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Kinetics and mechanism of phosphate-catalyzed hydrolysis of benzoate esters: comparison with nucleophilic catalysis by imidazole and *o*-iodosobenzoate

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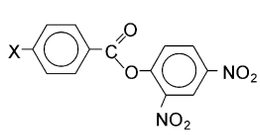
Phosphate-catalyzed hydrolysis of 2,4-dinitrophenyl 4-X-benzoate, and 3- or 4-Y-phenyl 3,5-dinitrobenzoates, where X and Y are substituents, has been studied spectrophotometrically. The following conclusions are based on catalytic rate constants, solvent kinetic isotope effect, detection of a mixed anhydride by FTIR, and application of the Hammett equation: (i) the catalytically active species is HPO_4^{2-}, (ii) the mechanism of catalysis is nucleophilic, the reaction proceeds *via* the irreversible formation of acyl phosphate, (iii) the formation of a tetrahedral species by attack of the HPO_4^{2-} on the ester CO group is rate limiting. Comparison of these results with our previous data on hydrolysis of benzoate esters with imidazole, or *o*-iodosobenzoate anion showed that: (i) the catalytic efficiency observed, *o*-iodosobenzoate > imidazole > phosphate, is due to a combination of steric and solvation effects, and the enhancement of the nucleophilicity of the former catalyst by the α-effect, (ii) the nonlinear Brønsted-type plot between log (catalytic constant) and pK_a of the leaving 4-Y-phenol indicates that the rate-limiting step for *o*-iodosobenzoate changes as a function of changing Y, (iii) the reaction rate-limiting steps are different for the above-mentioned nucleophiles.

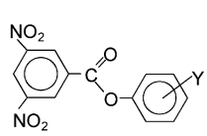
Introduction

Acyl-transfers are important reactions in chemistry and enzymology.[1–5] Previously, we have studied the hydrolysis of benzoate esters of the general structure X–C_6H_4–CO_2–C_6H_4–Y, where X and Y are substituents, with two powerful nucleophiles, namely, imidazole, Imz, and *o*-iodosobenzoate anion, IBA. We now report on phosphate-catalyzed hydrolysis of the same benzoate esters. Phosphate acts as a general base in hydrolysis of esters with poor leaving groups (LG), *e.g.*, ethyl dichloroacetate.[2] The nucleophilic-catalysis pathway is favored, however, for esters with better LG, *e.g.*, phenyl carboxylates. Here we show that this is indeed the case for phosphate-catalyzed hydrolysis of the following esters: (i) 2,4-dinitrophenyl 4-X-benzoates (hereafter designated as series I), where X = methyl (I-a), hydrogen (I-b), chloro (I-c), cyano (I-d) and nitro (I-e), respectively, and 3- or 4-Y-phenyl 3,5-dinitrobenzoates (hereafter designated as series II), where Y = 4-methyl (II-a), hydrogen (II-b), 3-cyano (II-c), 4-cyano (II-d) and 4-nitro (II-e), respectively.

We show that: HPO_4^{2-} is the active catalytic species; the mechanism of catalysis is nucleophilic; the rate limiting step for the *first part* of the reaction is attack of the catalyst on the ester CO group. We also compare nucleophilic catalysis by HPO_4^{2-}, Imz, and IBA.



General structure of series I



General structure of series II

Experimental

Synthesis

Reagents and solvents were purchased from Aldrich and Merck, and were purified as described elsewhere.[6] Series I was that available from a previous study,[4b] whereas series II was synthesized by reacting 3,5-dinitrobenzoyl chloride with the appropriate phenoxide under phase-transfer conditions.[4a] Esters II-a, II-b and II-e gave melting points that agree with literature values,[7] whereas esters II-c (mp 170–172 °C) and II-d (mp 225–226 °C) gave satisfactory elemental analysis, and the expected ^{1}H NMR spectra (acetone-d_6, Bruker AC-200).

Tetrabutylammonium di- and/or mono-hydrogenphosphate were prepared by reacting phosphoric acid (85%) with aqueous tetrabutylammonium hydroxide (40%). The final solution pH was adjusted to 4.3 or 7.4 for the former and the latter compound, respectively. Dry salts were obtained by lyophilization.

