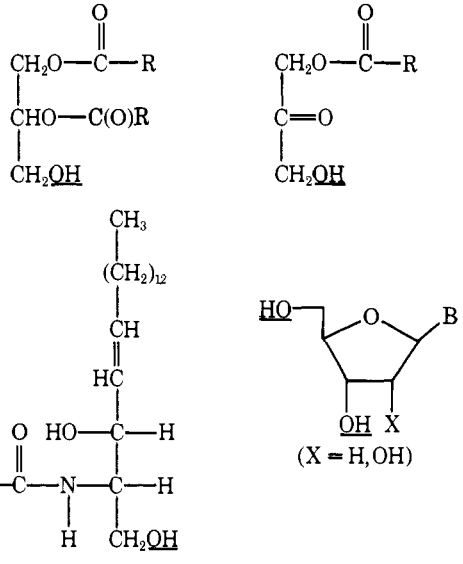
# One-Flask Synthesis of Unsymmetrical Phosphodiesters. Selective Amine Catalysis of the Phosphorylation of Primary vs. Secondary Alcohols

**Fausto Ramirez,*[1] James F. Marecek, and Hiroshi Okazaki**

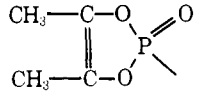
*Contribution from the Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794.* *Received January 29, 1976*

**Abstract:** Two different alcohols, $R^1OH$ and $R^2OH$, are converted into an unsymmetrical phosphodiester, $(R^1O)(R^2O)P(O)OH$, without isolation of intermediates. Alternatively, the two alcohols are converted into a phosphotriester, $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$, which is isolated and hydrolyzed to the phosphodiester with or without further purification. The procedures are made possible by the efficient imidazole catalysis of the phosphorylation of alcohols by alkyl cyclic enediol phosphates. The phosphorylation of a primary OH in the presence of an unprotected secondary OH in a diol can be performed with a 98:2 selectivity using triethylamine as catalyst. The reagents for the new phosphorylative coupling procedures are cyclic enediol *N*-phosphorylimidazoles and pyrophosphates, *N*-(1,2-dimethylethenylenedioxyphosphoryl)imidazole and di(1,2-dimethylethenylene) pyrophosphate, which are readily available from biacetyl and trimethyl phosphite via a stable pentaoxyphosphorane.

Some of the most important biological phosphates are unsymmetrical phosphodiesters, $(R^1O)(R^{11}O)P(O)OH$, derived from two fairly complex alcohol moieties, $R^1OH$ and $R^{11}OH$. For example, in many of the phospholipids of biological membranes, $R^1OH$ is a 1,2-diglyceride, a monoacyldihydroxyacetone, or an *N*-acylaminopolyol of the sphingosine type, while $R^{11}OH$ is a derivative of ethanolamine, serine, glycerol, or *myo*-inositol. In the polynucleotides, $R^1OH$ and $R^{11}OH$ are nucleosides with one primary and one or two secondary alcohol functions. In principle, a phosphodiester of this type can be synthesized from $R^1OH$ and $R^{11}OH$ according to the sequence $R^1OH = R^1OH$, $R^2OH = R^{11}OH$, or $R^1OH = R^{11}OH$, $R^2OH = R^1OH$, where $R^1OH$ and $R^2OH$ refer to the order in which the two alcohol moieties are submitted to the phosphorylation process. The choice of sequence depends on the availability of suitably protected $R^1OH$ and $R^{11}OH$, and on the capabilities of the phosphorylating reagents at hand.



We have described a series of derivatives of the 1,2-dimethylethenylenedioxyphosphoryl group,

