SHORT PAPER

Kinetics and mechanism of the intramolecular substitution of acetate in 2′-hydroxyphenacyl acetate: 2′-hydroxyphenacyl as a potential protective group for carboxylic acids

Colin R. Ogle and Lyndsay Main*

Chemistry Department, University of Waikato, Private Bag 3105, Hamilton, New Zealand

2-Acetoxy-2′-hydroxyacetophenone (**1c**) undergoes cyclisation in water via its phenolate ion to release acetate and coumaran-3-one (**2**) at rates defined by the equation $k_{obs} = k_1/[1+(10^{-pH})/K_a]$ where k_1, the first order rate coefficient for the cyclisation of the phenolate ion, is 8.6×10^{-4} s^{-1} and K_a, the ionisation constant for 2′-OH is 2.0×10^{-9} (pK_a 8.70) at 30°C.

Keywords: 2-acetoxy-2′-hydroxyacetophenone, intramolecular substitution

There have been few kinetic studies of intramolecular substitution reactions at phenacyl carbon by *ortho*-phenolate groups (Scheme 1). Bell and coworkers found[1] that the rates of chloro- and bromo-substitution in 2-chloro- (**1a**) and 2-bromo-2′-hydroxyacetophenone (**1b**) to form coumaran-3-one [3(2H)-benzofuranone; **2**] were very fast in water, but measurable at pH values in which the phenol was incompletely ionised. By using an estimated value for the phenol acid dissociation constant of 10^{-10}, they calculated first order rate coefficients at 25°C for cyclisation of the fully ionised phenolate ions of about 0.7 and 7 s^{-1} (half lives of 1 and 0.1 s) for chloro- and bromo-substitution respectively. The only related data that we are aware of for oxygen leaving groups apply to some 2′-hydroxy-6′-methoxychalcone epoxides (2′-hydroxy-6′-methoxy-α,β-epoxy-β-phenylpropiophenones), the phenolate ions of which cyclise preferentially to the α-carbon with rate coefficients of around 1 to 2 s^{-1} in 1:1 water/MeCN at 30°C.[2]

The study reported here is of the reactivity of this system with acetate as leaving group. The rate of the reaction is a guide to the ease of removal under mildy basic conditions of *o*-hydroxyphenacyl, a potential protective group for carboxylic OH in synthetic chemistry. Such a protective group could be attached to carboxylate ions using the phenacyl bromide (see Scheme 2 for the trivial case of acetate protection). The rate profile across the neutral to mildly basic pH region for the cyclisation reaction of 2-acetoxy-2′-hydroxyacetophenone [1-(2-hydroxyphenyl)-2-acetoxyethanone; **1c**] was therefore investigated.

The reaction of **1c** was monitored by UV spectroscopy at 30°C in 0.02 mol/l aqueous bicine [*N,N*-bis-(2-hydroxyethyl)glycine)] buffers (pH 7.8–8.9) and carbonate buffers (pH 8.8–10.6). Repetitive scanning showed formation of **2** (λ_{max} *ca* 330 nm), but further slow spectral changes indicated subsequent reaction of **2**, as was confirmed by separate study with **2** itself. Kinetic analysis of the cyclisation reaction was carried out by monitoring absorbance decrease with time at 310 or 360nm, depending on pH and the degree of ionisation of the phenol. The data used for kinetic analysis were restricted to about the first 75% reaction and analysed by the Guggenheim method[3] so as to circumvent the problem of lack of a steady infinity absorbance resulting from the subsequent slow reaction of initial product **2**. First order rate coefficients

for the cyclisation reaction (k_{obs}) were reproducible to within 6% between duplicate runs and were independent of buffer concentration and ionic strength at the low (<0.02 mol/l) buffer concentrations employed. The pH-rate profile (Figure) has the form of an ionisation curve consistent with the phenolate (2′-O-) species being the only significant contributor to the reaction. Quantitatively, the rate data (boxes in the Fig.1) fit the theoretical curve, which is defined by the equation

$$k_{obs} = k_1/[1+(10^{-pH})/K_a]$$

where k_1, the first order rate coefficient for the cyclisation of the phenolate ion is 8.6 (±0.3) x 10^{-4} s^{-1} and K_a, the ionisation constant for 2′-OH, is 2.0 (±0.4) x 10^{-9} (pK_a 8.7 ± 0.1).

The rate coefficient for cyclisation of the unionised phenolate was too small to be measured but is clearly no greater than the measured k_{obs} of 1.2×10^{-5} s^{-1} at the lowest pH studied (6.84).
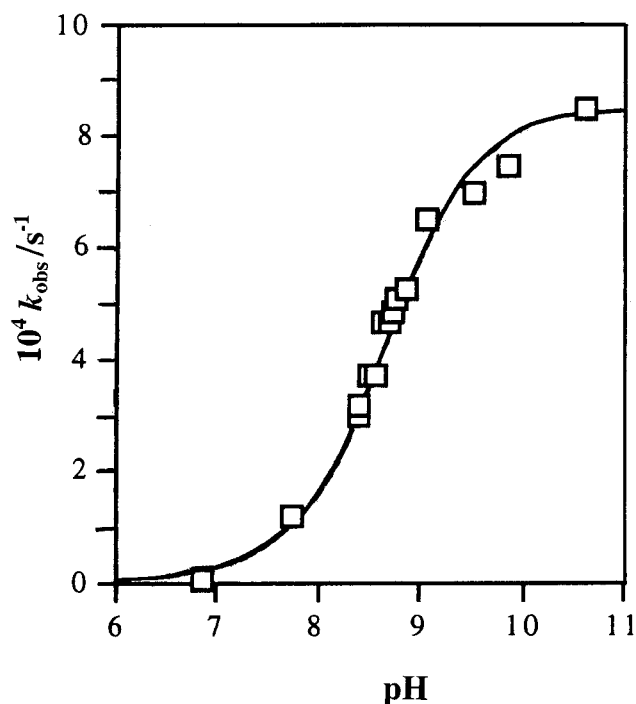
Fig.1 First order rate coefficient (k_{obs}) vs pH for the reaction of **1c** in buffered aqueous solution at 30°C. The line of best fit is based on equation (1) with a pK_a of 8.70 for **1c** and rate coefficient (k_1) for cyclisation of the phenolate ion of **1c** of 8.6×10^{-4} s^{-1}.