The mixed carboxylic-phosphoric anhydrides were synthesized *in situ*,[8b] by reacting 1.0 mol of 4-X-benzoyl chloride (X = CN and NO_2) with 1.05 mol of tetrabutylammonium dihydrogenphosphate in anhydrous acetonitrile, at room temperature. Reaction progress was followed by monitoring the disappearance of the ester $\nu_{C=O}$ band and the appearance of the carbonyl group of the mixed anhydride (Perkin-Elmer 1750 FTIR spectrophotometer, 0.2 mm ClearTran cell, Wilmad Glass). We have obtained an excellent linear correlation (correlation coefficient, r = 0.997) between $\nu_{C=O}$ of these mixed anhydrides, 1700 (X = H),[8c] 1733 (X = 4-CN), 1741 cm^{-1} (X = NO_2) and the Hammett σ_p value of X. The same IR equipment and cell were employed in the detection of the produced acyl phosphoric

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anhydride, *vide infra*, under the following experimental conditions: reaction medium, 65% CD_3CN plus 35% of 0.1 M $((C_4H_9)_4N)_2HPO_4$ in D_2O, pD = 7.8, [I-e] = 0.05 M. The IR cell was kept at *ca.* 40 °C, and the spectrum of the reaction mixture was recorded as a function of time. The spectra of authentic samples were recorded in 65% CD_3CN plus 35% D_2O.

Kinetic measurements

Kinetic measurements were carried out with Zeiss PM6KS or Beckman DU-70 Uv-vis spectrophotometers, fitted with thermostated cell holders whose temperature was kept constant at ± 0.05 °C (4000A digital thermometer, Yellow Springs Instruments). All runs were carried out in triplicate, under pseudo-first-order conditions, and were initiated by injecting the ester solution in anhydrous acetonitrile into the phosphate buffer, under the following experimental conditions: solvent, 10% CH_3CN in water (v/v, N_2-saturated); ionic strength, 1.0 M, maintained with NaCl; $[\text{phosphate buffer}]_{total}$ = 0.05 to 0.25 M; reaction pH = 7.8 to 8.2. We have verified that observed rate constants, k_{obs}, were independent of [ester] in the range 1–6 × 10^{-5} M, and used final [ester] = 1–3 × 10^{-5} M. The reaction mixture was homogenized with a micro-stirrer (type 338.004, Hellma). Reaction progress was followed by monitoring liberation of the appropriate phenol as a function of time, at the following λ: 362 nm, series I; 224, 227, 226, 270, and 400 nm for esters II-a to II-e, respectively. Plots of log (absorbance) *versus* time were rigorously linear over more than five half-lives, their slopes offered k_{obs}. For the same run, the relative standard deviation in k_{obs}, *i.e.*, ((standard deviation/k_{obs}) × 100) was ≤ 0.2%; for triplicate runs, the difference between k_{obs} was ≤ 1%.

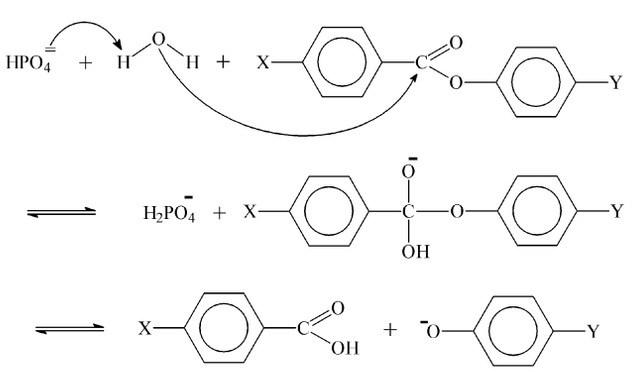
Results and discussion

Nature of the catalytically-active species

Independent of the reaction mechanism, the catalytically active species can be $H_2PO_4^-$, or HPO_4^{2-}, or both. Hydrolysis of ester I-e was studied at 40 °C, at three pHs, where the buffer ratios, *i.e.*, $[H_2PO_4^-]/[HPO_4^{2-}]$ were: 80 : 20; 50 : 50; and 20 : 80, respectively. Second order, *i.e.*, catalytic rate constants, k_c, were calculated from plots of k_{obs} *versus* $[H_2PO_4^-]$ and/or $[HPO_4^{2-}]$, respectively, giving: 0.004, 0.019, and 0.088 $M^{-1}s^{-1}$ ($H_2PO_4^-$); 0.019, 0.020, and 0.020 $M^{-1}s^{-1}$ (HPO_4^{2-}). The constancy of the latter k_c indicates that HPO_4^{2-} is the catalytically active species.

