The Three-Phase Test: Intermediates in Phosphate Transfer Reactions

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Abstract: Experimental details are given for the detection of intermediates in phosphate transfer reactions. The methods involve the use of polymer-bound reagents to detect reactive intermediates in solution. Evidence requiring the existence of polymer-free intermediates in reactions of phosphoramidates, acyl phosphates, and halophosphonates is presented.

I. Introduction

Reactions of phosphate derivatives have been extensively investigated and numerous mechanistic pathways have been described. The number of easily accessible ionic forms of phosphates in water, the varied geometries available for second-row elements, and the lability of these structures through pseudorotation results in a mechanistic complexity and richness unknown in first-row chemistry. A recurrent theme in the chemistry of phosphate transfer reactions concerns the intermediacy of the evanescent monomeric metaphosphate (Figure 1) and its derivatives.[2] In this paper we describe experiments which bear on this question for reactions involving phosphoramides, acyl phosphates and β-halophosphonates.

Phosphoramides. Basic hydrolysis of phosphorodiamides bearing at least one ionizable N-H function proceeds orders of magnitude more rapidly than the hydrolysis of the fully alkylated derivatives (Figure 2). Heath[3] attributed this to a steric effect, but Westheimer[4] interpreted these results in terms of a change in mechanism: the acidic N-H group permits a facile elimination-addition mechanism involving a metaphosphorodiimidate, **1**, whereas the fully substituted derivatives hydrolyze via biomolecular[5] or other dissociative[6] mechanisms. Supporting evidence for this interpretation was provided by the remarkable rate differences observed between **2** and **3** (Figure 3) by Traylor and Westheimer.[7] Additionally, Williams and Douglas[8] have recently examined the hydrolytic behavior of substituted esters **4**, which show most of the earmarks of ElcB reactions. That structures related to **1** are reasonable intermediates in these reactions was finally established in 1974 with the isolation[9] and characterization[10] of the first monomeric metaphosphate derivative **5**.

Acyl Phosphates. A considerable body of evidence has supported the intermediacy of the parent monomeric metaphosphate ion during the hydrolysis of phosphate esters.[15] The behavior of acyl phosphates is particularly revealing and has been studied by Jencks.[16] Hydrolysis occurs with P-O fission and decomposition occurs via the monoanion **6** or dianion **7** (Figure 4). In media of low water concentration or high salt concentration pyrophosphate is formed, suggesting that intermediate metaphosphate can be trapped under these conditions. In esters of acyl phosphates **8** hydrolysis is much slower and even then C-O fission occurs, indicating the difficulty of producing a metaphosphate lacking electron donors on the phosphorus atom.

β-Halophosphonates. A second process in which the intermediacy of metaphosphate has been strongly implicated is the fragmentation reaction of β-halophosphonates (the Conant-Swan reaction, Figure 5). The ready fragmentation of **9**,[18] the phosphorylation of *tert*-butyl alcohol by **10**,[19] and the stereospecificity of **11** → **12**[20] are all consistent with and most economically accounted for by unimolecular decomposition of the phosphonate anions with the formation of metaphosphate.[21] That even monoesters of β-halophosphonates are capable of such fragmentation was recently shown by Satterthwait and Westheimer,[22] who found identical product distributions from **13** and **14** in trapping experiments involving aromatic amines. The ester **15** appears to be unsually unselective in its reaction with nucleophiles.

II. Methods and Results

Our own studies were directed at the detection of intermediates in these reactions, and we had devised an unambiguous method to distinguish between associative and dissociative (elimination-addition) mechanisms. The method involves the generation of reactive intermediates from insoluble, polymer-bound precursors and their detection by trapping on a second solid support suspended in the same solution (Figure 6).

Direct reaction between the two solid phases is physically precluded; therefore any observed adducts must arise from polymer-free intermediates in solution. Inferences regarding the structure of the intermediate are more difficult to support than those concerning the existence of the intermediate; observation of an adduct provides prima facie evidence for the latter, but only the usual mechanistic exegeses are available for the former. Such inferences must be supported by establishing the structure of the adducts, a task best accomplished by removal of the adduct from the solid phase, using reagents which minimize undesired structural changes, followed by comparison with authentic samples.

