

expansolide B, R_f 0.40. The EtOAc extract was evaporated to dryness, and the residue (1.20 g), crystallized in MeOH, gave pure patuline that was characterized by comparison of its melting point (110 °C) and spectroscopic data with already published values.³⁻⁵

Expansolide A (1, C₁₇H₂₂O₅): Colorless crystals; mp 111–112 °C (MeOH); $[\alpha]_D^{24}$ -67.5° ($c = 0.4$, CHCl₃); IR (KBr; ν , cm⁻¹) 2951, 1778, 1743, 1647, 1444, 1381, 1362, 1345, 1231, 1204, 1132, 1037, 1025, 995, 926, 692, 613; CI-MS (NH₃, HR) m/z 307.1530 [M + H]⁺, C₁₇H₂₂O₅ (calcd m/z 307.1545); EI-MS, m/z (%) 307 ([M + H]⁺, 16), 262 (18), 246 (19), 218 (8), 217 (6), 200 (4), 187 (5), 182 (6), 180 (6), 173 (5), 155 (11), 154 (10), 134 (28), 117 (29), 115 (25), 91 (100), 77 (23), 69 (29).

Expansolide B (2, C₁₇H₂₂O₅): not crystallized; $[\alpha]_D^{24}$ -14.8° ($c = 0.5$, CHCl₃); IR (KBr; ν , cm⁻¹) 2950, 1771, 1737, 1654, 1468, 1442, 1372, 1343, 1245, 1199, 1128, 1045, 990, 970, 925, 766, 691, 605; CI-MS (NH₃) m/z 307 [M + H]⁺; EI-MS, m/z (%) 307 ([M + H]⁺, 100), 262 (17), 246 (31), 218 (13), 217 (10), 200 (6), 187 (7), 182 (6), 180 (11), 173 (7), 155 (10), 154 (7), 134 (21), 117 (30), 115 (26), 91 (68), 77 (15), 69 (18).

X-ray crystal analysis: C₁₇H₂₂O₅; molecular weight 306.36; crystals obtained by slow crystallization of expansolide A from methanol; monoclinic system, space group P2₁; Z = 4 (two epimer molecules in the asymmetric unit: A and B); $a = 14.747$ (7), $b = 6.504$ (4), and $c = 17.743$ (8) Å; $\beta = 108.55$ (2)°; $V = 1613.4$ Å³; d_c 1.26 g·cm⁻³; $F(000) = 656$; λ (Cu K α) = 1.5418 Å; $\mu = 6.7$ cm⁻¹ (absorption ignored).

Data were collected on a Phillips PW 1100 diffractometer with graphite-monochromated Cu K α radiation. From the 2969 reflections measured by the θ - 2θ scan technique up to $\theta = 65^\circ$, only 1596 were considered as observed and kept in refinement calculations having $I \geq 3\sigma(I)$, $\sigma(I)$ from counting statistics.

The structure was solved by direct methods with the program SHELX86⁸ and refined by blocked full-matrix least-squares minimizing the function $\sum w(|F_o| - |F_c|)^2$ with the program SHELX76.⁹ Difference Fourier maps

showed the methyl group on the lactone ring in molecule B and the acetyl group of each molecule to be disordered. The respective occupancy factors were refined and confirmed to be 0.50 for the two positions of C13B and 0.75 and 0.25 for the major and the minor positions of the acetyl groups in both molecules. Constraints were applied to fix the geometry of the acetyl groups. The hydrogen atoms, except those fixed on the disordered methyl groups not located in difference maps, were introduced in the refinement at theoretical positions (C - H = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at $R = 0.077$, $R_w = 0.096$ (with $R_w = \{\sum w(|F_o| - |F_c|)^2 / \sum w F_o^2\}^{1/2}$ and $w = 1/\sigma^2(F_o) + 0.01305F_o^2$). No residual was higher than 0.33 e Å⁻³ in the final difference map.

Patuline (3): mp 110 °C (MeOH); IR (KBr; ν , cm⁻¹) 3421, 3090, 1772, 1655 sh, 1623, 1464, 1385, 1284, 1217, 1013; EI-MS, m/z (%) 154 ([M⁺], 14), 136 (10), 126 (35), 110 (33), 97 (25), 84 (32), 82 (22), 71 (12), 69 (17), 57 (100), 55 (52); ¹H NMR (CD₃COCD₃, TMS) δ , (J , Hz) 2.90 sl (OH), 4.367, dd (17.2, 4.0, H5a), 4.643, dd (17.2, 2.8, H5b), 6.02–6.10, m (H1, H4, and H7); ¹³C NMR (CD₃COCD₃) δ , 59.6 (C5), 89.3 (C1), 108.9 (C4), 110.6 (C7), 147.2 (C2), 152.8 (C3), 169.5 (C8).

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Registry No. 1, 129240-51-3; **2,** 129311-85-9; patuline, 149-29-1.

Supplementary Material Available: Tables of fractional coordinates of the non-hydrogen atoms, fractional coordinates of the H atoms, anisotropic thermal parameters, bond lengths, bond angles, and torsion angles of molecules A, **1**, and B, **2** (8 pages); list of the observed and calculated structure factors (5 pages). Ordering information is given on any current masthead page.