Nature of catalysis by the buffer: general-base or nucleophilic?

Catalysis by the buffer (B/BH, B = HPO_4^{2-}) can be general base (Scheme 1) or nucleophilic (Scheme 2). In all subsequent discussion, we concentrate on the part of the reaction that leads to formation of the phenoxide anion. The reason is that the nucleophilic catalysis pathway, if it applies, involves the formation of acyl phosphoric anhydride (*Int2*, Scheme 2) whose (slow) hydrolysis,[8b] is outside the scope of the present work.



Scheme 1 General-base catalysis by phosphate buffer.

As shown, we take the view that the reaction mechanism is stepwise,[9–11] involving the formation of a tetrahedral intermediate, *e.g. Int1* in Scheme 2, as given elsewhere for the reaction of acetate and benzoate esters with nucleophiles.[9]

The main difference between Schemes 1 and 2 is the formation of *Int2*, a carboxylic-phosphoric anhydride in the nucleophilic catalysis pathway. Formation of *Int2* does not involve direct participation of water, consequently, a small (secondary) kinetic solvent isotope effect is expected. Indeed, k_{cH_2O}/k_{cD_2O} for hydrolysis of esters I-d and I-e, at 40 °C were found to be 1.4 and 1.1, respectively, in agreement with a nucleophilic catalysis mechanism. For comparison, k_{cH_2O}/k_{cD_2O} were found to be (catalyst, ester, respectively): 1.4 and 1.3 (IBA, 4-nitrophenyl 4-nitrobenzoate, I-e), 1.3, 1.0, and 3.0 (Imz, I-e, 4-nitrophenyl acetate, ethyl dichloroacetate).[1,4] For the last ester, the catalysis is *general base*.[1]

We sought direct experimental evidence for the formation of *Int2*. FTIR was employed to follow changes in the $\nu_{C=O}$ region for the phosphate-catalyzed hydrolysis of ester I-e, Fig. 1. Part A of this figure shows $\nu_{C=O}$ for the following *authentic samples* in 65% CD_3CN in D_2O: ester I-e, $\nu_{C=O}$ = 1762 cm^{-1}, the *initial* product if the catalysis were nucleophilic, *i.e.*, 4-nitrobenzoyl phosphate, $\nu_{C=O}$ = 1741 cm^{-1}, and the *final* reaction products, *i.e.*, an equimolar mixture of the potassium salts of 4-nitrobenzoic acid and 2,4-dinitrophenol, $\nu_{C=O}$ = 1722 and 1709 cm^{-1}, respectively. Part B of Fig. 1 shows changes in the same spectral region for phosphate-catalyzed hydrolysis of ester I-e after 10 minutes, 6 h and 18 h, respectively. A trace of *Int2* can be detected after 10 minutes, and is clearly seen after 6 hours, whereas the final reaction products are the only species present after 18 hours.[12] These changes show clearly the formation, and subsequent decomposition of *Int2*, 4-nitrobenzoyl phosphoric anhydride, in agreement with a nucleophilic catalysis mechanism.

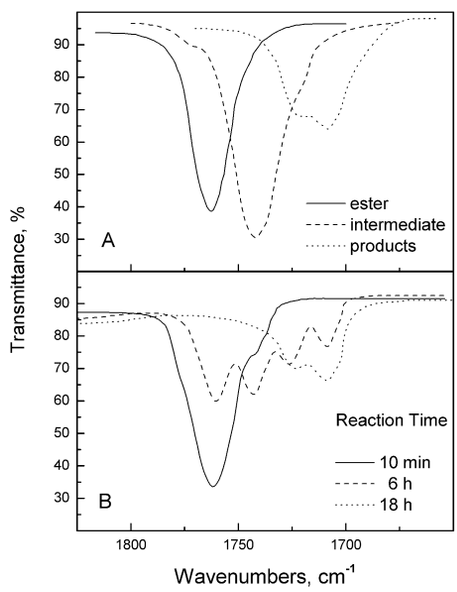


Fig. 1 IR spectra of the $\nu_{C=O}$ region. Part A shows peaks of *authentic* 2,4-dinitrophenyl 4-nitrobenzoate, Ester; 4-nitrobenzoyl phosphate, Intermediate; an equimolar mixture of potassium salts of 4-nitrobenzoic acid and 2,4-dinitrophenol, Products. Part B shows the dependence on time of the spectrum of I-e in the presence of phosphate buffer in CD_3CN–D_2O solvent, see Experimental for details.

