NBS were brominated from 10% to 20% completion. The reaction mixture was analyzed by GC for remaining starting material. Relative rates were calculated from the following equation:

$$\frac{k'}{k} = \frac{\log (A_0'/V_0) - \log (A_f'/V_f)}{\log (A_0/V_0) - \log (A_f/V_f)}$$

where A_0' and A_0 represent the original moles of the two compounds, A_f' and A_f represent the final moles of the two compounds, and V_0 and V_f represent the original and final volumes.

Acknowledgment. Support for the work was provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Associates of Point Loma Nazarene College.

Registry No. **1**, 78-94-4; **2**, 768-03-6; **3**, 3102-33-8; **4**, 814-78-8; **5**, 930-68-7; **6**, 106-51-4; **7**, 96-33-3; **8**, 623-43-8; **9**, 80-62-6; NBA, 79-15-2; NDBA, 598-93-6; NBMA, 51094-87-2; $BrCH_2CH(OCH_3)COCH_3$, 113704-67-9; $CH_3OCH_2CHBrCOCH_3$, 64151-19-5; $BrCH_2CHBrCOCH_3$, 25109-57-3; $BrCH_2CH(OCH_3)COPh$, 113704-68-0; $CH_3OCH_2CHBrCOPh$, 85083-55-2; $BrCH_2CHBrCOPh$, 51011-65-5; (R^*,R^*)-$CH_3CHBrCH(OCH_3)COCH_3$, 113725-87-4; (R^*,S^*)-$CH_3CHBrCH(OCH_3)COCH_3$, 113704-78-2; (R^*,R^*)-$CH_3CH(OCH_3)CHBrCOCH_3$, 85083-56-3; (R^*,S^*)-$CH_3CH(OCH_3)CHBrCOCH_3$, 85083-57-4; (R^*,R^*)-$CH_3CHBrCHBrCOCH_3$, 113704-69-1; (R^*,S^*)-$CH_3CHBrCHBrCOCH_3$, 113704-79-3; $BrCH_2C(OCH_3)(CH_3)COCH_3$, 113704-70-4; $CH_3OCH_2CBr(CH_3)COCH_3$, 113704-71-5; $BrCH_2CBr(CH_3)COCH_3$, 85526-21-2; CH_3OBr, 28078-73-1; $C_5H_5NHBr_3$, 39416-48-3; $C_5H_5NBr_2$, 6081-86-3; $BrCH_2CH(OCH_3)COOCH_3$, 60456-17-9; $CH_3OCH_2CHBrCOOCH_3$, 27704-96-7; $BrCH_2CHBrCOOCH_3$, 1729-67-5; $CH_3CHBrCH(OCH_3)COOCH_3$, 113704-75-9; (R^*,R^*)-$CH_3CH(OCH_3)CHBrCOOCH_3$, 26839-92-9; (R^*,S^*)-$CH_3CH(OCH_3)CHBrCOOCH_3$, 29247-01-6; (R^*,R^*)-$CH_3CHBrCHBrCOOCH_3$, 26708-42-9; (R^*,S^*)-$CH_3CHBrCHBrCOOCH_3$, 22426-04-6; $BrCH_2C(OCH_3)CH_3COOCH_3$, 82270-54-0; $CH_3OCH_2CBr(CH_3)COOCH_3$, 113704-76-0; $BrCH_2CBr(CH_3)COOCH_3$, 3673-79-8; $CH_2{=}C(OCH_3)COCH_3$, 51933-10-9; $CH_2{=}C(OCH_3)COPh$, 54123-71-6; $CH_3O(CH_2)_2COCH_3$, 6975-85-5; $CH_3O(CH_2)_2COPh$, 55563-72-9; $CH_3CH(OCH_3)CH_2COCH_3$, 13122-52-6; $CH_3OCH_2CH(CH_3)COCH_3$, 14539-67-4; $Br(CH_2)_2COCH_3$, 28509-46-8; $Br(CH_2)_2COPh$, 29636-75-7; $CH_3CHBrCH_2COCH_3$, 113704-77-1; $BrCH_2CH(CH_3)COCH_3$, 109539-55-1; 3-bromo-2-methoxycyclohexanone, 113704-72-6; 2-bromo-3-methoxycyclohexanone, 113704-73-7; 2-bromo-2-cyclohexen-7-one, 50870-61-6; 2,3-dibromo-1,4-benzoquinone, 25705-58-2; 2,6-di-*tert*-butylpyridine dibromide, 113704-74-8; 3-methoxycyclohexanone, 17429-00-4.