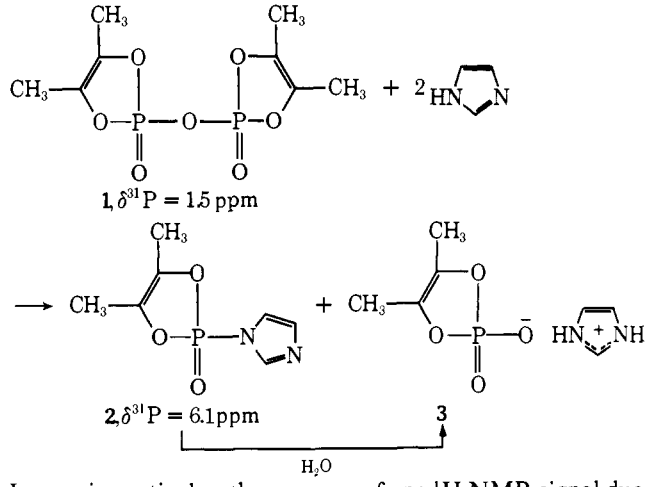


abbreviated[2] X=P(O)-, which can be used as reagents for the phosphorylation of alcohols. The methyl ester, X=P(O)-$OCH_3$, is available from the reaction of the biacetyl trimethyl phosphite *oxyphosphorane* with water[3] or acetyl bromide.[4] The pyrophosphate, $[X=P(O)]_2O$, is prepared[6] by reaction of the methyl ester with pyridine and phosgene.[5] The aryl esters, X=P(O)OAr, are obtained from the pyrophosphate and phenols, e.g., *p*-nitrophenol and pentafluorophenol.[6] A two-stage synthesis of unsymmetrical dialkyl (1-methylacetonyl) phosphates by means of the pyrophosphate has been reported in previous papers.[5,7] The 1-methylacetonyl group can be easily removed from the triesters, and this sequence of reactions constitutes a three-stage synthesis of unsymmetrical phosphodiesters[8-11] from the alcohols, $R^1OH$ and $R^2OH$.

This paper describes a procedure to convert a pair of alcohols into the diester $(R^1O)(R^2O)P(O)OH$ without the isolation of any intermediate ("one-flask" synthesis). Moreover, the two alcohols can be converted into the triester, $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$, in "one flask", and the triester can be hydrolyzed to the unsymmetrical dialkyl phosphate with or without an intervening purification step.

## Results

**Preparation of *N*-(1,2-Dimethylethenylenedioxyphosphoryl)imidazole (2).** The pyrophosphate[5] **1** reacts with imidazole to give the stable,[12-17] crystalline phosphorylimidazole,[18] **2**, in 90% yield. The structure of **2** rests on the data given in Table

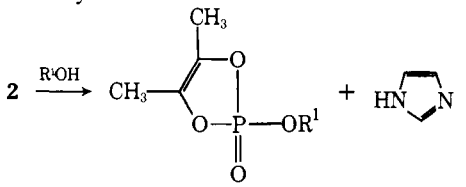


I; note, in particular, the presence of one $^1H$ NMR signal due to the two methyl groups on the 1,3,2-dioxaphosphole ring. The structure of the pyrophosphate **1** has been confirmed by x-ray crystallography.[19]

In agreement with structure **2**, the phosphorylimidazole reacts instantaneously with 1 mol equiv of water in aprotic solvents and generates imidazolium (1,2-dimethylethenylene) phosphate (**3**), i.e., the product of hydrolysis with complete ring retention.

**One-Flask Phosphorylative Coupling of Two Different Alcohols.** The phosphorylimidazole **2** is a reagent for the direct conversion of two different alcohols into an unsymmetrical phosphodiester without the isolation of any intermediate ("one-flask" reaction). The synthesis is carried out in acetonitrile solution as described in the Experimental Section (procedure 1) and is made possible by two properties of the system: (i) alcohols react much faster with the phosphorylimidazole **2** than with the alkyl cyclic enediol phosphate, **4**, which is the product of their reaction; and (ii) imidazole autocatalyzes the reaction of the first alcohol, $R^1OH$, with **2** and is also a very effective catalyst for the reaction of the second alcohol, $R^2OH$, with the cyclic triester **4**. This point will be discussed subsequently. Several examples of this new and convenient phosphodiester synthesis are given in Table II.

The phosphorylimidazole **2** can also be utilized for the conversion of the two alcohols into the acyclic triester **5** in one laboratory operation; **5** is subsequently hydrolyzed to the diester **6** with or without an intervening purification step. The synthesis is carried out in dichloromethane solution, as detailed in the Experimental Section (procedure 2A). Several examples of the synthesis are included in Table II.



**4**, $\delta^{31}P = -10$ to $-14$ ppm

$\xrightarrow{R^2OH}$ $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$

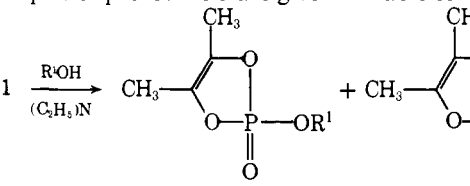
**5**, $\delta^{31}P = 0$–$3.5$ ppm

$\xrightarrow{H_2O}$ $(R^1O)(R^2O)P(O)OH + HOCH(CH_3)COCH_3$

**6**

The phosphorylimidazole **2** need not be isolated in the phosphotriester synthesis because it is generated rapidly and quantitatively from imidazole and the pyrophosphate **1** in dichloromethane solution, and because the salt **3**, which is formed as by-product, does not react with alcohols at appreciable rates.[20] The salt **3** is readily separated from the triester **5** in the work-up. Several applications of this procedure 2B are listed in Table II.

