

KINETICS AND MECHANISM OF THE HYDROLYSIS OF SUBSTITUTED PHENYL BENZOATES CATALYZED BY THE *o*-IODOSOBENZOATE ANION

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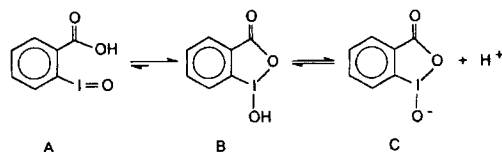
The *o*-iodosobenzoate (IBA^-)-catalyzed hydrolysis of the following esters was studied spectrophotometrically: 4-nitrophenyl 4-X-benzoate (series I, a–e, X = CH₃, H, Cl, CN, NO₂), 4-Y-phenyl 4-nitrobenzoate (series II, a–d, Y = CH₃, H, Cl, CN), 2,4-dinitrophenyl 4-X-benzoate (series III, b–e, X = H, Cl, CN, NO₂) and 4-Y-phenyl 2,4-dinitrobenzoate (series IV, a–e, Y = CH₃, H, Cl, CN, NO₂). Direct detection of a reaction intermediate, viz 1-(4-nitrobenzoyloxy)-1,2-benzodioxol-3(1*H*)-one, the absence of (general base) catalysis by the leaving group, the small kinetic solvent isotope effect and the fast catalyst ‘turnover’ show that the mechanism of catalysis by IBA^- is nucleophilic. Catalytic rate constants, activation parameters and application of the Hammett equation show the following mechanistic features: the first step of the reaction, i.e. that leading to the formation of the above-mentioned intermediate is irreversible, the leaving group is the phenol and the rate-limiting step is the collapse of the tetrahedral intermediate that is formed by attack of IBA^- on the ester. A comparison of the results of hydrolysis by IBA^- and by imidazole (Imz) revealed that IBA^- and Imz differ in their sensitivity toward an ester structure and, for the same ester series, IBA^- is a much more efficient catalyst. The reasons for the higher catalytic activity of IBA^- include nucleophilicity enhancement due to the α -effect, a smaller influence of steric effects and a more favorable entropy of activation.

INTRODUCTION

At pH values close to 7, the spontaneous and OH^- -mediated hydrolysis of simple esters, e.g. phenyl acetates and phenyl benzoates, is negligible, but their hydrolysis is efficiently catalyzed by nucleophiles, e.g. imidazole (Imz). This reaction has been studied in detail because of the importance of acyl-transfer reactions in chemistry and enzymology.^{1–7} Recently, the catalytic effect of *o*-iodosobenzoates has received much attention, mainly because these catalysts efficiently hydrolyze phosphorylated compounds, a fact that can be exploited, e.g., in the cleaning of contaminated areas.^{8–15}

o-Iodosobenzoic acid exists essentially as tautomer B, 1-hydroxy-, 1,2-benzodioxol-3(1*H*)-one, IBA^- (alter-

natively named 1-hydroxy-1,2-benzodioxolin-3-one), both in the solid state and in solution.^{16,17} Its anion (C , IBA^-) is a powerful nucleophile which hydrolyzes esters of carboxylic and phosphoric acids in aqueous solution, and in the presence of organized surfactant assemblies, e.g. simple and functionalized micelles, oil-in-water microemulsions and vesicles. With field applications in mind, it has been covalently bonded to silica gel, titanium dioxide and latexes, and the catalytic efficiency of the produced immobilized IBA^- has been determined.^{8–15,18,19}

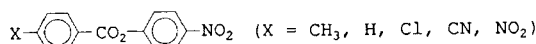


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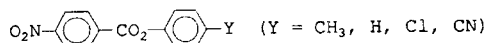
This potential use of IBA^- as a decontaminant requires a detailed knowledge of the hydrolysis reaction mechanism. This information can best be obtained from a systematic study of the effect of the structure of the substrate on reactivity. This study has not been carried out, and the only carboxylate esters so far employed were *p*-nitrophenyl hexanoate and substituted phenyl acetates.^{8-10,19}

We report here on the first part of the hydrolysis reaction of ester series I–IV by IBA^- , i.e. the step that leads to the formation of the intermediate 1-(4-X-benzoyloxy)-1,2-benzodioxol-3(1*H*)-one, 4-X-BzO-IBA. Note that the ester 4-nitrophenyl 4-nitrobenzoate (hereafter denoted **Ie**) is common to series I and II.

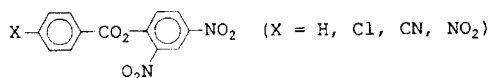
I (a-e)



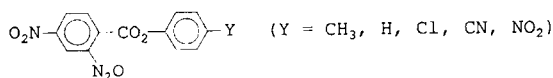
II (a-d)



III (b-e)



IV (a-e)



It was expected that the use of these compounds would yield important mechanistic information regarding, e.g., the nature of the rate-limiting step and the effect of structure on reactivity. We have recently studied details of the Imz-catalyzed hydrolysis of ester series I–IV in aqueous acetonitrile.^{20,21} We were interested, therefore, in comparing the results (e.g. catalytic rate constants, activation parameters and the Hammett ρ values) for the hydrolysis of the same substrates by these two widely different catalysts, namely IBA^- (oxygen nucleophile, anionic) and Imz (nitrogen nucleophile, neutral). This comparison should shed light on the relative contributions to the catalytic efficiency of factors such as steric effects and solvation of the nucleophile.