Phosphoramides. For the case of phosphoramides a suitable precursor was found in the ester **16** (Figure 7) prepared by phosphoramidation of the polymer-bound nitrophenol[11] as shown. Reaction of **16** with cyclohexylamine in solution gave the known[12] phosphoramide **18**, and confirmed that **6** was indeed capable of phosphate transfers to solvent-borne amines.

Our initial trapping agent was the polymer-bound amine **19**, accessible from the commercially available chloromethylated polystyrene (Merrifield's resin) by Gabriel synthesis (Figure 8). Phosphoramidation as before gave the reference susbtance **10**.

That phosphate transfer between the two solid phases could be catalyzed with a nonnucleophilic base in solution was established (qualitatively) by stirring a mixture of **16** and **19** in dioxane containing 1,8-bis(dimethylamino)naphthalene (proton sponge). At room temperature no transfer could be detected by IR, but at 50 °C (2 h), **20** slowly appeared. For analytical purposes, the polymer-bound leucine derivative **21** (Figure 9) was prepared by the well-established methods of solid-phase peptide synthesis.[13] Phosphoramidation afforded **22**, which could be cleaved from the resin by transesterification[14] with dimethylaminoethanol/DMF and then MeOH to give **23**. This latter substance was also prepared by phosphoramidation of leucine methyl ester in solution.

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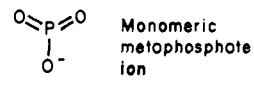
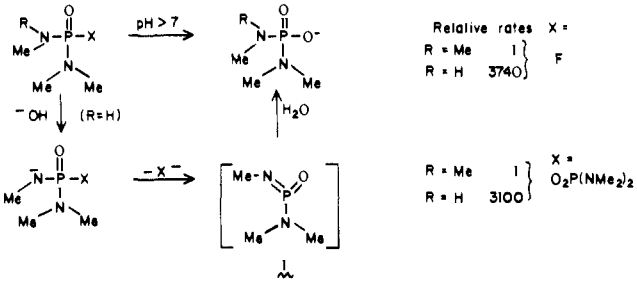


Figure 1.



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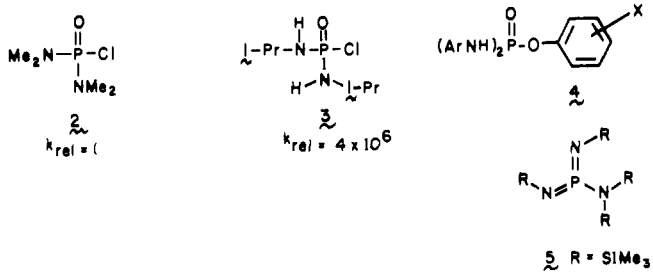

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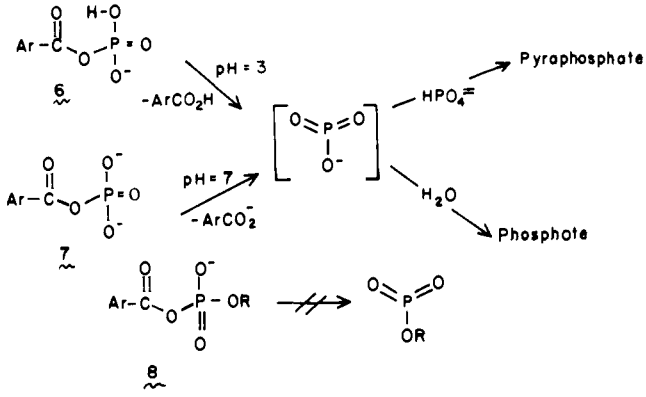
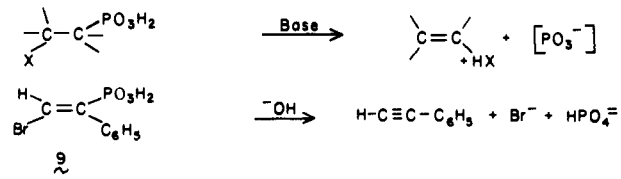
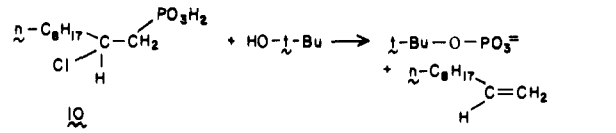


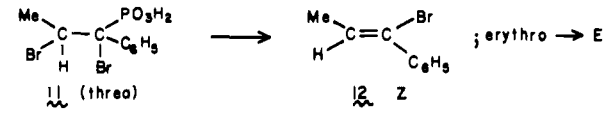
Figure 4.

