Intramolecular Catalysis in the Detritiation of 2′,6′-Dihydroxyacetophenone and 2′-Hydroxyacetophenone

By **Ronald P. Bell** * and **Derek W. Earls**, University of Stirling, Stirling FK9 4LA, Scotland

The kinetics of detritiation of 2′,6′-dihydroxyacetophenone have been studied at 25° in aqueous buffers and sodium hydroxide solutions in the pH range 6.0—13.8, and similar studies were made for 2′-hydroxyacetophenone between pH 12 and 13.8. The rates of the intramolecular processes for the two compounds have been determined, and do not indicate any special effects arising from simultaneous acid and base catalysis in the monoanion of 2′,6′-dihydroxyacetophenone. The results suggest an unusually large hydrogen isotope effect for intramolecular proton transfer in the anion of 2′-hydroxyacetophenone.

THE present work continues earlier studies[1-4] on the abstraction of protons bound to carbon by basic groups present in the same molecule. In the anion of 2′-hydroxyacetophenone[4] intramolecular proton transfer was found to occur with a velocity constant of 2.4×10^{-3} s^{-1} at 25°. In the monoanion of 2′,6′-dihydroxyacetophenone the possibility exists of intramolecular processes involving both acid and base catalysis. There is evidence[5-7] that the non-ionized form of this compound contains a strong hydrogen bond between one hydroxy-group and the carbonyl oxygen, and it is likely that this hydrogen bond persists in the monoanion. In the present investigation rates of intramolecular detritiation were determined for the mono- and di-anion of 2′,6′-dihydroxyacetophenone, and also for the anion of 2′-hydroxyacetophenone.

EXPERIMENTAL

2′-Hydroxyacetophenone giving a single g.l.c. peak was prepared by partially freezing a commercial sample. Commercial 2′,6′-dihydroxyacetophone was purified by vacuum sublimation, m.p. 155° (lit.,[8,9] 156—157°). Buffer components were of AnalaR grade. The tritiated substrates were prepared by allowing to stand for 24 h at room temperature substrate (0.2 g), tritiated water (20 mm^3; 5 Ci cm^{-3}), and one pellet of sodium hydroxide in AnalaR dioxan (1 cm^3). The precipitated sodium salt of the substrate was filtered off and added to an excess of dilute hydrochloric acid, after which the substrate was filtered off and dried.

The values of pK_1 and pK_2 for 2′,6′-dihydroxyacetophenone were determined at 25° from the measured pH values (glass electrode) of self-buffered solutions kept under nitrogen. The stoicheiometric buffer ratios were corrected for hydrolysis. Activity coefficients were estimated from equation (1) where I is the ionic strength. The mean of 15

$$\lg f_z = -0.5\, z^2 \frac{I^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} - 0.2I \qquad (1)$$

determinations between pH 7 and 9 (I 4×10^{-4}—5×10^{-3}) gave pK_1 8.12 ± 0.01; similarly, 12 determinations between pH 11.5 and 12.4 (I 0.12—0.20) gave pK_2 12.6 ± 0.1. Values reported previously[6] are pK_1 7.94 ± 0.05, pK_2 12.35 ± 0.2, by extrapolation from pH measurements in aqueous ethanol, and pK_1 8.00 ± 0.05, pK_2 12.7 ± 0.1, by spectrophotometry.

Rates of detritiation were measured by procedures described previously,[10] an Intertechnique SL30 scintillation counter being used. Good first-order plots were obtained throughout. If the molecule of 2′,6′-dihydroxyacetophenone is represented by SH_2, the reaction velocity is given by equation (2), where B is any basic species in the buffer

$$v = k_i'[SH^-] + k_i''[S^{2-}] + \Sigma k_B[B][SH_2] \qquad (2)$$

solution, including water, and the observed first-order rate constant k by equation (3). In these expressions the terms in k_i' and k_i'' may relate to the intramolecular processes in

$$k = \frac{k_i'K_1[H^+] + k_i''K_1K_2 + \Sigma k_B[B][H^+]^2}{[H^+]^2 + K_1[H^+] + K_1K_2} \qquad (3)$$

SH^- and S^{2-}, or to the kinetically indistinguishable reaction of hydroxide ions with SH_2 and SH^- respectively. Less probable processes, such as the reaction of B with the ionized substrate species, have not been included.