Single Transition State in the Transfer of a Neutral Phosphoryl Group between Phenoxide Ion Nucleophiles in Aqueous Solution

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Abstract: The second-order rate constants (k_{ArO}) for reaction of substituted phenoxide ions with 4-nitrophenyl diphenyl phosphate obey a linear equation over a range of 18 substituents with pK_{ArOH} values spanning the pK_a of the leaving 4-nitrophenolate ion: $\log k_{ArO} = 0.53pK_{ArOH} - 6.6$. The linear plot is consistent with a mechanism involving a single transition state or a two-step process with a very reactive intermediate with two almost identical transition states for its formation and breakdown; the value of the exponent (0.53) is also not consistent with a regular stepwise process with a discrete intermediate. The symmetrical reaction of 4-nitrophenolate ion with the 4-nitrophenyl ester is slightly imbalanced whereby bond formation does not keep up with bond fission in the transition state; the transition state, therefore, has some phosphorylium ion character. Transfer of the diethylphosphoryl group between weakly basic oxyanion nucleophiles is probably a concerted process with a transition state with more of the character of the pentacoordinate intermediate than it has in the corresponding diphenylphosphoryl group transfer.

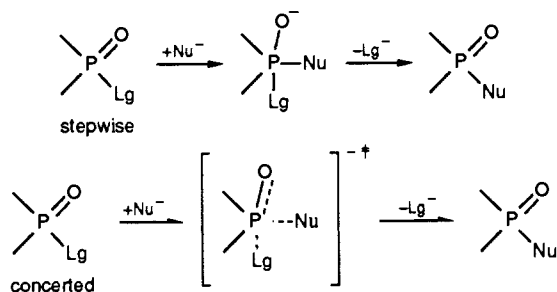
Introduction

Reaction of nucleophiles with neutral phosphoryl species has long been considered to involve pentacoordinate intermediates,¹ and the existence of pentacoordinate oxyphosphoranes² lends

credence to this belief. This and other laboratories have provided substantial evidence for concerted processes in transfer reactions of general acyl groups between nucleophiles.³⁻⁵ A concerted

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Scheme I. Stepwise and Concerted Routes for Nucleophilic Displacements at Phosphoacyl Centers^a

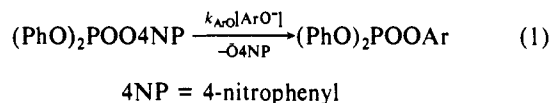
^a That the displacement is "in-line" in the concerted process can be revealed by stereochemical probes but not by polar substituent effects.

mechanism is defined as a reaction pathway with only a single transition state between reactants and products.^{6,7} We decided to investigate the possibility that transfer of the neutral phosphoryl group between nucleophiles could also be concerted (Scheme I). There is precedence that this might be so because reactions of phosphopyridines with substituted pyridines have been shown to be concerted for aqueous solution⁴ and transfers of the diphenylphosphinoyl^{5b} and dimethylphosphinoyl^{5b} groups also involve a single transition state. Nucleophilic attack at many acyclic phosphorus acyl groups has stereochemistry that is consistent with concertedness.^{14,8}

The oxygen ligands to phosphorus in phosphopyridines could assist expulsion of the leaving group⁴ and, hence, in some way force a concerted mechanism to take place. The steric requirements of the phenyl groups in the diphenylphosphinoyl group transfer could also favor a concerted pathway over a regular stepwise process with the pentacoordinate intermediate. Such arguments may not have substantial force in view of the concertedness of the transfer of the dimethylphosphinoyl species.^{5b} Reaction of aryl oxide ions with aryl diphenyl phosphate esters in aqueous solution does not possess any special electronic or steric conditions (as described above) that might force a concerted mechanism to operate.

Aryl diphenyl phosphates are readily obtained and react at relatively fast rates with phenolate ion.⁹ The esters have also been studied by many other groups in micelle-catalyzed reactions and in other models of enzymic catalysis.¹⁰

We have studied the reaction of substituted phenolate ions with 4-nitrophenyl diphenyl phosphate (eq 1). A stepwise path with a pentacoordinate intermediate should yield a nonlinear Brønsted dependence of k_{ArO} on pK_{ArOH} with a "break point" at the pK_a of the 4-nitrophenolate anion leaving group. Provided that



phenolate ions are employed with pK_{ArOH} values ranging well above and below that of the leaving nucleophile, a nonlinear Brønsted dependence is good evidence for a change in the rate-limiting step.⁷ Conversely, a linear plot over such a range of pK_a would indicate constancy of the transition-state structure so far as the forming bond is concerned⁷ and, hence, provides good evidence for a single transition state. The pK_a of the conjugate acid of a nucleophile is recognized to be a poor indicator of absolute nucleophilicity; there is much precedent that, within structurally identical groups of compounds (such as phenols, alcohols, pyridines, amides, and the like), pK_a gives a good comparative measure of the nucleophilicity. Provided there is no mechanistic change, no change in the rate-limiting step, or a substantial steric effect (with particular substituents), good linear free energy relationships will be obtained.

