Kinetics of the Intramolecular Displacement of Alcohols from *o*-Hydroxyaminobenzoates

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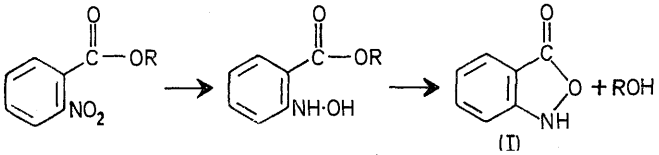
The kinetics of the liberation of benzyl and aliphatic alcohols from esters of *o*-hydroxyaminobenzoic acid, with formation of 2,1-benzisoxazol-3(1*H*)-one, have been investigated in acidic and in basic solution. In alkaline solution the reactions are very rapid, the displacement of the alcohol from the hydroxyamino-esters in dilute alkali occurring *ca.* 10^4 times more rapidly than from the corresponding unsubstituted benzoates. The observed kinetics are consistent with a rate-determining reaction between the anion of the hydroxyamino-group and the neighbouring ester group, with the pK_a for the ionisation of the hydroxyamino-group in the various esters close to 12.0. The reactions are considerably slower in acid solution, but comparison with the acid-catalysed hydrolysis of unsubstituted benzoates again suggests direct involvement of the hydroxyamino-group. The pK_a of the product benzisoxazolone, is 7.63.

RECENTLY reported synthetic studies on the use of *o*-nitrobenzoate as a protecting group for alcohols and phenols [1] have demonstrated that reduction of the 2-nitro-group to give the corresponding *o*-hydroxyaminobenzoate results in rapid intramolecular displacement of the alcohol with formation of 2,1-benzisoxazol-3-(1*H*)-one (I) (see Scheme 1). The ease with which the



SCHEME 1

alcohol is liberated suggests that the *o*-hydroxyamino-group acts as an extremely effective intramolecular catalyst. Although the intermolecular reaction between hydroxylamine and a number of esters (to give the appropriate alcohol and *O*-acylhydroxylamine) have been studied,[2,3] comparable studies on the effectiveness of the *o*-hydroxyamino-group as an intramolecular catalyst have not been reported.

In the present paper, rates of cleavage of methyl, ethyl, and benzyl esters of *o*-hydroxyaminobenzoic acid in both acidic and basic solutions are reported. These are compared with the rates of hydrolysis of the corresponding unsubstituted benzoates and where possible with other comparable systems known to exhibit intramolecular catalysis.

EXPERIMENTAL AND RESULTS

Materials.—Methyl, ethyl, and benzyl *o*-hydroxyaminobenzoate were prepared by reduction of the corresponding *o*-nitrobenzoates with zinc–ammonium acetate as previously described.[1] An attempted preparation of the phenyl ester by an analogous route gave phenol and 2,1-benzisoxazole-3(1*H*)-one. Solutions of the *o*-hydroxyamino-esters, when left for a few minutes at room temperature, gave n.m.r. spectra which suggested the presence of stable paramagnetic species. This was confirmed by e.p.r. studies, and the structure of the paramagnetic species is under investigation.

Esters of *o*-nitrobenzoic and benzoic acids were prepared by reaction of the acyl chloride with the appropriate alcohol.

2,1-Benzisoxazol-3(1*H*)-one was prepared from ethyl *o*-hydroxyaminobenzoate by alkaline hydrolysis.

Inorganic materials were of AnalaR grade.

pK_a *Value of* 2,1-*Benzisoxazol*-3(1H)-*one.*—The product benzisoxazolone ionizes readily in dilute alkali, and the acidic and basic forms have different u.v. spectra: acidic form, $\lambda_{max.}$ (H_2O) 308 nm (ε 4 190 $dm^3\ mol^{-1}\ cm^{-1}$); base form, $\lambda_{max.}$ (H_2O) 368 nm (ε 5 770 $dm^3\ mol^{-1}\ cm^{-1}$). Its pK_a was determined by spectrophotometric measurements at 308 and 368 nm on solutions in aminotris(hydroxymethyl)-methane (tris) buffers of varying buffer ratio. All measurements were carried out at 25(± 0.2) °C using a Gilford 2 400 spectrophotometer to give (at ionic strength $I = 0.015$) $K_a/K_{tris} = 3.61$ (± 0.06). By using the known value of K_{tris} ($pK_{tris} = 8.076$),[4] this gives (corrected to $I = 0$), 10^8K_a (2,1-benzisoxazolone) = 2.36, *i.e.* $pK_a = 7.63$.