Transfer of the Diethoxyphosphoryl Group [$(EtO)_2PO$] between Imidazole and Aryloxy Anion Nucleophiles

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Received September 30, 1987

Rate constants have been measured for reaction of imidazole with aryl diethyl phosphate (k_1) and of aryloxy anions with N-(diethoxyphosphoryl)imidazolium ion (k_{-1}) in aqueous solution at 25 °C; they obey the following linear Brønsted equations: $\log k_1 = -1.02\mathrm{p}K_{\mathrm{ArOH}} + 1.83$ ($n = 6$, $r = 0.989$); $\log k_{-1} = 0.85\mathrm{p}K_{\mathrm{ArOH}} - 0.48$ ($n = 10$, $r = 0.957$). The value of β_{eq} (1.87) obtained from β_{lg} and β_{nuc} supports a previously determined value (1.83) for the transfer of the neutral phosphoryl group [$(HO)_2PO$] from phenolate ion nucleophiles. The pK_a of (diethoxyphosphoryl)imidazolium ion is 6.04. The equilibrium constant for reaction of 4-nitrophenyl diethyl phosphate with imidazole is 5.9×10^{-6}; in the case of the aryl ester from phenol with $\mathrm{p}K_{\mathrm{ArOH}} = 4.34$ the equilibrium constant is calculated to be unity. The Brønsted β_{eq} data are used to calibrate effective charges derived from previously measured β_{lg} values for attack of nucleophiles at phosphorus bearing phenolate ion leaving groups.

Polar substituent effects on reaction rates and equilibria remain one of the most useful tools for investigating charge changes in organic reactions.[1] The effects, when compared with those for a standard equilibrium involving an ionization, give rise to the quantity defined as the effective charge change[1,2] from reactant to transition or product states. Effective charge values have little significance when considered alone;[1] in order to apply effective charge changes to investigate the extent of bond fission in a transition state, it is necessary to calibrate them with the change in charge on the atom in question when the reaction is completed. The polar substituent effect on such a calibration equilibrium compared with that of the standard ionization equilibrium is often quantified as a β_{eq} parameter (provided the reaction is amenable to the Brønsted approach).[1]

The value of β_{eq} has been determined by a number of different methods for carbonyl group (RCO) transfer between various types of nucleophile, and such values are relatively well understood. β_{eq} values for transfer of the phosphoryl group (PO_3^{2-}) between substituted pyridines have been determined by two independent groups[3,4] and these values are in agreement, but there is only one value of β_{eq} for transfer between oxyanions that has been estimated by a bonafide method.[5] Values of β_{eq} for transfer of phosphoryl groups between nucleophiles are very important in studies of bonding and charge in phosphorylation reactions in solution especially as there are now many values of β_{nuc} and β_{lg} in the literature that are available

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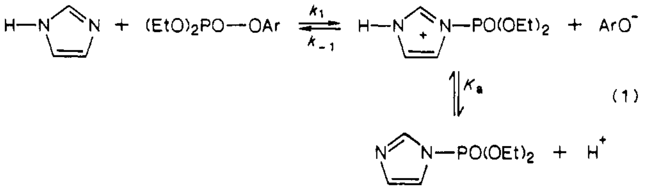
to be calculated. It is therefore of use to obtain the β_{eq} value for the transfer of a diethoxyphosphoryl group [$(EtO)_2PO$] between phenolate ion acceptors. Such a β_{eq} might be expected to be similar to that for transfer of the neutral phosphoryl function [$(HO)_2PO$] because replacing H by Et usually has little effect on reactivity, particularly when the group is remote from the center in question. The obtention of a β_{eq} value for the diethoxyphosphoryl group for transfer between aryl oxide ions would thus be of importance in supporting the single previously determined value.

We choose to obtain β_{eq} by application of the method of Jencks and Gerstein,[6] making use of the forward and reverse rate constants of the reaction (eq 1) that may be



(1)

determined each under its respective forcing conditions. The "forward" rate constant (k_1) is essentially that for reaction of imidazole with aryl diethyl phosphate esters in aqueous solution; this is known to have a nucleophilic mechanism although general-base-catalyzed hydrolysis is observed for some esters in other phosphyl series.[7] The reverse rate constant may be measured by reacting the aryl oxide ion with (diethoxyphosphoryl)imidazole in aqueous solution. Knowledge of K_a for the ionization of the phosphorylimidazole, which may be obtained by pH titration, enables us to calculate k_{-1}. The value of the equilibrium constant may be determined from k_1 and k_{-1} ($K = k_1/k_{-1}$), and β_{eq} may be obtained from a plot of log K versus pK_{ArOH}. In the event the equilibrium constant was not able to be determined over a sufficiently wide range of pK_{ArOH}; it is not essential to know K to measure β_{eq}, which is also given by the expression $\beta_{eq} = \beta_{nuc} - \beta_{lg}$. A Brønsted value measured by the latter method is likely to be more accurate because its components may be estimated over a much larger range of pK_{ArOH}. The term β_{nuc} refers to k_{-1} and β_{lg} to k_1.

In this investigation we employ the Leffler index ($\alpha = \beta_{lg}/\beta_{eq}$)[1] as a measure of the change in effective charge from ground to transition state relative to the overall change in charge for full bond fission.

