

Catalysis of the ethanolysis of aryl methyl phenyl phosphinate esters by alkali metal ions: transition state structures for uncatalyzed and metal ion-catalyzed reactions†

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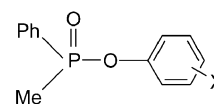
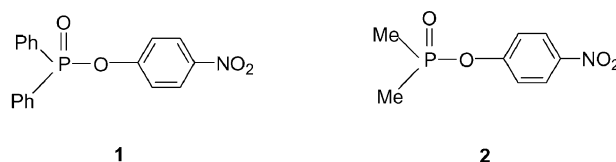
This paper reports on a spectrophotometric kinetic study of the effects of the alkali metal ions Li^+ and K^+ on the ethanolysis of the aryl methyl phenyl phosphinate esters **3a–f** in anhydrous ethanol at 25 °C. Rate data obtained in the absence and presence of complexing agents afford the second-order rate constants for the reaction of free ethoxide (k_{EtO^-}) and metal ion-ethoxide ion pairs (k_{MOEt}). The sequence $k_{\text{EtO}^-} < k_{\text{MOEt}}$ is established for all the substrates, contrary to the generally observed reactivity order in nucleophilic substitution processes. The quantities δG_{ip} , δG_{is} and ΔG_{cat} , which quantify the observed alkali metal ion effect in terms of transition state stabilization through chelation of the metal ion, give the order $\delta G_{\text{is}} > \delta G_{\text{ip}}$ for Li^+ and K^+ . Hammett plots show significantly better correlation of rates with σ and σ° substituent constants than with σ^- , yielding moderately large $\rho(\rho^\circ)$ values that are consistent with a stepwise mechanism in which formation of a pentacoordinate (phosphorane) intermediate is the rate-limiting step. The range of the values of the selectivity parameter, $\rho_n (= \rho/\rho_{\text{eq}})$, 1.3–1.6, obtained for the uncatalyzed and alkali metal ion catalyzed reactions indicates that there is no significant perturbation of the transition state (TS) structure upon chelation of the metal ions. This finding is relevant to the mechanism of enzymatic phosphoryl transfer involving metal ion co-factors. The present results enable one to compare structural effects for nucleophilic reactions of several series of organophosphorus substrates. It is shown that the order of reactivity of the substrates: 4-nitrophenyl dimethyl phosphinate (**2**) > **3a** > 4-nitrophenyl diphenyl phosphinate (**1**) is determined mainly by the steric effects of the alkyl/aryl substituents around the central P atom in the TS of the reaction.

Introduction

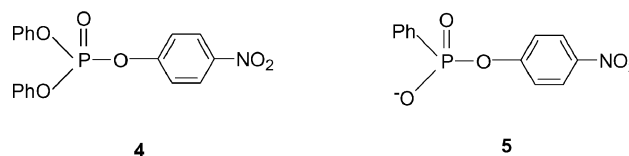
An understanding of the influence of metal ions on the transfer of the phosphoryl group from phosphate esters and related substrates to nucleophiles is desirable because of the importance of these substrates in biological energy transport and the propagation of genetic information.^{1–4} A significant body of information on the effects of divalent metal ions on phosphoryl transfer processes is available in the literature.^{5,6} The more recent work of Brown and coworkers⁷ has demonstrated very large catalytic effects of La^{3+} on the methanolysis of phosphate di- and triesters.

We have devoted attention mainly to the study of alkali metal ion effects in phosphorus-based systems for which there was scant information prior to our work. Significantly, we have demonstrated catalysis by alkali metal ions of the ethanolysis of the following phosphorus-based esters in anhydrous ethanol: 4-nitrophenyl diphenylphosphinate (**1**),⁸ 4-nitrophenyl dimethylphosphinate (**2**),⁹ 4-nitrophenyl diphenylphosphate (**4**)¹⁰ and 4-nitrophenyl phenylphosphonate (**5**).¹¹ A characteristic feature of the reaction of these substrates with alkali metal ethoxides in ethanol is the upward curvature of plots of the observed first-order rate constant (k_{obs}) against metal ethoxide (MOEt) concentration, indicating concurrent reaction of free and ion-paired ethoxide with the substrate. Analysis of our kinetic results has provided, in each case, values of the second-order rate constants for the reactions of free ethoxide (k_{EtO^-}) and metal ethoxide ion-pair (k_{MOEt}). The relative magnitude of these rate constants ($k_{\text{MOEt}} > k_{\text{EtO}^-}$) points to a catalytic role for the alkali metal ions. Using the transition state theory,

in conjunction with a model for the characterization of the transition states of catalyzed reactions which was developed by Kurz¹² and applied in different forms by Mandolini¹³ and Tee,¹⁴ we have shown^{8–11} that the catalytic action of the alkali metal ions derives from better stabilization of the transition state of the reaction rather than the initial state through chelation with the metal ion.



- 3** (a) X = 4-NO₂
 (b) X = 3-NO₂
 (c) X = 4-COCH₃
 (d) X = 4-Cl
 (e) X = H
 (f) X = 4-CH₃



We report in this paper data obtained from a kinetic study of the nucleophilic reactions of aryl methyl phenyl phosphinate esters **3a–f** with LiOEt and KOEt in anhydrous ethanol. Upward curvature in the k_{obs} vs. $[\text{MOEt}]$ plots is indicative of catalysis of the title reaction by the alkali metal ions Li^+ and K^+ .

† Electronic supplementary information (ESI) available: kinetic data for the reaction of aryl methyl phenyl phosphinates with various nucleophilic reagents in differing media. See <http://www.rsc.org/suppdata/ob/b5/b501537e/>

Systematic variation in structure in going across the substrate series **1**, **3a** and **2** is informative from the structure–reactivity relationship point of view, especially in evaluating how electronic and steric factors in the substrates affect both reactivity with the nucleophile and the catalytic action of the metal ions. It was also of interest to obtain information on the effect of metal ion binding on TS structure in these reactions. Such information will be useful in evaluating the mechanistic details of certain enzymatic phosphoryl transfers involving metal ion co-factors.^{2,3} The finding in this study, that alkali metal ion binding does not significantly perturb the TS of the catalyzed reaction, underlines the importance of electrostatic stabilization of the TS of enzyme catalyzed reactions by charges suitably disposed in the enzyme active site.

