

Effective Charge Distribution for Attack of Phenoxide Ion on Aryl Methyl Phosphate Monoanion: Studies Related to the Action of Ribonuclease

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The reaction of phenoxide ion with aryl methyl phosphate monoanions and aryl diethyl phosphates obeys second-order kinetics in aqueous solution at 39 °C and 1 M ionic strength. The second-order rate constants ($M^{-1} s^{-1}$) for these reactions obey the following Brønsted equations:

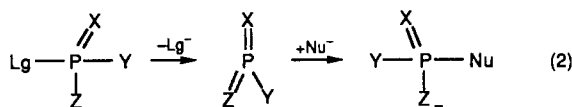
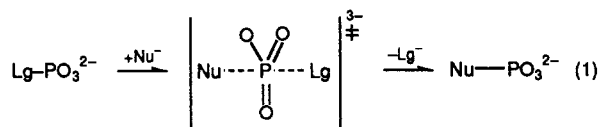
$$\log k_2 = -0.51pK_{lg} + 0.72 \quad (r = 0.970) \quad (\text{aryl diethyl phosphate})$$

$$\log k_2 = -0.64pK_{lg} - 2.53 \quad (r = 0.898) \quad (\text{aryl methyl phosphate monoanion})$$

The monoanion is some 10^4 -fold less reactive toward attack by phenolate ion than is the diethyl ester with 4-nitrophenol leaving group, consistent in part with the operation of an electrostatic effect. The similarity between the Brønsted exponents in both reactions indicates that the effective charge change on the leaving oxygen from ground state to transition state is similar in both cases; this indicates that the oxyanion in the monoanion case does not assist leaving group expulsion. The data are consistent with little coupling between proton abstraction from the 2'-hydroxyl group and the leaving group expulsion in the ribonuclease reaction.

Introduction

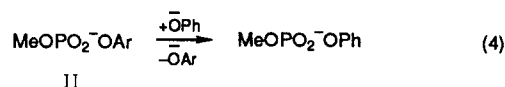
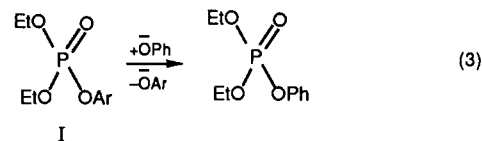
Transition states with considerable metaphosphate monoanion character (eq 1) are well-established for transfer reactions of the phosphomonoester dianion.¹ Trapping evidence has been obtained for "metaphosphate-like" intermediates (eq 2) when ligands other than oxygen are involved.² The transition states for nu-



cleophilic reactions at the phosphoryl group (PO_3^{2-}) in water have weak bonding between central phosphorus and entering and leaving groups.³ There is evidence that non-nucleophilic solvents or indeed complete absence of solvent promote complete separation of the metaphosphate monoanion species.⁴ Part of the rationale for the existence of weak bonding between entering and leaving atoms and the phosphorus ("exploded" transition state)^{5a} is the ability of the negatively charged oxygens attached to the central atom to satisfy the pentavalency of the phosphorus; the "internal nucleophilicity"^{5b} of these oxygens assists departure of the leaving group prior to bond formation.

Reactions of nucleophiles with neutral phosphate⁶ and phosphinate⁷ esters possess concerted mechanisms. A phosphodiester monoanion is intermediate in charge between that of a monoester dianion and neutral ester; it is therefore pertinent to consider whether the internal nucleophilicity^{5b} of the attached oxygen is sufficient to force the transfer mechanisms of these species to have "metaphosphate-like" character.^{8a} Such considerations are important in the study of phosphodiester transfer processes in biochemistry because of the possibility of charge neutralization by complexation of the monoanion.

We report here a study of the reaction of phenolate ion with the neutral esters aryl diethyl phosphate (I) and with aryl methyl phosphates (II) (eq 3 and 4) to determine the effective charge change on the leaving oxygen relative to the change in charge in the ionization of phenols.^{8b} The data for the charge changes are of use in determining the state of bonding in the transition states although it must be emphasized that solvation is also implicated in the charge "seen" by the substituents.