We used Fourier transform (FT) IR spectrometry to show the formation of a reactive intermediate, namely 4-O₂N-BzO-IBA. This indicates that catalysis by IBA^- is nucleophilic. Other evidence, e.g. absence of catalysis by the leaving group (the phenoxide ion), and small kinetic solvent isotope effect, also support this mechanistic conclusion. The catalytic efficiency of IBA^- , relative to that of Imz, is explained as a combination of the α -effect and smaller steric interactions. The reaction

activation parameters clearly reflect the stronger solvation of IBA^- relative to that of Imz.

EXPERIMENTAL

Synthesis. All reagents and solvents were obtained from Aldrich and Merck and were purified as described elsewhere.²² Esters were those available from a previous study.²⁰ IBA was synthesized by the oxidation of *o*-iodobenzoic acid with potassium peroxydisulfate in cold sulfuric acid.²³ The product gave a satisfactory m.p. of 229–230 °C (reported m.p., 228–230 and 231–232 °C^{23,24}) and microanalysis (Perkin-Elmer CHN-2000 analyzer). Its IR spectrum (Perkin-Elmer FT-1750 spectrometer, KBr) showed a peak at 1619 cm⁻¹, in agreement with the previously reported ν_{CO} of IBA, 1620 cm⁻¹.²⁵

The intermediate 4-NO₂-BzO-IBA was prepared as described elsewhere,²⁶ and gave a satisfactory m.p., 206–207 °C (lit. m.p., 204–205 °C) and microanalysis. Its IR spectrum (KBr) showed peaks at 3073, 1717, 1633, 1528 and 1329 cm⁻¹.

Determination of the pK_a of IBA. The pK_a of the acid in aqueous acetonitrile [14% (v/v) organic solvent] was determined spectrophotometrically from the Henderson–Hasselbach equation. The absorption of the conjugate base (309 nm, pH 12), obeyed Beer's law in the concentration range 3×10^{-4} – 17×10^{-4} M (correlation coefficient = 0.9997, $\epsilon = 700 \text{ l mol}^{-1} \text{ cm}^{-1}$). The pK_a was determined from the dependence of $[\text{IBA}^-]$ on the pH of the solution, in the presence of *N*-methylmorpholine buffer (NMeM, pH range 7.2–8.2, $\mu = 0.1$). Its value, 7.53, is close to that determined in the presence of organized assemblies by Moss *et al.*⁸ (7.25) and Mackay *et al.*¹¹ (7.02).

Kinetic measurements. The ester stock solutions were 3×10^{-3} – 5×10^{-3} M in anhydrous acetonitrile. A solution of IBA^- could not be used as a buffer because of its intense UV–visible absorption. Therefore, the pH of the reaction medium was maintained with NMeM. Hydrolysis by this buffer, in the absence of IBA^- , was found to be negligible. The reaction solution conditions were 14% (v/v) acetonitrile in water, $[\text{IBA}^-] = 2 \times 10^{-4}$ – 20×10^{-4} M, $[\text{NMeM}] = 0.05$ M, $\mu = 0.2$ (KCl) and pH range = 7.8–8.3. The pH values of these solutions were calculated as given elsewhere,²⁷ and checked with a Fisher Accumet-50 pH meter.

Kinetic runs were carried out with the aid of microcomputer-controlled Zeiss PM6KS and Beckman DU-70 spectrophotometers and an Applied Photophysics MV 17F stopped-flow apparatus. All spectrophotometers were equipped with thermostated cell holders

whose temperatures were kept constant to $\pm 0.05^\circ\text{C}$ (checked with a Lauda R 42/2 digital thermometer).

All reactions were carried out under pseudo-first-order conditions and were initiated by injecting 3–5 μl of the ester stock solution into the thermally equilibrated, buffered IBA solution. The final [ester] was 1.5×10^{-5} – 2.5×10^{-5} M. Cells with the appropriate path length (10–40 mm) were used to ensure a reasonable variation in the absorbance per unit time. [This point is important because the use of [ester] $> 5 \times 10^{-5}$ M resulted in irreproducible rate data, owing to limited solubility of the substrates in the aqueous buffer (the effect of solution inhomogeneity on the accuracy of rate data was discussed in, e.g., Refs. 28 and 29). Under our experimental conditions, the value of k_{obs} did not change when [ester] was decreased to half its value.] The reactions were conveniently followed by monitoring the appearance of either phenol or phenoxide ion at 400 nm (series I), 265 and 284 nm (esters **IIa–c** and **d**, respectively), 360 nm (series **III**) and 270 nm (series **IV**). Each run was carried out in triplicate. The log(absorbance) vs time plots were rigorously linear over more than five half-lives. Observed first-order rate constants (k_{obs}) were determined from the slopes of these plots, and were reproducible to within $\pm 0.2\%$. Second-order (catalytic, k_1) rate constants were obtained from linear plots of k_{obs} versus [IBA $^-$]. The relative standard deviation in k_1 , i.e. (standard deviation/ k_1) $\times 100$, was $< 2\%$.