The crystalline pyrophosphate[5] **1** is a convenient reagent for the one-flask conversion of two alcohols into the dialkyl (1-methylacetonyl) phosphates **5**. The synthesis is carried out in dichloromethane solution in the presence of triethylamine according to procedure 3 (Experimental Section). The synthesis is possible because the triethylammonium (1,2-dimethylethenylene) phosphate (**7**) formed as by-product does not react with the alcohols at any appreciable rate,[20] and because triethylamine is an effective catalyst for the reaction of certain alcohols with the cyclic triesters **4** (see below). Examples of procedure 3 are given in Table II.

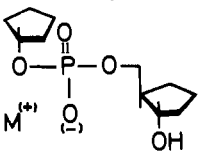


**4** **7**

$\xrightarrow[(C_2H_5)_3N]{R^2OH}$ $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$

**5**

Triethylamine catalyzes the reaction of primary alcohols, $R^2OH$, with the cyclic triesters **4**, *but it does not catalyze the reaction of secondary alcohols with* **4**. This remarkable specificity permits the synthesis of compound **6a′** (M = $C_6H_{11}NH_3^{(+)}$) from cyclopentanol ($R^1OH$) and unprotected *trans*-2-hydroxymethylcyclopentanol ($R^2OH$) by procedure 3. The selectivity in the phosphorylation of the primary vs. the secondary hydroxyl functions of the diol is 98:2; the previous synthesis[5] of **6a′** without triethylamine involved a 90:10 selectivity and required much longer time. Imidazole reduces the selectivity to 80:20 (Table VI).



**6a′**

The first alcohol, $R^1OH$, in the phosphorylative couplings of Table II is a relatively hindered primary or secondary acyclic alcohol, such as neopentyl alcohol, 3-pentanol, or 2,4-dimethyl-3-pentanol, an alicyclic secondary alcohol, like cyclopentanol or cyclohexanol, an unsaturated alcohol, isopentenyl alcohol, or a negatively substituted alcohol, e.g., 2-bromoethyl alcohol. The second alcohol, $R^2OH$, in the couplings is usually a primary alcohol of relatively low steric requirements. Such combinations produce less than 2% of undesirable *symmetrical* dialkyl (1-methylacetonyl) phosphates. The symmetrical triesters are the result of a transesterification in the second step of the synthesis, i.e., of a substitution on the cyclic phosphate with ring retention:

$$R^2OH + X{=}P(O)OR^1 \rightarrow X{=}P(O)OR^2 + R^1OH$$

$$R^1OH + X{-}P(O)OR^1 \rightarrow (R^1O)_2P(O)OCH(CH_3)COCH_3$$

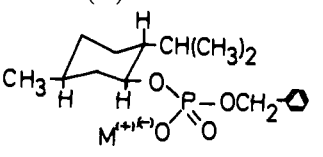
$$R^2OH + X{=}P(O)OR^2 \rightarrow (R^2O)_2P(O)OCH(CH_3)COCH_3$$

That the formation of symmetrical triesters in the syntheses of Table II is negligible (<2%) is shown in independent studies of the reaction of the alcohols $R^2OH$ with preformed cyclic triesters,[21] $X{=}P(O)OR^1$, in deuterated solvents, by means of $^1H$ NMR spectrometry (next Section). In most of the examples of Table II, the *uncatalyzed* reaction $R^2OH + X{=}P(O)OR^1$ generates less than 3–5% of symmetrical triesters, and the presence of imidazole or triethylamine reduces that amount even further.

One secondary alcohol, 2-propanol, is included, as the second alcohol $R^2OH$ in Table II. The highly sensitive 3,3-dimethylallyl alcohol, as well as the negatively substituted 2-bromoethanol and 2,2,2-trichloroethanol, also give good results as $R^2OH$ in the amine catalyzed syntheses.

With two exceptions, the dialkyl (1-methylacetonyl) phosphates (**5**) included in Table II can be deblocked to yield the desired unsymmetrical dialkyl phosphates, containing less than 2% of undesirable alkyl (1-methylacetonyl) phosphate. The exceptions are the triesters which contain either a trichloroethyl or dimethylallyl group. The 2-bromoethyl and the isopentenyl groups do not interfere in the deblocking step.