Results

The rates of the reaction of the aryl methyl phenyl phosphinate esters **3a–f** with LiOEt and KOEt were studied spectrophotometrically in anhydrous ethanol at 25 °C by monitoring the release of the relevant phenoxide ion under first-order conditions, with the nucleophilic reagent in significant excess relative to the substrate. In all cases, good first-order kinetics were obtained and formation of the phenoxide ion was quantitative, indicating that nucleophilic attack at the phosphorus center was the only reaction pathway. First-order rate constants, k_{obs} , were reckoned from linear plots of $\ln(A_{\infty} - A_t)$ vs. t . Kinetic data for the ethanolysis of the substrates **3a–f** with LiOEt and KOEt are provided in the supplementary information.

Plots of k_{obs} vs. total metal ethoxide concentration, $[\text{MOEt}]_0$ ($M = \text{Li}, \text{K}$), show an upward curvature in all cases. Typical plots, for the ethanolysis of **3a** by LiOEt and KOEt, are shown in Fig. 1. The upward curvature of the plots indicates the greater reactivity of the alkali metal ethoxide ion pairs than of free ethoxide ions, contrary to the generally observed reactivity order in nucleophilic substitution processes. The relative order of reactivity, $\text{LiOEt} > \text{KOEt}$, is qualitatively evident in Fig. 1 for the reaction of **3a**.

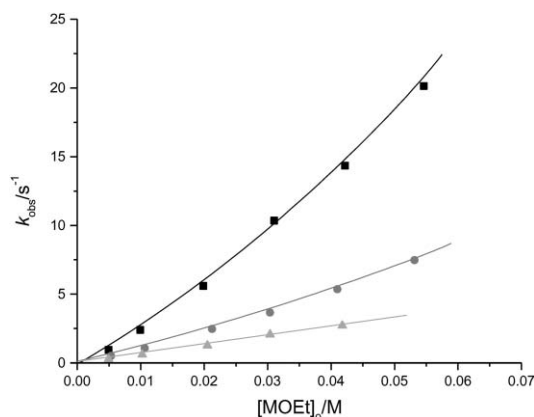


Fig. 1 Plots of k_{obs} vs. $[\text{MOEt}]_0$ for the reaction of **3a** with LiOEt (■) and KOEt (●) and with KOEt in the presence of excess [2.2.2]cryptand (▲) in EtOH at 25 °C (see supplementary information for data on this and other substrates investigated).

The reactions of **3a–f** with KOEt were also investigated in the presence of excess [2.2.2]cryptand in order to obtain kinetic data for the reactions of free ethoxide ion; additional experiments were conducted with excess dicyclohexyl-18-crown-6 ether (DC-18-C-6) for **3e** and **3f** and with excess 18-crown-6 ether (18-C-6) for **3e**. The kinetic data obtained for reactions in the presence of these macrocycles are assembled in the supplementary information. Plots of k_{obs} vs. $[\text{KOEt}]_0$ in the presence of these complexing agents are linear and pass through the origin, without exception. A typical plot, for the reaction of **3a**, is included in Fig. 1. The significance of this observation

is that these experiments establish that free ethoxide is the only nucleophilic reagent under conditions of excess complexing agent.

In a complementary set of experiments, the effects of added complexing agents [2.2.2]cryptand, 18-C-6 and DC-18-C-6 on the reactions of **3e** with KOEt and of added [2.1.1]cryptand on the reaction of **3e** with LiOEt were examined, in order to further substantiate that the reaction in the presence of these ligands involves free ions. The data are given in the supplementary information, and plotted in Fig. 2 for the reaction of **3e** with KOEt in the presence of increasing amounts of [2.2.2]cryptand, DC-18-C-6 and 18-C-6. A plot (not shown), which is similar to those displayed in Fig. 2, was also obtained for the effect of increasing amounts of [2.1.1]cryptand in the reaction of **3e** with LiOEt (refer to the supplementary information). In all cases, the rate decreased linearly as a function of added complexing agent at constant $[\text{MOEt}]_0$, until the addition of one equivalent of the ligand relative to $[\text{MOEt}]_0$. Further additions of the complexing agent beyond this point essentially had no effect on k_{obs} .

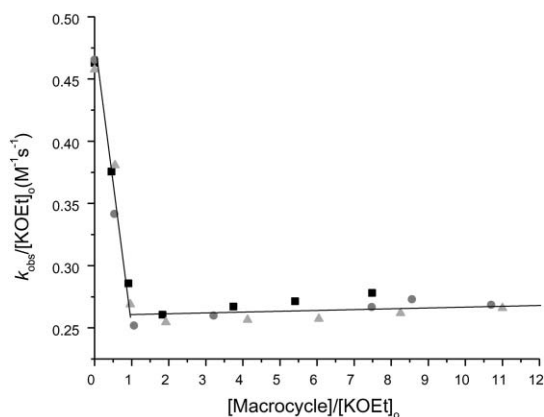


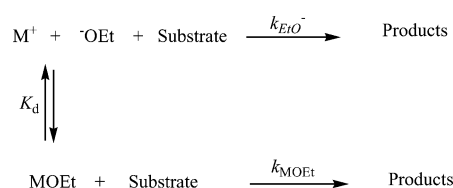
Fig. 2 Plots of $k_{\text{obs}}/[\text{KOEt}]_0$ vs. $[\text{macrocycle}]/[\text{KOEt}]_0$ for the reaction of **3e** with KOEt in the presence of increasing amounts of [2.2.2]cryptand (■), DC-18-C-6 (●) and 18-C-6 (▲) in EtOH at 25 °C (refer to the supplementary information).