RESULTS AND DISCUSSION

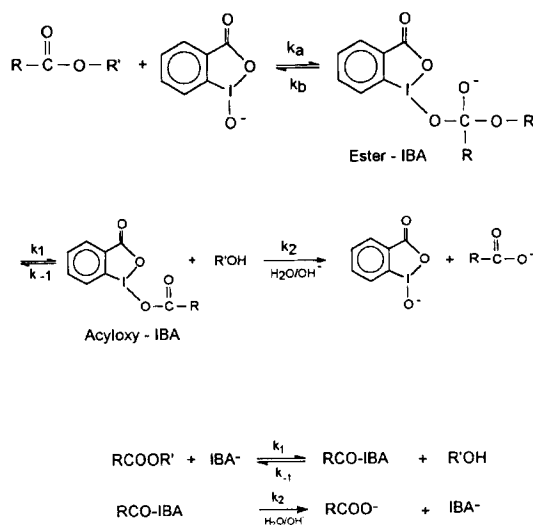
Mechanism of catalysis by IBA $^-$

Catalysis by IBA $^-$ is either of the general base or the nucleophilic type. The latter mechanism is depicted in Scheme 1. RCOOR' and R'OH refer to substituted benzoate ester and substituted phenol, respectively. The second step of the reaction, i.e. that leading to hydrolysis of 4-X-BzO-IBA will not be considered here, and so is shown in Scheme 1 as a single step, characterized by the rate constant k_2 . The main feature of this reaction pathway is the formation of the intermediate 4-X-BzO-IBA. Under identical conditions ($T = 25^\circ\text{C}$, $\text{pH} = 7.70$, [IBA $^-$] = 3.2×10^{-4} M), the observed rate constant for the hydrolysis of ester **Ie** and that of the corresponding (authentic) intermediate were found to be 0.0046 and 0.059 s^{-1} , respectively. That is, under the conditions of the kinetic experiment, the reaction intermediate, if it is formed, cannot be detected.

The following evidence shows, however, that catalysis by IBA $^-$ is nucleophilic.

(i) Direct spectroscopic detection of the reaction intermediate.

Using FT-IR spectrometry we were able to detect the



Scheme 1

formation of 4-NO $_2$ -BzO-IBA during the reaction of **Ie** and IBA in DMSO- d_6 . Figure 1(A) shows the absorption of authentic samples in the 1800–1600 cm^{-1} region. The bands shown are due to the stretching vibration of the carbonyl groups of ester **Ie** (curve 1), the hydrolysis final product, 4-nitrobenzoic acid (curve 2), the intermediate of the nucleophilic catalysis mechanism 4-NO $_2$ -BzO-IBA (curve 3) and IBA (curve 4). Figure 1(B) shows the variation of the spectrum as a function of time of a mixture of 0.056 M **Ie** and 0.32 M IBA in DMSO- d_6 . The formation of 4-X-BzO-IBA right from the start of the reaction is clearly shown at 1686 cm^{-1} . The disappearance of the intermediate after 5 h is probably due to its hydrolysis by traces of water present in the organic solvent. Using ^1H NMR spectroscopy, Moss *et al.*³⁰ reached a similar conclusion for the reaction of 4-nitrophenyl acetate with IBA in dry DMSO- d_6 . We attempted to detect the formation of 4-X-BzO-IBA by ^1H NMR spectroscopy (Bruker AC-200, 200 MHz, DMSO- d_6) but because all protons of reactants, intermediate and products are aromatic, we were unable to reach an unambiguous conclusion regarding the formation of this intermediate. On the other hand, the use of FT-IR spectrometry is particularly attracting because ν_{CO} of relevant species are well separated, as shown in Figure 1(A). To our knowledge, this is the second time that IR spectrometry has been employed to detect the formation of a reaction intermediate in an acyl-transfer reaction.²⁰

Desolvation enhances nucleophilicity and basicity, probably unequally. For example, the acetate ion acts as a general base in the hydrolysis of 4-X-phenyl acetates in aqueous solution.^{3,4,6} In dry acetonitrile,