The one-flask synthesis of the dicyclohexylammonium salt, **6a″**, in 72% yield from (±)-menthol and benzyl alcohol by



**6a″**

Table I. Elemental Analyses and Spectral Data[a] of Derivatives of the 1,2-Dimethylethenylenedioxyphosphoryl Group, X=P(O)Y, X=P(O)OR, and Dialkyl(1-methylacetonyl) and Dialkyl Phosphates

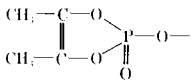
| Compd. no. | Substituent | M | Mp, bp, °C (mm) | Molecular formula | % calcd C | % calcd H | % calcd P | % found C | % found H | % found P | $^1$H NMR τ, ppm (J, Hz) | $^1$H NMR τ, ppm (J, Hz) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Y | | X=P(O)Y[b] | | | | | | | | $CH_3C{=}C$ | Signals in Y |
| 1 |  | | 84–86 | *c* | | | | | | | 8.02 | |
| 2 |  | | 62–64[d] | $C_7H_9O_3N_2P$ | 42.0 | 4.5 | 15.5 | 41.9 | 4.7 | 15.3[e] | 7.95 (0.5)[f] | 2.07; 2.78 |
| | R | | X=P(O)OR[g] | | | | | | | | $CH_3C{=}C$ | Signals in R |
| 4 | $(CH_3)_3CCH_2$ | | 90 (0.1)[h] | $C_9H_{17}O_4P$ | 49.1 | 7.8 | 14.1 | 49.2 | 7.9 | 14.0 | 8.07 | 6.20 (7); 9.04 |
| 4 | $CH_2{=}C(CH_3)CH_2CH_2$ | | 55 (0.005) | $C_9H_{15}O_4P$ | 49.5 | 6.9 | 14.2 | 49.5 | 7.0 | 14.1 | 8.09 | 5.15; 5.75; 7.51 (7); 8.24 |
| 4 | $(CH_3)_2C{=}CHCH_2$ | | *i* | | | | | | | | 8.07 | 4.64; 5.40 (10); 8.14 (3) |
| 4 | $(C_2H_5)(CH_3)CH$ | | 65 (0.025) | $C_8H_{15}O_4P$ | 46.6 | 7.3 | 15.0 | 46.9 | 7.2 | 14.8 | 8.06 | 5.46; 8.39 (7); 8.61 (6.5); 9.04 (7) |
| 4 | $(C_2H_5)_2CH$ | | 45 (0.005) | $C_9H_{17}O_4P$ | 49.1 | 7.8 | 14.1 | 49.3 | 8.0 | 14.2 | 8.04 | 5.50; 8.34 (7); 8.99 (7) |
| 4 | $[(CH_3)_2CH]_2CH$ | | 90 (0.1) | $C_{11}H_{21}O_4P$ | 53.2 | 8.5 | 12.5 | 53.1 | 8.6 | 12.3 | 8.07 | 5.85 (9.6); 9.03 (7) |
| 4 | c-$C_6H_{11}$ | | 60 (0.005) | $C_{10}H_{17}O_4P$ | 51.7 | 7.4 | 13.3 | 51.9 | 7.4 | 13.2 | 8.06 | 5.55; 8.34 |
| | $R^1$; $R^2$ | | $(R^1O)(R^2O)P(O)OCH(CH_3)(COCH_3)$[i] | | | | | | | | $CH_3CO$ | $CH_3CH$[k] |
| 5 | $(CH_3)_3CCH_2$; $(CH_3)_3CCH_2$ | | 90 (0.1) | $C_{14}H_{29}O_5P$[l] | 54.5 | 9.5 | 10.0 | 54.3 | 9.3 | 9.9 | 7.77 | 8.55 (7) |
| 5 | $(CH_3)_3CCH_2$; $C_6H_5CH_2$ | | 100 (0.1) | $C_{16}H_{25}O_5P$ | 58.5 | 7.7 | | 59.3 | 8.1 | | 7.83; [m] 7.86 | 8.58 (7); 8.60 (7) |
| 5 | $CH_2{=}C(CH_3)CH_2CH_2$; [n] $(CH_3)_2C{=}CHCH_2$ | | *i* | | | | | | | | 7.77 | 8.53 (7) |
| 5 | $(C_2H_5)_2CH$; $(CH_3)_2CHCH_2$ | | 90 (0.2) | $C_{13}H_{27}O_5P$ | 53.0 | 9.2 | 10.5 | 52.9 | 9.3 | 10.5 | 7.76 | 8.54 (7) |