Discussion

Dissection of rate data

The reactions of **3a–f** with LiOEt and KOEt are discussed in terms of the reaction sequence given in Scheme 1, which assigns kinetic activity to both free and ion-paired ethoxide according to eqn. (1), with $K_d (= 1/K_a)$ defined in eqn. (2). The rate constants k_{EtO^-} and k_{MOEt} in eqn. (1) pertain to the processes involving free ethoxide ion (the uncatalyzed reaction) and the metal alkoxide ion pair (the catalyzed reaction), respectively, depicted in Scheme 1. It is to be noted that the metal ion effects in this study, discussed below, arise from ground state and transition state interactions involving metal alkoxide ion pairs, which are distinct from the rate-enhancing effect of added divalent metal salts recorded for the reactions of a number of organophosphorus esters.^{5,6}

$$k_{\text{obs}} = k_{\text{EtO}^-}[\text{EtO}^-]_{\text{eq}} + k_{\text{MOEt}}[\text{MOEt}]_{\text{eq}} \quad (1)$$



Scheme 1

Table 1 Calculated second-order rate constants for the ethanolsis of **3a-f** by free EtO⁻ (k_{EtO^-})^a and the ion pairs KOEt (k_{KOEt}) and LiOEt (k_{LiOEt}) in anhydrous ethanol at 25 °C

Substrate	$k_{\text{EtO}^-}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{KOEt}}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{LiOEt}}/\text{M}^{-1}\text{s}^{-1}$	$k_{\text{LiOEt}}/k_{\text{KOEt}}$
1 ^b	0.980 ^b	4.84 ^b	24.0 ^b	4.96
2 ^c	230 ± 8 ^c	255 ± 8 ^c	648 ± 21 ^c	2.54
3a	67.6 ± 2.0	184 ± 8	492 ± 14	2.67
3b	32.8 ± 0.8	89.4 ± 8.6	215 ± 3	2.40
3c	9.50 ± 0.10	30.0 ± 2.3	58.8 ± 1.4	1.96
3d	2.15 ± 0.53	6.46 ± 0.46	8.85 ± 0.17	1.37
3e	0.37 ± 0.02	1.23 ± 0.04	1.39 ± 0.09	1.13
	0.38 ± 0.02 ^d			
	0.32 ± 0.01 ^e			
3f	0.17 ± 0.01	0.58 ± 0.02	0.64 ± 0.02	1.10
	0.18 ± 0.01 ^d			

^a Determined in the presence of excess [2.2.2]cryptand relative to [KOEt]₀ (see text). ^b Taken from ref. 8. ^c Taken from ref. 9. ^d Determined in the presence of excess DC-18-6 relative to [KOEt] (see text). ^e Determined in the presence of excess 18-C-6 relative to [KOEt] (see text).

In the presence of excess complexing agent relative to MOEt, the condition [MOEt]_{eq} = 0 exists and eqn. (1) simplifies to $k_{\text{obs}} = k_{\text{EtO}^-}[\text{EtO}^-]_{\text{eq}}$. Plots of k_{obs} vs. [KOEt]₀ in the presence of [2.2.2]cryptand for the substrates **3a-f**, using the data in the supplementary information, are all linear and furnish the values of k_{EtO^-} given in Table 1.

In order to obtain k_{MOEt} in Scheme 1, eqn. (1) is rearranged to obtain eqn. (3). It is the expectation from eqn. (3) that a plot of $k_{\text{obs}}/[\text{EtO}^-]_{\text{eq}}$ vs. [EtO⁻]_{eq} should yield a straight line with slope = $k_{\text{MOEt}}/K_{\text{d}}$, from which k_{MOEt} can be evaluated, since K_{d} values at 25 °C are known from the literature ($\text{Li}^+ = 0.00472 \text{ M}$, $\text{K}^+ = 0.0111 \text{ M}$).¹⁵ Values of [EtO⁻]_{eq}, calculated from eqn. (4) and (5), are included in the supplementary information.

$$k_{\text{obs}}/[\text{EtO}^-]_{\text{eq}} = k_{\text{EtO}^-} + k_{\text{MOEt}}[\text{EtO}^-]_{\text{eq}}/K_{\text{d}} \quad (3)$$

$$[\text{EtO}^-]_{\text{eq}} = 0.5\{-K_{\text{d}} + (K_{\text{d}}^2 + 4K_{\text{d}}[\text{MOEt}]_0)^{1/2}\} \quad (4)$$

$$[\text{MOEt}]_0 = [\text{EtO}^-]_{\text{eq}} + [\text{MOEt}]_{\text{eq}} \quad (5)$$

According to eqn. (3), plots of $k_{\text{obs}}/[\text{EtO}^-]_{\text{eq}}$ vs [EtO⁻]_{eq} for the reactions of the substrates with LiOEt and KOEt are all linear; a typical plot, for the reaction of **3a** with LiOEt, is displayed in Fig. 3. Values of k_{MOEt} obtained through application of eqn. (3) as described above are included in Table 1. In principle, k_{EtO^-} values can also be accessed as intercepts of the $k_{\text{obs}}/[\text{EtO}^-]_{\text{eq}}$ vs. [EtO⁻]_{eq} plots obtained using eqn. (3). However, such intercept values are usually small and have large associated errors, hence k_{EtO^-} values obtained from experiments done in the presence of complexing agents (*vide supra*) are preferred.

The values of the rate constants k_{EtO^-} , k_{KOEt} , and k_{LiOEt} obtained for the ethanolsis of **3a-f** by the three nucleophilic entities EtO⁻, KOEt, and LiOEt are assembled in Table 1, together with corresponding data for **1** and **2** from our previous studies^{8,9} for comparison. The values of k_{LiOEt} and k_{KOEt} in Table 1, when compared with the values of k_{EtO^-} , show moderate catalysis of the ethanolsis reaction by Li⁺ and K⁺ for all the substrates. The values of the ratio $k_{\text{LiOEt}}/k_{\text{KOEt}}$ given in Table 1 quantify the

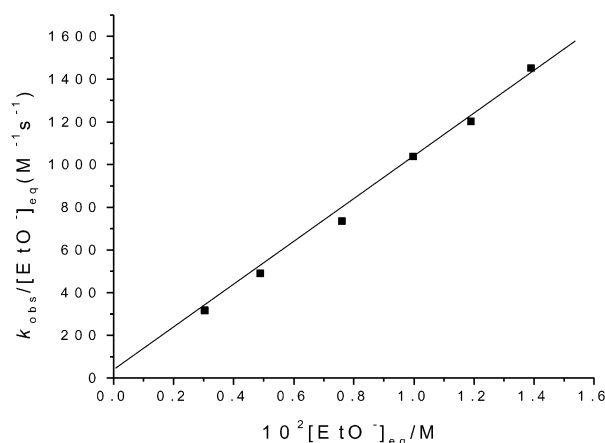


Fig. 3 Plot of $k_{\text{obs}}/[\text{EtO}^-]_{\text{eq}}$ vs. [EtO⁻]_{eq} for the reaction of **3a** with LiOEt in EtOH at 25 °C according to the ion-pairing treatment of eqn. (3) (see text and the supplementary information).

relative catalytic effectiveness of the alkali metal ions Li⁺ and K⁺ and show that the catalytic activity of Li⁺ is diminished as the electron-withdrawing power of the substituents in the phenyl ring decreases (see below).