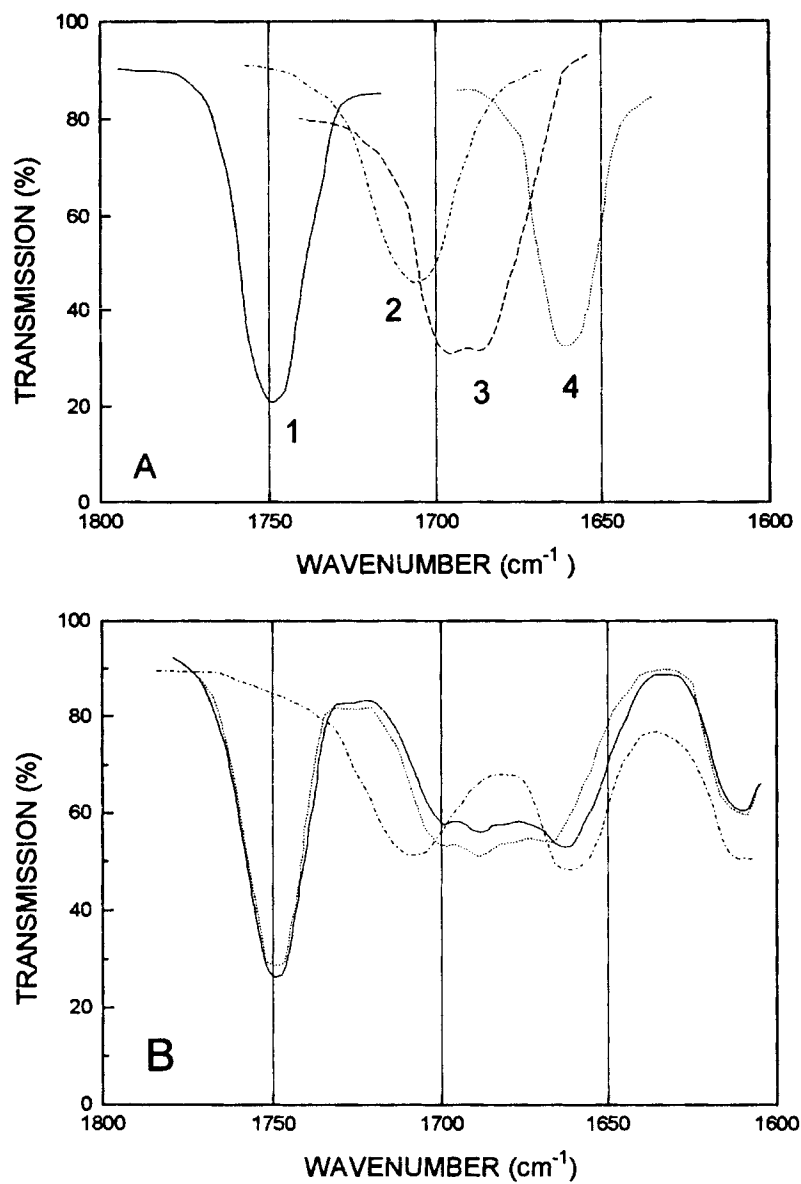


Figure 1. IR spectra in the 1800–1600 cm^{-1} region. (A) Absorption bands for authentic samples of (1) ester **1e**, (2) 4-nitrobenzoic acid, (3) 4- NO_2 -BzO-IBA and (4) IBA. (B) Variation of the spectrum of a mixture of 0.056 M **1e** and 0.32 M IBA after (—) 0.4, (·····) 1.5 and (---) 300 min. Conditions: in $\text{DMSO}-d_6$, 0.1 mm Itran-2 cell

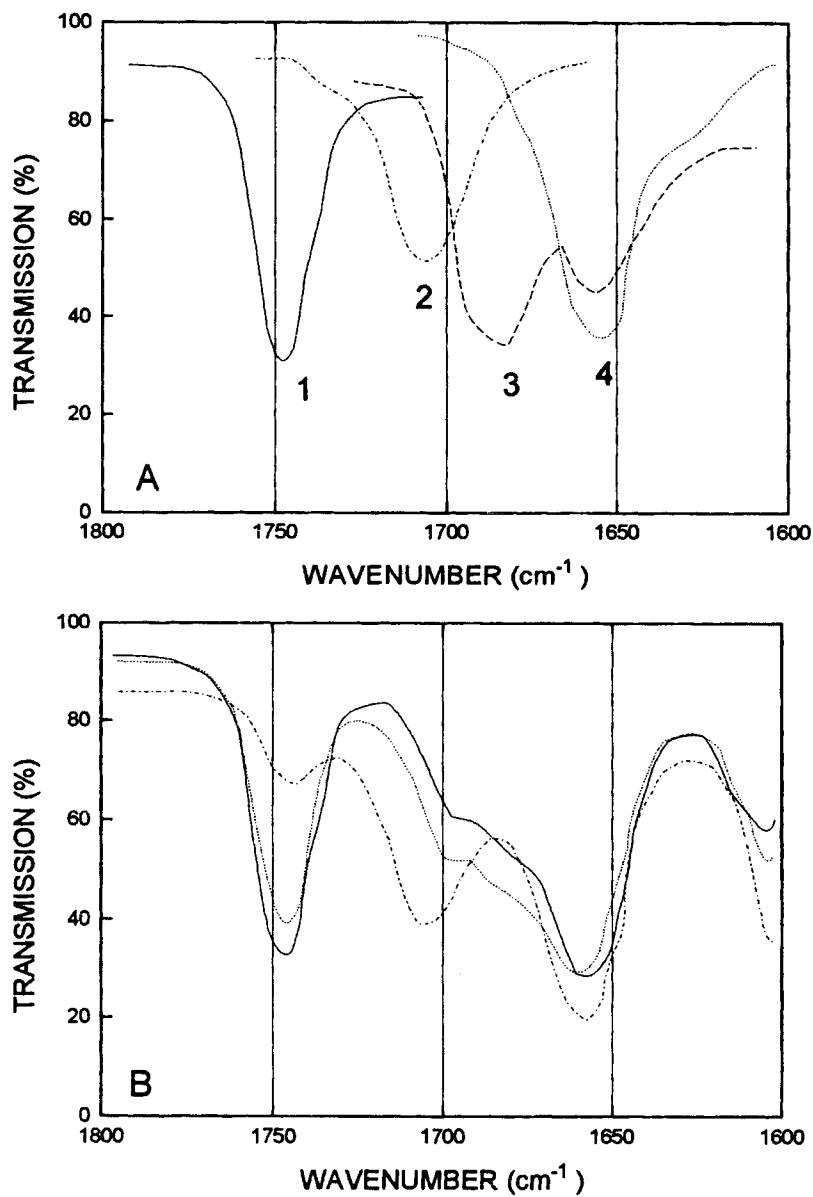


Figure 2. IR spectra in the 1800–1600 cm⁻¹ region in the presence of D₂O. (A) Absorption bands for authentic samples of (1) ester **1e**, (2) 4-nitrobenzoic acid, (3) 4-NO₂-BzO-IBA and (4) IBA. (B) Variation of the spectrum of a mixture of 0.043 M **1e** and 0.031 M IBA after (—) 1, (·····) 4 and (---) 60 min. Conditions: 3% D₂O in DMSO-*d*₆, 0.1 mm Itran-2 cell

however, the reaction between potassium acetate and 4-nitrophenyl *o*-toluate, in the presence of a crown ether, produces acetic-*o*-toluic mixed anhydride. This shows that the acetate anion, when completely desolvated, can act as a nucleophile.³¹ Therefore, we repeated the IR experiment in presence of the highest D₂O concentration, 3% (v/v), at which the intermediate can still be detected. Figure 2 shows the results obtained, where the formation and subsequent disappearance of 4-NO₂-BzO-IBA can be readily seen at ν_{max} 1684 cm⁻¹.

