessity for the reaction in TFA to parallel precisely that in water; nevertheless, a SKIE is equally expected for rate-limiting ketonisation as is postulated below, while substrate protonation of whatever sort will show similar substituent effects. The Baldwin's Rule[3] implications of this work[38] are considered later.

The Reaction in Alkali.—This is simpler to the extent that the product K_1K_D equals the fitting constant K_C of eqn. (3), which in turn approximates K_A for **1**, so that for kinetic purposes, no dissection of these terms is necessary. From Scheme 3 we obtain



1A **9A** **2**

Scheme 3

the full steady-state eqn. (10). For k_f, the plateau rate simplifies

$$k_{obs} = k_f + k_r = k_4K_1K_D/([H^+] + K_1K_D) + k_{-4}K_a^K([H^+] + K_a^K) \quad (10)$$

to $k_f = k_4 = 10^{-2.7}$ s^{-1}. At low pH, such that ($[H^+] \gg K_1K_D$ or K_a^K), we obtain the relation of eqn. (11) which is soluble if we

$$K_{eq} = k_f/k_r = K_4K_1K_D/K_a^K = 10^{0.9} \quad (11)$$

can estimate K_a^K. This equals K_a^E/K_T where $K_T = 10^{6.4}$. Dubois and co-workers[32] have measured pK_a^E 10.34 for PhC(OH)=CH$_2$ which, adjusted for 30% isopropyl alcohol to the same extent as pK_D above, becomes $K_a^E = 10^{-10.6}$ for **9**. Hence $K_a^K = 10^{-17.0}$ from which $K_4 = 10^{-5.5}$ and $k_{-4} = 10^{2.8}$ s^{-1}.

In making this derivation we have assumed that acetophenone is likely to be a good model for **2** in terms of proton transfer rates to and from oxygen, but not for the equivalent rates at carbon; this is in line with our explanation for the differences in K_T noted above. We now extend this argument. Kresge[30] has analysed the alkali-catalysed deprotonation of PhCOMe, and its spontaneous reprotonation at oxygen, in terms of the rate constants k_{OH}^E and k_o', respectively, where these quantities are related as $k_o'K_a^K = k_{OH}^EK_w$. By hypothesis, we may use $k_o' = 10^{3.9}$ s^{-1} for acetophenone[30a] to model the reprotonation rate of **9A**; given $K_a^K = 10^{-17.0}$ and the experimental K_s (for K_w) $= 10^{-13.6}$, we obtain $10^{0.5}$ dm^3 mol^{-1} s^{-1} for k_{OH}^E. This is over tenfold greater than $k_{OH}^E = 0.25$ dm^3 mol^{-1} s^{-1} for acetophenone[30a] and reflects the postulated destabilisation of the keto-form. Hence Scheme 4 can be constructed, from which follows eqn. (12). Given the values

$$k_r = k_{OH}^Ek_{-4}/(k_o' + k_{-4}) \quad (12)$$

deduced for k_{OH}^E, k_o' and k_{-4}, this equation solves to give

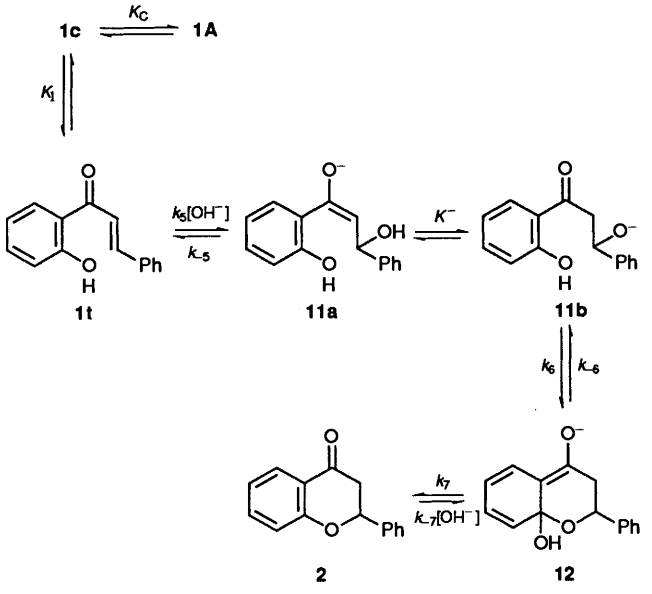
$k_r = 0.25\ s^{-1}$, not far from the observed value of $0.466\ s^{-1}$: a highly satisfactory outcome considering the extrapolations and approximations involved.

