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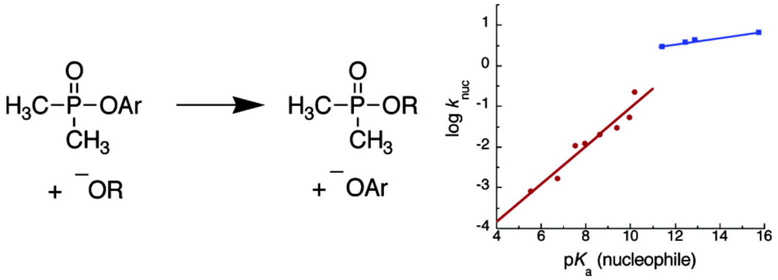

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A Concerted Mechanism for the Transfer of the Thiophosphinoyl Group from Aryl Dimethylphosphinothioate Esters to Oxyanionic Nucleophiles in Aqueous Solution

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Abstract: Earlier work on the hydrolysis of aryl phosphinothioate esters has led to contradictory mechanistic conclusions. To resolve this mechanistic ambiguity, we have measured linear free energy relationships (β_{nuc} and β_{lg}) and kinetic isotope effects for the reactions of oxyanions with aryl dimethylphosphinothioates. For the attack of nucleophiles on 4-nitrophenyl dimethylphosphinothioate, $\beta_{nuc} = 0.47 \pm 0.05$ for phenoxide nucleophiles (pK_a < 11) and $\beta_{nuc} = 0.08 \pm 0.01$ for hydroxide and alkoxide nucleophiles (p$K_a \geq 11$). Linearity of the plot in the range that straddles the pK_a of the leaving group (4-nitrophenoxide, pK_a 7.14) is indicative of a concerted mechanism. The much lower value of β_{nuc} for the more basic nucleophiles reveals the importance of a desolvation step prior to rate-limiting nucleophilic attack. The reactions of a series of substituted aryl dimethylphosphinothioate esters give the same value of β_{lg} with the nucleophiles HO$^-$ ($\beta = -0.54 \pm 0.03$) and PhO$^-$ ($\beta = -0.52 \pm 0.09$). A significantly better Hammett correlation is obtained with σ^- than with σ or $\sigma°$, as expected for a transition state involving rate-limiting cleavage of the P−OAr bond. The ^{18}O KIE at the position of bond fission ($^{18}k = 1.0124 \pm 0.0008$) indicates the P−O bond is ~40% broken, and the ^{15}N KIE in the leaving group ($^{15}k = 1.0009 \pm 0.0003$) reveals the nucleofuge carries about a third of a negative charge in the transition state. Thus, both the LFER and KIE data are consistent with a concerted reaction and disfavor a stepwise mechanism.

Introduction

Phosphoryl transfer reactions are widespread in biological systems where they are involved in energy transport, transmission of genetic information, and a host of other essential regulatory processes at the cellular level. As a consequence of their ubiquity, an understanding of the mechanism of biological phosphoryl transfer has been an important preoccupation in chemical biology. Although phosphinate esters do not occur naturally, they are structurally related to phosphate and phosphonate esters that function as pesticides, neurotoxins, and other biologically active substances.[1] A number of appropriately substituted phosphinic acids have found use as metalloprotease inhibitors.[2] Investigations of the reactions of phosphinates with a variety of nucleophiles have been undertaken to characterize the influence of structure on the reactivity of organophosphorus esters, as part of the effort to understand the detailed mechanism of uncatalyzed phosphoryl transfer.[3]

Earlier reports[4,5] concluded that the rates of hydrolysis of aryl dimethylphosphinothioate esters and related substrates correlate well with σ and $\sigma°$ substituent constants rather than σ^-. (The $\sigma°$ substituent constant is based on phenyl acetic acid and its substituted derivatives, originally devised by Taft, to correlate purely inductive effects. The σ and σ^- substituent constants are the more familiar Hammett constants based on the ionization of benzoic acids.) This result is consistent with an associative, addition−elimination ($A_N + D_N$) mechanism in which the formation of a pentacoordinate (phosphorane) intermediate[6] is rate determining (see Pathway A, Scheme 1). On the other hand, data from these studies[4,5] also provide Brønsted-type correlations with β_{lg} values in the range of −0.30 to −0.50 in water and 50% water−50% ethanol solvent. The magnitude of the β_{lg} values could be interpreted to indicate little-to-moderate separation of the leaving group in the TS of a concerted (A_ND_N) reaction[7] (Pathway B, Scheme 1). Thus, a mechanistic ambiguity exists for these reactions. The discrepancy noted above may be due in part to differences in the mixed solvent systems used in some of these studies and, in other cases, to limited numbers of substituents used in the construction of the LFER.

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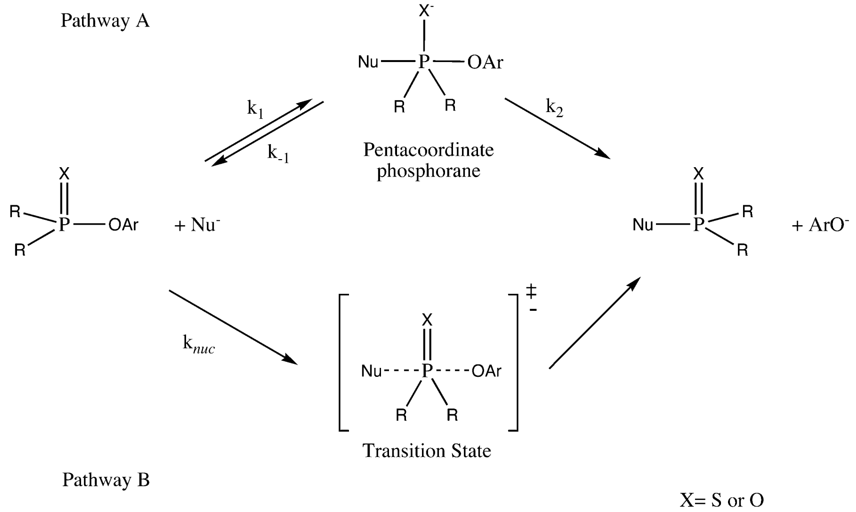
Scheme 1. Alternative Mechanisms, an Addition−Elimination ($A_N + D_N$) Pathway with the Formation of a Pentacoordinate (Phosphorane) Intermediate (Pathway A) and a Concerted (A_ND_N) Reaction (Pathway B)



Literature data show that the rates of hydrolysis of the oxygen analogues of the title compounds, the aryl dimethylphosphinate esters **1**, correlate satisfactorily with σ^- substituent constants.[8] This result is consistent with either a concerted mechanism or an addition−elimination mechanism in which the departure of the leaving group is rate limiting. A kinetic imperative for the latter mechanism requires that the condition $k_{-1}/k_2 > 1$ holds in Pathway A, Scheme 1. Since hydroxide ion is a poorer leaving group than aryloxide ions, a concerted mechanism was advocated for this system in preference to rate-limiting separation of the leaving group in an addition−elimination mechanism.[8] Furthermore, the transition states for the hydrolysis of alkyl[9] and aryl[10] phosphate and phosphorothioate triesters are very similar,[11] even though the thio triester hydrolyzes at a slower rate than its oxygen counterpart (the so-called "thio effect"). By analogy, it seemed unlikely to us that the aryl dimethylphosphinothioate esters of the type depicted in **2** would react by a stepwise, associative mechanism when a concerted mechanism has been demonstrated for **1**.