(ii) *Absence of general base catalysis by the leaving group.*

Observed rate constants for the following reactions were determined in 10% acetonitrile in water at 25 °C: [Id] = 2×10^{-5} M, [IBA⁻] = 20×10^{-5} M, pH = 8.33, in the absence and presence of [4-cyanophenol] at 0.6×10^{-4} – 6×10^{-4} M; [Ie] = 2×10^{-5} M, [IBA⁻] = 37.7×10^{-5} M, pH = 7.99, in the absence and presence of [4-nitrophenol] at 0.5×10^{-4} – 3×10^{-4} M; [IVe] = 2×10^{-5} M, [IBA⁻] = 23×10^{-5} M, pH = 7.80, in the absence and presence of [4-nitrophenol] at 0.5×10^{-4} – 3×10^{-4} M. The k_{obs} values ($\times 10^{-3}$ s⁻¹) obtained were 1.96 ± 0.01 , 6.12 ± 0.03 and 5.91 ± 0.03 for esters Ie, Id and IVe, respectively. Consider the pH employed, and p*K*_a values of 7.53, 7.95 and 7.15 for IBA, 4-cyanophenol and 4-nitrophenol, respectively, the concentrations of conjugate bases are 70.6% 4-cyanophenoxide and 86.3% IBA⁻ (ester Id). The corresponding values for the experiments in the presence of additional 4-nitrophenol are 87.4% 4-nitrophenoxide and 74.3% IBA⁻ (ester Ie), and 81.7% 4-nitrophenoxide and 65% IBA⁻ (ester IVe). That is, although in all experiments [4-X-phenoxide] ≥ [IBA⁻], the reaction rate was insensitive to the presence of the additional base, namely 4-X-phenoxide. Absence of catalysis by the leaving group is a clear indication that IBA⁻ is not acting as a general base, because if this were the case, then k_{obs} should have increased as a function of [phenol] which was added at the start of the kinetic run.^{3,4,6,32,33}

(iii) *Small kinetic solvent isotope effect.*

Hydrolysis of esters Ie and IIIId was studied in H₂O and in D₂O at 25 °C and pH (pD) = 8.0 and 7.8 respectively. The ratios between the catalytic rate constants (k_1 , see below) were 1.4 and 1.3, respectively. Typical general base catalyzed reactions are associated with much higher kinetic solvent isotope effects.¹⁻⁷

(iv) *Rapid catalyst 'turnover'.*

The reaction of ester Id and IBA⁻ was carried out at 35 °C and pH 7.80, at ester-to-IBA⁻ ratios of 1:1, 1:10 and 1:30. The value of k_{obs} , $(2.53 \pm 0.02) \times 10^{-3}$ s⁻¹,

was insensitive to changes in the ratio of the reactants, and this fast turnover shows that IBA⁻ is a true nucleophilic catalyst.³⁴

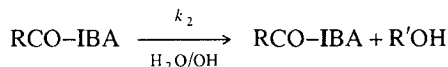
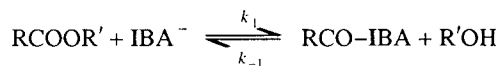
Kinetics of the hydrolysis of ester series I–IV by IBA⁻

According to the preceding discussion, the reaction under consideration follows Scheme 1. The latter can be simplified if it is shown that the intermediate ester-IBA does not accumulate along the reaction pathway. This conclusion can be reached from the following observations:

(i) Identical rate constants were obtained by following either the disappearance of reactants or the appearance of products of the first step of the reaction. For example, values of k_{obs} for the reaction of Ie (2×10^{-5} M) with IBA⁻ (57.3×10^{-5} M) at 25 °C, pH = 8.0, were 9.16×10^{-3} s⁻¹ (disappearance of Ie, followed at 265 nm) and 9.17×10^{-3} s⁻¹ (appearance of 4-nitrophenoxide, followed at 400 nm).

(ii) Isosbestic points were observed in the UV-visible spectra of the reaction. For example, sharp isosbestic points were observed at 309 and 312 nm in the UV-visible spectra of the reaction of IBA⁻ with Ie and Id, respectively.

These results can be explained by the fact that the species ester-IBA does not accumulate during the reaction,³⁵ and consequently Scheme 1 can be simplified by deleting the steps given by the rate constants k_a and k_b . This result is similar to that observed for reaction of Imz with the same ester series.²⁰ In the latter case, we extracted all rate constants by following the dependence of the absorption of the reaction intermediate, namely 4-X-benzoyl-Imz, on time.²⁰ This approach cannot be used for the present reaction because 4-X-BzO-IBA does not accumulate. The problem can be easily solved, however, if k_{-1} were negligible, this can be shown as follows. The reaction scheme (with symbols as in Scheme 1) is



We found that the hydrolysis of 4-NO₂-BzO-IBA is not subject to catalysis by the NMeM buffer or by IBA⁻, i.e. the term k_2 is the observed rate constant for spontaneous and OH⁻-catalyzed hydrolysis. From the preceding discussion, RCO-IBA can be considered as a reactive intermediate. Application of the steady-state approximation yields³⁶

$$\begin{aligned} -d[\text{RCOOR}']/dt &= d[\text{RCOO}^-]/dt = k_2[\text{RCO-IBA}] \\ k_1[\text{RCOOR}'][\text{IBA}^-] &= k_{-1}[\text{RCO-IBA}][\text{R}'\text{OH}] + k_2[\text{RCO-IBA}] \end{aligned}$$

and therefore

$$-d[\text{RCOOR}']/dt = k_1[\text{RCOOR}'][\text{IBA}^-]/r[\text{R}'\text{OH}] + 1$$

where $r = k_{-1}/k_2$. Now, if $k_{-1} > k_2$, then the reaction rate should show an inverse dependence on the amount of phenol which was added at the beginning of the kinetic run. This was not observed experimentally (see above, absence of catalysis by the leaving group). If, on the other hand, $k_2 > k_{-1}$, then conversion of the ester into 4-X-BzO-IBA can be described by a single, irreversible step. This result is similar to that observed for the reaction of these esters with Imz.²⁰