Experimental Section

N-(Diethoxyphosphoryl)imidazole was prepared by the method of Cramer, Schaller, and Staab[8] and Baddiley, Buchanan, and Letters.[9] Diethyl chlorophosphonate (0.1 mol) was added dropwise to imidazole (0.02 mol) in dry acetone (120 mL) over a period of 2 h. The resulting precipitate of imidazolium chloride was filtered, and the filtrate was evaporated at room temperature in vacuo. The product was liquid and had n^{20}_D 1.466 (lit. n^{23}_D 1.4605[10] and 1.4475[11]). The material was not distilled because Ranganathan and Brinigar[10] have shown that decomposition occurs even under high-vacuum conditions. Degterev and Nikolenko,[11] however, obtained the amide by distillation at 0.3 Torr. The oil had the following ^1H NMR spectrum: ^1H NMR ($CDCl_3$) δ 8.1 (s, 1 H), 7.4 (s, 1 H), 7.2 (s, 1 H), 4.1–4.4 (complex multiplet, 4 H), 1.35 (t, 6 H, J = 7 Hz). The spectrum is in agreement with that observed by Ranganathan and Brinigar.[10]

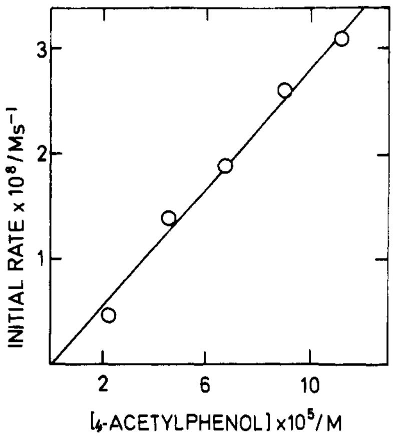


Figure 1. Reaction of 4-acetylphenol with *N*-(diethoxyphosphoryl)imidazole in tris(hydroxymethyl)aminomethane buffers. See Table III for conditions; line is calculated from k_{-1} (Table III).

The aryl diethyl phosphate esters were prepared by the following general procedure, paying particular attention to the fact that some of the esters are real and potential nerve gas agents: the phenol (0.02 mol) was dissolved in benzene (100 mL) to which was added triethylamine (0.02 mol). Diethyl chlorophosphonate (0.02 mol) was added, and the mixture was warmed at 70–80 °C overnight. The product was cooled and the crystalline $NEt_3{\cdot}HCl$ salt filtered; the solution was washed with dilute HCl, and the benzene layer was dried with $MgSO_4$ and evaporated. The product was then either recrystallized or redistilled under vacuum. Boiling points, melting points, and analytical data for these known esters are recorded in the supplementary table. Infrared and NMR spectra were determined with a Perkin-Elmer 297 and a JEOL JNM PS 100 MHz instrument, respectively; the spectra are consistent with the proposed structures.

Water used throughout the investigation was doubly distilled from glass. Buffer materials were of AR grade or were redistilled or recrystallized from bench-grade products. Dioxane (AR grade) was purged of peroxide impurities by its passage through a column of alumina.

The reaction under investigation was studied initially by scanning the UV–visible spectrum of the reaction to choose the best wavelength for following the kinetics. Ester reactions were followed by adding an aliquot of the ester in dioxane solvent (ca. 20 μL) to 2.5 mL of a buffer containing the reagent species (imidazole or hydroxide ion). The kinetics were followed by measuring the absorbance at the predetermined wavelength. First-order rate constants were obtained from the absorbance A by plotting $A_\infty - A_t$ versus time on two-cycle semilogarithmic graph paper. The pH was measured after the reaction with a Radiometer PHM 26 pH meter calibrated with EIL standard buffers to ±0.01 unit.

Reaction of the phenolate anion with *N*-(diethoxyphosphoryl)imidazole is complicated by the hydrolysis of the latter substrate so that we were forced to study initial rates of disappearance of the nucleophile. Phenolate ion buffers were prepared as stock solutions by dissolving the phenol in buffer and adjusting the pH to the appropriate value with concentrated HCl or NaOH. The final concentration of buffer (tris(hydroxymethyl)aminomethane) was 0.2 M and the ionic strength was kept at 0.5 M with KCl. A separate solution was made up to the identical specification except that the phenol was omitted. Dilution of the two stock solutions with each other gives varying concentrations of phenol at constant buffer concentration and ionic strength. An aliquot of *N*-(diethoxyphosphoryl)imidazole in dioxane (0.1 mL to give a final concentration of ca. 0.05 M) was added to 2.5 mL of buffer containing the phenol (at a concentration of between 0.03 and 2 mM), and the initial rate of disappearance of the phenol was measured at an appropriate wavelength. The extinction coefficient of the absorption change was measured separately. The first-order rate constant relative to phenol was obtained from the slope of the plot of the initial rate against phenol concentration (Figure 1), and this, divided by the concentration of *N*-(dieth-