The esters of diphenyl phosphoric acid have sufficient reactivity,⁹ compared to that of the esters of a dialkyl phosphoric acid,⁹⁻¹² to enable accurate rate data to be collected rapidly for a range of phenolate ion nucleophiles; dialkyl phosphate esters are not such attractive vehicles to study since they are less reactive and there is the possibility of dealkylation reactions.¹¹

Experimental Section

Materials. 4-Nitrophenyl diphenyl phosphate was prepared from equivalent amounts of diphenylphosphoryl chloride (Aldrich), 4-nitrophenol, and triethylamine in dichloromethane solvent. The product was obtained by extracting the dichloromethane with dilute HCl, drying the organic layer (MgSO_4), and evaporating. Recrystallization from ethanol gave needles: mp 48–9 °C (lit.¹³ mp 49–51 °C). Phenols were from commercial sources and, except where of AR grade, were recrystallized, resublimed, or redistilled. Inorganic salts, methanol, and buffer materials were of AR grade; water was doubly distilled from glass. Deuterium oxide (>99.8% D) was from Aldrich. Acetonitrile was purified according to the method of Lewis and Smyth.¹⁴

Methods. Measurement of pH was carried out with a Radiometer PHM 62 pH meter equipped with a Russell CMAWL CL5 combination electrode calibrated with EIL standard buffers to ± 0.01 pH unit.

Identities of the products of reaction of phenolate ions with the 4-nitrophenyl ester were determined by extraction of the product buffer with CH_2Cl_2 without acidification, evaporation of the organic extract, and TLC analysis with aluminum-backed silica gel plates (5% MeOH/95% benzene); esters for standardization (see Results) were prepared by the method used for the 4-nitrophenyl diphenyl phosphate by substituting the appropriate phenol. HPLC analysis was carried out with a Pye system equipped with a Zorbax reversed-phase column; the eluent had the composition 80%/MeOH 20%. The retention times for phenol, diphenyl phosphoric acid, and triphenyl phosphate were 2.05, 1.75, and 3.75 min, respectively, with a flow rate and pressure set at 1.5 mL/min and 164 psi. An ultraviolet detector set at 267 nm was employed to assay the effluent.

Buffer solutions containing aryl oxide ions for reaction with 4-nitrophenyl diphenyl phosphate were prepared by adding dilute KOH solution to the phenol in buffer and KCl solution to give a defined pH between 6.5 and 11.5; the composition of the stock phenolate ion buffer solution involved approximately 0.1 M phenol, 0.5 M ionic strength, and 0.1 M buffer concentration. The pH was chosen so that the phenol would be mostly in its basic form. Solutions with varying concentrations of phenol with identical pH, ionic strength, and buffer concentration were obtained by diluting the stock phenol buffer with a stock solution of buffer prepared in the same way as the phenol buffer but without adding phenol. In order to retain both product ester and the reactant in solution, it was

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necessary to employ a solvent composition containing 16% (v/v) methanol/water.

The buffer solution was prepared by adding the appropriate amount of phenol-containing buffer (as prepared above), diluent buffer (as prepared above), and then Analar methanol. Addition of methanol after the stock buffer had been prepared ensured that the phenolate ion concentration was able to be calculated with pK_a values for aqueous solution. Addition of methanol to 16% (v/v) had a negligible effect on the pH (measured by glass electrode standardized against standard aqueous buffers) compared to the same dilution with water. The procedure outlined above was taken to obviate our having to measure pK_a values at 16% (v/v) methanol and also having to standardized the pH probe under these conditions. Buffer components employed throughout were as follows: pH 6.5–7.5, KH_2PO_4 ; pH 7.5–9.5, tris(hydroxymethyl)aminomethane (Tris); pH 9.5–11.5, $KHCO_3$. Buffers containing phenolate ions were not kept for more than 1 day during use, owing to oxidation problems with the more basic species. The water employed in making up the buffer solutions was degassed immediately prior to its use.

A typical kinetic experiment involved adding an aliquot (20–50 μ L) of a stock solution of the ester in acetonitrile to the aqueous solution (2.5 mL) of aryl oxide ion in buffer in a 10-mm path length silica cell. The ester solution was added on the flattened tip of a glass rod, and mixing was effected by rapid vertical strokes. The reaction was followed spectrophotometrically; initially the UV/vis spectrum was scanned repetitively with a Unicam SP800 or Perkin-Elmer Lambda 5 instrument to obtain the best single wavelength for study. The wavelength for the 4-nitrophenyl ester is 400 nm, but in later studies (to be submitted for publication) with substituted phenyl esters it was necessary to employ different wavelengths. The pH of the solution was measured after the reaction was complete with the pH probe in the reaction cell, and the run was discarded if the pH differed from the initial pH by more than 0.05 pH unit.

Experiments with D_2O solvent were carried out in essentially the same way as above except that 1-mL cells with 10-mm path lengths were employed. The pD of solutions in D_2O was measured with a regular pH probe standardized against protio standard buffers; the value of pD was computed from the pH meter reading by eq 2.^{15a} Calculations on kinetic data were carried out with a BBC microcomputer in BASIC language.

$$pD = \text{pH meter reading} + 0.40 \quad (2)$$

Results

Reaction of 4-nitrophenyl diphenyl phosphate in phenolate ion buffers exhibited excellent first-order kinetics up to about 90% of the total release of 4-nitrophenol. The observed rate constants are linear in total phenol concentration; the slopes of the plots of rate constant versus phenol concentration depend on the fraction of phenol present as base (FB, eq 3; see table in the supplementary material).

$$dk_{\text{obs}}/d[\text{phenol}]_{\text{total}} = k_{\text{ArO}}\text{FB} \quad (3)$$

It is assumed reasonably that this rate law holds for all the substituted phenols, and in these cases k_{ArO} was calculated by dividing the slope ($dk_{\text{obs}}/d[\text{phenol}]_{\text{total}}$) by FB; the value of FB was determined from the pH and the pK_a of the phenol in question. The derived parameters, k_{ArO} , are recorded in Table I with conditions of pH, concentration ranges of phenols, and ranges of the observed rate constants. Rate constants for reaction of acetate ion, imidazole, and hydroxide ion with the 4-nitrophenyl ester were measured and are also recorded in Table I.