To obtain definitive information regarding the mechanism and structure of the TS for these reactions, and to resolve the discrepancy noted above, we have undertaken a study of the dependence of rate on nucleophile pK_a for the reaction of 4-nitrophenyl dimethylphosphinothioate (**2a**) with a series of oxyanionic nucleophiles, which include phenoxides, alkoxides, and hydroxide ion. The pK_a values of these nucleophiles straddle that of the leaving group, 4-nitrophenoxide (pK_a = 7.14). Such LFER experiments have been found to have diagnostic utility in determining the relative timing of bond formation and bond fission in a number of nucleophilic substitution reactions.[12] A change in the rate-limiting step will be expected to occur in the mechanism of Pathway A, Scheme 1 when $\Delta pK_a = pK_{nuc} - pK_{lg} = 0$, especially when the nucleophiles involved are structurally related. Such a change will manifest a nonlinear Brønsted plot, with a break at $\Delta pK_a = 0$, since different amounts of charge will be located on the O atom of the nucleophile in the transition states for bond formation (k_1) and bond cleavage (k_2).[7] We have also measured the dependence of rate on leaving group pK_a for reactions of **2** with HO^- and PhO^-, to enable a determination of the extent of cleavage of the P−OAr bond in the TS of the reaction.

LFER experiments have been supplemented with heavy-atom (^{18}O and ^{15}N) kinetic isotope effect (KIE) measurements as probes of TS structure. The primary ^{18}O KIE at the position of bond fission, $^{18}k_{bridge}$, gives a measure of the extent of P−O bond cleavage in the TS. The ^{15}N KIE in the leaving group NO_2, ^{15}k, is sensitive to the amount of charge delocalized into the aromatic ring of the nucleofuge in the TS. The origin of ^{15}k lies in contributions from a quinonoid resonance form in the nitrophenolate anion, and differences in stiffness of N−O bonds and N−C bonds. Because N−O bonds are stiffer, the nitrogen atom is more tightly bonded in neutral 4-nitrophenol than in the phenolate anion. The ^{15}K equilibrium isotope effect for deprotonation of 4-nitrophenol is thus normal, 1.0023 ± 0.0002.[13]

The corresponding isotope effects have been measured for other group transfer reactions with the 4-nitrophenyl leaving group. These include acyl transfer reactions of 4-nitrophenyl acetate;[14] the hydrolysis of 4-nitrophenyl phosphate monoester, and diesters and triesters with the same nucleofuge;[15] and the hydrolysis of 4-nitrophenyl sulfate monoester and diesters.[16] The maximum value of $^{18}k_{bridge}$, with the 4-nitrophenyl leaving group, is in the range of 1.02−1.03 in a late transition state with significant bond fission, such as the hydrolysis of 4-nitrophenyl sulfate and 4-nitrophenyl phosphate.[15] In the late TS of the hydrolysis of 4-nitrophenyl phosphate dianion, where close proximity to the anionic phosphoryl group in the TS enhances delocalization of charge, $^{15}k = 1.0028 \pm 0.0002$.[17] In hydrolysis reactions of phosphodiesters and triesters, which are concerted with tighter transition states and less bond fission to the

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nucleofuge, ${}^{18}k_{\mathrm{bridge}}$ ranges from 1.004 to 1.006, and ${}^{15}k$ ranges from 1.0007 to 1.0016.[15]

If the reaction is concerted, large KIE values would be expected at both positions. If, on the other hand, the reaction is stepwise, then formation of the intermediate is expected to be rate limiting in the region where nucleophile $pK_a \gg$ leaving group pK_a (7.14), and the KIEs will then reflect formation of the intermediate. In this case, no ^{15}N KIE should be observed, and the ^{18}O KIE would likely be inverse, reflecting compression of bending modes.

LFER and KIE methods are both powerful tools for the diagnosis of reaction mechanism, and relatively few reactions have been studied combining both methodologies. The results obtained in the LFER and KIE studies, herein reported and discussed below, provide good evidence for a concerted mechanism in the reaction of these phosphinothioate esters and enable a description of the TS structure.

Experimental Section

Materials. Distilled, deionized water was degassed under vacuum just prior to use. 1,4-Dioxane was passed through an alumina column to remove peroxides. Phenols and alcohols were commercial products and were purified by either recrystallization from a suitable solvent or by distillation. Analytical grade NaOH was standardized, using phenolphthalein as indicator. Buffer materials used were of analytical reagent grade. The syntheses of the compounds **2a**−**g**, including the isotopic isomers used for kinetic isotope effects experiments, are reported in Supporting Information.

Kinetic Measurements. Kinetic measurements were made on a Cary 50 Bio spectrophotometer equipped with a Lauda E100 thermostat. Reactions in which HO^- was the nucleophile were carried out in CAPS buffer solutions in the pH range of 10.57−11.01. For alcoholates and phenolates, except 2,4,5-Cl_3PhO^- and 2,3,5,6-F_4PhO^-, self-buffered solutions of the nucleophiles (Nuc^-) were obtained by partially neutralizing the conjugate acid of the relevant nucleophile (NucH) with NaOH, such that a NucH:Nuc^- ratio of 2:1 resulted. In the case of 2,4,5-Cl_3PhO^- and 2,3,5,6-F_4PhO^-, the phenolate nucleophiles were obtained by dissolving the parent phenols in MOPS and Bis-Tris buffer solutions, respectively. The nucleophile solution in each case was prepared from two stock solutions, one containing the phenol and the buffer component and the other being an identical solution of the buffer adjusted to the same pH as the former but without the phenol. These two stock solutions were mixed in the appropriate proportions to obtain different concentrations of the phenolates, while the parameters of buffer concentration, ionic strength, and pH remained constant. All nucleophile solutions for kinetic runs were maintained at ionic strength, $I = 1$ M (KCl).

Reaction was initiated in each case by injecting 25−50 μL of a stock solution of the substrate in 1,4-dioxane into a 1 cm cuvette containing 3 mL of the desired run concentration of the nucleophile. The run solution of the nucleophile was equilibrated thermally at 25.0 ± 0.1 °C in the cuvette holder of the spectrophotometer for 30 min before the kinetic run was initiated. It was ensured that the substrate concentration in the kinetic runs was kept in the region of $3.0-4.0 \times 10^{-5}$ M and that the nucleophile concentration was in sufficient excess of the substrate to maintain pseudo-first-order conditions. Nucleophile concentrations were kept in the range of 0.001−0.005 M for the alcoholates and 0.005−0.025 M for the phenolates.