Experimental Section

Materials. Aryl diethyl phosphates had been prepared from the appropriate phenol for a previous study⁹ by reaction with diethyl phosphoryl chloride. These species are real and potential nerve gas agents, and particular attention was paid to this in their use.

Aryl methyl phosphates were prepared by demethylation of aryl dimethyl esters with LiCl in dry acetone.¹⁰ The aryl dimethyl phosphates (also potential nerve gas agents) were prepared from

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(5) (a) Jencks, W. P. *Chem. Soc. Rev. London* 1981, 10, 345. (b) Williams, A.; Douglas, K. T. *Chem. Rev.* 1975, 75, 627.

(6) Ba-Saif, S. A., unpublished data, University of Kent, 1989.

(7) Bourne, N.; Chrystiuk, E.; Davis, A. M.; Williams, A. *J. Am. Chem. Soc.* 1988, 110, 1890.

(8) (a) Kirby, A. J.; Younas, M. *J. Chem. Soc. B* 1970, 510. (b) Williams, A. *Acc. Chem. Res.* 1984, 17, 425. Thea, S.; Williams, A. *Chem. Soc. Rev. London* 1986, 16, 125.

(9) Ba-Saif, S. A.; Williams, A. *J. Org. Chem.* 1988, 53, 2204.

(10) Kirby, A. J.; Younas, M. *J. Chem. Soc. B* 1970, 1165.

Table I. Attack of Phenolate Ion on Substituted Phenyl Diethyl Phosphates^a (eq 3)

substituent	pK^{ArOH}	pH ^b	k_{obs}^c s ⁻¹	[total phenol] ^d M	N ^e	$k_2^{f,i}$ M ⁻¹ s ⁻¹
2,4-(NO ₂) ₂	4.09	7.55 ^f	3.5–4.25	6.9–17.3	4	34
4-NO ₂ -2-Cl	5.45	8.5 ^f	2.3–6.75	3.6–18	5	10
2-NO ₂ -4-Cl	6.46	11.1 ^h	74–130	7–17.6	4	4.8
4-NO ₂	7.14	11.14 ^h	8.9–19	3.7–18.5	5	0.67
3-NO ₂	8.38	10.3 ^h	1.7–3.2	3.9–14.7	4	0.25

^a Conditions: 39 °C and ionic strength maintained at 1 M with KCl. ^b Average of all the runs; pH did not vary by more than 0.03 units. ^c Range of observed pseudo-first-order rate constants ($\times 10^6$). ^d Range of total phenol concentrations used ($\times 10^2$). ^e Number of data points not including duplicate runs. ^f Tris(hydroxymethyl)aminomethane buffer. ^g Second-order rate constant for attack of phenolate ion ($\times 10^3$). ^h Bicarbonate buffer. ⁱ Uncertainty is no more than 10%.

the phenol and dimethyl phosphoryl chloride. Dimethyl phosphoryl chloride was synthesized in the following manner: dimethyl phosphite (37 g) was added to CCl₄ (150 mL) and cooled to less than 0 °C with an ice-salt bath. Dry Cl₂ was bubbled through the solution (protected with drying tubes) until it acquired a permanent yellow color. Dry air was passed for 30 min to remove residual Cl₂, and the solvent was removed in vacuo. The residual oil was dissolved in CCl₄ (150 mL), and the solution was again evaporated. The residue was distilled in vacuo to give a colorless oil, bp 76–7 °C at 16 Torr (lit.¹¹ bp 70–1 °C at 15 Torr).