The data for the unhindered phenolate ions (this includes 2-substituted phenols) obey a linear Brønsted-type equation (4), which is illustrated in Figure 1; 2,6-disubstituted phenolate ions are not included in the correlation. A plot of the "residuals" for the linear correlation of eq 4 is illustrated in Figure 2.

$$\log k_{\text{ArO}} = (0.53 \pm 0.05)pK_{\text{ArOH}} - 6.6 \pm 0.4 \quad (4)$$

$$n = 18, r = 0.930$$

The mechanism involving an intermediate (eq 5) should give rise to the theoretical eq 6⁵ where $\Delta\beta = \beta_2 - \beta_{-1}$, $\Delta pK = pK_{\text{ArOH}} - pK_{\text{4NPOH}}$, and β_1 , β_2 , and β_{-1} refer to Brønsted-type equations

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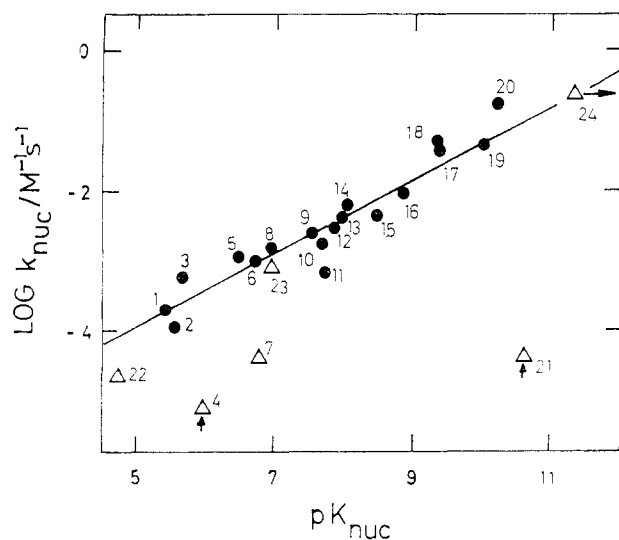


Figure 1. Brønsted plot for reaction of 4-nitrophenyl diphenyl phosphate in buffers containing substituted phenols. The points are identified in Table I, which records the conditions. The line is calculated from eq 4, which correlates phenolate ion data represented by open circles. Arrows indicate upper limits; the data points Δ are excluded from the correlation. Second-order rate constants for nucleophiles other than phenolate ions are illustrated.

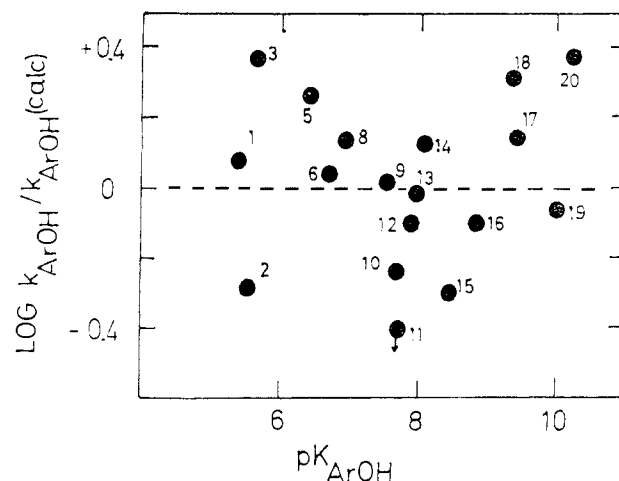
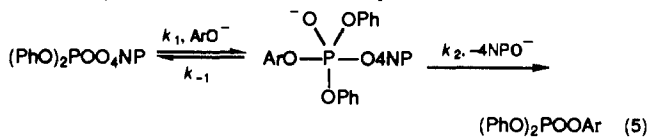


Figure 2. Plot of the "residuals", the difference between calculated and observed values of $\log k_{\text{ArO}}$ (see text), against pK_{ArOH} .

for k_1 , k_2 , and k_{-1} in eq 5. Equation 6 has the same form as that derived by other workers for the stepwise mechanism.^{15b}



Equation 6 predicts a Brønsted-type correlation consisting of two linear portions intersecting at the pK_a of the 4-nitrophenol leaving group (7.14 in this case); eq 6 gives a linear plot only if $\Delta\beta = 0$. Fit of the unhindered data in Table I to eq 6 was done

$$k_{\text{ArO}}/k_0 = 10^{\beta_1 \Delta pK} / (1 + 10^{-\Delta\beta \Delta pK}) \quad (6)$$

with a grid search program.⁵ The best fit was searched within the limits of β_1 from 0.4 to 0.6 in increments of 0.02, $\Delta\beta$ from 0 to -0.2 in units of -0.04, and $\log k_0$ from -2 to -3 in increments of 0.1. The best values of the parameters are 0.56, 0, and -2.5, respectively, and we take the uncertainty as being the unit of variation within each limit.