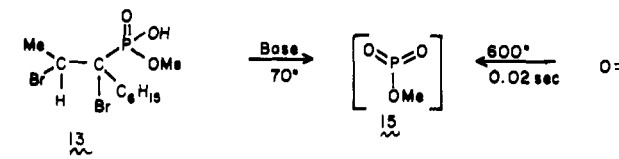
With the tractable system in hand, transfer of phosphate between **16** and **21** could be determined. In either hot dioxane or acetonitrile efficient (>90%) transfer occurred, and the structure of the adduct was established, through cleavage from the resin, to be the reference substance **23** (Figure 10). Under identical conditions no transfer of phosphorus could be detected from the fully substituted **24**.

Acyl Phosphates. We turned next to the examination of acyl phosphates and an appropriate derivative was prepared as shown in Figure 11. In this preparation we were aided by the site-site interactions[17] of carboxylic acids bound to polystyrenes with low degrees of cross-linking. Carbodiimide gave the anhydride, from which the acyl phosphate **24** was formed by cleavage with radioactive phosphate introduced as its Me_4N^+ salt. Again, a polymer-bound amino acid **25** served as a trapping agent. A mixture of **24** and **25** in dioxane or MeCN resulted in slow phosphate transfer at 70 °C. Radioassay of the polymer **26** and solution indicated the fate of the phosphate released; 40-60% was found to be trapped as glycine *N*-phosphate.









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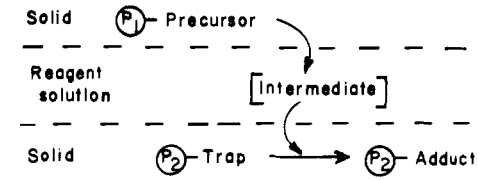

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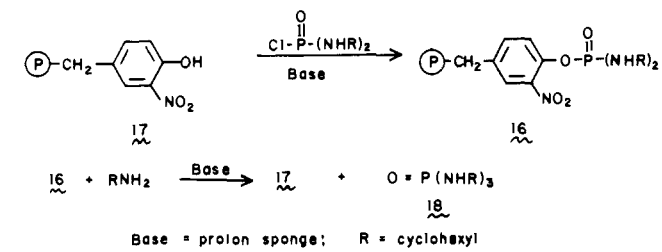


Figure 7.

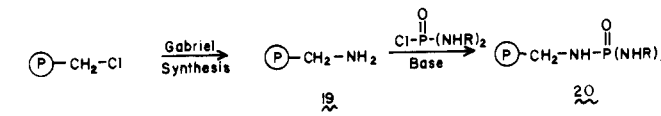


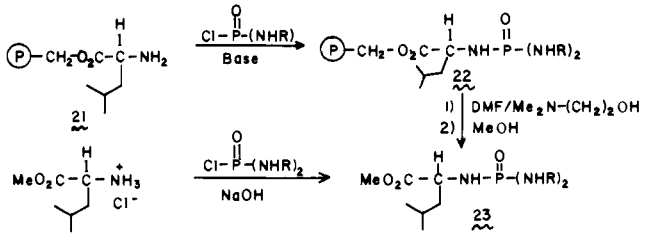
Figure 8.

A tedious and low-yield synthesis[23,24] gave the acyl phosphate ester **29**, from which only traces of phosphate were transferred (Figure 12), and control experiments with pyrophosphate **30** in solution failed to show phosphorylation of **25** under these conditions.

β-Halophosphonates. A second likely precursor for the parent metaphosphate ion required a polymer-anchored β-halophosphonate, and we prepared this substance from chloromethylated polystyrene via Wittig reaction and phosphorylation as shown (Figure 13). Using the glycine derivative **25** and Et_3N as base, phosphate transfer through solution was observed, the product being characterized as before by conversion to monophosphorylated glycine.