Hammett correlations and mechanism

We have constructed Hammett plots for the reactions of **3a-f** with the three nucleophilic species EtO⁻, KOEt, and LiOEt from the data assembled in Table 1, using σ , σ° and σ^{-} substituent constants from the literature.¹⁶ Table 2 gives the ρ values derived from such plots and shows that correlations with σ and σ° substituent constants are significantly better than with σ^{-} substituent constants. The plots obtained with σ constants for the reactions of the three nucleophilic entities EtO⁻, KOEt, and LiOEt are displayed in Fig. 4.

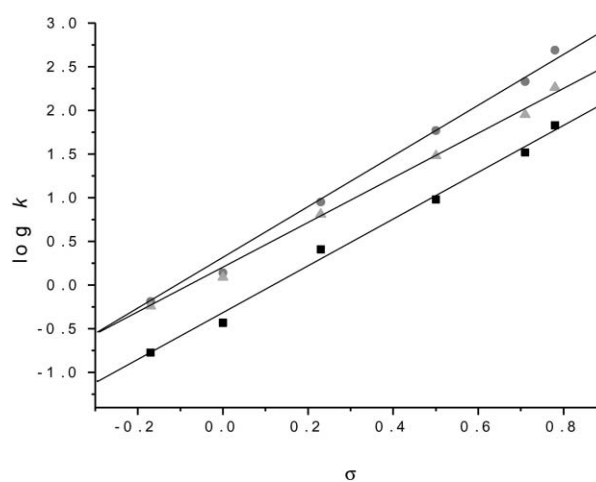


Fig. 4 Hammett σ - ρ plots for the reactions of **3a-f** with free EtO⁻ (■) and the ion-pairs KOEt (▲) and LiOEt (●) in EtOH at 25 °C. The different sigma substituent constants used in the construction of the Hammett plots were taken from ref. 16.

Table 2 Hammett ρ values (R^2) for leaving group variations in the ethanolsis of aryl methyl phenylphosphinates **3a-f** by free EtO⁻ and the ion pairs KOEt and LiOEt in anhydrous ethanol at 25 °C^a

Substituent constant	ρ value (R^2)		
	EtO ⁻	KOEt	LiOEt
σ	2.71 ± 0.10 (0.994)	2.61 ± 0.08 (0.996)	3.20 ± 0.19 (0.986)
σ°	2.78 ± 0.08 (0.997)	2.68 ± 0.09 (0.995)	3.10 ± 0.11 (0.995)
σ^{-}	1.79 ± 0.30 (0.901)	1.74 ± 0.26 (0.917)	2.03 ± 0.30 (0.920)

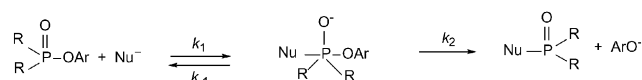
^a The different sigma substituent constants used in the construction of the Hammett plots in Fig. 4 were taken from ref. 16.

Table 3 Hammett ρ values for the reaction of EtO^-/HO^- with some aryl phosphinates in ethanol or predominantly aqueous solvents

Reaction system	Solvent	Temp/ $^{\circ}\text{C}$	Hammett ρ value
$\text{Me}_2\text{P}(\text{O})\text{-OPhX}/\text{EtO}^-^a$	EtOH	25	$\rho(\rho_n)^b$, 2.69(1.37)
$\text{Ph}_2\text{P}(\text{O})\text{-OPhX}/\text{EtO}^-^c$	EtOH	25	$\rho(\rho_n)^b$, 2.6(1.3)
$\text{MePhP}(\text{O})\text{-OPhX}/\text{EtO}^-^d$	EtOH	25	$\rho(\rho_n)^b$, 2.71(1.38)
$\text{MePh}(\text{O})\text{-OPhX}/\text{EtO}^-/\text{Li}^+^d$	EtOH	25	$\rho(\rho_n)^b$, 3.20(1.63)
$\text{MePh}(\text{O})\text{-OPhX}/\text{EtO}^-/\text{K}^+^d$	EtOH	25	$\rho(\rho_n)^b$, 2.61(1.33)
$\text{Ph}_2\text{P}(\text{O})\text{-OPhX}/\text{HO}^-^e$	H_2O	25	ρ^o , 1.40
$\text{Ph}_2\text{P}(\text{O})\text{-OPhX}/\text{HO}^-^f$	90% H_2O –10% dioxane	25	ρ , 1.55
$\text{Ph}_2\text{P}(\text{O})\text{-SPhX}/\text{HO}^-^g$	80% H_2O –20% MeOH	25	ρ , 1.46
$\text{Me}_2\text{P}(\text{S})\text{-OPhX}/\text{HO}^-^h$	H_2O	25	ρ^o , 1.28
$\text{Ph}(\text{MeSO}_2\text{CH}_2)_2\text{P}(\text{O})\text{-OPhX}/\text{HO}^-^i$	80% H_2O –20% dioxane	25	ρ , 1.45

^a Taken from ref. 9. ^b The quantity $\rho_n (= \rho/\rho_{\text{eq}})$ is the normalized ρ value to enable comparison of this parameter in water. ^c Taken from ref. 19. ^d This work. ^e Taken from ref. 20. ^f Taken from ref. 21. ^g Taken from ref. 22. ^h Taken from ref. 23. A recent LFER and KIE re-investigation of this system (ref. 18) shows that the mechanism of reaction is concerted rather than stepwise. ⁱ Taken from ref. 24.