Equation 6, substituted for the parameters for best fit, reduces to eq 7, which is very close to the forced linear correlation of eq 4.

$$\log k_{\text{ArO}} = (0.56 \pm 0.02)pK_{\text{ArOH}} - 7.0 \pm 0.1 \quad (7)$$

Table I. Reaction of Substituted Phenolate Ions with 4-Nitrophenyl Diphenyl Phosphate^a

no.	substituent ^k	pK _{A,OH} ^b	pH ^c	k _{obs} × 10 ⁴ /s ⁻¹ ^d	ArOH/mM ^f	N ^g	k _{ArO} × 10 ⁴ /M ⁻¹ s ⁻¹ ^j
1	2,3,4,5,6-F ₅	5.40	8.16	4.8–5.9	29–73	4	2.2
2	2,3,5,6-F ₄	5.53	7.50	0.5–1.5	18–93	5	1.1
3	2,3,4,5-Cl ₄	5.64	8.20	1.9–6.6	5–31	8	5.6
4	2,4,6-Cl ₃	5.99	7.52		5–20	4	<0.066 ^e
5	2,3,5-Cl ₃	6.43	8.56	6.5–8.2	12–29	4	11
6	2,4,5-Cl ₃	6.72	8.30	3.2–4.4	2–12	5	10
7	2,6-Cl ₂	6.78	6.5	0.1–0.22	5–26	5	0.38
8	2,3,4-Cl ₃	6.92	8.73	7–10	9–46	5	16
9	2,5-Cl ₂	7.51	8.63	8–18	11–53	5	26
			8.14 ^h	2.5–6.5	9–40	5	22 ^g
10	4-CHO	7.66	9.60	34–43	35–88	4	17
11	2,3-Cl ₂	7.71	8.50	11–14	26–64	4	7.0
12	2,4-Cl ₂	7.85	8.15	14–17	24–61	4	30
13	4-CN	7.95	10.0	5.6–15	3–28	5	42
14	4-CH ₃ CO	8.05	9.00	14–43	12–62	5	67
15	2-Cl	8.48	9.00	8–33	19–93	5	39
16	2-F	8.82	9.00	15–48	20–69	5	93
17	4-Cl	9.38	11.22	115–305	2.2–45	5	380
18	4-COOH	9.31	11.5	2.7–29	4.8–24	4	500
19	parent	9.99	9–10.45	1.0–50	20–104	25	430 ⁱ
20	4-CH ₃ O	10.20	11.5	18–56	2–41	6	1800
21	2,6-(CH ₃) ₂	10.63	10.96		0.58–6.1	4	<0.33 ^e
22	acetate ion	4.76 ⁿ	7.24	0.4–0.8	100–250 ^l	4	0.22 ^m
23	imidazole	6.95 ⁿ	8.05	40–75	240–790 ^l	4	8.9 ^m
24	hydroxide ion	16.4 ^p		22–78	80–320 ^l	5	2600 ^m

^a Conditions: 25 °C, 0.5 M ionic strength maintained with KCl, 0.1 M buffer concentration (for identity of buffer see Experimental Section), 16% MeOH/water. ^b Value of the pK_a of the attacking nucleophile. Parameters from: Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry*; Sober, H. A., Ed.; The Chemical Rubber Co.: Cleveland, OH, 1970; J-150. ^c Average pH. ^d Range of observed rate constants. ^e Upper limit. ^f Range of nucleophile concentrations employed (total acid plus base forms). ^g Number of data points not including duplicates. ^h Value of pD. ⁱ Parameter derived from data at a number of pH values. ^j Error in this parameter is no more than ±10%. ^k Nucleophiles recorded as nos. 22–24 are not phenolate ions. ^l Concentration range of the appropriate nucleophile. ^m Refers to second-order rate constant for attack of nucleophile on the ester. ⁿ pK_a of the conjugate acid of the appropriate nucleophile. ^p pK_a of water taken from: Sauer, C. K.; Jencks, W. P.; Groh, S. *J. Am. Chem. Soc.* **1975**, *97*, 5546. ^q Value for deuterium oxide solvent.

Table II. Effect of Ionic Strength on the Alkaline Hydrolysis of 4-Nitrophenyl Diphenyl Phosphate^a

ionic strength ^e	[OH ⁻] × 10 ² /M ^c	k _{obs} × 10 ⁴ /s ⁻¹	k _{OH} /M ⁻¹ s ⁻¹	N ^b
0.5	0.8–3.2	2–7.8	0.26	5
0.4	1.4–11	50–370	0.33	5
0.3	1.5–10	68–440	0.44	5
0.2	1.5–11	69–430	0.40	5
0.1	1.5–11	58–430	0.42	5

^a 25 °C and 16% MeOH/water (v/v). ^b Number of data points not including duplicates. ^c Range of hydroxide ion concentration made up with KOH. ^d Range of observed rate constants. ^e Ionic strength made up with KCl.

The effects of change in ionic strength and methanol concentration on the rate constants for attack of hydroxide ion and phenolate ion, respectively, are recorded in Tables II and III. A deuterium oxide solvent isotope effect of 1.2 is observed for the reaction of 2,5-dichlorophenolate ion with the 4-nitrophenyl ester (see Table I).

Product analysis studies with TLC indicate that the aryl ester is the major product (>99% yield) for reactions with the 4-nitrophenyl ester in buffers containing phenolate ion. TLC spots positively identifying the aryl ester as product were observed for buffers with 4-methoxyphenolate ion, 4-chlorophenolate ion, 4-cyanophenolate ion, and 2,5-dichlorophenolate ion; a trace of the diphenyl phosphoric acid was observed in all cases.