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Table I. Reaction of Imidazole with Substituted Phenyl Diethyl Phosphates at 25 °C and 0.5 M Ionic Strength[a]

substituent	pK_{ArOH}	$k_1/(M^{-1}\ s^{-1})$[c]	N[d,e]	[imidazole]/M[g]	k_{obsd}/s^{-1}[f]	10^4[ester]/M[h]
2,4-$(NO_2)_2$	4.09	1.7×10^{-2}	6	0.1–0.9	$(2–14) \times 10^{-3}$	7.9
2-Cl-4-NO_2	5.45	1.3×10^{-4}	12	0.1–0.9	$(1.5–9) \times 10^{-5}$	2.1
2-NO_2-4-Cl	6.46	1.3×10^{-5}	4	0.4–0.9	$(5–10) \times 10^{-6}$	1.35
4-NO_2	7.14	2.2×10^{-6}	7	0.1–0.9	$(0.5–6) \times 10^{-3}$	20
3-NO_2	8.38	3.3×10^{-8}	4	0.4–0.9	$(1.5–3) \times 10^{-7}$	96
F_5[b]	5.40	2.4×10^{-4}	4	0.25–0.9	$(0.4–2.5) \times 10^{-4}$	7.0

[a] Made up with KCl; except where noted the wavelength for kinetics was 400 nm. [b] Wavelength for kinetics 300 nm. [c] Error no greater than ±5%. [d] Number of data points not counting duplicates. [e] Average pH 8.05 for all the runs. [f] Range of observed pseudo-first-order rate constants. [g] Range of total imidazole concentrations employed. [h] Ester concentration.

Table II. Alkaline Hydrolysis of Substituted Phenyl Diethyl Phosphates at 25 °C and 0.5 M Ionic Strength[a]

substituent	pK_{ArOH}	$k_{OH}/(M^{-1}\ s^{-1})$[b]	N[c]	$[OH^-]/M$[d]	$10^4\ k_{obsd}/s^{-1}$[e]
3-NO_2	8.34	8.0×10^{-5}	4	0.03–0.16	1–7
4-NO_2	7.14	8.6×10^{-3}[f]	4	0.05–0.16	5–14
2-NO_2-4-Cl	6.46	3.9×10^{-2}	4	0.03–0.16	10–80
2-Cl-4-NO_2	5.45	4.5×10^{-2}	4	0.02–0.15	10–70
2,4-$(NO_2)_2$	4.09	3.2×10^{-1}	4	0.03–0.16	100–500

[a] Made up with KCl; ester concentrations as in Table I; wavelength for kinetics 400 nm. [b] Deviations no greater than ±5%. [c] Number of data points not including duplicate runs. [d] Range of hydroxide ion concentrations employed. [e] Range of observed pseudo-first-order rate constants. [f] Literature value for 50% EtOH/water at 37.5 °C: $1.6 \times 10^{-2}\ M^{-1}\ s^{-1}$.[12]

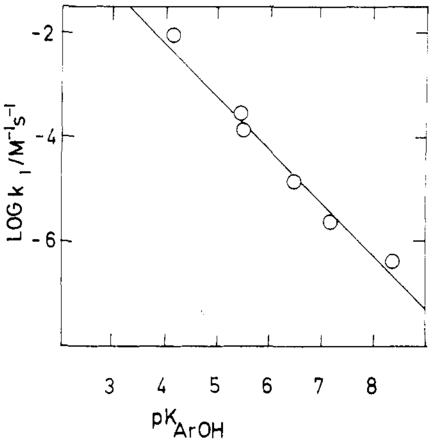

Figure 2. Brønsted dependence of k_1 for reaction of imidazole with substituted phenyl diethyl phosphate esters. Conditions as in Table I; line is calculated from eq 3.

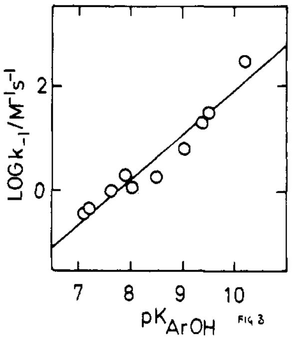

Figure 3. Brønsted dependence for the reaction of substituted phenolate anions with N-(diethoxyphosphoryl)imidazolium ion (k_{-1}). Conditions as in Table III; line is calculated from eq 4.

oxyphosphoryl)imidazolium ion and the fraction of phenol present as phenolate ion, gives the second-order rate constant k_{-1}. The pH was measured on each reaction solution at zero time on a control solution that was not used to measure absorbance changes; this is necessary because the pH changes with time due to the hydrolysis of the phosphorylimidazole and cannot be completely controlled even by the relatively high buffer concentrations employed here.

The pK_a of N-(diethoxyphosphoryl)imidazolium ion was measured with a Radiometer pH titration set comprising a Radiometer digital pH meter PHM 26, REC 61 Servograph, REA Titratigraph, TTT 60 Titrator, and ABU Autoburette. The data that were obtained in less than 1 min for each titration were fitted to eq 2. [A] is the concentration of free acid and [B] is that for free base at the pH in question.

$$pK - pH = \log ([A]/[B]) \qquad (2)$$

Results

Reaction of aryl diethyl phosphates in imidazole and hydroxide ion buffers exhibited excellent pseudo-first-order kinetics up to about 90% of the total reaction. The pseudo-first-order rate constants are linear in total imidazole concentration ($[Im_{tot}]$); second-order rate constants were determined by division of the slope of the plot of k_{obsd} against total imidazole concentration by FB, the fraction of total imidazole present as the free base. It has previously been shown that the reaction depends on the base form of imidazole.[7] The derived parameters are recorded in Table I. First-order rate constants for hydrolysis are linear in hydroxide ion concentration, and the slope of the plot gives the second-order rate constant (k_{OH}) recorded in Table II. The value of k_{OH} for the hydrolysis of the 4-nitrophenyl ester agrees with that measured by Ketelaar, Gersmann, and Hartog[12] under slightly different conditions.