In the preceding discussion, we described IBA⁻-catalyzed hydrolysis in terms of a two-step mechanism, as given elsewhere for the reaction of acetate and benzoate esters with nucleophiles,³⁷⁻⁴⁰ although another mechanistic possibility, e.g. that it is 'enforced concerted,' cannot be ruled out. Distinction between these two possibilities is not trivial and is beyond the scope of this study. For example, a decision may be made from a Brønsted-type correlation ($\log k_{\text{nucleophile}} = \beta_{\text{nucleophile}} \text{p}K_{\text{a}} + C$), a non-linear plot indicates a two-step mechanism. It is difficult, however, to predict unambiguously the position of the break point

in a plot of $\log k_{\text{nucleophile}}$ versus $\text{p}K_{\text{a}}$, except when the entering and leaving groups have similar structures,⁴¹ and cases are known (e.g. pyridinolysis of ester **IIIe**) where no break was observed, although other pieces of evidence indicate a two-step mechanism.³⁹ Additionally, some mechanisms which were given as concerted (e.g. the reaction of phenoxides with substituted phenyl acetates)⁴² were later shown to proceed via a two-step mechanism.⁴³

Table 1 shows the catalytic rate constants (k_1) and the Hammett ρ values for the reaction of IBA⁻ with ester series I–IV, and the corresponding activation parameters are given in Table 2. As stated in the Introduction, we are interested in comparing Imz and IBA⁻ as nucleophilic catalysts for hydrolysis. Such a comparison is shown in Table 3 for catalytic rate constants and in Table 4 for activation parameters. Regarding these data, the following points are relevant:

(i) IBA⁻ and Imz differ in their sensitivity toward structure of the ester. The rate constant for the IBA⁻-catalyzed reaction is more sensitive to the structure of the ester. For example, at 25 °C the values of k_1 for Imz-catalyzed hydrolysis of esters **Ie** and **Ive** are 0.082 and 0.083 l mol⁻¹ s⁻¹,²⁰ whereas they are 16.1 and

Table 1. Catalytic rate constants (k_1) and Hammett ρ values for the reaction of IBA⁻ with ester series I–IV^{a-c}

Ester series (group varied)	X or Y	k_1 (l mol ⁻¹ s ⁻¹)			
		18 °C	25 °C	35 °C	45 °C
I (acyl)	CH ₃	0.25	0.38	0.67	1.12
	H	0.50	0.76	1.35	2.17
	Cl	0.96	1.48	2.50	4.15
	CN	6.80	10.20	17.99	28.70
	NO ₂	8.70 ^d	16.10	26.90	43.0
	ρ	1.63	1.68	1.67	1.65
II (phenol)	CH ₃	0.21	0.36	0.64	1.10
	H	0.35	0.53	1.05	1.66
	Cl	0.93	1.53	2.89	4.23
	CN	6.03	9.16	15.04	26.52
	ρ	1.72	1.74	1.68	1.69
	ρ	6.11	9.86	18.17	34.12
III (acyl)	Cl	15.96	23.57	46.06	79.83
	CN	112.17	177.68	307.97	544.57
	NO ₂	181.27	270.43	468.72	845.60
	ρ	1.82	1.80	1.76	1.74
	CH ₃	0.53	0.78	1.40	2.48
	H	0.92	1.39	2.54	4.18
IV (phenol)	Cl	2.51	3.69	6.87	10.90
	CN	19.30	27.50	46.44	76.0
	NO ₂	32.07	46.36	77.56	124.76
	ρ	1.88	1.87	1.82	1.78

^a Reactions conditions: [NMeM] = 0.05 M, μ = 0.2, 14% (v/v) acetonitrile in water. The buffer pH values were 8.0 (series I), 8.1 (series II and IV) and 7.8 (series III).

^b The average Hammett ρ values are 1.66 ± 0.02 , 1.71 ± 0.03 , 1.78 ± 0.04 and 1.84 ± 0.05 for ester series I, II, III and IV, respectively.

^c Hammett ρ values for the Imz-catalyzed hydrolysis of these esters are 1.09, 1.59, 1.71 and 1.59 for ester series I, II, III and IV, respectively.²⁰

^d Measured at 15 °C.

Table 2. Activation parameters for the reaction of ester series I–IV with IBA^{−a}

Ester series (group varied)	X or Y	Activation parameters		
		ΔH^*	ΔS^*	ΔG^*
I (acyl)	CH ₃	9.6	−28.2	18.0
	H	9.5	−27.2	17.6
	Cl	9.3	−26.5	17.2
	CN	9.3	−22.9	16.1
	NO ₂	9.1	−22.7	15.8
II (phenol)	CH ₃	10.6	−25.0	18.1
	H	10.6	−24.8	18.0
	Cl	9.8	−24.8	17.2
	CN	9.4	−22.8	16.1
	NO ₂	9.1	−22.7	15.8
III (acyl)	H	11.1	−16.9	16.1
	Cl	10.5	−16.8	15.6
	CN	10.1	−14.5	14.4
	NO ₂	9.9	−14.2	14.1
IV (phenol)	CH ₃	10.0	−25.4	17.6
	H	9.8	−25.0	17.3
	Cl	9.6	−23.8	16.7
	CN	8.7	−22.7	15.5
	NO ₂	8.7	−21.9	15.2

^a Activation parameters are given in kcal mol^{−1} (ΔH^* and ΔG^*) and calk^{−1} mol^{−1} (ΔS^*) (1 kcal = 4.184 kJ). The errors are ± 0.1 kcal mol^{−1} (ΔH^* and ΔG^*) are 0.5 e.u. (ΔS^*).