$$2 \underset{k_o'}{\overset{k_{OH}^E}{\rightleftharpoons}} \mathbf{9A} \underset{k_4}{\overset{k_{-4}}{\rightleftharpoons}} \mathbf{1A}$$

Scheme 4

Alternative Reaction Pathway. Tirouflet and Corvaisier[5] suggest, but do not favour, an alternative pathway involving hydroxide ion addition followed by its elimination *via* an intramolecular S_N2 displacement. This pathway overcomes the objection[2] that Scheme 3 involves a disfavoured 6-*endo-trig* ring closure, since 6-*exo-tet* processes are favourable.[3] Johnson[39] has observed that, while 2′-hydroxychalcone can be cyclised by MeO^-/MeOH, the reaction does not take place in Bu^tO^-/Bu^tOH, consistently with the fact that Bu^tO^- is not a nucleophile.[19]

This mechanism as it stands can be rejected since the S_N2 displacement of OH, except from ROH_2^+ under strongly acid conditions, is unknown.[40] However, Johnson[39] has suggested an ingenious variant which is shown as Scheme 5. This involves



Scheme 5

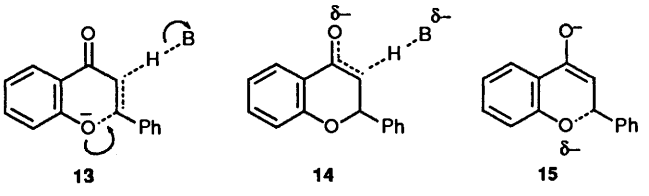
hydration of the double bond followed by intramolecular *ipso*-attack to give the Meisenheimer-type adduct **12** which then expels hydroxide ion. Here K^- is composite of $K_a^K = 10^{-17.0}$ and a re-ionisation step for which benzyl alcohol, pK_a[19] = 15.4, is a reasonable model, so that $K^- \approx 10^{1.6}$. Full steady-state treatment of the forward reaction leads to an expression that simplifies to eqn. (13) for the plateau rate, *i.e.* when $K_C \gg [H^+]$. Eqn. (13) may be further simplified by noting that, if **11** and **12**

$$k_f = k_5k_6k_7K^-K_1K_S/K_C(k_{-5}k_{-6} + k_{-5}k_7 + k_6k_7K^-) \quad (13)$$

are true steady-state intermediates, *i.e.* do not accumulate, all steps leading away from the sequence **11a** $\rightleftharpoons$ **11b** $\rightleftharpoons$ **12** must be much faster than those entering it. Given $k_{-5} \gg k_6$, it follows that the denominator term in $k_6k_7K^-$ disappears. It is more difficult to decide between k_{-6} and k_7 since both steps are likely to be very fast. Solving for known terms as previously, this leaves $k_6K_5 = 10^{2.0}$ or $k_7K_5K_6 = 10^{2.0}$ as rival solutions. Given $K_5 \ll 1$, the first possibility entails $k_6 \gg 10^2\ s^{-1}$. Rates of this order are known[41] for the formation of *spiro*-Meisenheimer complexes, but only for substrates much more activated than **12**. For example,[41a] while $k \approx 2 \times 10^7\ s^{-1}$ for the cyclisation of 1-hydroxy-2-(2,4,6-trinitrophenoxy)ethane, loss of one nitro-group reduces this to $k \approx 50\ s^{-1}$, so that for a single carbonyl substituent, $k \ll 10^{-3}\ s^{-1}$ may be anticipated. In addition, the substitution of a six- for a five-membered ring adduct reduces k (and K) by *ca.* 10^3. It follows that an impossible value for k_7 would probably be required to make the second possibility viable. Since K_5 must be very small, the first possibility entails $k_6 > 10^5\ s^{-1}$. In fact, k_5 is the obvious first step in retro-aldol fission of a chalcone, for which addition of hydroxide ion is known[16] to be rate-determining. As noted above, we observe a reaction which is probably this and for which $k_{OH} = 4.57 \times 10^{-5}\ dm^3\ mol^{-1}\ s^{-1}$ (Table 1). Since no reaction can be faster than its slowest step, this argument also eliminates Scheme 5 from consideration. Given that PhOH is a much weaker nucleophile than PhO^-, a parallel process to replace Scheme 2 is still less likely. This pathway can be dismissed at any pH. Most probably, Johnson's observation[39] is simply explained by the extremely high basicity of the reaction medium,[19] leading to scarcely any of the flavanone product as we have observed.