Reaction of N-(diethoxyphosphoryl)imidazole in phenolate ion buffers gives initial rates of phenol consumption that are linear in total phenol concentration (Figure 1) and in phosphorylimidazole concentration. The 2,4-dinitrophenol nucleophile was found not to have any effect on the solution of the phosphorylimidazole; this is indicated later to be due to an unfavorable equilibrium constant for ester formation. Initial rate measurements also obviate problems due to hydrolysis of N-(diethoxyphosphoryl)imidazole and its reaction with amine buffer. The parameter k_{-1} determined as described in the methods section is recorded with the conditions in Table III together with the value of pK_a for the phosphorylimidazole determined by titration. No interference due to the hydrolysis of the phosphorylimidazole was observed in the pH titration presumably due to the low hydrolysis rate at the pHs involved and the speed of the measurements.

The rate parameters obey linear Brønsted dependencies (eq 3–5) and these are illustrated in Figures 2–4. The

$$\log k_1 = (-1.02 \pm 0.09)pK_{ArOH} + 1.83 \pm 0.29 \quad (n = 6, r = 0.989) \qquad (3)$$

$$\log k_{-1} = (0.85 \pm 0.09)pK_{ArOH} - 0.48 \pm 0.77 \quad (n = 10, r = 0.957) \qquad (4)$$

$$\log k_{OH} = (-0.44 \pm 0.06)pK_{ArOH} + 1.24 \pm 0.36 \quad (n = 5, r = 0.974) \qquad (5)$$

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Table III. Reaction of *N*-(Diethoxyphosphoryl)imidazolium Ion with Substituted Phenolate Anions at 25 °C and 0.5 M Ionic Strength[a]

substituent	[substrate]/M	pK_{ArOH}	pH^b	N^c	$10^5[ArOH]/M^d$	10^8(init rate)/(M $s^{-1})^e$	$k_{-1}/(M^{-1}\ s^{-1})^f$	$K \times 10^{6\,h}$
4-NO_2	0.0413	7.14	7.80	4	3–11	0.5–3	0.37	5.9
4-CN	0.0457	7.9	8.50	6	2–12	5–20	2.0	0.30^g
2-Cl	0.0481	8.48	7.91	5	2–12	5–30	1.7	
4-MeO	0.0457	10.20	9.93	5	1–5	3–30	280	
2-NO_2	0.0520	7.23	7.85	5	1–5	2–12	0.45	6.4^g
4-CHO	0.0456	7.66	7.90	5	2–10	1–4	0.98	1.0^g
4-CH_3CO	0.0487	8.05	7.95	5	2–11	0.5–3	1.1	3.8^g
4-C_6H_5	0.0487	9.51	8.89	5	5–30	3–10	31	
4-Cl	0.0487	9.38	8.91	5	40–210	15–52	20	
3-Cl	0.0487	9.02	8.50	5	40–200	10–44	5.8	

[a] Made up with KCl. [b] Average pH. [c] Number of data points not including duplicates. [d] Range of total phenol concentrations employed. [e] Initial rate values over the range of phenol concentrations. [f] Deviations no greater than ±5%. [g] Using k_1 calculated from eq 3. [h] $K = k_1/k_{-1}$.

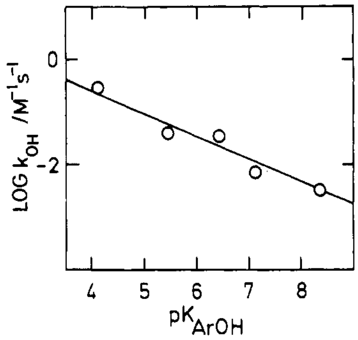


Figure 4. Dependence on pK_{ArOH} of the reaction of hydroxide ions with substituted phenyl diethyl phosphate esters (k_{OH}). Conditions as in Table II; line is calculated from eq 5.

value of β_{lg} for hydroxide ion attack (−0.44, eq 5) is similar to that obtained by Rowell and Gorenstein (−0.4)[13] and by Khan and Kirby (−0.36 to −0.41)[14] for aryl dialkyl phosphate hydrolysis in alkali. Lazarus and Benkovic[15] found a β_{lg} (using a two-point Brønsted plot) for attack of imidazole on aryl phosphates that was higher (−0.75) than the one determined here (−1.02, eq 3).