III. Discussion

In any of the observed phosphorus transfers between the two



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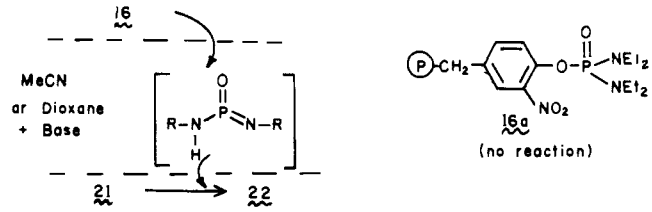

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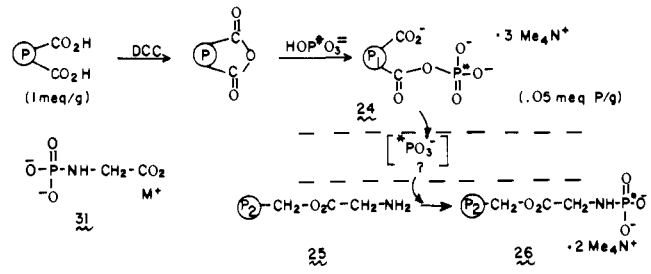

Figure 11.

solid phases the structure of the actual phosphorylating agent cannot be assigned with certainty. For example, disproportionations within the polymer-bound precursors could lead to polymer-free oligomers of metaphosphate which might act as carriers in a catalytic sense. Even though this possibility is weakened because of the high degree of monophosphorylation observed in the adducts, it cannot be rigorously excluded. Moreover, Westheimer[22] has pointed out that a species as electrophilic as metaphosphate might never be "free" in solution, and could form complexes with dioxane, as does the isoelectronic SO_3,[25] or even acetonitrile. In this regard the enhanced degree of phosphate transfer in the presence or proton sponge is noteworthy, though this base is not readily formulated as a nucleophile, and the role of halide ions in the Conant-Swan reaction remains obscure.

Finally, it is tempting to compare the present results with those found for phosphate transfer reactions by previous workers. The facile reactions of the polymer-bound phosphoramidate, acyl phosphate, and β-chlorophosphonate and the slow reaction of the acyl phosphate ester all have their parallels in solution chemistry. Yet the relevance of reactions occurring in hydrocarbon matrices to those occurring in largely aqueous media is limited and does not warrant direct comparison. Moreover, the three-phase method excludes mechanisms, e.g., association, which may represent the lowest energy pathway for a reaction in solution. On the other hand, the technique reveals mechanistic possibilities which may be difficult to detect in solution. At worst our results may have no relevance outside their own context; at best they may reflect the events in hydrophobic enzyme interiors; at the very least they may be considered complementary to classical kinetic studies in aqueous media.

Experimental Section

General methods for manipulating the polymers and multiphase

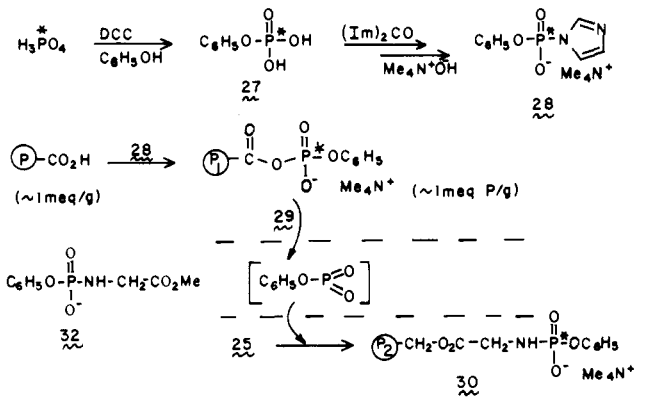

Figure 12.