46.3 l mol^{−1} s^{−1} for the IBA[−]-catalyzed reaction. Introduction of a second nitro group in the *ortho* position of the acyl moiety of **Ie**, leading to **IVd**, is expected to increase the rate because of its electron-withdrawing effect. The same structural modification, however, may decrease reactivity owing to hindrance to the attack of the nucleophile, and steric inhibition of resonance between the CO group and the 2,4-dinitrophenyl ring. Both effects result from steric crowding at the reaction

Table 3. Comparison of the values of the catalytic rate constant, k_1 , for ester hydrolysis by IBA[−] (k_{IBA^-}) and Imz (k_{Imz}) for ester series I–IV^{a,b}

Substituent (X or Y)	$k_{\text{IBA}^-}/k_{\text{Imz}}$			
	Series I (acyl) ^c	Series II (phenol) ^c	Series III (acyl) ^c	Series IV (phenol) ^c
CH ₃	54	821		1907
H	78	745	20	1856
Cl	84	970	20	2183
CN	173	274	25	895
NO ₂	197	199	29	571

^a Reaction conditions: temperature = 25 °C (series I and III), 35 °C (series II) and 40 °C (series IV); μ = 0.2 (IBA[−]) or 0.07 (Imz); acetonitrile in water, 14% (v/v) (IBA[−]) or 10% (v/v) (Imz).

^b Data for the Imz-catalyzed ester hydrolysis were taken from Ref. 20.

^c The group whose structure is being varied is given in parentheses.

center which forces both *o*-nitro and CO groups out of the plane of the acyl benzene ring.^{20,21} The relative importance of steric interactions also depends on the structure of the attacking nucleophile. Our previous results for Imz (a rigid heterocycle) indicated that polar and steric effects of the *o*-NO₂ group almost cancel out, leading to rate constants for ester series II and IV that differ by, at most, 8%.²⁰ For the IBA[−]-catalyzed reaction, the steric retarding effect is less, owing to the favorable disposition of the nucleophilic center (the oxygen of the I–O[−] bond). The latter protrudes *ca* 2 Å from the heterocyclic five-membered ring almost linearly (the O–I–O[−] angle is 165°).¹⁶

(ii) For the same ester series, IBA[−] is a much more efficient catalyst. This is clearly seen from the data in Table 3. This is a very interesting result, because Moss *et al.*³⁷ found that the nucleophilicities of IBA[−] and Imz are similar toward 4-nitrophenyl acetate! Their conclusion was based on an estimation of the

Table 4. Comparison of the activation parameters for ester hydrolysis by IBA[−] and Imz for ester series I–III^{a–c}

Substituent (X or Y)	Series I (acyl) ^d		Series II (phenol) ^d		Series III (acyl) ^d	
	$\Delta\Delta H^*$	$T\Delta\Delta S^*$	$\Delta\Delta H^*$	$T\Delta\Delta S^*$	$\Delta\Delta H^*$	$T\Delta\Delta S^*$
CH ₃	−0.2	2.18	0.8	4.8		
H	−0.1	2.45	1.3	4.9		
Cl	0.3	2.98	0.9	4.9	2.2	4.2
CN	0.7	3.68	0.1	3.4	1.8	3.7
NO ₂	0.5	3.58	0.5	3.2	1.0	3.0

^a $\Delta\Delta H^*$ (kcal mol^{−1}) = $\Delta H^*\text{IBA}^- - \Delta H^*\text{Imz}$.

^b $T\Delta\Delta S^*$ (kcal mol^{−1}) = $T\Delta S^*\text{IBA}^- - T\Delta S^*\text{Imz}$.

^c Data for the Imz-catalyzed reaction were taken from Ref. 20.

^d The group whose structure is being varied is given in parentheses.

nucleophilicity constant, n , of the Swain–Scott equation, its values being 3.88 and 3.58 for IBA^- and Imz , respectively. It is known, however, that the value of n also depends on the structure of the reagent.^{3,35} This dependence is probably the reason for the difference in reactivity between the two nucleophiles toward 4-nitrophenyl acetate and the benzoate esters, respectively. In this regard, it is also interesting that $k_{\text{IBA}^-}/k_{\text{Imz}} > k_{\text{OH}^-}/k_{\text{Imz}}$ for the hydrolysis of series **III**.³⁸

(iii) Application of the Hammett equation shows differences between catalysis by both nucleophiles. Application of the Hammett equation to the rate data for Imz -catalyzed hydrolysis required the use of either the σ scale (series **I** and **III**) or the σ^- scale (series **II** and **IV**). Use of the latter shows that the leaving group is the phenoxide ion. From calculated ρ_X (1.09 and 1.71 for series **I** and **III**, respectively) and ρ_Y (1.59 and 1.59 for series **II** and **IV**, respectively), it was concluded that the rate-limiting step is decomposition of the tetrahedral intermediate that precedes N-4-X-benzoylimidazole (series **I**, **II** and **IV**) or attack of Imz on acyl group of the ester (series **III**).²⁰

All rate constants for the IBA^- -catalyzed reaction correlated well with the σ -scale (attempts to correlate values of $\log k_1$ with the Hammett σ_p^- scale for ester series **II** and **IV** resulted in curved plots in all cases). This shows that the leaving group is 4-Y-phenol. Additionally, the fact that $\rho_Y > \rho_X$ (Table 1) indicates that the reaction is more sensitive to the nature of the leaving group than to the structure of the acyl moiety. This means that the rate-limiting step is the same for all four series, namely collapse of the ester– IBA tetrahedral intermediate.