Kinetic Measurements.—The cleavage of the *o*-hydroxyaminobenzoates can be conveniently followed by observing spectrophotometrically the appearance of the product benisoxazolone. In alkaline solution the reactions were followed at 368 nm with a Durrum–Gibson stopped flow spectrophotometer. In acidic solution, where the reactions were considerably slower, they were followed at 308 nm with a Gilford 2 400 spectrophotometer.

The rates of hydrolysis of the corresponding unsubstituted benzoates in alkaline solution were measured spectrophotometrically by observing the rate of disappearance of ester absorption at 235 nm, using a Gilford 2 400 spectrophotometer. All kinetic measurements were made at 25(±0.2) °C.

Ester Hydrolyses in Alkaline Solution.—The rates of cleavage of the methyl, ethyl, and benzyl *o*-hydroxyaminobenzoates were measured in sodium hydroxide solutions, with 0.002 mol $dm^{-3} \leqslant [NaOH] \leqslant 0.1$ mol dm^{-3}. Ester concentrations were *ca.* 8×10^{-5} mol dm^{-3}. Under these conditions the observed rate law was of the form shown in equation (i), where E represents the ester. The observed

$$-\mathrm{d}[E]/\mathrm{d}t = k_e[E] \qquad \text{(i)}$$

rate constants, k_e, for the hydrolyses in various sodium hydroxide solutions are listed in Table 1.

For the hydrolyses of the parent benzoates ester concentrations were *ca.* 10^{-4} mol dm^{-3} and hydroxide concentrations between 0.02 and 0.2 mol dm^{-3}. The rate law was again as shown in equation (i), with the first-order rate constant, k_e, given by equation (ii). Table 2 lists observed values of

$$k_e = k_{OH^-}[OH^-] \qquad \text{(ii)}$$

[1] D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J.C.S. Perkin I*, 1973, 599.

[2] T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, ch. I.

[3] W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969.

[4] R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' 2nd edn., Butterworths, London, 1965.

k_e together with values calculated from equation (ii) with the following values of k_{OH^-}: $PhCO_2Me$ $6.9_0 \times 10^{-2}$; $PhCO_2Et$ $3.0_5 \times 10^{-2}$; $PhCO_2{\cdot}CH_2Ph$ $6.3_5 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}. The value for ethyl benzoate may be compared with a reported value [5] of 2.93×10^{-2} dm^3 mol^{-1} s^{-1}.

Ester Hydrolyses in Acid Solution.—Phenylhydroxylamines are known to rearrange in acid solution to give *p*-hydroxyanilines.[6] However, what little kinetic evidence exists [7,8] suggests that such reactions are very slow and the observed spectral changes during the reactions were consistent with complete conversion of the esters into the alcohol and benzisoxazalone. The rate of cleavage of ethyl *o*-hydroxyaminobenzoate was measured in perchloric acid solutions with [$HClO_4$] = 0.22, 1.1, or 5.5 mol dm^{-3}. The observed first-order rate constants for the reactions in these solutions were 1.53×10^{-5}, 2.17×10^{-5} and 3.90×10^{-5} s^{-1}, respectively. At the acid concentrations used for the cleavage, the ester is *N*-protonated to a considerable extent and the relatively low rate of reactions enabled the pK_a of the protonated ester EH^+ to be determined spectrophotometrically. The results were as follows: EH^+, $\lambda_{max.}$ 276 nm (ε 1 420 dm^3 mol^{-1} cm^{-1}); E, $\lambda_{max.}$ 318 nm (ε 4 700 dm^3 mol^{-1} cm^{-1}); pK_a = 0.60. This value for the pK_a was obtained in fairly dilute acid solutions ($\leqslant$0.3M) where it was assumed that $y_{H^+} = y_{EH^+}$. In solutions of higher acid concentration, the extent of protonation followed the H_0 acidity function. The above value of the pK_a may be compared with that of protonated phenylhydroxylamine, estimated [7] as 3.2.

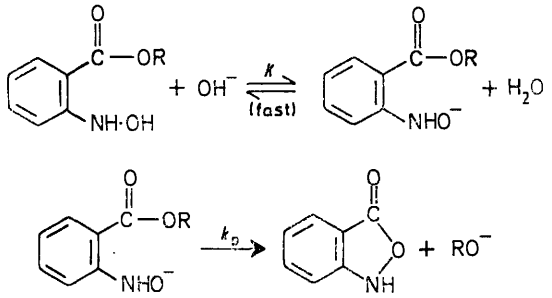
The rate of cleavage of benzyl *o*-hydroxyaminobenzoate in acid solution was found to be similar to that of the ethyl ester.