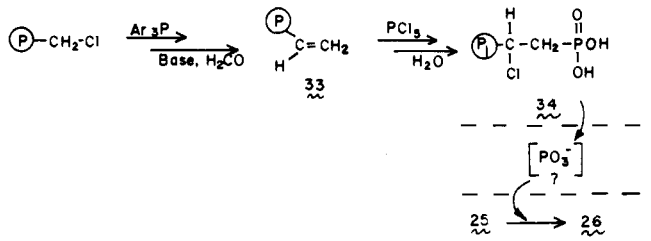

Figure 13.

systems have been described.[26] Radioactive phosphorus was determined by scintillation counting using disintegration curves and checked against standards.

I. Reference Substances. Methyl *N*-(*N,N'*-Dicyclohexyldiaminophosphoryl)leucinate (23). Leucine methyl ester hydrochloride (20 mg) was dissolved in 8 mL of 10% NaOH and *N,N'*-dicylohexylphosphorodiamidic chloride[27] (DPDC, 37 mg) was added. After 1 h at ambient temperature the solution was extracted with 40 mL of CCl_4. The organic phase was dried and evaporated to give crystalline **23**: mp 180–182 °C (30% yield); NMR δ 3.5 (s, 3 H), 1–2.1 (broad, 31 H); IR 1740, 1240 cm^{-1}. Anal. Calcd for $C_{19}H_{38}N_3O_3P$: C, 58.73; H, 10.12. Found: C, 58.50; H, 10.17.

Sodium and barium salts of glycine-*N*-phosphate 31 and *N*-monophenylphosphoroglycine salts and methyl ester **32** were prepared by standard procedures; physical properties agreed with literature[29] values.

II. Preparation and Characterization of Polymer-Bound Reagents. Phosphorodiamidic Ester 16. A suspension of polymer-bound nitrophenol[11] **17** (2.1 g, 6 mequiv) in 60 mL of dioxane was treated with 4 g of DPDC and 1.3 g of proton sponge at room temperature for 16 h, then at 45 °C for 4 h. After washing with dioxane, acetone, and ethanol, the resin showed IR 1240, 1010 cm^{-1}. Anal. N, 3.9; P, 1.38 (0.45 mequiv/g). A 1-g sample was treated with 86 mg of cyclohexylamine and 188 mg of proton sponge in 8 mL of dioxane at 50 °C for 5 h to give *N,N',N''*-tricyclohexylphosphorotriamide (**18**), mp 245 °C dec (lit.[12] mp 246 °C dec).

Phosphorodiamidic Ester 16a. The polymer-bound nitrophenol[11] **17** (1 g, 3 mequiv) was treated with a mixture of $POCl_3$ (0.9 g), diethylamine (0.8 g), and 1 mL of pyridine in 6 mL of $CHCl_3$ at 0 °C for 1 h. After stirring for an additional 2 h at room temperature the mixture was heated at 45 °C for 2 h. Washing with acetone and ethanol gave **16a**, the resin showing IR 1240, 1220 cm^{-1}. Anal. P, 3.18 (1.02 mequiv/g). A 470-mg sample of the resin was suspended in 3 mL of 25% $Me_4N^+\bar{O}H$ in H_2O at 50 °C for 5 h, then allowed to stir at 25 °C overnight; addition of acetone to the solution phase precipitated the Me_4N^+ salt of *N,N'*-tetraethylphosphorodiamidic acid, mp 223 °C (lit.[28] mp 222 °C).

Aroyl Phosphate 24. Polymer-bound benzoic acid[17] (0.16 g, 0.16 mequiv) was stirred at room temperature for 5 h with a solution of 200 mg of DCC in 5 mL of CH_2Cl_2. After washing with CH_2Cl_2 the resin showed IR 1785 and 1720 cm^{-1}, characteristic of the anhydride.[17] A 120-mg sample was suspended in 2.5 mL of pyridine and a solution of $(Me_4N^+)_2\ H^*PO_4^{2-}$ in 4 mL of H_2O and 4 mL of dioxane was added. After heating at 60 °C for 1 day the resin was washed with

Table I

	mg **23**	mg **25**	solvent	proton sponge	temp, h	% transfer	% recov **24**
(1)	116	30	6 mL dioxane	4 mg	60 °C, 21	23	50
(2)	133	30	5 mL dioxane	4 mg	70 °C, 27	63	10
(3)	295	67	5 mL dioxane	none	70 °C, 27	33	51
(4)	1116	251	5 mL MeCN	none	70 °C, 27	30	50

dioxane, ethanol, and acetone, then dried. Analysis indicated 0.15 P (0.05 mequiv/g) whereas radioactivity indicated 0.07 mequiv/g. The acyl phosphate resin showed IR 1690 and 1380 cm^{-1}. (Approximately 1/20 of the original carboxylates were converted to acyl phosphates.)