Nucleophilic catalysis by phosphate buffers in aqueous solutions has been demonstrated for, *e.g.*, hydrolysis of 4-nitrophenyl acetate,[13a] phosphoryl transfer from phosphorylated pyridine monoanions,[13b] hydrolysis of guanosine 5′-phosphate 2-methylimidazole,[13c] hydrolysis of bis(4-nitrophenyl) methyl phosphonate,[13d] and esterolysis of 2,4-dinitrophenyl acetate in the presence of micellar benzyltrimethylammonium *n*-decyl phosphate.[13e] The first study had a very limited scope, and the

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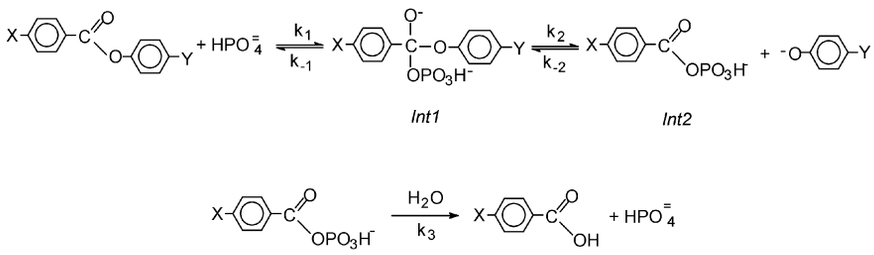
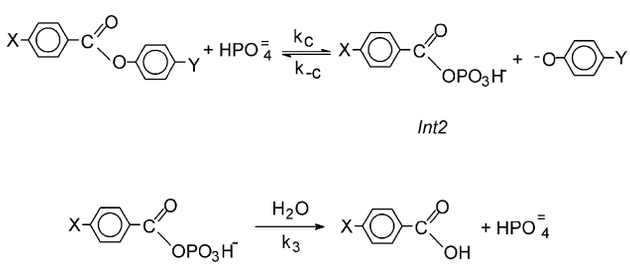


Scheme 2 Nucleophilic catalysis by phosphate buffer.

question of the catalytically-active species has not been addressed.[13a] The second and third reactions are catalyzed by both buffer species, albeit more efficiently by HPO_4^{2-},[13b,c] the fourth reaction is catalyzed by HPO_4^{2-}, whereas the last reaction shows the formation of the mixed anhydride in a micellar solution.

Details of the reaction mechanism

We now address the relative stabilities of *Int1* and *Int2*, respectively. Uv-vis spectra recorded during the hydrolysis of several esters showed sharp isosbestic points that lie between peaks of the ester and the phenol produced, *e.g.*, at 295 and 242 nm for esters I-e and II-d, respectively. Additionally, identical rate constants were obtained when hydrolysis of I-c was studied by following either the disappearance of the ester, or the appearance of 4-chlorophenol. Both observations indicate that *Int1* does not accumulate, so that Scheme 2 can be simplified, as depicted in Scheme 3.



Scheme 3 Simplified scheme for nucleophilic catalysis by phosphate buffer.

An obvious experiment to judge the reversibility of the reaction, *i.e.* whether k_{-c} is relevant, is to determine the (common ion) effect of the leaving phenol, added at the *start* of the run, on k_{obs}. Because pK_a of HPO_4^{2-} and the leaving phenol (*e.g.*, 4-nitrophenol) are practically the same, their concentrations should be comparable (≥0.1 mol L^{-1}), in order to clearly see the effect of reversibility on k_{obs}. Experimentally, however, this phenol concentration cannot be employed because of its strong Uv-vis absorption.