The explicitly determined equilibrium constants (K) are determined from experimental values of k_{-1}; k_1 was estimated by *interpolation* from eq 3 except in the case of the 4-nitrophenyl ester, where an experimental value is employed. Values of k_1 requiring *extrapolation* from eq 3 are not used. The equilibrium constants obey a Brønsted equation (eq 6); since the values of pK_{ArOH} are only over

$$\log K = (-1.55 \pm 0.2)pK_{ArOH} + 5.89 \pm 1.5 \qquad (n = 5,\ r = 0.976) \quad (6)$$

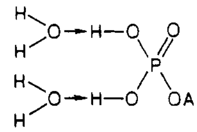
a small range, not much reliance can be placed on the value of β_{eq} from eq 6 even though a reasonably good correlation coefficient is indicated.

Discussion

In order to utilize β_{lg} and β_{nuc} to determine β_{eq}, it is required that these parameters be measured for reactions that are the microscopic reverse of each other. This criterion is fulfilled in the present case. A further requirement is that the parameters should be for ranges of substituent where the same rate-limiting step is operating. There is considerable overlap of phenolate ion identity in both k_1 and k_{-1} (Figures 2 and 3). The equilibrium constant, K, may be determined directly for the 4-nitrophenyl ester; *interpolation* of k_1 is possible from eq 3 to enable K to be estimated reliably from the experimental k_{-1} for the 4-acetyl-, 4-formyl-, 2-nitro-, and 4-cyanophenyl esters. The Brønsted dependence of this set of equilibrium constants has an exponent −1.55 ± 0.2. This value is subject to considerable error because it is obtained over a small range of pK_{ArOH} values; nevertheless it is within deviation limits of the preferred value of β_{eq} (−1.87 ± 0.18) obtained from β_{lg} and β_{nuc} over much wider pK_{ArOH} ranges.

In order to be sure that the same rate-limiting step is being measured in k_1 and k_{-1}, it is necessary to determine whether the Brønsted line for k_{-1} (Figure 3) can be extrapolated linearly from about $pK_{ArOH} = 7$ to pK_{ArOH} 4 to overlap with the data for the lower pK_{ArOH} substituents in Figure 2. If a pentacoordinate intermediate exists, it could have a break point at $pK_{ArOH} = pK_{imidazole}$ so that β_{nuc} would refer to the addition step whereas β_{lg} would refer to the breakdown steps under the two conditions. This is unlikely because the imidazolium ion is generally a better leaving group than is a phenolate or alcoholate of the same pK_a.[16] Thus the pK_a of the phenol attacking group would have to be lower than 7 before a change in rate-limiting step occurs, and we judge that the data in Figure 3 refers to a rate-limiting step that is maintained down to $pK_{ArOH} = 4$.

Replacing Et for H has little effect on the charge change on the oxygen. Any hydrogen-bonding differences between the phosphoryl and diethoxyphosphoryl species are not felt significantly at the oxygen (I and II). The value of β_{eq} for



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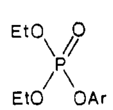

II

the diethyl species is slightly larger than that for the neutral phosphoryl group but this is considered insignificant considering the deviations on both values.

The effective charge induced by neutral phosphoryl groups on oxygen in esters (0.83–0.87) is more positive than that induced by the diphenylphosphinoyl species (+0.2).[17] Presumably the extra P–O dipoles are responsible for the increased charge in the phosphoryl case.

The essential confirmation of the result for β_{eq} from our previous work[5] gives us confidence to use this value to calibrate β_{lg} for reactions measured in other laboratories and in our own. The value of β_{lg} for attack of imidazole

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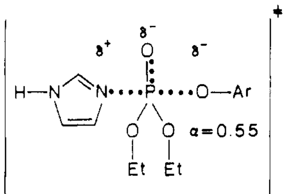
[14] Khan, S. A.; Kirby, A. J. *J. Chem. Soc. B* **1970**, 1172.

[15] Lazarus, R. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 4300.

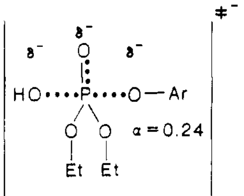
[16] (a) Al-Rawi, H.; Williams, A. *J. Am. Chem. Soc.* **1977**, *99*, 2671. (b) Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 499.

[17] Bourne, N.; Chrystiuk, E.; Davis, A. M.; Williams, A. *J. Am. Chem. Soc.* **1988**, *110*, 1890.

on aryl diethyl phosphate esters (−1.02) compared with β_{eq} for the overall fission of the ArO–P bond indicates that there is considerable bond fission in the transition state. The value of the Leffler index (β_{lg}/β_{eq}) is 0.55 (III). The large change in charge is consistent with *either* a concerted process *or* a stepwise process where the second step (release of aryl oxide ion) is rate limiting. Although a concerted mechanism is possible, a putative zwitterionic intermediate in this reaction could be stable enough to exist as a kinetically significant species. Structure III illustrates the transition state for the rate-limiting step, and this holds for either concerted or stepwise mechanisms; even though the transfer may be a stepwise process, it is evident that both bond formation and bond fission are still only partially completed. Intermediates analogous to the ones for the stepwise mechanism have been shown to exist in carbonyl group transfer, and the explanation of this, although the ligands were good leaving groups, is proposed to be electrostatic stabilization of the zwitterions.[18]