| 5 | $(C_2H_5)_2CH$; $C_6H_5CH_2$ | | 97 (0.01) | $C_{16}H_{25}O_5P$ | 58.5 | 7.7 | 9.4 | 58.4 | 7.6 | 9.5 | 7.67; [m] 7.70 | 8.62 (7); 8.64 (7) |
| 5 | $[(CH_3)_2CH]_2CH$; $C_6H_5CH_2$ | | 95 (0.005) | $C_{18}H_{29}O_5P$ | 60.7 | 8.2 | 8.7 | 60.8 | 8.2 | 8.7 | 7.82; [m] 7.88 | 8.60 (7); 8.67 (7) |
| 5 | c-$C_5H_9$; $C_2H_5$ | | 70 (0.02) | $C_{11}H_{21}O_5P$ | 50.0 | 8.0 | 11.7 | 50.0 | 8.1 | 11.9 | 7.75 | 8.55 (7) |
| 5 | c-$C_5H_9$; [n] $CCl_3CH_2$ | | *i* | $C_{11}H_{18}O_5PCl_3$ | 35.9 | 4.9 | 8.4 | 36.2 | 5.1 | 8.2 | 7.75 | 8.57 (7) |
| 5 | c-$C_6H_{11}$; $C_6H_5CH_2$ | | 120 (0.2) | $C_{17}H_{25}O_5P$ | 60.0 | 7.4 | 9.1 | 59.7 | 7.5 | 9.2 | 7.77; [m] 7.79 | 8.60 (7); 8.61 (7) |
| 5 | (±)-3-*p*-Menthanyl; $C_6H_5CH_2$ | | 117 (0.005) | $C_{21}H_{33}O_5P$ | 63.6 | 8.4 | 7.8 | 63.4 | 8.4 | 7.6 | 7.85; [m] 7.88 | 8.60 (7); 8.64 |
| 5 | c-$C_6H_{11}$; $(CH_3)_2CH$ | | 66 (0.001) | $C_{13}H_{25}O_5P$ | 53.4 | 8.6 | 10.6 | 53.3 | 8.8 | 10.4 | 7.75 | 8.56 (7) |
| 5 | $(CH_3)_3C$; [n] $(CH_3)_2CHCH_2$ | | 50 (0.005) | $C_{12}H_{25}O_5P$[o] | 51.4 | 9.0 | 11.1 | 51.6 | 8.9 | 11.1 | 7.78 | 8.58 (7) |
| 5 | $(CH_3)_3C$; [n] c-$C_5H_9$ | | *i* | $C_{13}H_{25}O_5P$ | 53.4 | 8.6 | 10.6 | 53.3 | 8.7 | 10.6 | 7.75 | 8.55 (7) |
| 5 | $(CH_3)_3C$; [n] $(CH_3)_3CCH_2$ | | *i* | $C_{13}H_{27}O_5P$ | 53.1 | 9.2 | 10.5 | 52.8 | 9.3 | 10.4 | 7.74 | 8.54 (7) |
| | $R^1$; $R^2$ | M | $(R^1O)(R^2O)P(O)(OM)$[j] | | | | | | | | Main signals in $R^1$, $R^2$ | |
| 6 | $(CH_3)_3CCH_2$; | H | | | | | | | | | 6.33 (5); 9.03 | |
| 6a | $(CH_3)_3CCH_2$ | $(C_6H_{11})_2NH_2^{(+)}$ | 211–214[p] | $C_{22}H_{46}O_4NP$ | 63.0 | 11.0 | 7.4 | 63.0 | 11.2 | 7.5 | 6.55 (5); 8.4; 9.04 | |
| 6 | $(CH_3)_3CCH_2$; | H | | | | | | | | | −2.00; 2.70; 5.00 (7); 6.37 (5); 9.05 | |
| 6a | $C_6H_5CH_2$ | $(C_6H_{11})_2NH_2^{(+)}$ | 104–105[q] | $C_{24}H_{42}O_4NP$ | 65.6 | 9.6 | 7.0 | 65.4 | 9.8 | 7.1 | 0.6; 2.70; 5.10 (7); 6.50 (5); 9.10 | |
| 6 | $(C_2H_5)_2CH$ | H | | | | | | | | | 5.75; 6.23 (6); 8.4; 9.00 (4); 9.10 (3) | |
| 6a | $(CH_3)_2CHCH_2$ | $(C_6H_{11})_2NH_2^{(+)}$ | 164–165[p] | $C_{21}H_{44}O_4NP$ | 62.2 | 10.9 | 7.6 | 62.2 | 11.0 | 7.7 | 5.95; 6.40 (6); 7.04; 8.35; 9.04 (4); 9.10 (3) | |
| 6 | $(C_2H_5)_2CH$; | H | | | | | | | | | −1.13; 2.70; 5.00 (7); 5.82 (6); 8.40 (7); 9.08 (7) | |