Aroyl Phosphate Ester 29. Radioactive monophenyl phosphate, mp 96–97 °C, was prepared in 8% yield from the action of DCC (2.7 g) on phenol (0.74 g) and $H_3P^*O_4$ (3.4 g) in dioxane followed by hydrolysis (lit.[23] mp 98 °C). The monoester (0.36 g) in $MeCN/C_6H_6$ was treated with 0.35 g of *N,N'*-bisimidazolecarbonyl at room temperature, followed by heating for 30 min at 100 °C. The resulting imidazolium salt[24] **28** was converted by titration to the Me_4N^+ salt, crystallized from acetone–ether, mp 120 °C dec, and used directly in the next step. The salt was added to a suspension of the polymer-bound benzoic acid (140 mg, 0.14 mequiv) in 3 mL of dioxane and heated at 70 °C for 22 h. Washing with dioxane, ethanol, and acetone followed by drying gave **29** (IR 1700, 1600, 1375 cm^{-1}; radioassay 0.14 mequiv/g) implying nearly complete conversion of the acid sites to acyl phosphate esters.

β-Chlorophosphonate 34. Chloromethylated resin (1 g, 1.06 mequiv) was suspended in xylene containing 1 g of triphenylphosphine and stirred for 190 h. Washing with ethanol–ether and drying gave the polymer-bound phosphonium salt (1.3 g), which was treated with 10 g of Na_2CO_3 in aqueous dioxane containing excess formalin at room temperature for 70 h. The vinyl derivative **33**, which showed <0.1 P (600 mg), was treated with 0.8 g of PCl_5 in 30 mL of benzene at room temperature for 72 h, filtered, then slurried with H_2O at 0 °C. Washing with dioxane, acetone, and ether and drying gave **34** (P 2.6 (0.84 mequiv/g), Cl 2.9), IR 1250, 1120 cm^{-1}.

Amino Acid Derivative 21 and 25. The leucine derivative **21** was prepared by attaching the *N*-t-Boc derivative to the resin followed by deblocking with CF_3CO_2H (0.45 mequiv/g). The resin **21** (144 mg) was treated with a solution of 55 mg of DPDC and 86 mg of proton sponge in 6 mL of dioxane at 50 °C for 17 hr. Washing with dioxane and ethanol gave **22:** IR 1730, 1430, 1240 cm^{-1}. The resin **22** was stirred in a solution of 1.5 mL each of DMF and *N,N*-dimethylaminoethanol at 25 °C for 64 h, then filtered, and the filtrate was allowed to stand with 5 mL of MeOH for an additional 1 day at room temperature. Preparative TLC (silica, ether/ethanol, 9:1) was used to separate methyl leucinate from **23**; the latter was identical with that prepared in solution (vide supra).

The glycine derivative **25** was prepared as described for **21**, N 0.78 (0.56 mequiv/g).

Benzylamine 19. Preparation of **19** has been described in detail[26] (0.8 mequiv/g). A 500-mg sample was treated with 400 mg of DPDC and 100 mg of proton sponge in 40 mL of dioxane at 25 °C for 14 h. After heating at 45 °C for an additional 4 h the resin was filtered, washed with dioxane and ethanol, and dried to give **20:** IR 1220, 1120 cm^{-1}. P 0.58 (0.12 mequiv/g).

III. Three-Phase Tests. A. Phosphoramide Transfer from 16. 1. Qualitative Detection (IR) of Transfer between Ester 16 and Amine 19. A suspension of **16** (70 mg) and **19** (320 mg) was stirred in 5 mL of dioxane containing 600 mg of proton sponge at 25 °C. After 2 h no transfer could be detected by IR. The mixture was heated at 50 °C for another 2 h, the resins were separated (by flotation in ethanol), and IR revealed the presence of **20:** 1220, 1120 cm^{-1}.