A single HPLC study confirmed that triphenyl phosphate is the product of reaction for buffers containing phenol.

Discussion

Concerted Mechanism for Nucleophilic Displacement. The reaction of 4-nitrophenyl diphenyl phosphate in buffers containing phenolate ion involves nucleophilic displacement of the 4-nitrophenolate ion to give the corresponding substituted phenyl ester. There is ample evidence for this from product isolation studies and the absence of a deuterium oxide solvent isotope effect on the reaction of 2,5-dichlorophenolate ion with the ester. The existence of substantial steric effects on the values of k_{ArO} for

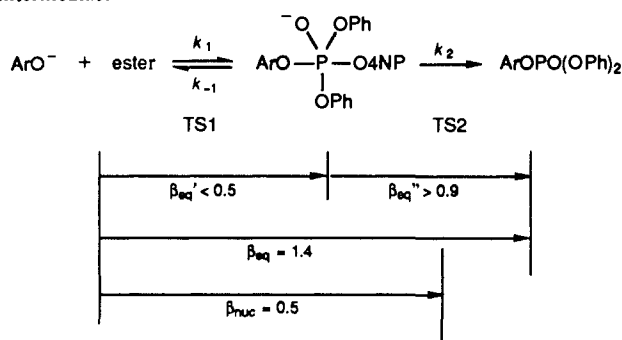
Table III. Effect of Methanol Concentration on the Reaction of Phenolate Ions with 4-Nitrophenyl Diphenyl Phosphate^a

% methanol	pH	k _{obs} × 10 ³ /s ⁻¹	[PhOH] × 10 ² /M ^b	k _{PhO} × 10 ² /M ⁻¹ s ⁻¹	N ^c
16				4.3 ^e	
22	11.25	1.5–4.0	0.5–10	3.4	5
27	11.23	1.6–3.3	1.4–7.0	3.2	5
32	11.04	1.2–2.7	1.3–6.5	2.6	5
40	11.23	1.5–3.2	1.6–8.2	2.5	5

^a 25 °C, 0.5 M ionic strength (made up with KCl), 0.1 M buffer species (see Experimental Section). ^b Range of phenol concentrations. ^c Number of data points not including duplicates. ^d Range of observed rate constants. ^e From Table I.

2,6-disubstituted phenolate ions excludes the possibility of general-base catalysis for the regular phenolate ions, which should yield only minor effects due to ortho substituent size in attack on water's protons. Solvent effects over the ranges studied are relatively small (Tables II and III) compared with the overall variation in k_{ArO}.

Curvature in the Brønsted dependence for nucleophilic attack of phenolate ions with the ester (Figure 1) is well below the uncertainty limits demanded by the data; the residuals for the linear correlation (eq 4) show no systematic variation (Figure 2) expected for force-fitting nonlinear data to a linear equation. The phenolate ions employed in this study have pK_a values ranging well above and below the pK_a of 4-nitrophenol. Either a concerted mechanism occurs or there is little difference in charge at attacking oxygen between the two transition states of the stepwise process. If the latter were so, then the difference in effective charge (Δβ, eq 6) on the attacking oxygen in the two putative transition states would be no greater than an upper limit of the value of Δβ which is (very conservatively) about -0.1. There is a difference of about 10% between the sum of the squares of the deviations for the best fit for Δβ = 0 and Δβ = -0.04. There is a preponderance of points for phenols with ΔpK values up to 3 units greater than zero. Phenols with ΔpK < 0 are not in great abundance, although there are many nitro-substituted species that cannot be used because they swamp the absorbance change for the substrate. The data

Scheme II. Effective Charge Map for Reaction via the Putative Intermediate

for points 9–20 give rise to a linear Brønsted-type line with slope +0.71 and intercept -8.18 ($\Delta pK > 0$), and all the nonsterically hindered phenolate ions with $\Delta pK < 0$ have values of k_{ArO} in excess of those predicted from this line. Increasing the range of values of pK_{ArOH} on either side of that for 4-nitrophenol will increase the confidence that there is a single transition state for the reaction.

Uncertainty in $\Delta\beta$ of 0.1 gives a confidence limit of $\approx 7\%$ of the overall change in effective charge on that oxygen ($\beta_{\text{eq}} = 1.4$).¹⁶ It is difficult to account for the stability of an intermediate where the difference in effective charge on the attacking oxygen between forward or reverse transition states must be less than 3.5% of the total change in effective charge.^{3c,d,4a,5,17}

In the region of pK_{ArOH} less than that of the 4-nitrophenolate ion leaving group, the slope of the Brønsted line (β_{nuc}) for the putative stepwise process (eq 6) should be equal to $\beta_1 - \beta_2$; in this region of pK_{ArOH} , the k_2 step becomes rate-limiting. The observed value of β_{nuc} is no greater than 0.5 in this region (see Figure 1). Thus, β_{eq}' for formation of the putative pentacoordinate intermediate must be less than 0.5 because β_{nuc} refers to the change in effective charge from the ground state to the transition state of the k_2 step, which marks a point on the reaction coordinate after the intermediate is formed (Scheme II). The value of β_{eq}'' will therefore be greater than $\beta_{\text{eq}} - \beta_{\text{nuc}}$ (that is, greater than 0.9). The k_2 step refers to only a rehybridization change in the P-OAr bond from pentacoordinate to tetracoordinate at phosphorus. The associated change in effective charge cannot, therefore, be greater than that for the k_1 equilibrium, which involves full P-OAr bond formation. The observed inequalities ($\beta_{\text{eq}}' < \beta_{\text{eq}}''$) are consistent with a mechanism with a single transition state but cannot be explained by a stepwise process.