III

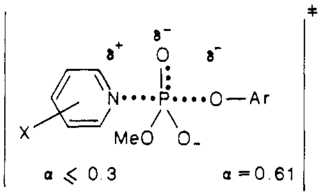


IV

The low β_{lg} value for reaction of hydroxide ion with aryl phosphate esters compared with that for imidazole attack is in accord with the hydroxide ion being the more powerful nucleophile; as expected the β_{lg} measured here and elsewhere[13,14] indicates that the ArO–P bond is little cleaved in the transition state (the Leffler value is 0.24 (IV)). This result is consistent with either a stepwise or a concerted mechanism but in this case, contrary to that of the imidazole reaction, there is no electrostatic stabilizing factor[18] for the putative intermediate. Reactions of phenolate ions with 4-nitrophenyl diphenylphosphinate[17] and with 4-nitrophenyl diphenyl phosphate[19] suffer no break in the respective Brønsted plots over the pK_{ArOH} where a change in rate-limiting step is predicted for a stepwise process; we therefore judge by analogy that the mechanism (IV) will be concerted.

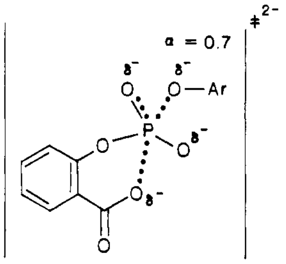
The substituent effect, β_{eq}, for transfer of the singly charged phosphoryl group between nucleophiles and aryl oxide ion acceptors is 1.74.[5] Since replacing the hydroxyl functions of the neutral phosphoryl groups by ethoxy groups has little effect on β_{eq}, it is reasonable that the same effect goes for hydroxyl group replacement in the [(H-O)(O⁻)PO] function; in that case the β_{eq} for (RO)(O⁻)PO will be −1.74.

Kirby and Younas[20] showed that pyridine attack on aryl methyl phosphate monoanion has a β_{lg} of −1.06; this gives a Leffler α value of 0.61 on the basis of our revised figure for β_{eq}. There is therefore considerable bond fission in the transition state. It is not possible to decide on charge balance in this reaction because we do not know β_{eq} for transfer of the $MeOPO_2^-$ group to pyridine acceptors. We know β_{eq} must be greater than that (1.07) for transfer of PO_3^{2-} to pyridine acceptors because of the reduced negative charge on the $MeOPO_2^-$ group. Thus the Leffler value will be less than the observed β_{nuc} (0.3), indicating that there must be charge imbalance in the transition state. It is not possible to compare "raw" β values to measure charge balance but when these are calibrated by β_{eq}, the resulting Leffler value (α) may be compared for charge balance.[1] The charge balance for the attack of pyridines on aryl methyl phosphate monoanions is shown in V. The positive charge required to balance up the charge distribution is presumably taken from the $MeOPO_2$ group of atoms. The reaction has an open or "exploded" transition state but the $MeOPO_2$ group has less metaphosphate ion "character" than has the PO_3 group of atoms in phosphoryl dianion transfer between pyridines and other nucleophiles.[21,22]



V

Intramolecular carboxylate ion attack on aryl phosphate monoanions has been studied by Benkovic[23] and Kirby.[24] These authors observed a β_{lg} of −1.17 and −1.26, respectively, for spontaneous hydrolysis but Benkovic found[23] that Zn^{2+} catalyst increased β_{lg} to −0.7. Application of the improved β_{eq} leads to Leffler values of 0.7 and 0.4, respectively, in agreement with the original conclusions[23] that the metal ion causes a lowering of negative charge at the reaction center. We cannot identify the mode of interaction from knowledge of the charge distribution except that it must be through space, direct, or through bond with the aryl oxygen atom; structure VI illustrates the transition state for the spontaneous hydrolysis. Indirect transmission of charge to the leaving oxygen through the phosphoryl oxygens from the zinc ion is unlikely to yield a change in β_{lg} of greater than 0.1; an analogous interaction involving complete neutralization of a phosphate monoanion is in protonation of aryl phosphate monoanion, which has a β_{eq} of <0.1. We therefore believe that the results indicate a direct interaction of the zinc ion with the developing charge on the leaving oxygen.



VI

For the first time we are able to present an equilibrium constant for transfer of the phosphoryl group from its cationic imidazolide to an aryl oxide ion. Formation of the 4-nitrophenyl ester has an equilibrium constant 1.7 × 10⁵, which is very favorable as is the equilibrium constant for

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[23] Steffens, J. J.; Siewers, I. J.; Benkovic, S. J. *Biochemistry* **1975**, *14*, 2431.