Lithium 2,4-dinitrophenyl methyl phosphate was prepared as follows: 2,4-dinitrophenol (6.3 g) and triethylamine (3.9 g) were added to a solution of dimethyl phosphoryl chloride (5 g) in dry acetone (50 mL); the mixture was stirred at room temperature with the exclusion of moisture. A precipitate of triethylammonium chloride formed almost immediately after the addition, and the suspension was stirred for 45 min. The suspension was filtered, and the filtrate was evaporated to yield the triester as an oil. The residual oil was taken up in a little dry acetone, and LiCl (1.5 g) dissolved in acetone (150 mL) was added. The mixture was refluxed for 60 min, and the resultant solution was evaporated. The residue was allowed to solidify, and the product was recrystallized from an acetone-methanol mixture.

Other aryl methyl phosphate esters were prepared by a similar procedure. All esters were isolated as their lithium salts except the 4-nitrophenyl and 2-nitro-4-chlorophenyl species, which were obtained as the free esters.¹⁰ All the materials gave satisfactory ¹H NMR and IR spectra consistent with their expected structures. Analytical data for the methyl esters are collected in the supplementary material.

Methods. Kinetics of reaction of phenolate ions with the aryl esters were measured by introducing an aliquot (0.02 mL) of a stock solution of the ester (in water if the methyl phosphates; in acetonitrile if the diethyl phosphates) on the flattened tip of a narrow glass rod to the buffer solution (2.5 mL) containing the phenol at the required concentration. The reaction was carried out in a 1 cm path length silica cell in the thermostatted cell compartment of either a Unicam SP 800 spectrophotometer or a Perkin-Elmer Lambda 5 instrument. The buffer solutions were prepared from stock solutions, one containing the phenol and buffer component (tris(hydroxymethyl)aminomethane or bicarbonate at 0.05 M) and an identical solution adjusted to the same pH but without phenol. Mixing the stock solutions in the appropriate proportions gives phenol at varying concentrations with identical parameters of buffer concentration, ionic strength, and pH. Solutions were degassed immediately prior to mixing and use. The pH was measured after each reaction with a Radiometer PHM 26 pH meter calibrated with EIL standard buffers to ± 0.01 pH units.

The absorbance change for the reaction of the diethyl phosphate esters was measured as a function of time, and the pseudo-first-order rate constant was obtained from a plot of $\log(A_\infty - A_t)$ against time. Initial rates were measured for the reaction of the methyl phosphate esters up to ca. 10% of the total reaction and were converted to pseudo-first-order rate constants by division by the ester molarity after converting absorbances to molarities.

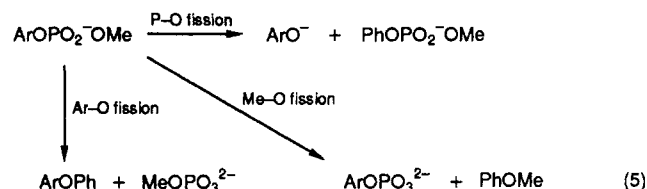
Extinction coefficients for the total absorbance change were measured from complete aryl oxide release from an ester sample in NaOH; the pH was adjusted to pH 10.55 and the absorbance measured.

Qualitative product analysis of the reaction between the aryl diethyl phosphate and phenolate ion was carried out by adding the ester (0.3 mg) in acetonitrile slowly to a solution of phenol (470 mg) in bicarbonate ion buffer at pH 10.0 and ionic strength 1 M. The reaction mixture was stirred for 3 h to ensure complete reaction of the ester, and the products were extracted with CH₂Cl₂ (15 mL). The extract was washed with water and then dried over MgSO₄. TLC analysis on silica gel plates using benzene as the eluent was employed to detect the formation of phenyl diethyl phosphate.