The Overall Reaction Mechanism.—As noted by Miles and Main,[8b] mechanistic discussion is most sensibly carried out in terms of the reverse reaction, which belongs to the much studied class of β-eliminations.[42,43] With at least approximate values of every microscopic rate and equilibrium constant for the present reaction, we are in a position not only to determine which are the rate-limiting steps, but also to indicate by means of Hammond's Principle,[44] if only qualitatively, the position of each transition state along its reaction co-ordinate.

For the reaction in alkali, Furlong and Nudelman[9a] postulate **13** as the transition state in the case of 2′-hydroxychalcone itself;



i.e. an E2 process, as has been noted.[8b] In terms of elimination this entails similar rates for proton removal and loss of phenoxide, *i.e.* $k_{OH}^E \approx k_{-4}$, which is far from the case (Table 4). Hence the E2 mechanism can be rejected. By contrast, Miles and Main[8] postulate rate-limiting deprotonation of the flavanone as depicted in the transition state **14**. This is the $(E1cb)_1$ mechanism[43] which will equally account for the SKIE's observed by both authors,[8,9] and also for general acid catalysis of the ring closure reaction as observed by Furlong and Nudelman.[9] In terms of Scheme 4, this requires $k_{-4} \gg k_o'$. We find just the reverse (Table 4).

Our postulated transition state is depicted as **15**. Given $k_o' \approx 10k_{-4}$ this lies on the ring-opening side of the enol anion **9A**, though only just, and its position is further substantiated[44] since, with $K_4 \approx 10^{-5.5}$, **9A** is a much higher energy species than **1A**. This then is the $(E1cb)_R$ mechanism which is unusual for PhCO as activating group and certainly unexpected for PhO^- as nucleofuge.[43] It is possible, of course, that the substituents in **1** have shifted the transition state slightly but significantly away from the position found for 2′-hydroxychalcone itself, though in fact Old and Main[7] do postulate what is essentially **15** in that case. It should also be noted that most subsequent work[8,9] has been carried out on 2′,6′-dihydroxychalcones where the mechanism may be different again. However, if we assume both general acid catalysis and an appreciable KIE to operate in the

Table 5 Estimates for the microscopic rate and equilibrium constants of Schemes 2–4

K_I	10^{-3}
k_i/s^{-1}	10^4
k_{-i}/s^{-1}	10^7
pK_D	7.3
pK_H	−4.0
pK_P	−6.5
k_1/s^{-1}	1.0×10^4
k_{-1}/s^{-1}	1.25×10^9
K_1	8×10^{-6}
k_3/s^{-1}	2.0
k_{-3}/s^{-1}	8×10^{-7}
$K_3 (= K_T)$	2.5×10^6
k_4/s^{-1}	2×10^{-3}
k_{-4}/s^{-1}	630
K_4	3.2×10^{-6}
pK_a^E	10.6
pK_a^K	17.0
$k_{OH}^E/dm^3\ mol^{-1}\ s^{-1}$	3.2
k_o'/s^{-1}	8×10^3