The reactions in which 4-nitrophenyl dimethylphosphinothioate was the substrate were monitored at 400 nm, the wavelength of maximum absorption of 4-nitrophenolate. With weakly basic phenolates as nucleophiles, the pH of the reaction medium was such that 4-nitrophenol was the product; under this condition, the reaction was monitored at 350 nm. In the reactions of the other substrates yielding the variously substituted phenolates as products, initial repetitive scans of the reaction mixture (substrate + nucleophile) were carried out prior to the kinetic determination to ascertain the appropriate wavelength for monitoring the appearance of the product. All reactions involving the alcoholates and hydroxide ion as nucleophiles were monitored for 10 half-lives. For these reactions, there was good agreement between the experimental and theoretical absorbances of the product at infinite reaction time. Pseudo-first-order rate constants, k_{obs}, were obtained by linear regression analysis, as slopes of plots of $\ln(A_\infty - A_t)$ vs time. Second-order rate constants, k_{nuc}, were reckoned from plots of k_{obs} vs [Nuc^-], which gave very good linearity in all cases. The rate constants of the reactions with the phenolate nucleophiles were determined by the initial rate method. The theoretical absorbance of the product at infinity was used to calculate the pseudo-first-order rate constant in such cases. Division of the initial rate of absorbance change by the theoretical absorbance at infinity gave the k_{obs}. In a few cases, e.g. reactions involving phenoxide and 4-methylphenoxide ions as nucleophiles, an internal check on the technique was made by allowing the reactions to go to completion. The rate constants obtained by both methods were in very good agreement.

Kinetic Isotope Effect Measurements. The solvent isotope effects on the reaction of 4-nitrophenyl dimethylphosphinothioate with one phenol and one alcohol were obtained. For the reaction with phenol, ester concentration was 3.4×10^{-5} M, and phenol concentration was 0.004 M. For the nucleophile 4,4,4,3,3,2,2-heptafluorobutanol, concentrations of 0.004 and 0.009 M were used, with an ester concentration of 1.8×10^{-5} M. The isotope effects were obtained from separate kinetic runs monitored at 400 nm in H_2O and D_2O, at 25 °C.

The experimental procedures employed for measurement of ${}^{15}k$ and ${}^{18}k_{\mathrm{bridge}}$ were very similar to previously reported methods used to measure KIEs in similar systems where 4-nitrophenol is the leaving group.[15] The product isolation procedures used below have been used previously, and control experiments have shown they do not result in isotopic fractionation. Reactions to measure ${}^{15}k$ were carried out using approximately 100 μmol (25 mg) of natural abundance **2a** in 100 mL of a 1:1 dioxane to buffer solution in capped beakers. (The cosolvent was required to solubilize the necessary quantity of the reactant.) The buffer solution used was 0.1 M CHES at pH 9.6. This pH was chosen to yield a convenient rate of reaction at ambient temperature.

The hydrolysis reactions were allowed to react at 25 °C for approximately one half-life (2 h). The reactions were then stopped by extraction three times with methylene chloride, which resulted in a two-phase mixture with the unconsumed reactant in the organic layer. The aqueous layer, containing the liberated 4-nitrophenolate, was titrated to pH 4 using 1 N HCl and extracted with diethyl ether to isolate the 4-nitrophenol product. The unreacted ester, which had been extracted into the organic layer, was completely hydrolyzed by addition of excess base (20 mL of 0.1 N NaOH), slow evaporation of the methylene chloride, and allowing the reaction to proceed at ambient temperature for >10 additional half-lives. The 4-nitrophenol liberated in the complete hydrolysis reaction mixture was also isolated via ether extractions, as previously described. Upon termination of the reaction, absorbance values were obtained at 410 nm. These values, in combination with the absorbance values obtained from assays of the 4-nitrophenol liberated at partial hydrolysis, were used to determine the fraction of reaction. All reactions fell within 46−48% of completion. (The rate in the 1:1 buffer:dioxane system is about 2.5-fold slower than that expected in aqueous buffer at the same pH as the buffer component of the mixed solvent. This most likely arises from pK_a shifts resulting from addition of the aprotic cosolvent, which would be expected to reduce the concentration of hydroxide ion.)

All reactions were performed in triplicate, and the 4-nitrophenol samples were purified by sublimation and analyzed by isotope ratio mass spectrometry using an ANCA-NT combustion system in tandem with a Europa 20-20 isotope ratio mass spectrometer.

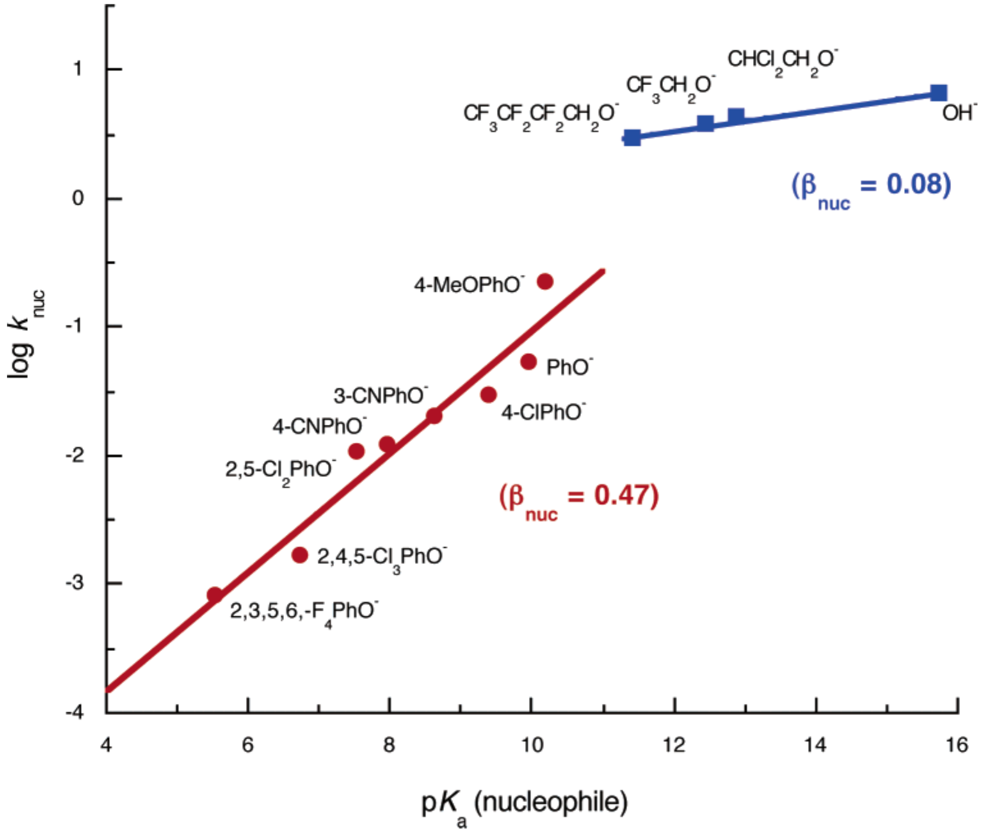

Figure 1. Plot of log k_{nuc} vs pK_a (nucleophile) for the reaction of **2a** with oxygen nucleophiles in water at 25 °C. The line for nucleophiles with pK_a < 11 is defined by eq 1, while the line for more strongly basic nucleophiles (p$K_a \geq 11$) is defined by eq 2.