[5] E. Tommila and I. Palenius, *Acta. Chem. Scand.*, 1963, **17**, 1980.

[6] C. K. Ingold, ' Structure and Mechanism in Organic Chemistry,' 2nd edn., Bell, 1969, p. 906.

DISCUSSION

The results for the base-catalysed cleavage of the *o*-hydroxyaminobenzoates (Table 1) show that k_e is approximately proportional to [OH^-] at low values of the latter, but levels off at higher values. This behaviour can most simply be interpreted in terms of a mechanism as in Scheme 2, in which the rate-determining step involves reaction of the anion formed on ionization of the hydroxyamino-group. This Scheme leads to the rate law as shown



SCHEME 2

in equation (i) with k_e given by equation (iii), which on inversion gives equation (iv).

$$k_e = k_0K[OH^-]/(1 + K[OH^-]) \quad \text{(iii)}$$

$$1/k_e = 1/k_0 + 1/k_0K[OH^-] \quad \text{(iv)}$$

The figure shows a plot of $1/k_e$ against $1/[OH^-]$ for the hydrolysis of benzyl *o*-hydroxyaminobenzoate (data from Table 1). Values of k_0 and K for the three esters,

[7] I. Bergman and J. C. James, *Trans. Faraday Soc.*, 1954, **50**, 60.

[8] S. Hashimoto, *Proc. Fac. Eng. Keigijuku Univ.*, 1948, **1**, 32.

TABLE 1

Rates of displacement of alcohols from *o*-hydroxyaminobenzoates in sodium hydroxide solutions at 25 °C.

Methyl ester			Ethyl ester			Benzyl ester		
10^2[NaOH]/ mol dm^{-3}	k_e/s^{-1}	k_e(calc.) [a]/ s^{-1}	10^2[NaOH]/ mol dm^{-3}	k_e/s^{-1}	k_e(calc.) [a]/ s^{-1}	10^2[NaOH]/ mol dm^{-3}	k_e/s^{-1}	k_e(calc.) [a]/ s^{-1}
0.2	6.78	7.11	0.188	2.13	2.09	0.2	21.1	21.0
0.3	10.0	9.95	0.25	2.41	2.66	0.3	28.7	29.5
0.4	12.2	12.4	0.375	4.04	3.64	0.4	37.1	36.8
0.5	15.0	14.6	0.50	4.15	4.47	0.5	45.1	43.2
1.0	26.2	22.3	0.75	6.36	5.77	1.0	68.5	66.2
2.0	29.1	30.3	1.0	7.38	6.76	2.0	90	90.5
5.0	36.2	38.7	1.5	7.82	8.18	3.0	105	103
7.5	39.3	41.2	3.0	9.65	10.3	5.0	114	116
10.0	43.2	42.6	5.0	11.4	11.5	10.0	129	128
∞		47.4 [b]	10.0	13.3	12.6	∞		143 [b]
			∞		14.0 [b]			

[a] Values calculated from equation (iv) using values of k_0 and K listed in Table 3. [b] k_0 (Scheme 2).

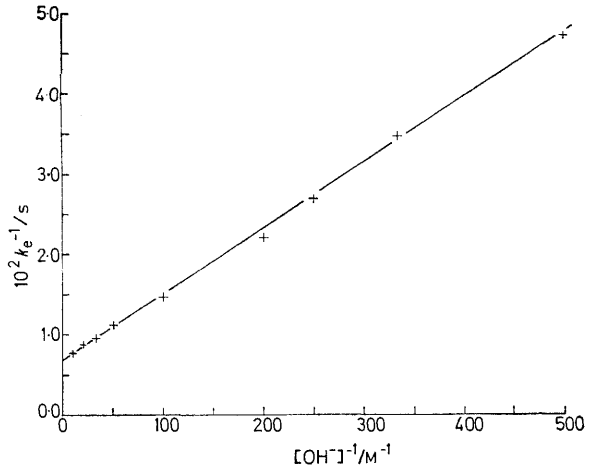
TABLE 2

Rates of hydrolyses of benzoates in hydroxide solutions at 25 °C

Methyl ester			Ethyl ester			Benzyl ester		
[KOH]/ mol dm^{-3}	10^3k_e/ s^{-1}	10^3k_e(calc.) [a]/ s^{-1}	[NaOH]/ mol dm^{-3}	10^3k_e/ s^{-1}	10^3k_e(calc.) [a]/ s^{-1}	[KOH]/ mol dm^{-3}	10^3k_e/ s^{-1}	10^3k_e(calc.) [a]/ s^{-1}
0.04	2.73	2.76	0.02	0.577	0.610	0.04	2.56	2.54
0.08	5.21	5.52	0.04	1.20	1.22	0.08	5.56	5.08
0.12	8.00	8.28	0.06	1.86	1.83	0.12	7.79	7.63
0.16	11.4	11.0	0.10	3.22	3.05	0.16	9.46	10.2
0.20	14.7	13.8				0.20	12.1	12.7