2. Between Ester 16 and Amine 21 (dioxane). A suspension of **16** (551 mg, 0.31 mequiv P) and **21** (940 mg, 0.4 mequiv) in 20 mL of dioxane containing 250 mg of proton sponge was heated at 90 °C for 6 h, then at 50 °C for 118 h. Washing, then separation of the resins, gave **22**, 0.86 P (0.29 mequiv P/g) or >90% phosphorus transfer. Transesterification and preparative TLC as described above gave the reference substance **23** (40%).

3. Between 16 and 21 (MeCN). A sample of **16** (240 mg, 0.1 mequiv), **21** (300 mg, 0.12 mequiv), and proton sponge (80 mg) was heated as before in 10 mL of MeCN. Phosphorus analysis showed 97% transfer.

4. Between 18 and 19 (Control). A suspension of **18** (74 mg) and **19** (740 mg) was heated as before in dioxane containing proton sponge (120 mg). Phosphorus analysis showed no loss of P from **18.** Identical results were found in MeCN as the solution phase.

B. Phosphate Transfer from Acyl Phosphate 24. All phosphate transfers in this series involved the radioactive **24** and the glycine derivative **25.** A suspension of 116 mg of **24** (0.006 mequiv P*) and 30 mg of **25** (0.016 mequiv) was heated at 60 °C for 21 h in 6 mL of dioxane containing 4 mg of proton sponge. Separation and washing gave recovered **24** (0.31 mequiv P by radioactivity) and **26** (0.017 mequiv P by radioactivity, 0.018 mequiv by P analysis). Therefore 50% of the phosphate of **24** was released and 23% was transferred (46% trapping). The identity of the product was established by stirring **26** with 30 mg of $Me_4N^+\bar{O}H$ in 2 mL each of H_2O and dioxane at 25 °C for 7 h followed by the addition of 60 mg of $BaCl_2$ to the solution phase. The precipitated Ba salts of glycine and its monophosphate derivative were assayed (radioactivity indicated that 48% by weight of this mixture was $Ba_3[O_2CCH_2N\text{-}P^*O_3]_2$ and that 90% of the original activity of **26** appeared as this salt). The salts were stirred with excess ion exchange resin (Na^+ form), then the solution was evaporated to dryness. TLC (silica support, EtOH/0.1 M Na_2CO_3 eluent) showed the radioactivity to be concentrated at R_f 0.16, corresponding to trisodium glycine *N*-phosphate. A sample of the dry sodium salts was subjected to isotopic dilution with unlabeled trisodium glycine *N*-phosphate. Radioassay confirmed that 90% of the released activity from the saponification of **26** appeared as glycine *N*-monophosphate. Results from these experiments are given in Table I.

C. From Acyl Phenyl Phosphate 29. 1. A mixture of 56 mg of **29** (0.0074 mequiv P*) and 30 mg of **25** was heated at 70 °C for 90 h in 6 mL of dioxane containing 7 mg of proton sponge. Radioassay indicated that 85% of the activity remained on **29** and 8% appeared on **30.** Transesterification followed by saponification gave the sodium salt of glycine-*N*-monophenyl phosphate, identical with reference substance **32.**

2. The experiment was repeated in the absence of proton sponge: 1.88 g of **29** and 1.12 g of **30** were heated at 70 °C for 160 h in dioxane. Radioassay showed 1% transfer and 80% recovered on **29.**

3. In acetonitrile as the solution phase, no detectable transfer (analysis, radioassay) occurred after 240 h at 70 °C.

D. From β-Chlorophosphonate 33 (Conant–Swan Reaction). The chlorophosphonate **33** (104 mg, 0.087 mequiv P) was stirred with the glycine derivative **25** (174 mg, 0.09 mequiv) in 8 mL of MeCN containing 1 g of Et_3N for 4 h at 25 °C. Separation of the resins gave **26,** 0.049 mequiv P (by analysis) or 56% transfer. The identification was performed by transesterification/saponification, then comparison with authentic sample **31** (sodium and barium salts).