Another approach is to investigate the reverse reaction, *i.e.*, that of *authentic* mixed anhydride with an appropriate phenoxide ion, in presence of a buffer, HB/B, whose B is a poor general base, and does not act as a nucleophile. We studied the reaction of equal amounts (4×10^{-5} M) of 4-nitrobenzoyl phosphate and 2,4-dinitrophenolate anion (to give ester I-e), in the presence of 0.05 mol L^{-1} *N*-methylmorpholine buffer, at pH = 6.8. The Uv-vis spectrum of this mixture did not change as a function of time, during one hour. The same reaction was also investigated by FTIR, under the following conditions: solvent 65% CD_3CN in D_2O buffered with 0.05 M *N*-methylmorpholine (pD = 7.2); [4-nitrobenzoyl phosphate] = 0.025 M; [2,4-dinitrophenolate anion] = 0.05 M, 0.05 mm path length ClearTran cell. The 1850–1650 cm^{-1} spectral region was periodically scanned during two hours; no ester appeared (at *ca.* 1762 cm^{-1}). Both experiments clearly indicate that: (i) the mixed anhydride, *i.e.*, *Int2*, is stable under these reaction conditions,[8b,12] (ii) the step of concern, *i.e.*, that leading to the formation of *Int2* plus the phenoxide ion is irreversible. That is, we need only be concerned with k_c of Scheme 3.

Table 1 shows the dependence of k_c of series I on temperature, along with the corresponding activation parameters. The Hammett plot (log k_c *versus* σ_p)[14] gave an excellent straight line ($r = 0.9981$, sum of the squares of the residues, $\Sigma Q = 0.068$) with $\rho_X = 2.23$. The reaction of series II was studied only at 50 °C; the following $10^3 k_c$, $M^{-1}s^{-1}$, were calculated: 5.01, 7.08, 22.2, 51.3, and 97.3 for II-a (Y = 4-CH_3), II-b (Y = H), II-c (Y = 3-CN), II-d (Y = 4-CN) and II-e (Y = 4-NO_2), respectively. For series II, the Hammett plot was satisfactory *only* when σ^-_p was employed ($r = 0.9992$, $\Sigma Q = 0.026$), giving $\rho_Y = 0.89$. The implications of these ρ for the rate-limiting step will be discussed in the next paragraph.

Comparison of nucleophilic catalysis by phosphate, imidazole and the *o*-iodosobenzoate anion

Comparison of hydrolysis of these benzoate esters by HPO_4^{2-}, Phos, Imz, and IBA is instructive because: (i) all three reactions proceed by nucleophilic catalysis, *via* an irreversibly formed acylated catalyst, *e.g.*, *Int2* for Phos, (ii) although the three catalysts have comparable pK_a (7.53, 7.05, and 7.20, for IBA, Imz, and Phos, respectively) their nucleophilic centers are different, nitrogen for Imz, and anionic oxygen for phosphate and IBA, respectively. An *outline* of the reactions of concern is depicted in Scheme 4 for an ester of the general formula $X–C_6H_4–CO_2C_6H_4–Y$, whereas relative rates, and differences between the activation parameters are listed in Table 2. Note that series I (2,4-dinitrophenyl 4-X-benzoates) is the *same* for the three catalysts, whereas series II for IBA and Imz, 4-Y-phenyl 2,4-dinitrobenzoates, is *different* from that employed with Phos, 3- or 4-Y-phenyl 3,5-dinitrobenzoates:

Imz and, specially, IBA are much more efficient nucleophiles than Phos (Table 2). This is due, in part, to differences in steric interactions, and of properties, *e.g.*, solvation, of the nucleophiles. Steric hindrance to the attack on the ester CO group (to give *Int1*) is relevant to reactivity because of the presence of the *o*-nitro group in the phenol moiety.[15] This effect is specially small for IBA due to the favorable disposition of its nucleophilic (oxygen) center, which protrudes unhindered from the heterocyclic five-membered ring (the O–I–O^- bond angle is 165°).[4b] This, in part, is responsible for the favorable entropy of activation of the IBA-catalyzed reaction, as manifested by the corresponding *negative* $T\Delta\Delta S^{\neq}$, Table 2. Heat of solvation, ΔH°_{solv}, of the nucleophile contributes to the activation enthalpy since it must be de-solvated, at least partially, before attacking the ester CO group. ΔH°_{solv} are 17.9,[4b] 5.6[16a] and 250 kcal mol^{-1}[16b] for IBA, Imz, and Phos, respectively. These data agree with the *positive* (*i.e.* favorable) $\Delta\Delta H^{\neq}$ of Imz, and the fact that $\Delta\Delta H^{\neq}$ for Imz is larger than the corresponding value for IBA. The higher ΔH°_{solv} of the latter nucleophile is more than compensated for by its enhanced nucleophilicity, due to the α-effect.[3]