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formation of the ester from the *neutral* reactants (1.2×10^4). The corresponding equilibrium constant for formation of 4-nitrophenyl acetate from acetylimidazole and 4-nitrophenol is 1.1.[6] Imidazole is thus a very efficient reagent for phosphorylation reactions to phenols and presumably to alcohols. The scope of the reagent is restricted by the pK_a of the phenol. The value of β_{eq} for the reaction of cation with anion is 1.87 so that it may be calculated that the equilibrium constant for formation will be unity for a phenol with $pK_{ArOH} = 4.34$. The reagent is therefore not effective for strongly acidic phenols. The fact that we found no reaction between 2,4-dinitrophenol and the *N*-(diethoxyphosphoryl)imidazole is presumably due to the equilibrium constant being too low for sufficient reaction to occur under the conditions prevailing.

Acknowledgment. We are grateful to the Government of Saudi Arabia (S.A.B.) and to S.E.R.C. (U.K.) (Grant GR/E/06558) for financial support.

Supplementary Material Available: Analytical and physical data for the aryl diethyl phosphate esters (1 page). Ordering information is given on any current masthead page.

Isolation and Reaction of New Aromatic Dications. 4-Thioniapyridinium Dications: 2-Aryl-(or 2-Alkyl-)4-methyl-3-oxo-2*H*-1,4-thiazin-2-ylium Tetrafluoroborates

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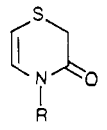
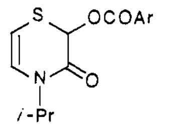
Received September 23, 1987

2-Hydroxy-4-methyl-2-aryl(or -2-*tert*-butyl)-2*H*-1,4-thiazin-3-ones (**5**) generate carbocations **6** in trifluoroacetic acid solution at room temperature. These ions are sufficiently stable to be observed spectroscopically in this solution. Reaction of **6** with some nucleophiles are described. Stable crystalline tetrafluoroborates of **6** were isolated. From ^1H NMR, ^{13}C NMR, and UV–vis spectral data it was concluded that these cations are aromatic in nature and should be depicted as **9** and called 4-thioniapyridinium dications.

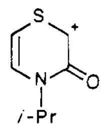
In the course of our investigation on the chemistry of 4-alkyl-2*H*-1,4-thiazin-3-ones **1**[1] and their derivatives,[2] in search for some biological activities of these compounds, it was found that reactions of esters **2**[3] with various nucleophiles occurred with exclusive alkyl–oxygen bond fission.[4] It was also found that the ester **2** (Ar = $m\text{-ClC}_6H_4$) is readily solvolyzed in various kinds of solvents and give m values as high as 1.53[5] for this compound in Grunwald–Winstein equation,[6] $\log k - \log k_0 = mY$. Since by definition $m = 1.00$ for *tert*-butyl chloride, the value 1.53 means solvolysis of the ester **2** (Ar = $m\text{-ClC}_6H_4$) is much more sensitive to the change in polarity of the solvents than is *tert*-butyl chloride.



1



2, Ar = Ph, $m\text{-ClC}_6H_4$



3

These facts strongly imply intermediacy of a very stable carbocationic species **3** during these nucleophilic displacements of the ester **2**. The generation and therefore its unusual stability of the ion **3** seemed quite surprising, since **3** is a secondary carbenium ion and its cationic center is directly linked to a carbonyl carbon. With this situation in mind the present work was undertaken to clarify structure and nature of the ion **3**, by observing it directly in strongly acidic media and if possible by isolating it as a stable salt.

Table I. Reaction of Grignard Reagents (R′MgX) with Diketone 4[4]

product	R	R′	yield, %	mp, °C	IR, cm^{-1}
5a	H	Ph	60	152	1628
5b	H	$p\text{-FC}_6H_4$	65	118	1634
5c	H	$p\text{-ClC}_6H_4$	58	137	1637
5d	H	$p\text{-MeC}_6H_4$	65	153	1628
5e	H	$p\text{-MeOC}_6H_4$	50	138	1645
5f	Me	Ph	100	145	1640
5g	Me	$p\text{-MeOC}_6H_4$	55	141	1620
5h	H	Me	56	oil	1640
5i	H	Et	74	oil	1628
5j	H	*t*-Bu	34	81	1617

Results and Discussion

Preparation of 2-Substituted 2-Hydroxy-4-methyl-2*H*-1,4-thiazin-3-ones (5). Attempted direct observation of the carbocation **3** failed; it proved insufficiently stable to exist in trifluoroacetic acid (TFA) at room temperature. Therefore 2-aryl-(and some 2-alkyl-)substituted cations **6** were chosen for present study.

Reaction of diketones **4**[4] with various alkyl- and arylmagnesium halides proceeded with perfect regioselectivity in ether or tetrahydrofuran as solvent at room temperature to give corresponding 3-keto 2-alcohols **5** as sole products. The results are shown in Table I.

Generation of Cations 6a–g in TFA from Corresponding Alcohols 5a–g. 2-Aryl-substituted keto alcohols

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(2) Masuda, R.; Hojo, M.; Ichi, T.; Adachi, F.; Yoshinaga, K. *Phosphorus Sulfur* **1983**, *16*, 143.

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