The value of $\rho(\rho^o) = 2.71$ (2.78) obtained in this study (see Table 2) for the ethanolysis of $\text{MePhP}(\text{O})\text{-OPhX}$ substrates (**3a–f**) is the same as that reported for the $\text{Me}_2\text{P}(\text{O})\text{-OPhX}$ system, 2.69 (2.77)⁸. In particular, the normalized value of $\rho_n = \rho/\rho_{\text{eq}} = 1.38$ obtained by using $\rho_{\text{eq}} = 1.96$ for the ionization of substituted benzoic acids in ethanol at 25 $^{\circ}\text{C}$,¹⁷ is the same as that obtained for the $\text{Me}_2\text{P}(\text{O})\text{-OPhX}$ system, $\rho_n = 1.37$.⁹ It is also of the same magnitude as $\rho(\rho^o)$ values reported in the literature for the alkaline hydrolysis of a number of substituted aryl phosphinates in wholly aqueous or predominantly aqueous binary solvent mixtures (see Table 3). These reactions were concluded, on the basis of linear Hammett $\sigma(\sigma^o)$ – ρ correlations and the magnitude of ρ values, to react by the stepwise mechanism of Scheme 2. A Hammett correlation that does not involve σ^- substituent constants, as in the present case, disfavors a dissociative [$\text{S}_{\text{N}}1(\text{P})$] mechanism as well as a concerted [$\text{S}_{\text{N}}2(\text{P})$]-type process, in which the separation of the leaving group is part of the rate-limiting TS. On the other hand, correlation of reaction rates with $\sigma(\sigma^o)$ substituent constants indicates that the incoming negative charge from the nucleophile is not delocalized onto the nucleofuge in the transition state (TS) of the reaction. Furthermore, a $\sigma(\sigma^o)$ – ρ correlation with a moderately large ρ as observed for substrates **3a–f** is consistent with a stepwise mechanism in which formation of the pentacoordinate phosphorane-type intermediate is rate-limiting (Scheme 2).



Scheme 2 The rate determining step depends on the magnitude of k_{-1}/k_2 . Formation of the intermediate is rate-limiting when $k_{-1}/k_2 < 1$, while its decomposition becomes rate-limiting when $k_{-1}/k_2 > 1$.

The ρ values in Table 3 for the diverse phosphinate substrates reacting with hydroxide ion or ethoxide ion lie in the range 1.3–1.6. The similarity in the value of $\rho(\rho_n)$ in these systems is good evidence for similarity in TS structure for the nucleophilic reactions of these phosphinate substrates^{8,9} (see below for a discussion of the magnitude of ρ for the uncatalyzed and catalyzed ethanolysis of **3a–f**).

Alkali metal ion catalysis and TS stabilization

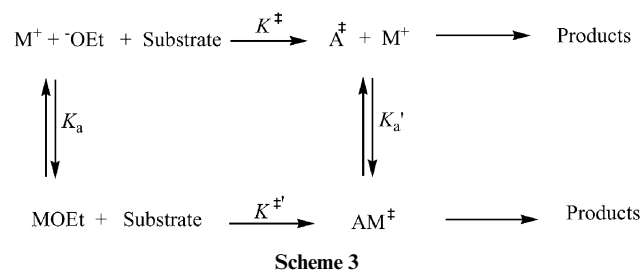
Our results (and specifically values of the rate ratio, $k_{\text{MOEt}}/k_{\text{EtO}^-}$), for **3a–f** calculated from the data in Table 1 show that Li^+ and K^+ exert moderate catalytic effects on the ethanolysis of these substrates. The selectivity sequence $\text{Li}^+ > \text{K}^+$ is clearly evident in the reactions of **3a–c**; the difference in the magnitude of the catalytic effect of these ions is less obvious in the substrates **3d–f**, judging from the values of the $k_{\text{LiOEt}}/k_{\text{KOEt}}$ ratios for these substrates. In the following treatment of alkali metal ion catalysis, it is assumed that the interaction between

the metal ions and the substrates is negligible and that the dominant ground state interaction is represented by M^+/EtO^- interaction.^{8,10,18} This ground state interaction is in the form of an ion-pair formation equilibrium, eqn. (2), which is quantified by $K_a (= K_d^{-1})$.

On the other hand, metal ion–TS interactions are discussed in terms of Kurz's model¹² for the characterization of the TS of catalyzed reactions, in which a virtual association constant, K_a' , of the alkali metal ion catalyst with the TS is calculated by means of the thermodynamic cycle in Scheme 3 and according to eqn. (6) [see also refs. 13 and 14 for different forms of this model]. The net catalytic effect of the metal ion, ΔG_{cat} , is obtained from eqn. (7), in which δG_{ts} and δG_{ip} are free energies of stabilization obtained from K_a' and K_a , respectively.

$$K_a' = k_{\text{MOEt}} K_a / k_{\text{EtO}^-} \quad (6)$$

$$\Delta G_{\text{cat}} = \Delta G_{\text{c}}^{\ddagger} - \Delta G_{\text{a}}^{\ddagger} = \delta G_{\text{ts}} - \delta G_{\text{ip}} \quad (7)$$



ΔG_{cat} values for the ethanolysis of **3a–f**, obtained by the procedure outlined above, are given in Table 4. Corresponding data reported earlier,^{8,9} for the reactions of **1** and **2**, are also supplied in Table 4 for comparison with the results for **3a** in the present study. In general, the selectivity order $\text{Li}^+ > \text{K}^+$ obtains in the reactions of the substrates **3a–f**, although, as noted above, the difference in the catalytic strength of the two ions appears to decrease as the electrophilicity of P in the substrate decreases in **3d–f**. Inspection of Tables 1 and 4 shows that the behavior noted above is a reflection of the reduced catalytic activity of Li^+ in reactions involving **3d–f**. This suggests that the driving force for Li^+ attachment is smaller when there is decreased electron withdrawal by the phenyl ring substituents.

The catalytic order $\text{Li}^+ > \text{K}^+$ argues for a mode of electrostatic stabilization of the TS in which the chelate effect of the metal ions is inversely proportional to their crystal radii.^{8,9,11,18} A linear relationship between $\delta G_{\text{ts}}(\text{M}^+)$ and the inverse of the crystal radius was reported⁸ for the phosphinate system **1**. Thus, the smaller Li^+ cation, with a higher charge/mass ratio, binds more strongly to the TS than the larger K^+ .