Table I (continued)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 6a | $C_6H_5CH_2$ | $(C_6H_{11})_2NH_2^{(+)}$ | 121–122[r] | $C_{24}H_{42}O_4NP$ | 65.6 | 9.6 | 7.0 | 65.7 | 9.6 | 7.1[s] | 0.5; 2.75; 5.04 (6); 5.94; 7.18; 8.42 (7); 9.10 (7) |
| 6 | $[(CH_3)_2CH]_2CH$; | H | | | | | | | | | –2.5; 2.70; 4.98 (7); 6.00; 8.1; 9.00 (6) |
| 6a | $C_6H_5CH_2$ | $(C_6H_{11})_2NH_2^{(+)}$ | 121–123[r] | $C_{26}H_{46}O_4NP$ | 66.8 | 9.9 | 6.6 | 66.7 | 10.1 | 6.5[t] | 0.3; 2.70; 5.05 (6); 6.10; 7.10; 8.4; 9.00 (6) |
| 6 | c-$C_5H_9$; | H | | | | | | | | | 5.20; 5.96 (7); ~8.2; 8.65 (7) |
| 6a | $C_2H_5$ | $(C_6H_{11})_2NH_2^{(+)}$ | 136–137[r] | $C_{12}H_{23}O_4NP$ | 60.8 | 10.2 | 8.2 | 60.8 | 10.2 | 8.1[u] | 0.4; 5.44; 6.18 (7); 7.13; 8.2; 8.72 (7) |
| 6 | c-$C_6H_{11}$; | H | | | | | | | | | –2.0; 2.70; 5.05 (6); 5.70; ~8.5; 8.6 |
| 6a | $C_6H_5CH_2$ | $(C_6H_{11})_2NH_2^{(+)}$ | 133–135[v] | $C_{25}H_{42}O_4NP$ | 66.5 | 9.4 | 6.7 | 66.2 | 9.5 | 7.1 | 0.4; 2.70; 5.05 (6); 5.85; 7.10 |
| 6 | (±)-3-*p*-Methanyl; | H | | | | | | | | | –1.77; 2.70; 5.07 (6); 5.95; 7.8; 8.7; 9.2 |
| 6a | $C_6H_5CH_2$ | $(C_6H_{11})_2NH_2^{(+)}$ | 195–196[r] | $C_{29}H_{50}O_4NP$ | 68.6 | 9.9 | 6.1 | 68.7 | 9.9 | 6.1[w] | 0.4; 2.70; 5.15 (6); 6.06; 7.18; 8.5; 9.17 (4); 9.20 (4) |
| 6 | c-$C_6H_{11}$; | H | | | | | | | | | 6.45; ~8.3; 8.63 (6) |
| 6a | $(CH_3)_2CH$ | $(C_6H_{11})_2NH_2^{(+)}$ | 180–182[p] | $C_{21}H_{42}O_4NP$ | 62.5 | 10.5 | 7.7 | 62.5 | 10.6 | 7.7 | 5.6; 7.05; ~8.4; 8.77 (6) |

[a] NMR spectra in $CDCl_3$ at 25 °C. $^1H$ signals in parts per million from $Me_4Si$ = 10 ($\tau$); coupling constants, $J$ in Hz; all integrated intensities agree with the proposed structures. $^{31}P$ signals in parts per million from $H_3PO_4$ = 0. [b] $\delta\ ^{31}P$ = 1.5 | –O(O)P–X |; –6.1 [imidazolyl]. [c] Reference 5. [d] From benzene–hexane or $CH_2Cl_2$–hexane. [e] N: calcd, 14.0%; found, 13.9%. [f] The salt X=P(O)O(–)$HNH_2^{(+)}$ has $\tau$ 8.10, (CDCl$_3$). [k] 1-Methylacetonyl methine, $^1H$: $\tau$ 5.2–5.4 ppm (m). Main signals in R$^1$, R$^2$ in Table VII. [l] High resolution mass spectrum; *m/e* 308.1754 (calcd for $C_{14}H_{29}O_5P$, 308.1754). [m] Two diastereomers are observable. [n] Hydrolysis to dialkyl phosphate is not possible. [o] High resolution mass spectrum; *m/e* 280.1458 (calcd for $C_{12}H_{25}O_5P$, 280.1441). [p] Salt made in and recrystallized from ethyl acetate. [q] Salt made in petroleum ether; recrystallized from petroleum ether–hexane. [r] Salt made in diethyl ether; recrystallized from cyclohexane. [s] N: calcd, 3.2%; found, 3.0%. [t] N: calcd, 3.0%; found, 2.9%. [u] N: calcd, 3.7%; found, 3.8%. [v] Salt made in diethyl ether; recrystallized from dichloromethane–cyclohexane. [w] N: calcd, 2.8%; found, 2.6%.

procedure 1 can be cited as an example of the potential of this technique. The precursor 1-methylacetonyl ester of **6a**″ is isolated in 93% yield from the alcohols by procedure 2A, and can be hydrolyzed to **6a**″ in a separate operation.