Table 6 Nucleofuge ranking orders for Z: in $G\text{-}CH_2CH_2\text{-}Z$[a]

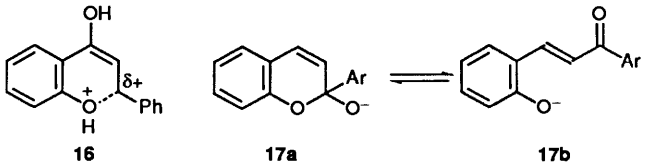
	G		
Z	CN	$PhSO_2$	PhCO
MeO^-	6.3	6.1	6.8
PhO^-	8.2	8.9	9.9[b]
$PhNMe_2$	10.7	9.2	

[a] Ref. 41. [b] This work.

present case, we have to explain their origin. Since the extent of C–O bond breaking is very slight, catalysis of this step is not expected, so that k_{OH}^E (and perhaps k_o') must be implicated. Stirling[43] notes that, in contradiction of simple theory, KIEs are in fact found for proton loss in detritiation reactions.[45] Their origin may lie in the substantial electronic reorganisation entailed when most of the developing anionic charge finishes away from the atom that loses its proton. Hence the argument from KIEs may be unsound. General acid catalysis might result from the same asymmetry, though as we note above, it is not very evident here (see Fig. 1) at buffer concentrations similar to those used by Furlong and Nudelman[9a] to demonstrate catalysis by glycine.

The unusual position for the transition state in this reaction, relative to more typical β-eliminations involving RCO as activating group,[43] may be some consequence of internal return; *i.e.*, the difficulty experienced by the phenoxide anion in attempting to diffuse away. Whatever its origin, it enables us to make an estimate of the hitherto inaccessible ranking order[43] of phenoxide as nucleofuge with PhCO as activating group. Using Stirling's formula,[43,45b] this value appears in Table 6 and is entirely in line with what might have been anticipated by cross-comparison with the other activating groups shown there.

For the reaction in acid (Scheme 2) there are effectively two transition states. For the reverse reaction, k_{-3} represents the plateau rate as seen above; this is much the slowest step in the reaction sequence. Hence the rate-limiting transition state lies



16 **17a** **17b**

on this path, and given $K_3 \approx 10^{6.4}$, then by Hammond's Principle[44] again, it must be very close to the enol **9** in structure. It may perhaps be represented as some protonated form of **14**; the mechanism of the spontaneous or water-catalysed ketonisation of enols is not known in any detail,[30a] so we defer further discussion. The other transition state lies on the path between **1H** and **9H**, and given $K_1 \approx 10^{-5.1}$, must be very close to the latter structure. We may represent it as **16**. This has an obvious similarity to **15**, in that fission of the C–O link has only just begun, and may share with it the same rationale, as stated above.