The $^{18}k_{bridge}$ was measured similarly, using the mixture of [^{14}N] 4-nitrophenyl and [^{15}N]-4-nitrophen[^{18}O]yl compounds. This method utilizes the remote label method,[18] in which the isotope ratio of the nitrogen atom serves as a reporter for oxygen isotope ratios. The observed isotope effect was corrected for ^{15}k and for incomplete isotopic incorporation (see Supporting Information).

Results

The solvent isotope effect for the reaction of 4-nitrophenyl dimethylphosphinothioate with phenoxide is 1.00 ± 0.02. The solvent isotope effect for the reaction of 4-nitrophenyl dimethylphosphinothioate with 4,4,4,3,3,2,2-heptafluorobutanol is 1.01 ± 0.05.

Second-order rate constants for the reaction of **2a** with a variety of oxyanions at 25 °C, obtained as described in the Experimental Section, are given in Table 1, together with the pK_a values of the conjugate acids of the nucleophiles in water. A value of $k_{-OH} = 6.63$ M^{-1} s^{-1} was obtained in this study for the hydrolysis of **2a** in aqueous solution at 25 °C. Istomin and Eliseeva reported a value of 5.12 M^{-1} s^{-1} under the same conditions.[5] A Brønsted-type plot of log k_{nuc} vs pK_a of the conjugate acid of the nucleophile is displayed in Figure 1. The plot is linear for the series of structurally related phenoxides in the pK_a range 5.5−10.2, which straddles the pK_a of the 4-nitrophenol leaving group (pK_a = 7.14). A β_{nuc} value of 0.47 ± 0.05 (R = 0.968) is obtained in this region. A change in slope is observed in the more basic region (p$K_a \geq 11$) where the nucleophiles are hydroxide and alkoxide ions; in this region, the much smaller value of $\beta_{nuc} = 0.08 \pm 0.01$ (R = 0.996) is calculated.

Table 1. Second-Order Rate Constants (k_{Nuc})[a] for the Reaction of Several Oxygen Nucleophiles with 4-Nitrophenyl Dimethylphosphinothioate in Water at 25 °C

entry	nucleophile	pK_a[b]	k_{nuc}/M^{-1}s^{-1}
1	HO^-	15.74	6.63 ± 0.23
2	$CHCl_2CH_2O^-$	12.89	4.28 ± 0.25
3	$CF_3CH_2O^-$	12.43	3.81 ± 0.12
4	$CF_3CF_2CF_2CH_2O^-$	11.4	3.01 ± 0.03
5	4-MeOPhO$^-$	10.20	$2.23 \pm 0.03 \times 10^{-1}$
6	PhO$^-$	9.95	$5.40 \pm 0.17 \times 10^{-2}$
7	4-ClPhO$^-$	9.38	$2.93 \pm 0.03 \times 10^{-2}$
8	3-CNPhO$^-$	8.61	$2.04 \pm 0.29 \times 10^{-2}$
9	4-CNPhO$^-$	7.95	$1.25 \pm 0.24 \times 10^{-2}$
10	2,5-Cl$_2$PhO$^-$	7.51[c]	$1.08 \pm 0.01 \times 10^{-2}$
11	2,4,5-Cl$_3$PhO$^-$	6.72[c]	$1.73 \pm 0.04 \times 10^{-3}$
12	2,3,5,6-F$_4$PhO$^-$	5.53[c]	$8.20 \pm 0.03 \times 10^{-4}$

[a] Measured at ionic strength, I = 1.0 M (KCl). [b] Values of pK_a at 25 °C, taken from Jencks and Regenstein.[19] [c] Values of pK_a at 25 °C, taken from Bourne et al.[7]

Polar substituent effects in the nucleophilic reactions of aryldimethylphosphinothioate esters **2a**−**g** for the attacking nucleophiles PhO$^-$ and HO$^-$ were evaluated at 25 °C. The relevant second-order rate constants are assembled in Table 2. Construction of a Brønsted-type plot of log k_{nuc} vs pK_a of the leaving group results in the linear relationships shown in Figure 2. Values of $\beta_{lg} = -0.54 \pm 0.03$ (R = 0.991) and -0.52 ± 0.09 (R = 0.974) were obtained for PhO$^-$ and HO$^-$ nucleophiles, respectively.

Hammett plots were also constructed using the data in Table 2, in conjunction with literature values of σ substituent constants.[20,21] The plots obtained using σ^- constants give a significantly better correlation in each case than those involving σ and $\sigma°$ substituent constants (see Table 3). The plots using

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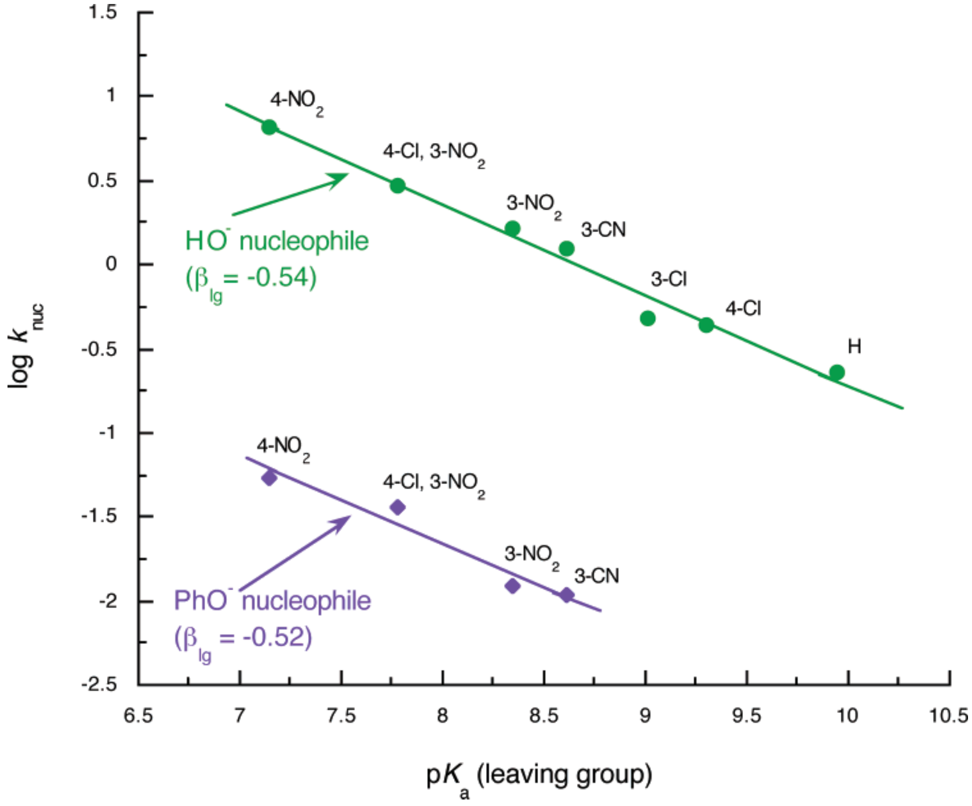

Figure 2. Plot of log k_{nuc} vs pK_a (leaving group) for the reactions of HO$^-$ and PhO$^-$ with aryl dimethylphosphinothioate esters **2a**−**g** in water at 25 °C. The lines for HO$^-$ and PhO$^-$ are defined by eqs 4 and 5, respectively.