RESULTS AND DISCUSSION

The kinetic results for 2′,6′-dihydroxyacetophenone and 2′-hydroxyacetophenone are presented in Tables 1 and 2 respectively. For the former the values of k_{calc} are those given by equation (3) with the following values of the constants: k_i' 2×10^{-6} s^{-1}, k_i'' 8×10^{-5} s^{-1}, $k_{H_2O}[H_2O]$ 2×10^{-7} s^{-1}, k_{HPO_4} 4.4×10^{-5} dm^3 mol^{-1} s^{-1}. The value of k_{obs} at pH 8.33 was obtained by extrapolating to zero buffer concentration the results for a series of self-buffered solutions: the same series gives 8×10^{-5} dm^3 mol^{-1} s^{-1} for the value of k_B in the term $k_B[SH^-][SH_2]$. The relative values of k_B for HPO_4^{2-} and SH^- are consistent with the values of pK_2 for phosphoric acid (7.21) and pK_1 for SH_2 (8.12). No catalysis by borate ions was detectable, since the concentrations of borate ion and SH_2 are never simultaneously large. In the experiments with 2′-hydroxyacetophenone (pK 10.27[4]) the solutions are sufficiently alkaline to convert it almost completely to the anion, and the values of k_{calc} in Table 2 are obtained from equation (4), with k_i 1.2×10^{-5} s^{-1} and k_{OH} 1×10^{-4} dm^3 mol^{-1} s^{-1}.

$$k = k_i + k_{OH}[OH^-] \qquad (4)$$

---

[1] R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, 1963, **59**, 1623.

[2] R. P. Bell, B. G. Cox, and J. B. Henshall, *J.C.S. Perkin II*, 1972, 1232.

[3] R. P. Bell and B. A. Timimi, *J.C.S. Perkin II*, 1973, 1518.

[4] R. P. Bell, D. W. Earls, and B. A. Timimi, *J.C.S. Perkin II*, 1974, 811.

[5] S. Bachleson and I. Bachleson, *Rev. Roumaine Chim.*, 1969, **14**, 3, 329.

[6] R. Arnaud, *Bull. Soc. chim. France*, 1967, **12**, 4541.

[7] V. A. Granzhan, S. F. Manole, S. K. Laktionova, and M. P. Filippov, *Zhur. strukt. Khim.*, 1971, **12**, 430.

[8] W. Baker, *J. Chem. Soc.*, 1934, 1953.

[9] A. Russell and J. R. Frye, ' Organic Syntheses,' Wiley, New York, 1955, Coll. vol. 3, p. 281.

[10] J. R. Jones, *Trans. Faraday Soc.*, 1965, **61**, 2456.

Although equation (3) gives a reasonably good representation of the results for 2′,6′-dihydroxyacetophenone over a wide pH range, there are significant discrepancies, probably due in part to side reactions occurring in the presence of oxygen. For example, at pH 13.82 failure to exclude oxygen led to a decrease of *ca.* 30% in the observed velocity constant, though a first-order course was still followed. This effect was diminished or absent at lower values of pH, though in general the u.v. absorption spectra of the solutions change slightly over the period of a detritiation experiment. No such spectral changes were observed for 2′-hydroxyacetophenone, which may explain why the agreement between k_{obs} and k_{calc} is better for this compound, since the single high value of k_{obs} in 1M-sodium hydroxide can be attributed to a kinetic salt effect.

TABLE 1

Detritiation rates for 2′,6′-dihydroxyacetophenone at 25°

pH (measured)	10^6k/s^{-1} obs.	10^6k/s^{-1} calc.	Solution
6.00	0.419	0.460	Phosphate buffer
6.06	0.444	0.341	Phosphate buffer
7.00	1.40	1.51	Phosphate buffer
7.05	1.22	0.95	Phosphate buffer
7.30	1.80	1.86	Phosphate buffer
7.34	1.43	1.18	Phosphate buffer
7.73	2.16	2.10	Phosphate buffer
7.77	1.65	1.48	Phosphate buffer
8.00	2.22	2.13	Phosphate buffer
8.02	1.75	1.62	Phosphate buffer
8.10	0.66	1.19	Phosphate buffer
8.33	1.50	1.35	Self-buffered
8.52	1.09	1.56	Borate buffer
8.52	1.14	1.56	Borate buffer
9.15	1.55	1.86	Borate buffer
9.16	1.60	1.86	Borate buffer
9.19	1.71	1.87	Borate buffer
10.28	2.47	2.47	Borate buffer
10.32	2.62	2.50	Borate buffer
10.40	3.36	2.62	Borate buffer
11.95 †	21.8	17.6	Sodium hydroxide
12.62 †	50.4 *	41.0	Sodium hydroxide
12.88 †	55.7	57.3	Sodium hydroxide
13.16 †	62.0	66.3	Sodium hydroxide
13.44 †	63.8		Sodium hydroxide
13.82 †	61.4 *		Sodium hydroxide

* These experiments were carried out under nitrogen with degassed solutions. † These values were calculated from the concentration of sodium hydroxide.