Results

Reaction of aryl diethyl phosphate esters in phenolate ion buffers exhibited excellent pseudo-first-order kinetics up to about 90% of the total reaction. The observed rate constants are linear in total phenol concentration; associated work on the reaction of aryl diphenylphosphinates⁷ and aryl diphenyl phosphates⁸ in phenol buffers indicates that for these esters the phenolate ion is the reactive species and that the phenyl ester is the product. It is reasonable to assume that in the present case the rate law involves attack of the phenolate ion, and the second-order rate constants were obtained by division of the slope of the plot of k_{obs} versus total phenol concentration by FB, the fraction of total phenol present as phenolate ion. The derived parameters are recorded in Table I. Qualitative analysis by TLC indicates that the phenyl diethyl phosphate is the product of the reaction in each case.

Kirby and Younas¹⁰ have indicated that reaction of phenolate ions with aryl methyl phosphate monoanion can be complicated by the existence of three paths (eq 5); they



showed that Me–O bond fission is not significant but that P–OAr and PO–Ar bond fission occur with similar rates. The pseudo-first-order rate constants obtained as described in the Experimental Section from initial rates of release of substituted phenolate anion and total ester molarity refer only to attack at phosphorus and are linear in overall phenol concentration; the slope of the linear plot is divided by the fraction of base for the phenolate ion (0.75, see Table II) to give the second-order rate constants as recorded in Table II.

The second-order rate constants (k_2) for attack of phenolate ion on aryl diethyl phosphates and aryl methyl phosphates obey the Brønsted laws given respectively by eq 6 and 7; the data are illustrated in Figure 1.

$$\log k_2^{\text{diethyl ester}} = (-0.51 \pm 0.07)pK^{ArOH} + 0.72 \pm 0.4 \quad (r = 0.970) \quad (6)$$

$$\log k_2^{\text{methyl ester}} = (-0.64 \pm 0.16)pK^{ArOH} - 2.53 \pm 0.88 \quad (r = 0.898) \quad (7)$$

Table II. Reaction of Substituted Phenyl Methyl Phosphate Esters in Phenolate Ion Buffers^a (eq 4)

substituent	mp, °C	pK ^a _{A⁻OH}	ε ^b	λ, ^c nm	k _{obs} × 10 ⁸ , ^d s ⁻¹	N ^e	k ₂ × 10 ⁸ , ^f M ⁻¹ s ⁻¹
2,4-(NO ₂) ₂ ^{g,i}	134-6	4.09	11100	400	268-964	5	1150
2,3-(NO ₂) ₂ ^{g,i}	248 dec	4.96	3650	420	301-1110	5	142
2,5-(NO ₂) ₂ ^g	250 dec	5.04	4300	445	48-150	4	225
2-Cl-4-NO ₂ ^g	230 dec	5.45	16350	400	5.4-17.1	4	25
2-NO ₂ -4-Cl ^h	119-20	6.46	4400	420	8.5-33.6	4	57
4-NO ₂ ^h	122-3	7.14	13100	400	1.3-4.9	5	6

^a Conditions: 39 °C and ionic concentration maintained with KCl. No buffer other than the phenol-phenolate ion mixture was employed. The concentrations of phenol (total) were varied from 0.2 to 1 M, and the fraction of phenolate ion was 0.75. The pH of the solutions averaged 10.55. ^b Extinction coefficient for the absorption change (units of absorption per cm per molar); the ester had negligible absorbance under these conditions. ^c Wavelength for kinetic study. ^d Range of first-order rate constants observed. ^e Number of data points not including duplicate runs. ^f The uncertainty of these rate constants is no more than 10%. ^g Lithium salt. ^h Neutral acid. ⁱ Has one molecule of acetone of crystallization. ^j Has one molecule of water of crystallization. ⁿ Melting points of the substituted phenyl methyl phosphate esters.