Table 2. Second-Order Rate Constants (k_{nuc})[a] for the Reactions of HO$^-$ and PhO$^-$ with a Series of Substituted Dimethylphosphinothioates in Water at 25 °C

entry	leaving group	pK_a[b]	k_{nuc}/M^{-1} s^{-1}
	A. Nucleophile = HO$^-$		
1	4-NO$_2$PhO$^-$	7.14	6.63 ± 0.23
2	4-Cl,3-NO$_2$PhO$^-$	7.78	2.94 ± 0.24
3	3-NO$_2$PhO$^-$	8.35	1.66 ± 0.07
4	3-CNPhO$^-$	8.61	1.25 ± 0.03
5	3-ClPhO$^-$	9.01	0.48 ± 0.04
6	4-ClPhO$^-$	9.30	0.44 ± 0.01
7	PhO$^-$	9.95	0.23 ± 0.01
	B. Nucleophile = PhO$^-$		
1	4-NO$_2$PhO$^-$	7.14	$5.40 \pm 0.17 \times 10^{-2}$
2	4-Cl,3-NO$_2$PhO$^-$	7.78	$3.65 \pm 0.0.18 \times 10^{-2}$
3	3-NO$_2$PhO$^-$	8.35	$1.22 \pm 0.02 \times 10^{-2}$
4	3-CNPhO$^-$	8.61	$1.10 \pm 0.02 \times 10^{-2}$

[a] Measured at ionic strength, I = 1.0 M (KCl). [b] Values of pK_a at 25 °C, taken from Jencks & Regenstein.[19]

σ^- for the reactions of the nucleophiles PhO$^-$ and HO$^-$ with aryl dimethylphosphinothioates are shown in Figure 3.

The kinetic isotope effects were measured for the hydroxide attack on compound **2a**, at the oxygen atom of the scissile P−O bond and at the nitrogen atom in the nitro group (Figure 4). These KIEs were found to be: $^{15}k = 1.0009 \pm 0.0003$ and $^{18}k_{bridge} = 1.0124 \pm 0.0008$.

Discussion

The kinetic behavior observed in these reactions is consistent either with nucleophilic attack or with general base catalysis.

Table 3. Hammett ρ Values with Correlation Coefficients (R) for Leaving Group Variation in the Reactions of HO$^-$ and PhO$^-$ with Substituted Aryl Dimethylphosphinothioates in Water at 25 °C (see text)

substituent constant[20, 22]	ρ value (R)	
	HO$^-$	PhO$^-$
σ	1.43 ± 0.26 (0.926) 1.45 ± 0.10 (0.996)[a]	1.62 ± 1.02 (0.745)
$\sigma°$	1.41 ± 0.24 (0.933) 1.37 ± 0.11 (0.993)[a]	1.80 ± 0.95 (0.802)
σ^-	1.17 ± 0.07 (0.991) 0.93 ± 0.02 (0.9997)[a]	1.05 ± 0.27 (0.940)

[a] Calculated from the data of Istomin and Eliseeva.[5]

The absence of a significant solvent isotope effect for the reaction of 4-nitrophenyl dimethylphosphinothioate with either phenoxide or with 4,4,4,3,3,2,2-heptafluorobutanol rules out the possibility that these nucleophiles act as general bases, since such a mechanism should result in a normal solvent isotope effect. Since the other aryl oxide and alcoholate nucleophiles follow the same Brønsted correlations as these two respective nucleophiles, it is concluded that the other reactions also proceed by nucleophilic attack at phosphorus.

LFER Correlations. (a) Brønsted-Type Correlations. Brønsted-type correlations have proved an invaluable mechanistic tool for probing the properties of the TS of numerous reaction types.[12,22−25] Values of β_{nuc} and β_{lg} obtained from such plots have been used to estimate TS structures and to evaluate the

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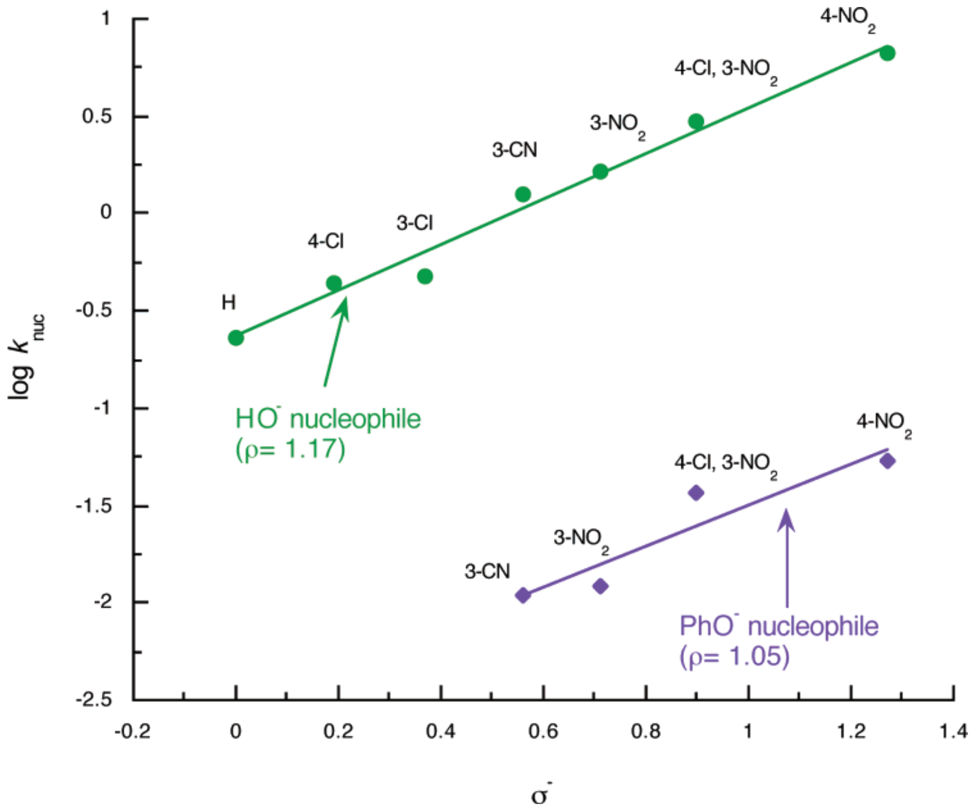


Figure 3. Hammett plots for the reactions of **2a**−**g** with HO⁻ and PhO⁻ in water at 25°C, utilizing σ^- substituent constants (see text).