TABLE 2

Detritiation rates for 2′-hydroxyacetophenone at 25°

10^3[OH$^-$]/M		10	25	50	75	100	1 000
10^5k/s^{-1}	obs.	1.33	1.39	1.74	1.93	2.19	17.1
	calc.	1.30	1.45	1.70	1.95	2.20	11.2

The low acidity (pK 10.27) of 2′-hydroxyacetophenone is due to stabilisation of the undissociated molecule by intramolecular hydrogen bonding, and it has been suggested [4] that intramolecular proton transfer in the anion (involving a configuration in which such hydrogen bonding is excluded) is more appropriately interpreted in terms of the pK of 4′-hydroxyacetophenone, namely 8.05. This value is close to the measured value of pK_1 8.12 for 2′,6′-dihydroxyacetophenone, for which hydrogen bonding is possible both in the undissociated molecule and the monoanion. It is therefore apparent that the value of k_i' found for this compound provides no evidence for rate enhancement due to a concerted acid–base process involving both phenolic groups, since it is considerably smaller than k_i for 2′-hydroxyacetophenone. In fact, the intramolecular process corresponding to k_i' is a very inefficient one, as may be seen by calculating the 'effective concentration', c_i, given here by the ratio of k_i' to k_B in the term $k_B[SH^-][SH_2]$. This gives $c_i = 2 \times 10^{-6}/8 \times 10^{-5} = 0.025$M, which is very much smaller than values obtained for a number of similar systems,[2-4,11,12] presumably because of a less favourable geometry.

It is doubtful whether the analogous constant k_1'' for the species S^{2-} can be attributed to an intramolecular process at all. It can also be interpreted in terms of the kinetically equivalent intermolecular reaction between hydroxide ions and the monoanion SH^-, with a rate constant of 2×10^{-3} dm^3 mol^{-1} s^{-1}, which is well within the range found for the detritiation of a number of substituted acetophenones in alkaline solution.[13] On the other hand, the corresponding calculation for k_i' gives 1.5 dm^3 mol^{-1} s^{-1} for the reaction between hydroxide ions and SH_2, so that it is reasonable to retain the intramolecular interpretation of this term.

A value for the kinetic hydrogen isotope effect can be derived by combining the value of k_i^T for the anion of 2′-hydroxyacetophenone [equation (4)] with k_i^H previously derived from iodination experiments.[4] In comparing $COCH_2T$ with $COCH_3$ a statistical correction of 3 must be included, and the true isotope effect is $k_i^H/3\ k_i^T = 2.4 \times 10^{-3}/3 \times 1.2 \times 10^{-5} = 67$. If the Swain–Schaad relation [14] is applicable, this corresponds to $k_i^H/k_i^D = 18.4$. These are unusually large isotope effects, and in particular are much larger than those recently measured [12] for analogous reactions of the anions of substituted 2′-carboxyacetophenones. Although there are precedents and possible theoretical explanations for isotope effects of this magnitude,[15] the above result requires confirmation in view of the different techniques used for the two isotopes. The interpretation of the iodination results was not entirely straightforward because of other possible routes for iodine consumption, and errors arising from this source could lead to a spuriously large isotope effect.

We thank the S.R.C. for a Fellowship awarded to D. W. E., and for other financial assistance.

[5/1001 *Received, 28th May, 1975*]

---

[11] E. T. Harper and M. L. Bender, *J. Amer. Chem. Soc.*, 1965, **87**, 5625.

[12] R. P. Bell, D. W. Earls, and J. B. Henshall, *J.C.S. Perkin II*, 1976, preceding paper.

[13] J. R. Jones, R. E. Marks, and S. C. Subba Rao, *Trans. Faraday Soc.*, 1967, **63**, 111, 993; J. R. Jones, *ibid.*, 1969, **65**, 2138.

[14] C. G. Swain, E. C. Stivers, J. F. Reuwer, and L. J. Schaad, *J. Amer. Chem. Soc.*, 1958, **80**, 5885.

[15] R. P. Bell, *Chem. Soc. Rev.*, 1974, **3**, 513.