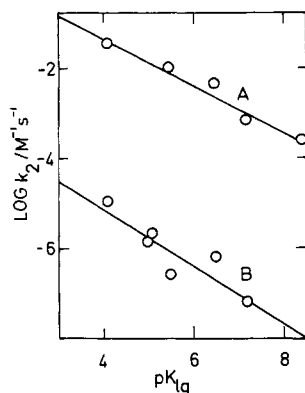
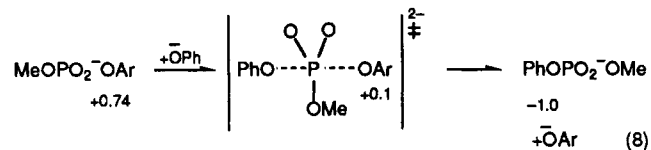


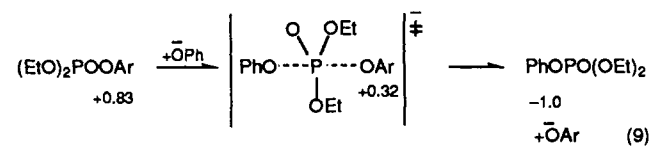
Figure 1. Brønsted dependence on the pK_a of the leaving phenol of the reaction of phenolate anion with A, substituted phenyl diethyl phosphates, and B, substituted phenyl methyl phosphate monoanions. Conditions as in Tables I and II and data from Tables I and II, respectively; the lines are calculated from eq 6 and 7. The identities of the points are, in increasing order of pK_a of the leaving phenols: 2,4-dinitrophenyl, 2,3-dinitrophenyl, 2,5-dinitrophenyl, 2-chloro-4-nitrophenyl, 2-nitro-4-chlorophenyl, 4-nitrophenyl, 3-nitrophenyl.

Discussion

The difference in reactivity of 10⁴-fold between phenolate ion attack on 4-nitrophenyl diethyl phosphate and 4-nitrophenyl methyl phosphate monoanion (Tables I and II) is explained in part by electrostatic repulsion. Comparison between the Lefler α values (Appendix 1)^{8b} for the bond fission (eq 8 and 9) for attack of the phenolate ion on esters with different leaving groups indicates that there is only a very small increase in charge change, consistent with a very small bonding change from neutral to monoanionic phosphoryl case ($\alpha = 0.28$ for the diethyl ester and 0.37 for the methyl species). The oxyanion attached to the phosphorus in the monoanionic ester therefore



$$\beta_{\text{lg}} = -0.64 \quad (\alpha = 0.37) \quad \beta_{\text{eq}} = -1.74$$



$$\beta_{\text{lg}} = -0.51 \quad (\alpha = 0.28) \quad \beta_{\text{eq}} = -1.83$$

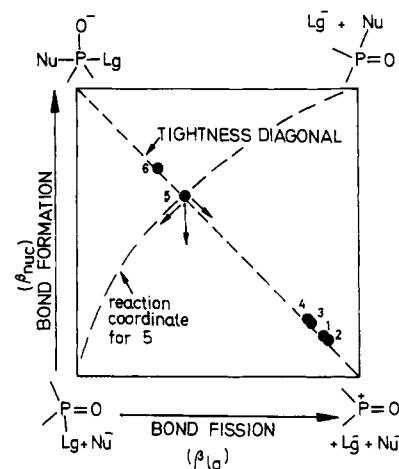


Figure 2. General reaction map for the transfer of a phosphorus acyl group between leaving group and nucleophile. Transition states for symmetrical concerted reactions lie along the "tightness" diagonal. The points refer to the transition-state structures of the following symmetrical reactions: (1) transfer of $-\text{PO}_3^{2-}$ between isoquinolines; (2-4) transfer of $(\text{PhO})_2\text{PO}^-$, Ph_2PO^- , and MeOPO_2^- between 2,4-dinitrophenolate anions; (5 and 6) transfer of MeOPO_2^- and $(\text{EtO})_2\text{PO}^-$ between phenolate ions. Vectors emanating from (5) indicate the resultant effect on β_{lg} of a decrease in pK_{nuc} .