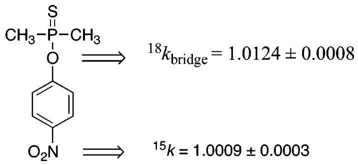


Figure 4. Compound **2a,** with the positions and magnitudes of KIE measurements indicated, and the notation used.

response of TS structures to changing substitution patterns and reaction conditions, especially when the nucleophiles are structurally related and possess the same atom at the nucleophilic site.[23,25−28]

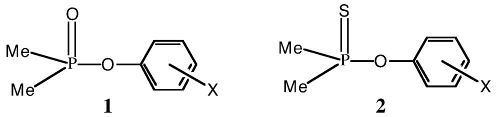
The Brønsted correlation in Figure 1 is linear for the phenoxide nucleophiles; the more basic alkoxide and hydroxide nucleophiles follow a different linear correlation, with a much smaller slope. The solid line defined by phenoxide nucleophiles in Figure 1 is given by eq 1, while eq 2 defines the solid line obtained with hydroxide and alkoxide nucleophiles, giving $\beta_{\text{nuc}} = 0.47 \pm 0.05$ ($R = 0.968$) and 0.08 ± 0.01 ($R = 0.994$), respectively, in the two regions.

$$\log k_{\text{nuc}} = (0.47 \pm 0.05)\text{p}K_{\text{a}} - (5.70 \pm 0.41) \qquad (1)$$

$$\log k_{\text{nuc}} = (0.08 \pm 0.01)\text{p}K_{\text{a}} - (0.37 \pm 0.08) \qquad (2)$$

The linear plot for phenoxide nucleophiles in the pK_a range 5.53−10.2, which straddles the basicity of the leaving group (pK_a of 4-nitrophenol = 7.14), is good evidence that the reaction of these nucleophiles with **2a** occurs by a concerted mechanism. The value of $\beta_{\text{nuc}} = 0.47$ obtained in this study may be compared to $\beta_{\text{nuc}} = 0.41$ measured in 90% water−10% dioxane for the hydrolysis of the oxygen analogue, **1a**, which also reacts via a concerted mechanism.[8]

Scheme 2. Compounds **1**(**a**−**j**) Were the Subject of a Previous Study[8] Concluding that Nucleophilic Attack Occurs by a Concerted Mechanism[a]



1 **2**

1 (a): X = 3,5-(NO$_2$)$_2$
(b): X = 4-NO$_2$
(c): X = 3-NO$_2$
(d): X = 4-CH$_3$CO
(e): X = 4-EtOCO
(f): X = 4-Cl
(g): X = 3-Cl
(h): X = H
(i): X = 4-Me
(j): X = 4-MeO

2 (a): X = 4-NO$_2$
(b): X = 4-Cl, 3-NO$_2$
(c): X = 3-NO$_2$
(d): X = 3-CN
(e): X = 3-Cl
(f): X = 4-Cl
(g): X = H

[a] Reactions of compounds 2(**a**−**g**) have also been studied previously, leading to contradictory mechanistic conclusions, and are the subject of this study.

The break at high nucleophile basicity is too sharp to be ascribed to a gradual change of selectivity with increasing nucleophilic reactivity, as would be expected from a Hammond effect.[29] As is evident from Figure 1, the break does not occur where $\Delta pK_a = pK_{\text{nuc}} - pK_{\text{lg}} = 0$, which might imply a change in rate-limiting step in a stepwise mechanism. These data are consistent with the well-documented effect of solvation on nucleophilic reactivity in hydroxylic solvents.[24,30,31] Brønsted

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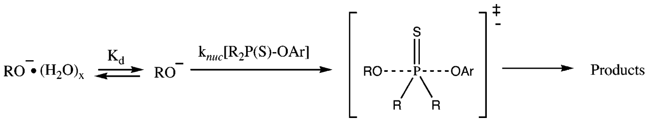
Scheme 3. More Effective Solvation of the Strongly Basic Nucleophiles Necessitates a Kinetically Significant Desolvation Step before Nucleophilic Attack on the Substrate Occurs



plots for reactions of phenoxide and alkoxide nucleophiles are frequently discontinuous, with a significantly smaller slope for the more basic alkoxides. The diminished slope is explained by more effective solvation of HO^- and strongly basic alkoxides, in comparison to the more weakly basic phenolate anions. Desolvation of the strongly basic nucleophiles, according to Scheme 3, is a requirement before nucleophilic attack on the substrate occurs in the concerted reaction;[31] K_d in Scheme 3 is the equilibrium constant for the desolvation step.

The foregoing considerations suggest that HO^- and the alkoxide ions react by the same mechanism as the phenoxides. According to this model, the decreased Brønsted-type slope for the reaction of the strongly basic nucleophiles is a manifestation of negative deviations of log k_{nuc} at high basicity according to eq 3.[31,32]

$$\Delta \log k_{nuc} = (1 - \beta_{nuc}) \log K_d \qquad (3)$$

Such solvational imbalance[30,31] has been observed in phosphoryl transfer reactions[31,33] and other group transfers,[29,34] as well as in the solvolysis of 1-phenylethyl carbocations.[35] Bernasconi[36] has proposed a model in which both partial desolvation of the nucleophile and bond formation occur in the same step, to account for decreased reactivity of strong bases in these processes. In this instance, the imbalance results from the necessity for desolvation of the nucleophile to progress ahead of nucleophilic attack in the TS.

Data for the dependence of rate of the reactions of the nucleophiles HO^- and PhO^- on leaving group pK_a are given in Table 2 and are displayed graphically in Figure 2. Equations 4 and 5, respectively, define the straight lines obtained in Figure 2 for HO^- and PhO^- as nucleophiles, giving $\beta_{lg} = -0.54 \pm 0.03$ ($R = 0.991$) for HO^- and -0.52 ± 0.09 ($R = 0.974$) for PhO^-.

$$\log k_{nuc} = (-0.54 \pm 0.03)\mathrm{p}K_a + (4.67 \pm 0.28) \qquad (4)$$

$$\log k_{nuc} = (-0.52 \pm 0.09)\mathrm{p}K_a + (2.48 \pm 0.68) \qquad (5)$$

It is noted that β_{lg} is similar for both nucleophiles, hence, for purposes of subsequent discussion, the average value of $\beta_{lg} = -0.53$ is adopted. The similar sensitivity of the reaction to substituents in the leaving group for attack by HO^- and PhO^- indicates that nucleophilic attack on phosphorus causes the same magnitude of decrease in the effective charge on the leaving group in the TS, irrespective of the apparent difference in β_{nuc} for phenoxides and alkoxides/HO^-. This is entirely consistent with the conclusion reached above, namely that the amount of bond formation in the TS is the same for the two groups of nucleophiles, phenoxides and alkoxides/HO^-, and that the different values of β_{nuc} mirror the difference in the ground state of the two nucleophile types due to strong solvation of the strongly basic nucleophiles.

To summarize, the Brønsted-type LFER data obtained in this study have yielded values of $\beta_{nuc} = 0.47$ and $\beta_{lg} = -0.53$. These values indicate that there is moderate bond formation and bond cleavage in the TS of a concerted mechanism for the reaction of aryl dimethylphosphinothioates with oxyanion nucleophiles. As will also be shown in the sections that follow using other mechanistic criteria, the data are not consistent with an associative, stepwise mechanism.

(b) Hammett Correlations. Hammett correlations have featured prominently in the discussion of the mechanisms of the reactions of aryl phosphinates.[3,8,37,38] Reactions in which rates are satisfactorily correlated with σ or $\sigma°$ substituent constants are deemed to react by an associative mechanism involving rate-limiting formation of the phosphorane intermediate. On the other hand, correlation of rates with σ^- constants point to either a concerted mechanism or an associative mechanism in which the decomposition of the phosphorane intermediate is rate-limiting. In the latter case, additional criteria are needed to decide for either mechanism.