There is scope for considerable discussion regarding the distinction between a mechanism with a single transition state and one with an intermediate that lies in a depression bounded by weak barriers to the forward and reverse reactions. There is no way at present of examining this difference experimentally for solution reactions, and "Occam's Razor"¹⁸ indicates that the simplest explanation holds, namely, that there is a single transition state. The alternative "stepwise" mechanism differs from a regular stepwise process where an intermediate has a real existence; the stepwise alternative to the concerted mechanism examined here would be described as an enforced concerted mechanism because the intermediate would have too short a lifetime to exist.

Strong cross-correlation effects may be inferred from a nonzero $d\beta_{\text{nuc}}/dpK_{\text{g}}$ from previous work from this laboratory;¹⁹ this observation is consistent with transition states not lying on the edges of the reaction map for the reaction (for example, see Figure 3) and is very good evidence for a concerted process.

Transition-State Structure. The absence of detectable curvature in the Brønsted dependence (Figure 1) indicates that the effective charge on the attacking oxygen is independent of the electron-

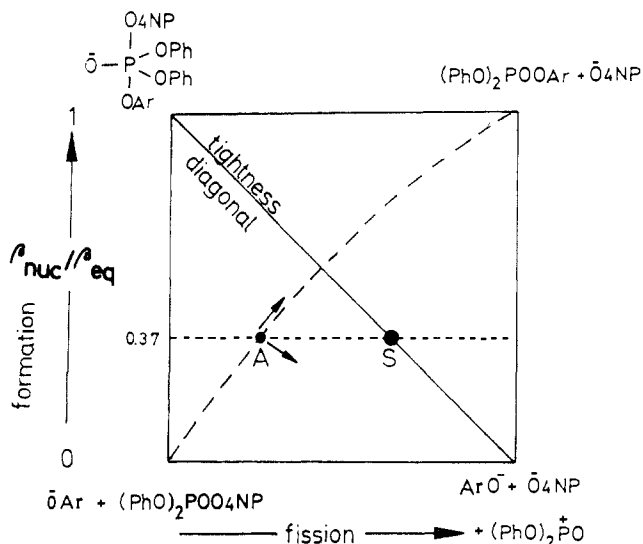


Figure 3. Reaction map for displacement of 4-nitrophenolate ion from 4-nitrophenyl diphenyl phosphate by a substituted phenolate ion. Energy coordinate is perpendicular to the plane of the paper. Bond fission and formation is measured by the appropriate Leffler parameter ($\alpha = \beta_{\text{nuc}}/\beta_{\text{eq}}$ or $\beta_{\text{nuc}}/\beta_{\text{eq}}$). The horizontal dashed line represents the locus of movement of the transition state as a function of change in substituent on the nucleophile. Point S represents the structure of the transition state for the symmetrical reaction. Point A is discussed in the text.

donating or -attracting power of the substituent. This effect can only be true for the concerted process if the change in energy of the nucleophile moves the transition state in the reaction map (Figure 3) in a horizontal direction. It is likely, on the basis of other works,^{4,5a,7} that the structure of the transition state varies with nucleophile; while effective charge on attacking oxygen remains constant for nucleophilic attack on the 4-nitrophenyl ester, the bonding of the phosphorus to the leaving oxygen weakens as the nucleophile becomes less basic. The direction of movement of the transition state A in the map is the vector sum of the "Hammond" and "anti-Hammond" effects, which involve movements along and perpendicular, respectively, to the reaction coordinate.

The extent of bonding for a particular bond in the transition state may be measured by the Leffler parameter, α , which is a dimensionless quantity.²⁰ α refers to a change in value of a physical quantity such as Brønsted β for the transition state compared to the change to the product state. Thus, for a reaction involving substituent change on the nucleophile, the value would be $\beta_{\text{nuc}}/\beta_{\text{eq}}$.²⁰ The transition-state structure lies on the diagonal (at S) for the symmetrical reaction involving displacement of 4-nitrophenolate ion by the 4-nitrophenolate ion nucleophile. The diagonal has been named "tightness diagonal" by Albery and Kreevoy²¹ and "disparity reaction" by Grunwald.²² The bonding at S is measured by the Leffler parameter; $\alpha = \beta_{\text{nuc}}/\beta_{\text{eq}} = 0.53/1.4 = 0.38$ for formation, and since the reaction under consideration is completely symmetrical, the bonding to the leaving group is also 0.38 of the way from product to reactant state.

The effective charge structure of S is given in structure I, indicating a slightly uncoupled displacement process and some phosphorylium ion character in the transition state for the symmetrical reaction. The structure of the transition state, as indicated by its position in the map (Figure 3), is not consistent with an enforced concerted process where a pentacoordinate intermediate is too unstable to have a real existence.