[a] Values calculated from equation (ii).

obtained from such plots, are listed in Table 3. Also listed are the acidity constants K_a for the esters, which are simply related to K by $K_a = KK_w$, where K_w is the



Rates of displacement of benzyl alcohol from benzyl *o*-hydroxyaminobenzoate in sodium hydroxide solutions at 25 °C

thermodynamic ionisation constant of H_2O. Values of k_e calculated from equation (iii), by using values of k_0 an K from Table 3, are included in Table 1.

In Scheme 2 it has been assumed that the hydroxylamine loses a proton from OH rather than from NH. Recent measurements [9] have however shown that 1-methoxyamino-2,4-dinitrobenzene ionizes with a pK_a

TABLE 3

Displacement of alcohols from *o*-hydroxyaminobenzoates in alkaline solution at 25 °C

Ester	k_0 [a]/s^{-1}	K/dm^3 mol^{-1}	pK_a
Methyl	47.4	88.6	12.05
Ethyl	14.0	93.6	12.03
Benzyl	143	86.3	12.06

[a] k_0 and K as defined in Scheme 2.

of *ca.* 10.0 and that the OH and NH protons of 1-hydroxyamino-2,4-dinitrobenzene have similar acidities. In these compounds, because of the possibility of direct conjugation with the negative charge on N̄–OH, the nitro-groups should have a much greater effect in stabilizing the N̄–OH than the NH–Ō group. In view of this it seems likely that for the hydroxyamino-esters studied here, the OH protons are considerably more acidic than the NH protons, as has been assumed in Scheme 2. However, the observed kinetic behaviour could also be consistent with NH ionisation. For example a mechanism analogous to Scheme 2 involving ionisation of the NH proton followed by nucleophilic addition of the OH group of N̄–OH leads to the same rate law. Such a mechanism would require the N̄–OH group to be considerably more reactive than NH–OH, but this is perhaps not unreasonable as it is frequently found that the presence of free electron pairs adjacent to nucleophilic atoms leads to unusually high nucleophilic activity (the ' α effect ').[10]

[9] A. C. Knipe, personal communication.

[10] Ref. 3, p. 107.

[11] M. L. Bender, 'Mechanisms of Homogeneous Catalysis from Protons to Proteins,' Interscience, New York, 1971, ch. 9.

Thus the interpretation of k_0 (Table 3), the maximum attainable rate constant for the reaction, is not unambiguous.

The presence of the *o*-hydroxyamino-group results in a remarkably easy liberation of the alcohol. Comparison with the results for the alkaline hydrolysis of the corresponding unsubstituted esters (Table 2) shows that for example in 10^{-2} mol dm^{-3} NaOH, the alcohol is produced *ca.* 10^4 times more rapidly from the *o*-hydroxyaminobenzoates than from simple benzoates. Comparison with other ester hydrolyses involving intramolecular catalysis is difficult as such studies have generally involved the more reactive phenyl esters.[11] For example investigations of the rates of hydrolysis of monoesters of phthalic acid [12] provided evidence of significant participation of the neighbouring carboxylate group only for those esters with good leaving groups (*e.g.* phenoxide, trifluoroethoxide). A similar comment applies to ester hydrolyses involving intermolecular catalysis by hydroxylamine. It was found that hydroxylamine is only about a factor of 10 less effective than hydroxide ion in the hydrolysis of *p*-nitrophenyl acetate,[13] this being attributed to reaction of the dipolar form of hydroxylamine ($H_3N^+–O^-$). Similar studies on the hydrolysis of the esters of simple aliphatic alcohols do not appear to have been reported.