Triesters **5** containing tertiary alkyl groups in combination with other groups can be synthesized by these methods. For example, the *tert*-butyl triesters in Table I are obtained in 90–94% yield by procedure 2B. The tertiary alcohol is the first substrate of the phosphorylation ($R^1OH$); the second step is complete in about 15 h in the case of $R^2OH$ = isobutyl and neopentyl alcohols, but requires longer periods of time (ca. 40–45 h) when $R^2OH$ = cyclopentanol. Removal of the 1-methylacetonyl group from the *tert*-butyl triesters fails, due to the lability of the *tert*-butyl group under the present deblocking conditions.

**Amine Catalysis of Phosphorylations.** The effect of amines on the reaction of alcohols with the preformed[21] cyclic triesters (**4**) was studied in several solvents, with the results shown in Tables III–V.

The data obtained in chloroform-*d* (Table III) disclose that imidazole is a very effective catalyst for the reaction of primary and secondary alcohols with cyclic triesters **4** of all types, i.e., those containing primary, secondary, and tertiary alkyl groups ($R^1$). Tertiary alcohols are not included because they are involved in side reactions with the catalyst, and because their uncatalyzed reactions are impracticably slow. Imidazole catalysis of the solvolysis of tetrabenzyl pyrophosphate in 1-propanol has already been noted by Westheimer and coworkers,[17] and the behavior of imidazole in nucleophilic catalysis of phosphoryl transfer in aqueous solution has been discussed extensively.[22–26]

Triethylamine is a catalyst for the phosphorylation of certain alcohols with the cyclic triesters **4** in chloroform-*d*, although it is less efficient than imidazole. Triethylamine exerts a selective catalysis of the reaction of primary alcohols with cyclic triesters **4** which contain primary or secondary alkyl groups ($R^1$). This amine does not increase the rate of the reaction of secondary alcohols with cyclic triesters of any type, or even of primary alcohols with triesters which contain tertiary alkyl groups ($R^1$); in some cases, the amine actually decreases the reaction rate somewhat.

Pyridine does not increase the rate of the reaction of any type of alcohol with the cyclic triesters, **4**, and when the amine is present in relatively large amounts (~100 mol %), the effect is a relatively small decrease in reaction rate. The reaction of alcohols with **4** is acid-catalyzed; therefore, the approximate half-times of the uncatalyzed reactions given in Tables III–V were checked also in the presence of 2–4 mol % of pyridine acting as a "proton sponge", since the cyclic triesters **4** are quite sensitive to moisture, and the hydrolysis generates a strong acid: $H_2O + X{=}P(O)OR^1 \rightarrow (R^1O)P(O)(OH)OCH(CH_3)\text{-}COCH_3$. The acid catalysis of the reaction $R^2OH$ + $X{=}P(O)OR^1$ is of no synthetic value and was not investigated further at this time.

The interplay of steric effects in both the amine catalyst and the two substrates of the reaction, $R^2OH$ and $X{=}P(O)OR^1$, is evident from the following observations: (a) Quinuclidine, which has nearly the same $pK_B$[27] as triethylamine (2.9 vs. 3.0), but has lower steric hindrance about the tertiary nitrogen, displays a catalytic pattern quite different from that of triethylamine and closer to that of imidazole ($pK_B$ = 6.9). (b) The rate enhancement of the primary alcohol phosphorylation by triethylamine decreases as the steric requirements of the alkyl group in $X{=}P(O)OR^1$ increase; this is seen in the behavior of $X{=}P(O)OC_5H_9$-c and $X{=}P(O)OCH[CH(CH_3)_2]_2$ toward $(CH_3)_2CHCH_2OH$.