We now compare the rate limiting steps, RLS, involved. Our data indicate that these hydrolyses follow a stepwise mechanism, with RL formation, or breakdown of the corresponding

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Table 1 Dependence of the catalytic rate constants, k_c, on temperature and activation parameters for phosphate-catalyzed hydrolysis of ester series I, 2,4-dinitrophenyl 4-X-benzoates[a]

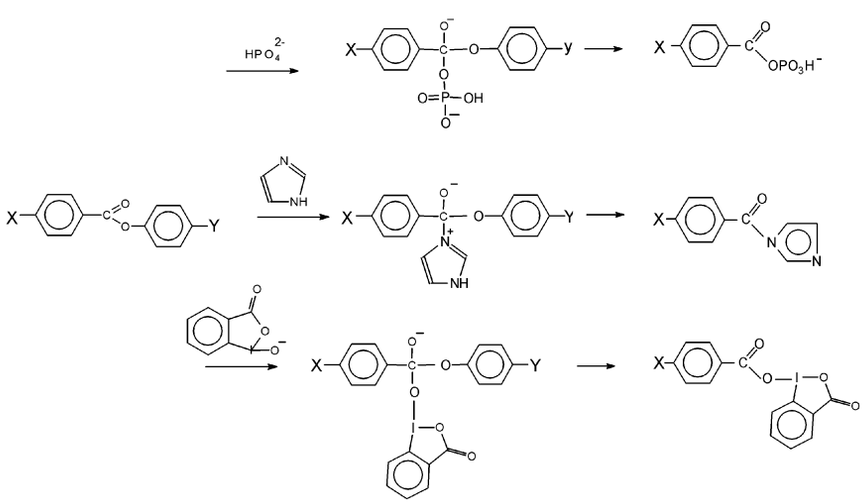
	$10^4\ k_c/M^{-1}s^{-1}$				
T/°C	X = CH_3	X = H	X = Cl	X = CN	X = NO_2
25.0	0.55	1.62	4.28	44.9	86.8
35.0	1.41	4.12	10.90	115.0	225.1
45.0	3.41	8.31	22.80	228.0	423.0
55.0	7.80	22.0	56.60	486.0	886.0
	Activation parameters[b]				
$\Delta H^{\neq}$/kcal mol^{-1}	16.6	16.0	15.9	14.6	14.2
$\Delta S^{\neq}$/cal K^{-1} mol^{-1}	−22.4	−22.3	−20.7	−20.1	−20.0
$\Delta G^{\neq}$/kcal mol^{-1}	23.3	22.6	22.1	20.6	20.2

[a] Reaction conditions: solvent, 10% acetonitrile in water, v/v; ionic strength = 1.0 M; $[\text{buffer}]_{\text{total}}$ = 0.05 to 0.25 M; reaction pH = 7.8 to 8.2. [b] The uncertainties in the activation parameters are ± 0.1 kcal mol^{-1} ($\Delta H^{\neq}$ and $\Delta G^{\neq}$) and ± 0.5 cal K^{-1} mol^{-1} ($\Delta S^{\neq}$).

Table 2 Comparison of the hydrolysis of series I, 2,4-dinitrophenyl 4-X-benzoates, at 25 °C, catalyzed by *o*-iodosobenzoate anion, IBA, imidazole, Imz, and HPO_4^{2-}, Phos

			$\Delta\Delta H^{\neq}$ [c]		$\Delta\Delta S^{\neq}$ [c]		$T\Delta\Delta S^{\neq}$ [c]	
X	$k_{\text{c-IBA}}/k_{\text{c-Phos}}$ [a]	$k_{\text{c-Imz}}/k_{\text{c-Phos}}$ [b]	IBA	Imz	IBA	Imz	IBA	Imz
CH_3	97363	4781	5.5	8.3	−4.1	11.4	−1.2	3.4
H	60864	2988	4.9	7.1	−5.4	7.7	−1.6	2.3
Cl	55070	2782	5.4	6.9	−3.9	7.3	−1.2	2.2
CN	39572	1604	4.5	6.3	−5.6	6.8	−1.7	2.0
NO_2	31155	1072	4.3	5.3	−5.8	4.2	−1.7	1.3

[a] Reaction conditions: Phos, μ = 1.0, solvent = 10% acetonitrile in water (v/v); IBA, μ = 0.2, solvent = 14% acetonitrile in water (v/v).[4b] [b] Reaction conditions: Imz, μ = 0.06, solvent = 10% acetonitrile in water (v/v).[4a] [c] $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{\text{Phos}} - \Delta H^{\neq}_{\text{Imz}}$, kcal mol^{-1}; $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{\text{Phos}} - \Delta S^{\neq}_{\text{Imz}}$, cal K^{-1} mol^{-1}; $T\Delta\Delta S^{\neq}$ is in kcal mol^{-1}.