participates to only a very small extent in assisting the expulsion of the leaving group. In gas-phase reactions the species ROPO_2 , which would be formed as a result of complete participation of the oxyanion, has been detected, albeit as an unstable entity.^{1b} The low pK_a of the hydroxyl function of the conjugate acid compared with that of the hydroxyls in the monophosphate ester dianion is consistent with its poor internal nucleophilicity.^{5b}

Phenolate ion attack on the aryl methyl phosphate monoanion probably involves a concerted process because the ester is intermediate in structure between a monophosphate ester dianion and a neutral phosphoryl ester. Both of these types of phosphoryl group have been shown to involve concerted transfer between nucleophiles.^{3,6,7} Bond fission is almost complete in the transition state for attack of nucleophiles on monophosphate dianions. Pyridine attack on phosphoryl pyridinium ions has a very "open" transition-state structure.^{3c} A useful way of looking at the electronic structure of the transition state in a displacement reaction is to view that for the case where entering and leaving groups are identical. When this condition holds for a concerted reaction the bonding of entering and leaving groups will be the same in the transition state which will lie on the "tightness" diagonal of Figure 2.¹² Attack of substituted pyridines on phospho-

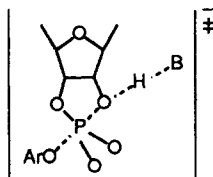
(12) Alberty, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* 1978, 16, 87.

rylisoquinolinium ion obeys a Brønsted law with slope (β_{nuc}) of 0.15;^{3b} the transition state of the symmetrical reaction will thus lie 0.15/1.07 of the way along the "tightness" diagonal from the bottom right corner.

Data from Kirby and Younas¹⁰ indicate that β_{nuc} for attack of oxyanions on 2,4-dinitrophenyl methyl phosphate monoanion is of the order 0.35. It is assumed that the value of α (0.2) is invariant over the range of phenolate ions employed as nucleophiles so that bond fission in the symmetrical reaction of ester with 2,4-dinitrophenolate anion will be 20% complete, and thus the transition state will lie 0.2 of the way along the "tightness" diagonal. The α value derived from β_{lg} for attack of phenolate ion on substituted phenyl methyl phosphates indicates that the bonds in the symmetrical transition state are 63% of the full bond consistent with a "tighter" transition state than when the nucleophiles are 2,4-dinitrophenolate ion. Such variation of electronic structure is not inconsistent with the observation of linear Brønsted plots for either nucleophile or leaving group variation; reference to the reaction map (Figure 2) indicates that if the nucleophile is constant and the leaving group basicity decreases, the resultant motion of the transition-state structure perpendicular and parallel to the reaction coordinate is such that β_{lg} may not vary significantly. The variation in transition-state structure in transfer of acyl functions between nucleophiles has also been observed in such systems as acetyl,^{13,14} diphenylphosphinoyl,⁷ and diphenylphosphoryl⁶ between phenolate ions; it has also been seen for transfer of the phosphoryl group between pyridines^{3a,c} and of the sulfur group between pyridines.^{3c}

The electronic transition-state structure for transfer of the methyl phosphoryl monoanion between 2,4-dinitrophenolate ion nucleophiles may be compared with those for the transfer of the diphenylphosphinoyl (Ph_2PO)⁷ and diphenylphosphoryl ($(\text{PhO})_2\text{PO}$)⁶ between these species. The values of α are 0.18 and 0.12, respectively, for bond formation from entering nucleophile and phosphorus and are derived from other work (Appendix 2).^{6,7} The transfer of the methylphosphoryl monoanion between phenolate ion nucleophiles has a transition-state structure close to that for the transfer of neutral phosphorus acyl groups between the same anionic nucleophiles.