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Multiple Structure–Reactivity Relationships in the Acid-Catalyzed Breakdown of Meisenheimer Complexes[1]

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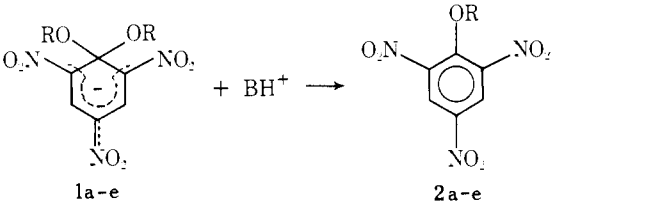
Abstract: Alkoxide ion departure from Meisenheimer complexes of the 1,1-dialkoxy-2,6-dinitro-4-X-cyclohexadianate type is catalyzed by pyridinium ions and by H_3O^+ with Brønsted α values ranging from 0.35 to 0.65, indicating concerted acid catalysis. α increases with increasing basicity of the leaving group and at the same time β_{1g} increases with increasing acidity of the catalyst, with $\partial\alpha/\partial pK_{1g} = -\partial\beta_{1g}/\partial pK_{BH^+} = p_{xy'} = 0.12$; β_{1g} increases with the basicity of the leaving group, with $-\partial\beta_{1g}/\partial pK_{1g} = p_{y'} = -0.34$; α also increases when the X substituent is made more electron withdrawing and this increase is accompanied by a corresponding increase in ρ with increasing acidity of the catalyst, with $\partial\alpha/\partial\sigma^- = -\partial\rho/\partial pK_{BH^+} = 1/c_4 = 0.087$ or $p_{xy} = 1/c_4\rho_{eq} = 0.014$. Qualitatively these trends in the structure–reactivity parameters can be rationalized in terms of changing bond lengths and effective charges in the transition state and are easily visualized by placing the transition state on a More O'Ferrall–Jencks diagram. The fact that $p_{xy'}/p_{xy} \gg 1$ indicates, however, that the development of effective charges and the changes in bond length are not synchronous. One contributing factor to this imbalance is attributed to an electrostatic interaction between the polar substituents on the acid catalyst and the leaving group ("Hine effect"). Other reasons for the imbalance are discussed. The water reaction also shows an increase of β_{1g} with increasing pK_{1g} which may be due to a solvation effect.

The transition state of chemical reactions has been one of the focal points of mechanistic interest for a long time. Structure–reactivity relationships have played a central role in attempts to define the structure of transition states,[2] and the ideas of Polanyi,[3] Bell,[4] Leffler,[5] and Hammond[6] have had a great influence on how chemists approach this question. In what is now commonly called the Leffler–Hammond postulate, the transition state is assumed to gradually change from a reactant-like structure in highly exothermic reactions to a product-like structure in highly endothermic reactions, with a intermediate structure in thermoneutral reactions.

There is a growing awareness that *concerted* reactions in which there is a strong coupling between two processes such as proton transfer and bond formation/cleavage between heavy atoms cannot be discussed in terms of simple Leffler–Hammond effects. For such reactions the three-dimensional energy maps introduced by Albery[7] and made popular by More O'Ferrall[8] and Jencks[9] constitute a very useful framework for the interpretation of structure–reactivity effects. This approach allows one to recognize that transition state structure is not only affected by effects along the reaction coordinate ("Leffler–Hammond effects") but by effects perpendicular to it ("Thornton effects"[10]). Failure to take the perpendicular effects into account may lead one to interpret certain results as being in apparent violation of the Leffler–Hammond principle[2b,11] whereas in fact they are not.[1b,2a]

In this paper we describe the study of reactions 1 and 2 and discuss the results within the framework of the More O'Ferrall–Jencks diagrams.



1a-e 2a-e

+ ROH + B (1)

a, R = CH_3CH_2; b, R = CH_3; c, R = $CH_3OCH_2CH_2$; d, R = $ClCH_2CH_2$; e, R = $HC{\equiv}CCH_2$

Results

All complexes except for **3a** could be isolated; **3a** was generated in situ as described in the Experimental Section. The rates were determined spectrophotometrically, either in the

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