The acid-catalysed cleavage of the esters is considerably slower than the corresponding basic cleavage. However, although accurate comparison with results for the simple benzoates is difficult, there is evidence of significant participation by the *o*-hydroxyamino-group. If the results of Tommila and Hinshelwood [14] on the acid-catalysed hydrolysis of ethyl benzoate in acetone–water over a range of (high) temperatures are extrapolated to 25 °C, then these give (allowing for a small solvent effect on the hydrolysis) [15] $k_{H^+} \simeq 10^{-7}$ dm^3 mol^{-1} s^{-1}, where k_{H^+} is the catalytic constant for the acid-catalysed hydrolysis. pK_a Measurements on the protonated hydroxyamino-ester shows that 75 and 28% of the unprotonated hydroxyamino-ester exists in 0.22 and 1.1 mol dm^{-3} perchloric acid solution, respectively. Combining this with the observed hydrolysis rates in these solutions gives $k_{H^+} \simeq 9 \times 10^{-5}$ dm^3 mol^{-1} s^{-1} for ethyl *o*-hydroxyaminobenzoate. This suggests that the *o*-hydroxylaminobenzoate is *ca.* 10^2—10^3 times more reactive towards acidic hydrolysis than ethyl benzoate. The mechanism of this hydrolysis presumably involves nucleophilic addition of –NH–OH to the protonated carbonyl group of the ester (Scheme 3). By analogy with the hydrolysis of simple alkyl benzoates, the reaction presumably proceeds *via* a tetrahedral intermediate (II), which after proton transfer can expel ROH leaving protonated benzisoxazolone.

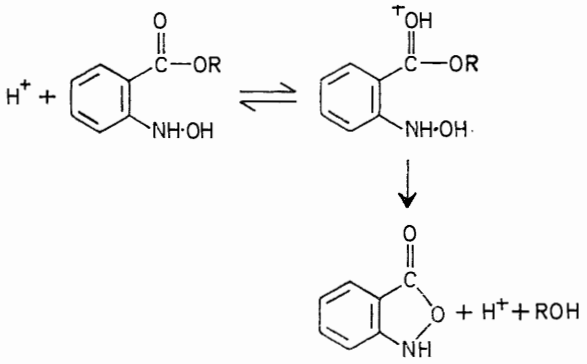
[12] J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, 1966, **88**, 747.

[13] T. St. Pierre and W. P. Jencks, *J. Amer. Chem. Soc.*, 1968, **90**, 3817.

[14] E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1938, 1801.

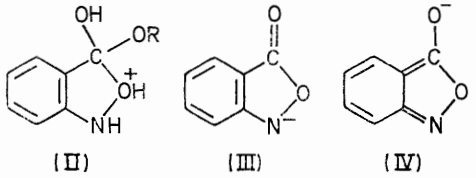
[15] E. Tommila and M. L. Murto, *Acta. Chem. Scand.*, 1963, **17**, 1957, and references therein.

Finally, the acidity of the product benzisoxazolone merits attention. The low pK_a (7.63) suggests considerable stabilisation of the negative charge of the anion (III).



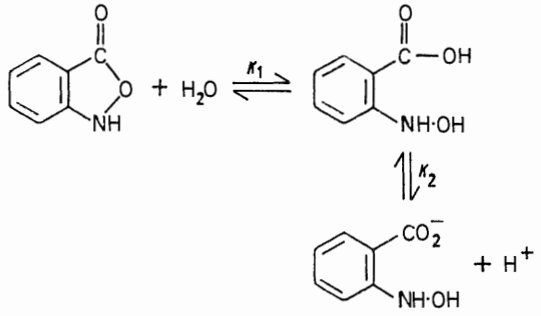
SCHEME 3

It is possible to draw a resonance structure (IV) involving delocalisation of the charge onto the carbonyl oxygen, but it is difficult to see why this should lead to such an increase in acidity over that normally expected for an NH group. It may be relevant that preliminary results for the alkylation of benzisoxazolone suggest



(II) (III) (IV)

O-alkylation rather than *N*-alkylation. We have considered the possibility that ionisation of the benzisoxazolone involves ring opening (Scheme 4). Assuming a value of pK_2 *ca.* 4, this could lead to an overall pK for the ionisation of benzisoxazolone of the observed magnitude if $K_1 \simeq 10^{-3}$ (*cf.* high pK_a values of *o*-formyl- and *o*-acetyl-benzoic acids, attributable to cyclisation of the acid form).[16] Several pieces of evidence however suggest that this is not the explanation for the high acidity of benzisoxazolone; (i) similar spectral changes are observed in addition of sodium ethoxide to benzisoxazolone in ethanol, where a process analogous to Scheme 4 cannot occur; (ii) benzisoxazolone only gives a positive hydroxylamine test (with triphenyltetrazolium chloride) in the presence of very strong base; (iii) *T*-jump studies show that the ionisation of benzisoxazolone is very rapid,



SCHEME 4

even at pH *ca.* 7 where the hydrolysis of ethyl *o*-hydroxyaminobenzoate (which should proceed at a similar rate to the back raction of K_1) is slow.

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[5/512 *Received*, 17*th March*, 1975]

[16] R. P. Bell, B. G. Cox, and B. A. Timimi, *J. Chem. Soc.* (*B*), 1971, 2247.