Hammett plots have been constructed for the reactions of HO^- and PhO^- with differently substituted aryl dimethylphosphinothioates in water, using the data in Table 2 in conjunction with values of σ, $\sigma°$, and σ^- obtained from the literature.[20,21] The results of these plots are summarized in Table 3, while Figure 3 shows the plots obtained for both nucleophiles using σ^- substituent constants. We have also included in Table 3 the result of an analysis of the Hammett plots obtained with the different substituent constants from the limited data of Istomin and Eliseeva for this system in pure water.[5] It is evident from Table 3 that significantly better correlations are obtained in our work with σ^- constants than with σ or $\sigma°$ constants, as would be expected when cleavage of the P−OAr bond is involved in the rate-limiting step. Thus, the results of the Hammett plots reinforce the conclusions drawn above on the basis of Brønsted LFER correlations.

Istomin and Eliseeva[4] concluded that the correlation of rates with $\sigma°$ indicated a stepwise $A_N + D_N$ mechanism. Hammett plots using the rate constant data of Istomin and Eliseeva[4] with σ, $\sigma°$, and σ^- substituent constants are all linear (see Table 3), the difference in correlation coefficients (R) of the different plots being within the range of the experimental error in the data. The fit is good in all cases, but within the narrow range of variation of R, the correlation with σ^- actually gives the best fit. Under these circumstances, we do not think that the scope of the original data of these authors warrants their definitive conclusion that the mechanism of reaction is $A_N + D_N$, since they relied on Hammett plots as the sole criterion of mechanism.

(c) Kinetic Isotope Effects. The kinetic isotope effects are those for hydroxide attack on **2a.** These data also indicate partial fission of the P−O bond in the transition state of the rate-limiting

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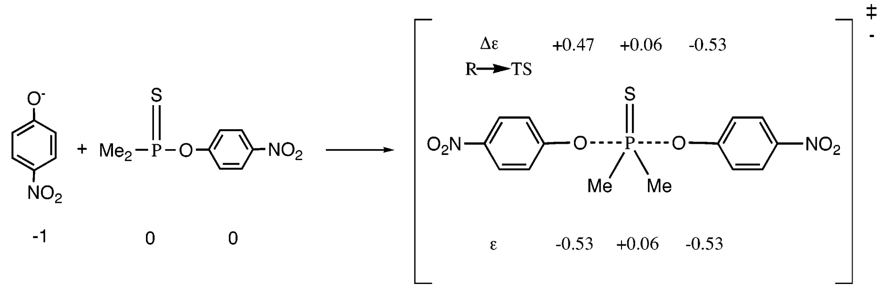

Figure 5. Effective charges in the transition state of the identity reaction in which the nucleophile and leaving group are 4-nitrophenol.

step. The magnitude of ${}^{18}k_{\mathrm{bridge}}$, 1.0124, is ~40% of the maximum value of this isotope effect, and ${}^{15}k$ is consistent with about a third of a negative charge on the nucleofuge. These data are entirely consistent with the LFER results. These data are not consistent with an addition−elimination mechanism, in which the first step should be rate-limiting, as a result of the much higher pK_a of hydroxide compared to 4-nitrophenol. In the rate-limiting TS of such a mechanism no negative charge should arise on the nucleofuge, and the P−O bond is little affected. Such a mechanism would exhibit KIEs for the rate-limiting formation of the intermediate. This could reasonably be expected to give rise to a small inverse value for ${}^{18}k_{\mathrm{bridge}}$, due to the compression of bending modes in the pentacoordinate intermediate. A precedent for such an effect has been observed in the amide-^{15}N isotope effect for the alkaline hydrolysis of 4-nitroanilide.[39] Under conditions where formation of a tetrahedral intermediate is rate-limiting, ${}^{15}k = 0.995$ in contrast to ${}^{15}k = 1.035$ when breakdown and accompanying C−N bond fission is rate-limiting.[39] The inverse KIE for intermediate formation in the amide reaction indicates that the isotope effect from compression of bending modes outweighs any reduction in C−N bond order from loss of amide resonance, which would give a normal isotope effect. In the present case, if a phosphorane intermediate forms, while some weakening of the P−O bond is expected on the basis of the observation of slightly longer P−O bonds in crystal structures of phosphoranes compared to analogous bonds in phosphate esters, this would not be enough to account for such a large normal ${}^{18}k_{\mathrm{bridge}}$, especially when compression of bending modes would give an inverse contribution to the observed KIE.

Effective Charge Distribution and Transition-State Structure. Having established a concerted mechanism for the reaction under discussion, we now proceed to determine the effective charge in the TS (ϵ_{TS}) on the entering nucleophile and leaving group to enable a discussion of the TS structure, using the methodology developed by Williams[12,27,28,40] and Jencks.[22,24,41] This procedure requires knowledge of the value of β_{eq}, according to eq 6, provided that the reactions for which β_{nuc} and β_{lg} have been measured are the microscopic reverse of each other, and that both parameters relate to the same rate-determining step. The reactions studied here utilize aryl oxides as the entering and leaving groups. The parameter β_{eq} is the overall charge change on the nucleofuge (or nucleophile) between the reactant and product states for the overall reaction, and is calculated according to eq 6 to be +1.00. Since in the product the nucleofuge has a defined charge of −1.0, this means that the aryl group has virtually no effective charge in the reactant.

$$\beta_{\mathrm{eq}} = \beta_{\mathrm{nuc}} - \beta_{\mathrm{lg}} \tag{6}$$

The quantity ϵ_{TS} is the effective charge on the nucleophile in the TS, and is related to β_{nuc} by eq 7, where ϵ_{R} is the effective

$$\epsilon_{\mathrm{TS}} = \beta_{\mathrm{nuc}} + \epsilon_{\mathrm{R}} \tag{7}$$

charge on the nucleophile in the ground state, i.e. −1. For the identity reaction, when nucleophile = leaving group = 4-nitrophenoxide, the charge on the nucleophile and the leaving group will be the same; hence, the effective charge on both equals −0.53 (Figure 5).

The total charge of nucleophile plus $Me_2P(S){-}OPhX$ in the reactant state is −1.0. In the TS, the charges on entering and leaving groups sum to −1.06. This leaves a charge imbalance of −0.06, which is balanced by +0.06 charge unit on the thiophosphinoyl group to maintain overall charge balance. The effective charges are displayed in the TS structure shown in Figure 5.