Transfer of Neutral Phosphoryl Groups. Nucleophilic displacements of diphenylphosphoryl derivatives are some 50-fold more reactive than those of corresponding diethylphosphoryl species.^{11,23} The difference in reactivity is probably due to the

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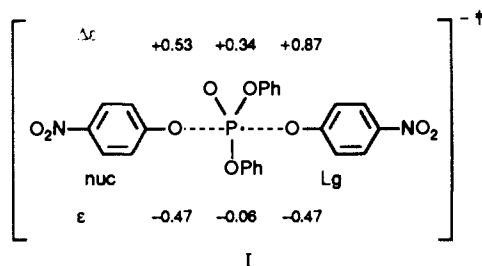
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increased electron-attracting power of the phenyl compared with the ethyl group; there is little steric requirement at phosphorus in the diphenyl series compared to that in the ethyl series. The reactivity difference, which is relatively small on an energy scale, is unlikely to result from a change in mechanism to a stepwise process in the diethyl case.

The conclusions of this paper refer to symmetrical and unsymmetrical displacements where at least one of the nucleophiles is weakly basic. Kinetically observable pentacoordinate phosphorus species from neutral phosphoacyl anions have always involved strong nucleophiles.² Addition intermediates observed in acid-catalyzed phosphoryl group transfer¹⁸ are neutral and thus possess no driving force to expel a ligand, and they can, thus, exist as observable entities.

General-Base Catalysis. The sterically hindered nucleophiles (2,4,6-trichlorophenolate ion, 2,6-dichlorophenolate ion, and

(23) Phenoxide ion attack on the 4-nitrophenyl ester of diethyl and diphenyl phosphoric acid has bimolecular rate constants $6.7 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ at 39°C ¹¹ and $4.3 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ at 25°C , respectively, with 32% MeOH/water.¹⁶ Hydroxide ion attack on these esters has the rate constants $8.6 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ ²⁴ and $0.26 \text{ M}^{-1} \text{ s}^{-1}$ ¹⁶ at 25°C in water.

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2,6-dimethylphenolate ion) and the data for acetate ion have reactivities well below those predicted from the regression line (eq 4) and may include some general-base component. The reactivity of the imidazole species, which comes close to that of a phenolate ion of similar $\text{p}K_{\text{a}}$, confirms previous conclusions that this reagent acts as a nucleophile.¹² Otherwise, the reactivity would be at least below that of the above sterically hindered phenolate anions.

Imidazole reacts with the hindered diphenylphosphinyl esters as a general base¹² and with the less hindered dimethylphosphinyl group as a nucleophile.^{5b} Our studies indicate that the oxyanion from 2-iodosobenzoic acid^{10m} is some 3.9×10^5 -fold more reactive against 4-nitrophenyl diphenyl phosphate than a phenoxide ion of similar $\text{p}K_{\text{a}}$; this is consistent with the nucleophile possessing the enhanced reactivity of an " α -nucleophile".

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Appendix

The parameters β_{eq}' , β_{eq}'' , and β_{eq} refer to the Brønsted-type parameter for the plot of the logarithm of the equilibrium constants for steps k_1 and k_2 and for the overall reaction against the $\text{p}K_{\text{a}}$ of the appropriate phenol.

The simple relationship $\beta_{\text{eq}} = \beta_{\text{eq}}' + \beta_{\text{eq}}''$ follows from the relationship between the three equilibrium constants. Thus, $\beta_{\text{eq}}'' = \beta_{\text{eq}} - \beta_{\text{eq}}'$ and β_{eq}'' must, therefore, be greater than 0.9 if $\beta_{\text{eq}}' < 0.5$ and $\beta_{\text{eq}} = 1.4$.

Supplementary Material Available: Table of reactivity data of 4-nitrophenyl diphenyl phosphate with buffers at different pH's containing phenol (1 page). Ordering information is given on any current masthead page.

The β Effect of Silicon in the Synperiplanar Geometry

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Abstract: The effect of silicon on the development of β positive charge has been measured for the synperiplanar geometry of the Si-C-C-X fragment in *endo*-3-(trimethylsilyl)-*endo*-2-norbornyl esters (3). Solvent effects were used to demonstrate that solvolysis took place by a carbocation mechanism. When the leaving group X was mesylate (3-OMs) and the solvent was 97% trifluoroethanol, the β effect was found to be about 10^5 by comparison of the solvolysis rate with the analogous structure lacking the trimethylsilyl group, *endo*-2-norbornyl mesylate (5-OMs). Thus, the synperiplanar β effect is much smaller than the antiperiplanar β effect (about 10^{12} under similar conditions). The effect may be smaller because of poorer vertical overlap in the synperiplanar geometry or because the syn leaving group prevents optimal vertical overlap. Alternatively, the antiperiplanar effect may be larger because of contributions from nonvertical participation.

One of the most important electronic properties of silicon is its substantial ability to stabilize positive charge on a β atom, the so-called β effect.² Positive charge may be produced solvolytically in solution or by various reactions in the gas phase. The presence of a β silicon atom can produce an acceleration (compared with hydrogen at the same β position) of up to 10^{12} (about 18 kcal mol^{-1}) for secondary systems in solution.³ Mass spectrometric

studies have assessed the β effect for primary systems ($\text{Me}_3\text{SiCH}_2\text{CH}_2^+$) at 39 or 48 kcal mol^{-1} ,^{4,5} the difference resulting from the chosen value of the heat of formation of Me_3Si^+ . Li and Stone found the effect to be about 28 kcal mol^{-1} for secondary systems.⁵ By ab initio calculation, Jorgensen and co-workers⁶ found the β effect to be about 38 kcal mol^{-1} for the primary case, 22 kcal mol^{-1} for the secondary case, and 16 kcal mol^{-1} for the

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