The value of α measuring the extent of bond fission for the ribonuclease-catalyzed cyclization of aryl 3'-phosphoridine esters is smaller than that for the reaction catalyzed by model catalysts such as hydroxide ion or imidazole (III) reflecting reduced change in effective charge on the aryl oxygen in the transition state of the rate-limiting step.¹⁵



- III $\alpha = 0.34$ (B = imidazole)
 $\alpha = 0.31$ (B = hydroxide ion)
 $\alpha = 0.11$ (B = ribonuclease)

The value of Leffler's α for leaving group bond fission for reaction of substituted phenyl methyl phosphate monoanions with phenolate ion (the nucleophile is a full anion) is similar to that for cyclization of the substituted phenyl 3'-phosphoridine esters catalyzed by either imidazole or hydroxide ion (III) where the effective nucleophile (the 2'-hydroxyl function) is still partially protonated in the transition state.¹⁶ The state of bonding between the proton on the 2'-hydroxyl group and the catalytic base (B) does not have significant coupling with the leaving group bond fission in the transition state. The reduced value of β_{lg} (or α) for the bond fission in the ribonuclease catalysis¹⁵ compared with that for the attack of oxyanions is not due to reduced bond fission caused by the change in nucleophile type.

Acknowledgment. The SERC is thanked for partial support of this work (GR/EO6558) and S.A.Ba-S. thanks the Government of Saudi Arabia for a studentship.

Appendix 1

The Leffler α value for a bond fission is given by the equation $\alpha = \beta_{\text{lg}}/\beta_{\text{eq}}$ and the α for bond formation by $\alpha = \beta_{\text{nuc}}/\beta_{\text{eq}}$. The Brønsted terms β_{lg} , β_{nuc} are respectively the Brønsted slopes for leaving group and nucleophile variation. The term β_{eq} is the slope for the Brønsted dependence of equilibrium constant with varying leaving group or nucleophile. Since these parameters are measured against the ionization of the corresponding substituted acid species (in our case phenols) in aqueous solution they derive from a difference in effective charge^{8b} between solvated states. It is important to note that the electronic structure of the transition state derived from α values includes solvation and is *not* simply gas phase "bond order".^{8b}

Appendix 2

In the case of the reaction of 2,4-dinitrophenolate ion with substituted phenyl diphenylphosphinates the β_{lg} has not been determined explicitly but it may be calculated from a linear relationship between β_{lg} and $\text{p}K_{\text{nuc}}$.⁷ The derived β_{lg} gives the extent of bond fission in the transition state and division by β_{eq} gives the α value which when subtracted from unity gives the Leffler α value for bond formation cited in the text.

Registry No. 2,4-(NO₂)₂C₆H₃OPO(OEt)₂, 54436-53-2; 4-NO₂-2-ClC₆H₃OPO(OEt)₂, 106644-72-8; 2-NO₂-4-ClC₆H₃OPO(OEt)₂, 113947-94-7; 4-NO₂-C₆H₄OPO(OEt)₂, 311-45-5; 3-NO₂-C₆H₄OPO(OEt)₂, 4532-06-3; 2,4-(NO₂)₂C₆H₃OPO₂OMe⁻, 122949-58-0; 2,3-(NO₂)₂C₆H₃OPO₂OMe⁻, 122949-59-1; 2,5-(NO₂)₂C₆H₃OPO₂OMe⁻, 122949-60-4; 2-Cl-4-NO₂-C₆H₃OPO₂OMe⁻, 122949-61-5; 2-NO₂-4-ClC₆H₃OPO₂OMe⁻, 122949-62-6; 4-NO₂-C₆H₄-OPO₂OMe⁻, 29314-21-4; 2,4-(NO₂)₂C₆H₃OH, 51-28-5; (MeO)₂POCl, 813-77-4; 2,4-(NO₂)₂C₆H₃OPO(OMe)OLi, 29267-37-6.

Supplementary Material Available: Combustion analytical and melting point data for the aryl methyl phosphate esters (1 page). Ordering information given on any current masthead page.

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(15) Davis, A. M.; Regan, A. C.; Williams, A. *Biochemistry* **1988**, *27*, 9042.

(16) Davis, A. M.; Hall, A. D.; Williams, A. *J. Am. Chem. Soc.* **1988**, *110*, 5105.