The selectivity sequence obtained in this study is similar to that obtained for the phosphorus-based esters **1–4**^{8–11,18}. It is the

Table 4 Free energies of alkali metal ion stabilization of EtO⁻ (δG_{ip}), transition states (δG_{ts}), and the net catalytic effect (ΔG_{cat}) for the reaction of EtO⁻ with **1**, **2** and **3a-f** in ethanol at 25 °C. Free energies are given in kJ mol⁻¹

	$-(\delta G_{ip})$ EtO ⁻	$(-\delta G_{ts})$							(ΔG_{cat})								
		1 ^a	2 ^b	3a	3b	3c	3d	3e	3f	1 ^a	2 ^b	3a	3b	3c	3d	3e	3f
Li ⁺	13.3	21.2	15.8	18.2	17.9	17.8	16.3	16.5	16.6	7.9	2.5	4.9	4.6	4.5	3.0	3.2	3.3
K ⁺	11.2	15.1	11.4	13.6	13.6	14.0	13.4	14.1	14.2	3.9	0.2	2.4	2.4	2.8	2.2	2.9	3.0

^a Data taken from ref 8. ^b Data taken from ref. 9.

reverse of the selectivity pattern ($Cs^+ > K^+ > Na^+ > K^+$) recorded for sulfonates,^{19,25-26} in which the larger cations demonstrated greater catalytic activity than the smaller ones. The selectivity order obtained in this work is in accord with the prediction based on Eisenman's theory of ion-exchange selectivity patterns of alkali metal cations for ion-exchange resins and glass electrodes, in which the sequence is determined mainly by electrostatic effects.²⁷ According to this theory, the strength of the interaction between a cation and a fixed anionic group is determined by two contending factors: (i) electrostatic interactions resulting from the approach of ions of opposite charge, and (ii) the difference in the solvation energies of the ions, accounted for by the energy required to rearrange the solvent molecules around the ions so that close contact can occur. The net standard free energy change ($\Delta G^{\circ}_{\frac{1}{2}}$) for the interchange of cations 1 and 2 at a fixed anionic site is the difference between the terms for electrostatic interactions and solvent rearrangement in eqn. (8), in which e is the electronic charge, r_1 , r_2 , and r_A are the radii of cations 1 and 2 and of the anion, respectively, and ΔG_1 and ΔG_2 the solvation energies of cations 1 and 2.

$$\Delta G^{\circ}_{\frac{1}{2}} = \left\{ \left[\frac{e^2}{r_A + r_2} \right] - \left[\frac{e^2}{r_A + r_1} \right] - (\Delta G_2 - \Delta G_1) \right\} \quad (8)$$

From eqn. (8), it can be predicted that for a high electric field strength, *i.e.* an anionic group with a localized charge, the electrostatic term would dominate over the solvation energy term, allowing ions with opposite charge to come into direct contact. This means that for such situations, smaller ions will bind more strongly, and *vice versa*, resulting in the selectivity sequence $Li^+ > Na^+ > K^+ > Cs^+$. The linear relationship between $\delta G_{ts}(M^+)$ and the inverse of the crystal radius of the metal ion noted above for the phosphinate system **1**⁸ is a direct consequence of this phenomenon.

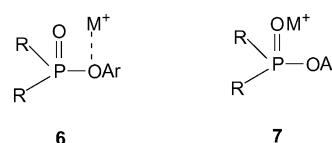
On the other hand, when the counter-ion has a low electric field strength, as in the sulfonate system,^{19,25-26} where the incoming negative charge is delocalized over two oxygens in the TS, it can be predicted that the solvation energy term in eqn. (8) would dominate over the term for electrostatic interaction. Under these conditions, the resulting selectivity sequence ($Cs^+ > K^+ > Na^+ > Li^+$) is opposite to that observed in the phosphorus esters and $\delta G_{ts}(M^+)$ correlates with the solvated (Stokes) radius of the metal ion.

TS structure for catalyzed and uncatalyzed ethanolsis reactions

The possible modes of catalytic intervention by alkali metal ions in the ethanolsis reaction of aryl methylphenylphosphinate esters (**3**) and similar substrates are now briefly considered, in order to assess the response of the selectivity parameter ρ to metal ion catalysis. Although polar substituent effects indicate charge or dipole changes resulting from differences in electronic structure between the ground state and the TS, and as these relate to bonding in the TS, care must be exercised in interpreting polar substituent effects in terms of the extent of bonding in the TS.²⁸ It is expected, nonetheless, that any significant change in TS structure or mechanism would be reflected in a change in the magnitude of ρ . We have shown⁹ that dissimilar values of ρ are obtained in the nucleophilic reactions of **2** where the

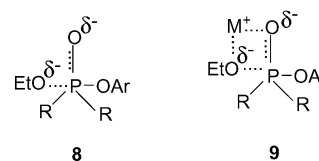
mechanism changes with change in solvent, from concerted [$S_N2(P)$] to stepwise involving a pentacoordinate intermediate.

A pre-association mechanism, in which binding of M^+ to the phenoxy O (see **6**) makes the leaving group a better nucleofuge (by lowering its pK_a) and stabilizes the incipient negative charge in the TS, is untenable in the present system, since the Hammett LFER data do not support a process in which detachment of the leaving group is part of the rate-limiting step.

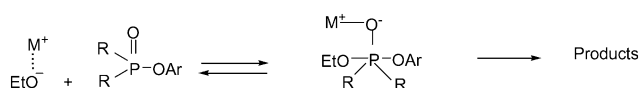


A second way in which alkali metal ions can catalyze the reaction is by coordinating with the P=O oxygen, as in **7**, resulting from a pre-association equilibrium. This will have the effect of increasing the electrophilicity of the P atom through P=O bond polarization, thereby promoting attack by the nucleophile at P. If this mechanism of catalysis operates to any significant extent, one could predict that reaction in the presence of the metal ions would involve transition states that are significantly different from that of the uncatalyzed reaction since the extent of nucleophilic participation will be different in the two situations. In fact, an extreme case of increased nucleophilic participation could conceivably result in a change of mechanism, from a situation in which formation of the pentacoordinate intermediate is rate-limiting to one in which its decomposition becomes the slow step of the reaction (see Scheme 2). For this mode of stabilization of the TS, one would therefore predict different ρ values for the catalyzed and uncatalyzed reactions.

A third way in which M^+ can facilitate the reaction is by reacting through the metal-alkoxide ion pair in a concerted fashion, to yield a pentacoordinate intermediate which is associated with the metal ion. This is depicted in Scheme 4. In this manner, the metal ion, while orienting the nucleophile in the best position for attack, also stabilizes the developing charge at the P=O oxygen mostly by electrostatic interaction. In this mode of catalysis, both ground state and TS interactions are mainly electrostatic in nature. Such a catalytic process could conceivably proceed through a TS that is not too different from that of the uncatalyzed reaction except for the presence or absence of the metal ion with its positive charge (compare TS structures for the concerted uncatalyzed and metal ion-catalyzed reactions, depicted by **8** and **9**, respectively), especially if electrostatic interactions are the dominant effect. For this mode of catalysis (Scheme 4), therefore, a reasonable expectation is a ρ value that is not significantly different for the catalyzed and uncatalyzed reactions.