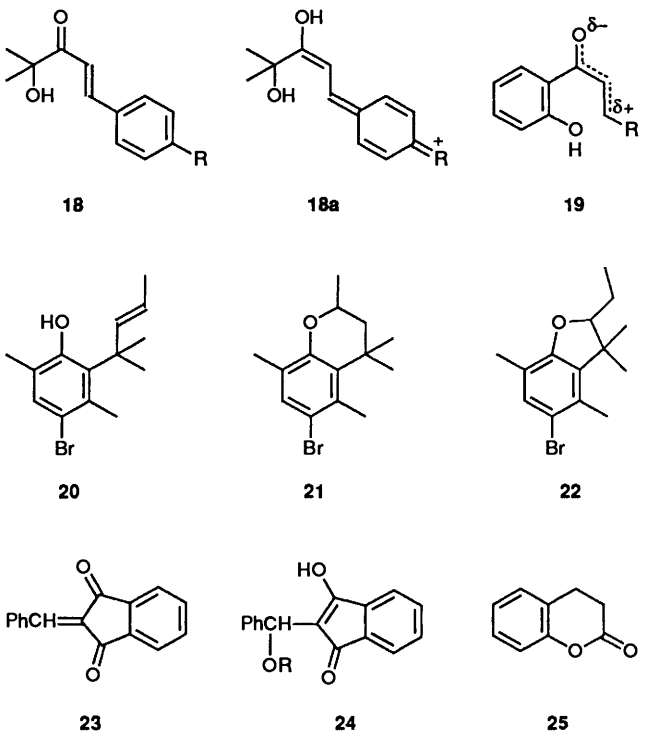
The fission step k_{-1} is so fast as to approach the diffusional limit to within an order of magnitude.[46] This step would not have to be very much faster for **16** to become an 'exploded transition state'[47a] of no significant lifetime. In fact, since the steady-state treatment of Scheme 2 actually works, we know that **9H** possesses a sufficient lifetime to equilibrate with **9**. Rates of this order for ring fissions are known; for example,[48] **17a** opens to **17b** in water at 25 °C at a rate of *ca.* $1 \times 10^9\ s^{-1}$. (Rather curiously, **17b** also is a chalcone, though cyclisation here takes a different form). It is possible that **9H** owes its relative stability to the multiplicity of electron-donor substituents that **1** contains. If so, this may be why the rate plateau at low pH has not been detected by previous investigators;[7–9] the acid-catalysed reaction studied by Tirouflet and Corvaisier[5] has an entirely different origin, in stoichiometric protonation of the substituted chalcone.

Since $pK_P \ll 0$, no catalysis is required for either step leading away from **9H**.[47b] Ketonisation can of course be acid-catalysed,[30] but that would distort the pH profile if it happened here, and no sign of it is visible (Fig. 1).

The extreme speed of step k_{-1} is no doubt connected with the status of the nucleofuge as an oxonium ion. No data exist for such species, but ammonium cations are among the very best nucleofuges in β-eliminations[43] (*cf.* Table 6), around 10^5 better than PhO^-, whereas loss of neutral amines (*i.e.* as the amine anion) is stated to be 'very slow.'[43] A qualitative indication is the 12 p*K* unit difference (5.07 to −7.04)[29] between $PhNMe_2$ and PhOH. The observed loss of PhOH from **9H** is *ca.* $10^{6.3}$ faster than that of PhO^- from **9A**, but the real gap in reactivity must be much greater than this since loss of the latter from **15** will be strongly assisted by the negative charge on enolate oxygen whereas loss of the former from **16** receives no such assistance. In the absence of better models, this argument cannot profitably be taken further.

Finally we consider the objection[2,49] noted at the start, that the present reaction as a 6-*endo-trig* cyclisation should be disfavoured, at any rate relative to the 5-*exo-trig* alternative product (**C**). Johnson and co-workers[49] find that **18** cyclises in acid but not in alkali and rationalise this in terms of the canonical form **18a**, which formally converts the acid-catalysed reaction into a 5-*exo-trig* cyclisation. The same argument could be used in the present case, and is indeed the reason why the alternative addition–elimination pathway for the reaction in alkali[5,39] was considered, and dismissed, above.

In fact, this argument is unnecessary. Any α,β-unsaturated ketone must be polarised in the sense of **19**, which places the partial positive charge on precisely that carbon atom which is attacked. There is even evidence that little advantage accrues to *exo-trig* mechanisms generally. Evans and Kirby,[50] in studying the cyclisation of the olefin **20**, find that the 5-*exo-trig* product **22** is favoured over the 6-*endo-trig* product **21** by a factor of merely 18. By analysing other cases,[50b] they demonstrate an even slimmer (*ca.* threefold) preference for the 6-*exo-trig* over the 6-*endo-trig* reaction pathway. Since these reactions all involve unactivated double bonds, and since polarisation of the double bond in **19** not only strongly favours the 6-*endo-trig* but must strongly disfavour the 5-*exo-trig* pathway, the preference



for flavanone **B** over aurone **C** as reaction product is not difficult to understand.