For series **I** and **III**, the ratio $k_{\text{IBA}^-}/k_{\text{Imz}}$ increases on going from $\text{X} = \text{CH}_3$ to NO_2 . For the other two series, however, value of $k_{\text{IBA}^-}/k_{\text{Imz}}$ first increases, then decreases considerably for $\text{X} = \text{CN}$ and NO_2 . The increase in $k_{\text{IBA}^-}/k_{\text{Imz}}$ as a function of the substituent is a consequence of the fact that $\rho_{\text{IBA}^-} > \rho_{\text{Imz}}$. The rates of the Imz -catalyzed hydrolysis of esters **Ie**, **IId**, **IVd** and **Ive** are ‘enhanced’ because there is a through-ring resonance between the substituent (CN and NO_2) and the negative charge on the oxygen of the phenoxide ion, this being the reason for the use of the σ^- scale. For the IBA^- -catalyzed reaction the leaving group is phenol, *i.e.* the rates are ‘normal,’ and this is responsible for the decrease in the ratio $k_{\text{IBA}^-}/k_{\text{Imz}}$ for these particular esters.

What are the reasons for the higher reactivity of IBA^- relative to that of Imz ? At the outset we stress that the reaction media are too similar, 14% and 10% acetonitrile in water, for the IBA^- and Imz -catalyzed reaction, respectively, to cause large rate differences, *e.g.*, due to desolvation of the nucleophile. The reactivity of IBA^- is due, in part, to the favorable disposition of the $\text{I}-\text{O}^-$ bond (see above). Note that IBA^- is a negatively charged nucleophile, whereas Imz is neutral.

The presence of a charge, however, does not explain the reactivity of the former, because for ester **Ie** we found that $k_{\text{IBA}^-}/k_{\text{phosphate}} = 3100$, although both nucleophiles have almost the same $\text{p}K_a$. [The phosphate buffer-catalyzed reaction was carried out at 25°C in 14% (v/v) acetonitrile–water. The absence of a kinetic solvent isotope effect for this reaction indicates that it is also proceeding via a nucleophilic catalysis mechanism.⁴⁴] The rate constants for hydrolysis of **Ie** by IBA^- and 4-nitrophenyl acetate by hydroxylamine or by hypochlorite ion are similar.² Note that the $\text{p}K_a$ values of these two nucleophiles are close to that of IBA (6.2 and 7.1, respectively) and their reactivity was attributed to the presence of the α -effect.^{2–4} We attribute a significant part of the reactivity of IBA^- to the same phenomenon.

Finally, we discuss the results shown in Table 4. The IBA^- -catalyzed reaction is associated with a higher $\Delta\Delta H^\ddagger$ term and a much higher $T\Delta\Delta S^\ddagger$ term. Ignoring the effect of solvation for the moment, one expects that $\Delta H^\ddagger(\text{IBA}^-) \leq \Delta H^\ddagger(\text{Imz})$ because the former is a slightly stronger base. A favorable (*i.e.* less negative) value of $\Delta S^\ddagger$ for the IBA^- -catalyzed reaction is also expected because of smaller steric interactions (see above).

Table 4 shows, however, that for all but two esters, $\Delta H^\ddagger(\text{IBA}^-) > \Delta H^\ddagger(\text{Imz})$, the difference in the free energy of activation being dominated by the $T\Delta\Delta S^\ddagger$ term. We now address the effect of solvation of the nucleophile. The heat of hydration of Imz was found to be 5.9 kcal/mol.⁴⁵ We are unaware of any theoretically calculated, or experimentally determined heat of solvation of IBA or IBA^- . We take 4-nitrophenol as a model compound because of its $\text{p}K_a$ is similar to that of IBA . The heat of hydration of this phenol is 5.7 kcal mol⁻¹ (1 kcal = 4.184 kJ),⁴⁶ very similar to that of Imz and also to that (6–7 kcal mol⁻¹) calculated for hydroxylamine,⁴⁷ a nucleophile which exhibits the α -effect. The latter effect, therefore, does not influence solvation. Consequently, 4-nitrophenol is a good model for IBA , and its conjugate base is a good model for IBA^- . The heat of solvation of the 4-nitrophenoxide ion was calculated as 17.9 kcal mol⁻¹,⁴⁶ and one expects a similar value for IBA^- . Consequently, in the IBA^- -catalyzed reaction the nucleophile is more strongly solvated, and the corresponding difference in solvation between the reactants and the transition state is most certainly smaller than that in case of Imz . Therefore, the fact that $\Delta H^\ddagger(\text{IBA}^-) > \Delta H^\ddagger(\text{Imz})$ may be due to the energy which is required to desolvate (partially) the attacking anion. The more favorable (less negative) $\Delta S^\ddagger$ values are probably due to a combination of (i) less steric hindrance to attack of IBA^- , (ii) a gain in the number of degrees of freedom of water molecules which are released due to the desolvation of IBA^- , before its attack on the ester, and (iii) a smaller difference in solvation between reactants and the transition

state. The latter effect is a consequence of the fact that reaching the transition state involves a charge formation in the case of Imz and a (negative) charge dispersion in case of iodosobenzoate-catalyzed hydrolysis.

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