Normalized values of ρ , *i.e.* ρ_n , are included in Table 3 for the metal ion catalyzed and uncatalyzed reactions. It is interesting to note that the value of ρ_n for the ethanolsis of the



Scheme 4

MePhP(O)-OPhX esters (**3a–f**) in the absence and presence of the cations Li^+ and K^+ lies within the narrow range of 1.3–1.6. Within this range, $\rho(\rho_n)$ is greater for the Li^+ -catalyzed reaction than for the K^+ -catalyzed process, while $\rho(\rho_n)$ for the uncatalyzed process is of the same order of magnitude as for the reaction under catalysis by K^+ . The data do not show a clear distinction in ρ values for catalyzed and uncatalyzed reactions. This similarity of $\rho(\rho_n)$ for the catalyzed and uncatalyzed reactions shows that the alkali metal ions do not significantly perturb the TS structure in the reactions of these esters. The similar $\rho(\rho_n)$ values therefore provide no indication of any significant change in TS structure upon binding of the metal ion to the TS of the reaction. This is an important conclusion, which supports the view that the presence of the alkali metal ions provides mainly electrostatic stabilization of the developing charge on the P=O oxygen and does not increase nucleophilic participation in the TS of the reaction. Herschlag and Jencks⁶ have used similar reasoning, based on the constancy of β_{unc} and β_{lg} values, to conclude that the TS structure is similar for uncatalyzed and Mg^{2+} -catalyzed bimolecular phosphoryl transfers from phosphorylated pyridine monoanions and *p*-nitrophenyl phosphate dianion. The significance of this finding is that it underscores electrostatic stabilization of the TS by suitably disposed charges in the enzyme active site as an important mechanism of catalysis in enzymatic phosphoryl transfers involving metal ion cofactors. Recent results on the ethanolysis of 4-nitrophenyl phenylphosphonate also demonstrate the importance of electrostatic stabilization of the TS for phosphoryl transfer that may be effected by multiple cations, either monovalent metal ions or amino acid residues.¹¹

Comparing sensitivities to metal ion catalysis in the phosphinate series of substrates, the sensitivity order **1** > **3a** > **2** emerges. This order contrasts with the reactivity order in the uncatalyzed reactions of these substrates towards EtO^- , **2** > **3a** > **1**, evident in Table 1. The implication of this observation is that the less reactive substrate is more susceptible to alkali metal ion catalysis. The differing sensitivity between **1** and **2** was explained⁹ on the basis of the more reactive substrate (**2**) having an earlier TS than the less reactive one (**1**) for the catalyzed reaction, consistent with the Hammond postulate. On this model, a late TS for the catalyzed reaction derives substantial stabilization through chelation with M^+ because of the larger amount of negative charge resident on the P–O oxygen. That **3a**, which is of intermediate reactivity relative to **1** and **2**, shows intermediate selectivity accords with this interpretation. The TS structure for **3a** is thus expected to lie between the TS structure for **1** and that for **2**. As will be shown below for the uncatalyzed reactions of these substrates, the steric characteristics of the substituents on P contribute substantially to the observed reactivity sequence and the TS structures.

Steric factors in the reactions of aryl phosphinates

An indication that the reactions of phosphinates with nucleophiles are subject to steric effects was provided by the early work of Cook *et al.*²⁹ and Hawes and Trippett³⁰ for the alkaline hydrolysis of a variety of alkyl phosphinates. In these reports, increasing the steric bulk of the alkyl substituent directly attached to P led to appreciable rate decreases. The results of Williams have also demonstrated a difference in the mode of imidazole catalysis of the hydrolysis of the substituted aryl phosphinates $\text{Me}_2\text{P(O)-OPhX}$ ³¹ and $\text{Ph}_2\text{P(O)-OPhX}$ ³² in aqueous media; this change in mechanism was ascribed to steric congestion in the transition state of the reaction of $\text{Ph}_2\text{P(O)-OPhX}$. Thus while imidazole manifests nucleophilic catalysis in the hydrolysis of $\text{Me}_2\text{P(O)-OPhX}$, general base catalysis is

observed for the reaction of $\text{Ph}_2\text{P(O)-OPhX}$. Steric crowding around the reaction center thus renders nucleophilic catalysis inefficient in the hydrolysis of $\text{Ph}_2\text{P(O)-OPhX}$ esters.

The second-order rate constants, k_{EtO^-} , for the ethanolysis of the phosphinates **1**, **3a** and **2** show a systematic increase across the series (see Table 1), giving relative rates of 1 : 69 : 235. The rate constants for the hydrolysis of the esters **1** and **2** give the relative rate of 1 : 100.^{31,32} This trend observed with the nucleophiles EtO^- and HO^- , in which phenyl substitution decreases the rate of the nucleophilic reaction of the phosphinates, does not accord with expectations for the electronic influence of substituents on the central P atom, bearing in mind that the Hammett σ_1 substituent constants³³ for Ph and Me groups are 0.12 and –0.01, respectively. Thus, if the inductive effect of Ph and Me groups were the sole factor determining reactivity, the reactivity trend would be **1** > **3a** > **2**, contrary to the experimental data given in Table 1. In fact, by comparing ρ^* values, Haake and co-workers²⁹ have shown that nucleophilic attack at P in phosphinates by HO^- is approximately as dependent on the acyl substituents as in the analogous reaction of carboxylates. The results outlined above therefore point to the importance of steric factors in the nucleophilic reactions of this series of phosphinate substrates.⁹

A plot (not shown) of $\log k_{\text{rel}}$ against Taft's steric constants (ΣE_s) according to eqn. (9)^{28,34,35} for the three phosphinate esters **1**, **3a**, and **2** is roughly linear (R^2 0.91), giving $\delta = 1.32$. The parameter δ is a similarity coefficient for the steric requirement of the reaction relative to the reference reaction.²⁸ Although the number of points used in the correlation above is limited, the magnitude of δ obtained is of qualitative significance, indicating that the reaction is subject to significant steric effects and that the reaction center is more crowded than that for the reference reaction.²⁸ On the other hand, the rate data for the ethanolysis of the substrates under discussion are not correlated by the Taft equation, eqn. (10),^{28,34,35} which combines both steric and polar effects, suggesting the relative unimportance of the electronic effects of the methyl and phenyl substituents on the central P in determining reactivity. It is therefore reasonable to conclude that the sequence of reactivity demonstrated above for the phosphinate esters is determined mainly by steric factors.