Scheme 4 Nucleophilic catalysis by Phos, Imz, and IBA buffers, respectively.

tetrahedral intermediate (*Int1*, see Scheme 2), depending on the nucleophile and/or the strength of the LG. Structures of the relevant (*i.e.*, rate-limiting) transition states, TS, are shown in Fig. 2, followed by corroborating evidence.

The extents of bond formation (between the nucleophile and the ester CO group) and bond breaking (between the CO group and LG) can be probed by considering: Hammett ρ_X (series I) and ρ_Y (series II), Brønsted-type plots (log k_c *versus* pK_a of the leaving phenol, β_{LG}), and plots of log k_c of the different nucleophiles. Examination of these data reveals the following:

(i) For Phos, the large magnitude of $\rho_X - \rho_Y$ (= 1.34) clearly indicates that the RLS is bond formation. For IBA and Imz, however, the corresponding differences are too small (≤ 0.12) to allow an unambiguous conclusion with regard to the nature of the RLS. Therefore, we draw our conclusions mainly from the above-mentioned Brønsted-type plots, log k_c–log k_c plots, and the activation parameters.

(ii) A Brønsted-type plot between log k_c IBA and pK_a of the leaving phenol exhibits a clear break (Fig. 3A), with β_{LG} changing from −0.78 for the poor LG to −0.26 for their good counterparts. Additionally, plots (not shown) of log k_c IBA *versus* log k_c Imz; log k_c IBA *versus* log k_c Phos; and log k_c IBA *versus* σ^- are clearly nonlinear. We have employed the Hammett σ^- scale with IBA in order to be consistent with a Brønsted-type plot, and with the corresponding Hammett plots of the other two nucleophiles. The two straight lines of the log k_c IBA *versus* σ^- plot yield ρ_Y that varies from 1.69 for poor LG, to 0.74 for their good counterparts. Therefore, there is a change in the RLS of IBA-catalyzed hydrolysis as a function of changing Y, the RLS being bond formation for

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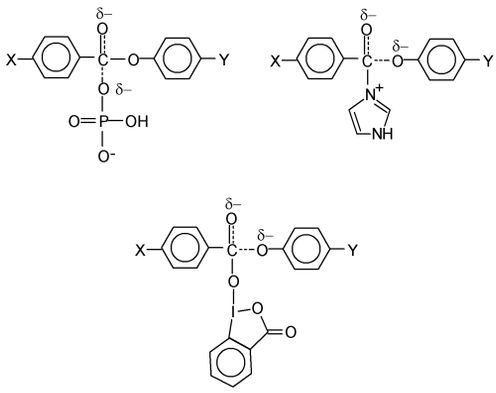

Fig. 2 Suggested structures for the rate-limiting transition states of nucleophile-catalyzed hydrolysis of benzoate esters.