β_{nuc} and β_{lg} values are normalized to obtain the Leffler indices[25−27,42] $\alpha_{\mathrm{formation}} = \beta_{\mathrm{nuc}}/\beta_{\mathrm{eq}}$ and $\alpha_{\mathrm{fission}} = \beta_{\mathrm{lg}}/\beta_{\mathrm{eq}}$, which measure the extent of bond formation and bond fission, respectively, in the TS. Since $\beta_{\mathrm{eq}} = 1.00$, $\alpha_{\mathrm{formation}} = \beta_{\mathrm{nuc}} = 0.47$ and $\alpha_{\mathrm{fission}} = \beta_{\mathrm{lg}} = 0.53$. These values locate the position of the TS as $T^{\ddagger}$ along the tightness diagonal[23,25,43] on the More O'Ferrall−Jencks diagram (Figure 6). The position of $T^{\ddagger}$ is only slightly displaced from the intersection of the synchronous route and the tightness diagonal, showing that the reaction in question is a concerted one in which bond cleavage is only very marginally advanced over bond formation in the TS. The present results are therefore clearly inconsistent with the formation of a phosphorane intermediate, as has been advocated for this reaction.[5] No intermediate, derived from an associative or a dissociative process, will be stable enough to have any real existence at this point of the potential energy surface.

Comparison of the Behavior of the $Me_2P(O){-}OPhX$ and $Me_2P(S){-}OPhX$ Systems. It is instructive to compare the behavior of the present system [$Me_2P(S){-}OPhX$] with that of its oxygen analogue [$Me_2P(O){-}OPhX$][8] to assess the influence of the thio effect on the mechanism and TS of the reaction of the title compounds. The rate constant ratio $k_{\mathrm{P=O}}/k_{\mathrm{P=S}}$ is found to be generally small, calculated as 2.4, 4.1, 5.0, 5.2, and 3.5 with 4-NO_2, 3-NO_2, 4-Cl, 3-Cl, and H, respectively, as the substituents in the phenoxide leaving group. These values for the thio effect may be compared with values of 4−11 and 12.4 obtained for the reaction of the methyl 2,4-dinitrophenyl

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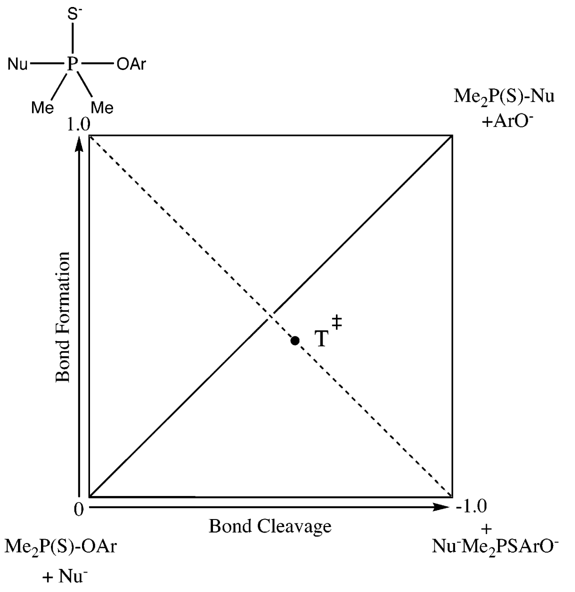

Figure 6. Location of the TS on a More O'Ferrall−Jencks diagram of the reaction of $Me_2P(S)-OAr$ with nucleophiles.

phosphate/phosphorothioate system with a variety of nucleophiles[44] and the alkaline hydrolysis of the triethyl phosphate/phosphorothioate system,[9] respectively. The present system is apparently less sensitive to S-substitution ($P = S$ versus $P = O$) than phosphates.[3] It is noted that Cook and co-workers[45] have reported a small rate-retarding effect, less than a factor of 10, for the replacement of O by S in a series of alkyl phosphinates.

The Leffler indices $\alpha_{\mathrm{formation}} = 0.47$ and $\alpha_{\mathrm{fission}} = 0.53$ have been calculated[37] from the data of Douglas and Williams[8] for the hydrolysis of $Me_2P(O)-OPhX$. The same values of these parameters have been obtained in the present study for the transfer of the thiophosphinoyl group from $Me_2P(S)-OPhX$ to oxyanions. The implication of this finding is that both substrate series demonstrate the same amount of bond making and bond fission in the TS of their reactions. This leads to the conclusion that S-substitution in the $P = O$ bond of $Me_2P(O)-OPhX$, while exerting a marginal rate-retarding effect, does not alter the TS structure in the reaction with oxygen nucleophiles. In this regard, the behavior of phosphinate/phosphinothioate system is similar to the phosphate/phosphorothioate system. In general, the TS for the hydrolysis of phosphates and phosphorothioates are similar,[3,11,46,47] the exception being the reaction of monoesters, where nucleophilic participation, that is absent in the $D_N + A_N$ reactions of phosphorothioates,[48] is a feature of the A_ND_N reactions of phosphate monoesters.[49]

The Associative Mechanism and Reactions of Phosphinates with Aryloxy Leaving Groups. Prior to this work, a number of reports on the reactions of oxygen nucleophiles with a range of phosphinate and phosphinothioate esters bearing aryloxy or arylthiolate leaving groups (e.g., $Ph_2P(Y)-OPhX$ ($Y = O$ or S), $Me_2P(Y)-OPhX$ ($Y = O$ or S), $Ph(Me)P(S)-SPhX$, and $Ph(MeSO_2CH_2)P(O)-OPhX$), have appeared in the literature.[4,5,7,8,37,38,50,51] The features of these reactions have been summarized.[3] The stepwise mechanism involving rate-limiting formation of the pentacoordinate intermediate has been advocated for the transfer of the (thio)phosphinoyl group in most of these reactions, based mainly on the results of Hammett correlations. The notable exceptions to this general trend are the alkaline hydrolysis of aryl dimethylphosphinates[51] and the reaction of aryl diphenylphosphinates with phenoxides in water,[7] which were shown to react by a concerted mechanism.

The present study, which has relied on Brønsted LFER, Hammett correlations, and heavy atom kinetic isotope effects as criteria for mechanism, has provided unambiguous evidence for a concerted mechanism for a reaction that was earlier proposed[5] to occur by an associative, stepwise mechanism. The question that needs be asked is: how general is the stepwise mechanism in the reactions of phosphinates? The corollary to this question is: how uncommon is the concerted mechanism? There are also subsidiary issues that need to be addressed. What factors promote one mechanism over another and at what point can a mechanistic changeover be anticipated? Clearly, more work is required to answer these questions and elucidate the factors that select for particular mechanisms.

Conclusions

The Brønsted β_{nuc} and β_{lg} parameters, measured for the reaction of aryl dimethylphosphinothioate esters with oxyanion nucleophiles in aqueous solution, and the Leffler indices derived from them describe a one-step process in which the bond to the incoming nucleophile is 47% formed and the bond to the nucleofuge is 53% cleaved in the TS. Correlation of the second-order rate constants for the reactions of HO^- and PhO^- with σ^- substituent constant supports a mechanism in which the bond to the nucleofuge is broken in the TS. This conclusion is strongly reinforced by the primary ^{18}O and secondary ^{15}N kinetic isotope effects measured in the hydrolysis reaction, thus removing the ambiguity in the literature concerning the mechanism of hydrolysis of aryl dimethylphosphinothioates.

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Supporting Information Available: Synthetic procedures and spectral data for compounds **2a−g**, preparation of isotopically labeled compounds, the equations used for calculation of the kinetic isotope effects, and complete citation to ref 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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