$$\log k_{\text{rel}} = \delta \Sigma E_s \quad (9)$$

$$\log k_{\text{rel}} = \rho^* \Sigma \sigma^* + \delta \Sigma E_s \quad (10)$$

According to the Hammond postulate, the faster reactions of $\text{Me}_2\text{P(O)-OPhX}$ esters in which steric effects are either absent or minimal indicate that these substrates have an earlier TS than those of $\text{Ph}_2\text{P(O)-OPhX}$ for which steric congestion has been demonstrated; the TS for MePhP(O)-OPhX esters lies in between these extremes. It is significant to note that although steric crowding occurs in the TS of the reaction of $\text{Ph}_2\text{P(O)-OPhX}$, this effect is not of sufficient magnitude to alter the mechanism of its substitution reaction, as observed in the solvolysis of phosphinyl chlorides where large steric effects alter the mechanism of reaction from concerted $[\text{S}_\text{N}2(\text{P})]$ -type to a dissociative $\text{S}_\text{N}2(\text{P})$ process.³⁶

Experimental

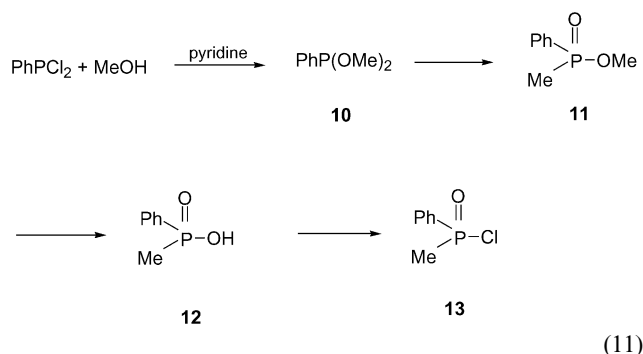
Materials

Anhydrous ethanol was obtained by refluxing absolute ethanol with magnesium turnings in the presence of iodine, followed by distillation. Potassium ethoxide solutions were prepared by dissolving clean potassium metal in dry EtOH at 0 °C in an atmosphere of N_2 ; lithium ethoxide solutions were made similarly using lithium hydride (Alfa-Ventron) instead, and filtering the resulting solution to remove any insoluble materials. Concentrations of the alkali metal ethoxide solutions were determined by titration with anhydrous potassium

hydrogen phthalate (Mathieson, Coleman/Bell). 18-Crown-6 ether (Parish Chemicals) was recrystallized from acetonitrile and stored over P₂O₅ *in vacuo* prior to use. Dicyclohexyl-18-crown-6 ether, [2.2.2]cryptand and [2.1.1]cryptand were Aldrich products which were used without further purification.

Synthesis of substrates

The substituted aryl methyl phenyl phosphinate esters investigated in this study were synthesized from the parent phenols and phenyl methyl phosphinyl chloride (**13**), the latter compound being obtained through a series of known reactions according to eqn. (11).



Dimethylphosphonite (**10**) was prepared according to the method of Harwood and Grisely.³⁷ The resulting crude oily product was vacuum distilled to yield a clear colorless liquid, bp 74 °C at 0.7 mm Hg (lit.,³⁷ 98 °C at 17 mm Hg). Methyl methyl phenylphosphinate (**11**) was obtained according to the method of Korpium *et al.*,³⁸ bp 106–108 °C at 0.78 mm Hg (lit., 119 °C at 3.5 mm Hg;³⁷ 94 °C at 0.05 mm Hg.³⁸ Methyl phenyl phosphinic acid (**12**) was obtained by the hydrolysis of **11**, using 6 M HCl; the crude product was recrystallized from ethanol, mp 132–133 °C (lit.,³⁹ 133–134 °C). The chloride **13** was then prepared by heating an equimolar mixture of **12** and freshly sublimed PCl₅ at 120 °C for 1 h under a stream of N₂; fractional distillation under reduced pressure yielded pure **13**, bp 103.5 °C at 0.79 mm Hg (lit., 155 °C at 11 mm Hg;³⁹ 105–110 °C at 0.05 mm Hg³⁹).

Phenyl methyl phenylphosphinate esters were then prepared by the general procedure described for 4-nitrophenyl methyl phenylphosphinate, using a modification of the method of Raevskii *et al.* as follows.⁴⁰ Equimolar quantities of 4-nitrophenol, triethylamine and **13** were stirred in diethyl ether at room temperature for 2 d in an atmosphere of N₂. The resulting suspension was filtered in an inert atmosphere in a glove box to remove the amine hydrochloride. The dark yellow oil obtained was triturated with acetone to remove any unreacted **13** and the resulting solution was dried over MgSO₄ and filtered. Rotary evaporation of the acetone gave a partially crystalline solid which was first recrystallized from a mixture of diethyl ether and petroleum ether (30 : 60); two subsequent recrystallizations from CCl₄ gave **3a** as the pure product, mp 86–87 °C (lit., 86–87 °C,⁴⁰ 85–86.5 °C⁴¹). The products gave ¹H/¹³C NMR spectra and elemental analysis consistent with the structures of the esters; their purity was checked by IR and ¹H NMR.

Kinetic method

The rates of reaction in anhydrous EtOH were investigated spectrophotometrically by monitoring the formation of the appropriate phenoxide ion at 25 °C under pseudo first-order conditions, with substrate concentrations in at least 20-fold deficit of the base. Kinetic measurements were performed, in part, using a Beckman DU-8 or Perkin-Elmer Lambda-5 spectrophotometer, equipped with thermostatted cell holders which maintained the temperature in the 10 mm quartz cuvette at 25 ± 0.1 °C. Relatively fast kinetics experiments were measured using a Hi-Tech stopped-flow module equipped with a thermostatted

water bath coupled to a McPherson monochromator and Can-Tech transient recorder. Spectral traces were displayed on a Hewlett-Packard oscilloscope; the data were treated directly by computer. The λ_{max} of the phenoxide ion being monitored was obtained in a separate experiment, prior to the kinetic determinations. Run solutions were generally made up just before the kinetic experiments; the kinetic experiments were performed in replicate and were followed for *ca.* 10 half-lives. First-order constants, *k*_{obs}, were reckoned from linear plots of ln(A_∞ - A_t) vs. time. The *k*_{obs} values are presented as in the supplementary information.

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