* To receive any correspondence. E-mail: l.main@waikato.ac.nz
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*
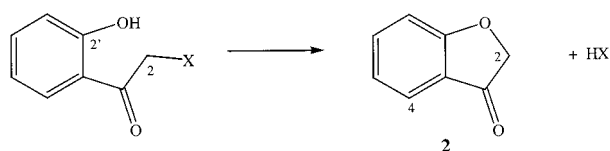
1 a X = Cl   d X = OC$_6$H$_4$(4-OMe)
  b X = Br   e X = OC$_6$H$_4$(4-CN)
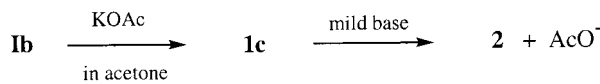 c X = OAc

Scheme 1

Scheme 2

At pH 10.0, where **1c** is almost fully ionised, it releases acetate with a half-life of about 15 minutes, and at pH 8.7 (half-ionisation) the half-life is about 30 min (30°C). By comparison, the second order rate coefficient reported for OH$^-$ with methyl acetate (at 25°C) indicates a half-life of about 10 hours (pH 10) and 2000 hours (pH 8.7).[4] Even allowing a factor of say 2 for the 5°C temperature difference, the 2′-hydroxyphenacyl ester at half-ionisation is around three orders of magnitude more reactive in releasing acetate than a methyl ester. As a protective group for a carboxylic acid, therefore, 2′-hydroxyphenacyl would have some considerable advantage over methyl in terms of mildness of basic conditions of removal. That 2′-hydroxyphenacyl esters are prepared under mildly basic conditions (see Experimental), may also be in their favour in some protective group applications.

In earlier unpublished work,[5] we found that displacement of 4-methoxyphenoxide from 2-(4-methoxyphenoxy)-2′-hydroxyacetophenone (**1d**) and of the better leaving group 4-cyanophenoxide from 2-(4-cyanophenoxy)-2′-hydroxyacetophenone (**1e**) are both immeasurably slow at pH 10, showing that 2′-hydroxyphenacyl has no application as a protective group for phenols. The reactivity limit for cyclisation at 30°C in the 2′-hydroxyphenacyl system in terms of oxygen leaving group ability therefore lies between acetate (pK_a of conjugate acid 4.75) and *p*-cyanophenolate (pK_a 7.95).

Experimental

2′-Hydroxyacetophenone was converted with CuBr in ethyl acetate-chloroform under reflux[6] to 2-bromo-2′-hydroxyacetophenone, which was dissolved in dry acetone and stirred with dry, powdered potassium acetate at room temperature for 90 min. before filtration, solvent removal and product purification on a silica layer (7:3 petro-

leum spirit/ether eluent). 2-Acetoxyacetophenone (**1c**) had m.p. 57°C (lit.[7] 171°C); IR (KBr) ν$_{C=O}$/cm^{-1} 1655, 1744; NMR (CDCl$_3$): ^{1}H δ 2.23 (s, 3H, CH$_3$), 5.35 (s, 2H, CH$_2$), 6.90–7.68 (m, 4H, Ar-H), 11.63 (s, 1H, OH); ^{13}C δ 20.5 (q, CH$_3$), 64.9 (t, CH$_2$), 117.1 (s, C-1′), 118.9 (d, C-3′), 119.3 (d, C-5′), 128.3 (d, C-6′), 137.1 (d, C-4′), 162.3 (s, C-2′), 170.4 (s, ester C=O), 197.3 (s, ketone C=O). Found: C, 62.07; H, 5.27%. C$_{10}$H$_{10}$O$_4$ requires C, 61.85; H, 5.19%.

Under conditions simulating those of the kinetic study, a sample of **1c** in ethanol was added to an aqueous carbonate buffered solution (0.13 mol/l in each of sodium carbonate and sodium bicarbonate; pH *ca* 9.4). After 30 min., the crude product was extracted and purified on a silica layer (7:3 petroleum spirit/ether eluent). Coumaran-3-one [**2**; 3(2H)-benzofuranone] had m.p. 95–98°C (lit.[8] 101-2°C); NMR (CDCl$_3$): ^{1}H δ 4.60 (s, 2H, CH$_2$) 7.0–7.7 (m, 4H, Ar-H); ^{13}C δ 74.7 (t, CH$_2$), 113.7 (d, C-7), 121.2 (s, C-3a), 122.0 (d, C-5), 124.1 (d, C-4), 137.9 (d, C-6), 174.0 (s, C-7a), 199.9 (s, C=O).

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