The Reaction Equilibrium.—We have remarked above on the fortunate accident that the chalcone–flavanone equilibrium is so closely in balance, a result echoed elsewhere[5,7–10] except where the flavanone product itself can ionise and this suppresses the reverse reaction. For example, 2′-hydroxychalcone itself possesses[10] $K = 3.5$ (in 33% ethanol) as against $K = 7.5$ in the present case. At first sight this is surprising, since conjugation is lost on cyclisation and the chalcone might well have been expected to be the more stable species. Pacheco and co-workers[10] indeed demonstrate that electron-donor substituents at the *para*-position of the styrene moiety (*i.e.* equivalent to *R* in **18**), which should increase the resonance energy of the system, do in fact stabilise the chalcone (though no significant effect of substituent was found in TFA[38]).

Given **1t** as the reactive species, the true $K_{eq} \approx 10^4$ in favour of the flavanone **2**. We require an intermolecular model for this process. For the hydration of simple activated alkenes in water, K_{eq} is typically found[51] in the range 1–10, *e.g.* $K_{eq} \approx 5$ for that of crotonic acid at 90 °C. At lower temperatures this value will be higher, hence $K_{eq} \approx 10$ may be taken as a reasonable estimate. A better model would be the addition of phenol, but there are no data. For the very activated molecule **23**, Bernasconi *et al.*[52] find $K_{eq} = 80.1$ dm^3 mol^{-1} for addition of PhO^- to give the anion of (**24**; R = Ph), with $K_{eq} \approx 10^4$ and $\approx 10^8$ for the formation of (**24**; R = H) and its anion by addition of water and hydroxide ion, respectively. While the difference in structure makes it impossible to transpose these results directly – in particular, **24** is still highly conjugated – they could imply that $K_{eq} \ll 1$ might be expected for the addition of PhOH to **1t**. On this argument, an effective molarity (EM)[53] of at least 10^5 appears to be present. EM values* of 10^4–10^8 are common for the formation of five-membered rings from conformationally-flexible systems in nucleophilic reactions,[53a] and a six-membered ring example is the lactonisation to yield **25** for which EM is[54] 4.7×10^5. Kirby notes[53b] that more rigid systems give higher EMs, and here **1** qualifies as more rigid than either **2** or the precursor to **25**. Here entropy is relevant. Our value for ΔS_{eq} of -9.3 cal K^{-1} mol^{-1} (Table 4) entails the overall reaction and not the process **1t** ⟶ **9** to which EM applies. A very rough estimate for the latter step may be derived from the dependence of rate on solvent composition. Since the increased k_f in 10% v/v isopropyl alcohol is largely the result of a weaker intramolecular hydrogen bond (see above), and since this is reflected in more negative $\Delta S^‡$ as well as $\Delta H^‡$ values (Table 3), we may reasonably conclude that ΔH and ΔS for the equilibrium **1t**/**1c** are both positive. If so, ΔS for the process **1t** ⟶ **9** is more negative than the measured ΔS_{eq} (we presume that the process **9** ⟶ **2** contributes inappreciably to its value). A value close to $\Delta S = -15$ cal K^{-1} mol^{-1} results. Since a value of ΔS near -5 cal K^{-1} mol^{-1} is expected[55] for simple cyclisation to give an alicyclic six-membered ring, it is difficult on this argument to reconcile the observed value of ΔS_{eq} with an exceptionally high EM. We conclude that, in this system, the observed *K* for intermolecular addition of water to simple α,β-unsaturated carbonyl compounds provides a better guide than that for PhOH based on the above rather dangerous extrapolation from **23** ⟶ **24**. The resulting estimate for EM of *ca.* 10^3 is probably the best that we can manage at the present time.

* While EM is in origin a kinetic concept, and the quoted value[54] is for a reaction rate, it should be noted that reverse rates *e.g.* for lactone hydrolysis are comparatively insensitive to structural factors,[53] so that EM can legitimately be used, as here, in the context of equilibria.

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