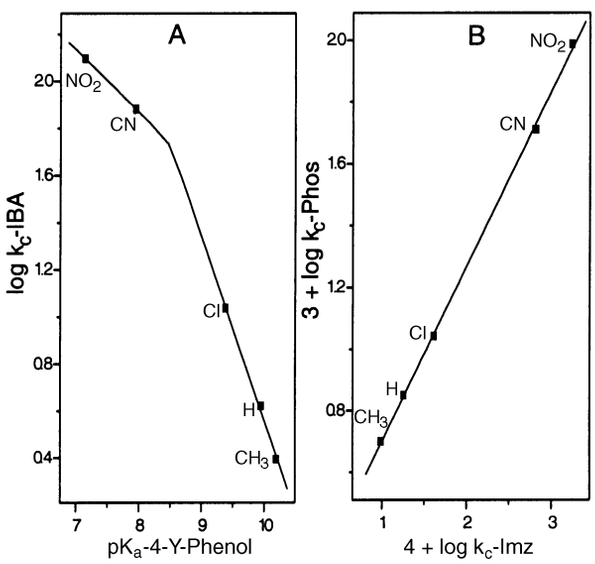

Fig. 3 Part A shows the relationship between the catalytic rate constant for hydrolysis of 4-Y-phenyl 2,4-dinitrobenzoates in the presence of IBA at 45 °C, k_c IBA,[4b] and the pK_a of the leaving phenol. Part B shows the relationship between the catalytic rate constants for hydrolysis of 4-Y-phenyl 2,4-dinitrobenzoates in the presence of Imz at 40 °C, k_c Imz,[4a] and those for the hydrolysis of 4-Y-phenyl 3,5-dinitrobenzoates catalyzed by phosphate at 50 °C, k_c Phos. For the latter series, the rate constant for Y = 4-Cl was calculated from the Hammett plot.

good leaving phenols, and bond breaking for poor leaving ones.

(iii) In contrast, there is an excellent linear correlation between log k_c Phos and log k_c Imz ($r = 0.9996$, $\Sigma Q = 0.017$, Fig. 3B), with a slope of 0.57. The corresponding Brønsted-type plots between log k_c and pK_a of the leaving phenol are also linear ($r = 0.9972$ and 0.9984, $\Sigma Q = 0.085$ and 0.036 for Imz and Phos, respectively), with β_{LG} of −0.75 and −0.40 for Imz and Phos, respectively. The effect of Y on rates of hydrolysis of series II by these two nucleophiles is also well described by the log $k_c = \rho_Y \sigma_Y^-$ relationship, with $\rho_Y = 1.59$ and 0.89 for Imz and Phos, respectively. Relative to Imz, β_{LG} and ρ_Y for the Phos-catalyzed reaction are markedly smaller; this indicates different magnitudes of bond breaking in their transition states, a conclusion that is consistent with a RL-formation and RL-breakdown of the tetrahedral intermediate for Phos and Imz, respectively.

(iv) In principle, the magnitude of bond formation between an attacking nucleophile and a reactant can be obtained from the slope, $\beta_{Nucleophile}$, of the Brønsted-type plot of log k_c *versus* pK_a of the attacking species. Since distinct classes of nucleophiles were employed (oxygen and nitrogen), $\beta_{Nucleophile}$ for the present reactions is not attainable by this approach. However, ρ_X is relevant to bond formation since it expresses the electronic demand on the X-substituted acyl moiety, in order to stabilize the partial negative charge on the acyl oxygen atom. Calculated ρ_X are 1.80, 1.71, and 2.23 for IBA, Imz, and Phos, respectively. These are consistent with a RL bond formation in the Phos-catalyzed reaction, with a demand on X larger than for the other two nucleophiles. Examination of the electrostatic interactions within the transition states shown in Fig. 2 corroborates this conclusion. For Phos, electrostatic repulsion is large in the dianionic TS, this being the reason for the large electronic demand on X,[13b] so that ρ_X is largest among the three nucleophiles.

(v) The activation entropies for hydrolysis of series I are consistent with the preceding discussion. As expected for bimolecular reactions, all $\Delta S^{\neq}$ are negative but $|\Delta S^{\neq}|_{Phos} < |\Delta S^{\neq}|_{Imz}$ in agreement with our previous conclusion regarding the importance of the bond formation (Phos), and bond breaking (Imz), steps respectively. The fact that $|\Delta S^{\neq}|_{Phos} > |\Delta S^{\neq}|_{IBA}$ is unexpected, at least for good LG, and may reflect: (i) the above-mentioned favorable disposition of the IBA nucleophilic center, (ii) more extensive solvent reorganization required to solvate the dianionic TS of the Phos-catalyzed reaction.

Conclusions

Phosphate-catalyzed hydrolysis of benzoate esters occurs *via* a stepwise mechanism, involving HPO_4^{2-} as a nucleophile, and the formation of acylated nucleophile, similar to Imz- and IBA-catalyzed hydrolysis of the same esters. The mechanism of catalysis and the nature of the RLS clearly depend on the structures of catalyst and substrate. Thus, increasing the strength of the LG from ethyl (in dichloroacetate)[1] to substituted phenyl (4-nitrophenyl acetate,[1,13a] series I and II) results in a change in the mechanism of catalysis by Phos and Imz from general base to nucleophilic. The weakest nucleophile, Phos, reacts with a RL-attack on the ester CO group, Imz reacts with RL phenol departure. The RLS of IBA, the strongest nucleophile, depends on the strength of the leaving phenol.

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