Steric effects are also in evidence in the uncatalyzed reactions, where the rates decrease in the order primary > secondary for $R^2$ in $R^2OH$, and primary > secondary ≫ tertiary for

Table II. One-Flask Syntheses of Unsymmetrical Phosphodiesters and Dialkyl (1-Methylacetonyl) Phosphotriesters from Alcohols by *N*-(1,2-Dimethylethenylenedioxyphosphoryl)imidazole (2), and Di(1,2-dimethylethenylene) Pyrophosphate (1)

| | | Procedure no. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 2[b] | | | | | | |
| | | 1,[a] Diesters from performed *N*-phosphoryl-imidazole | | 2A, Triesters from preformed *N*-phosphoryl-imidazole | | 2B, Triesters from phosphoryl-imidazole made in situ | | 3,[b] Triesters from pyrophosphate | | |
| $R^1$ in $R^1OH$ | $R^2$ in $R^2OH$ | Time in second step, h | % yield[c] | Time in second step, h | % yield[d] | Time in second step, h | % yield[d] | Time in second step, h | % yield[d] | Product characterization |
| $(CH_3)_3CCH_2$ | $(CH_3)_3CCH_2$ | 12 | 80 | | | 3 | 90 | | | Table I |
| $(CH_3)_3CCH_2$ | $(CH_3)_2CHCH_2$ | 6 | 74 | 2 | 90 | | | | | Ref 6 |
| $(CH_3)_3CCH_2$ | $C_6H_5CH_2$ | | | | | 2 | 90 | | | Table I |
| $CH_2{=}C(CH_3)CH_2CH_2$ | $(CH_3)_2C{=}CHCH_2$ | | | | | | | 6 | 92 | Table I |
| $(C_2H_5)_2CH$ | $(CH_3)_2CHCH_2$ | 15 | 74 | | | 3 | 90 | | | Table I |
| $(C_2H_5)_2CH$ | $C_6H_5CH_2$ | 14 | 74 | 2 | 95 | | | | | Table I |
| $[(CH_3)_2CH]_2CH$ | $C_6H_5CH_2$ | 12 | 70 | 3 | 95 | | | | | Table I |
| c-$C_5H_9$ | $CH_3CH_2$ | 5 | 68 | 2 | 94 | | | | | Table I |
| c-$C_5H_9$ | $(CH_3)_2CHCH_2$ | 15 | 78 | 2 | 93 | 2 | 93 | 15 | 95 | Ref 5 |
| c-$C_5H_9$ | $C_6H_5CH_2$ | 14 | 80 | 2 | 94 | | | 7 | 95 | Ref 5 |
| c-$C_5H_9$ | $CH_2{=}C(CH_3)CH_2CH_2$ | 6 | 70 | 2 | 94 | | | | | Ref 6 |
| c-$C_5H_9$ | $BrCH_2CH_2$ | | | | | 2 | 88 | 4 | 92[e] | Ref 6 |
| c-$C_5H_9$ | $CCl_3CH_2$ | | | | | 18 | 94 | | | Table I |
| $BrCH_2CH_2$ | (*trans*-2-hydroxycyclopentyl)methyl | | | | | | | 12 | 90[f] | Ref 5 |
| c-$C_5H_9$ | (*trans*-2-hydroxycyclopentyl)methyl | | | | | | | 15 | 92[g] | Ref 5 |
| c-$C_6H_{11}$ | $C_6H_5CH_2$ | 15 | 72 | | | 2 | 95 | | | Table I |
| c-$C_6H_{11}$ | $(CH_3)_2CH$ | 15 | 78 | 2 | 94 | | | | | Table I |
| (±)-3-*p*-Menthanyl | $C_6H_5CH_2$ | 15 | 72 | 3 | 93 | | | | | Table I |

[a] Synthesis of phosphodiesters **6**. [b] Syntheses of phosphotriesters 5. [c] Phosphodiester salt **6a**, based on $R^1OH$. [d] Phosphotriester 5, based on $R^1OH$. [e] $R^1OH$ and 2 mol equiv of $(C_2H_5)_3N$ added to pyrophosphate, followed by $R^2OH$. [f] $R^1OH$ added to pyrophosphate, followed by 2 mol equiv of $(C_2H_5)_3N$, and 1 mol equiv of $R^2OH$. The triester contains 95% of primary OH, and 5% of secondary OH phosphorylation products. [g] The triester contains 98% of primary OH and 2% of secondary OH phosphorylation products.

Table III. Half-Times of the Reaction of Cyclic Phosphotriesters with Alcohols in 0.2 M $CDCl_3$ at 25 °C:[a] $R^2OH + X{=}P(O)OR^1 \rightarrow (R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$

| Reaction | | Catalyst[b] | | | |
|---|---|---|---|---|---|
| $R^2$ | $R^1$ | None | Imidazole | Triethylamine | Quinuclidine |
| $(CH_3)_2CHCH_2$ | $(CH_3)_2CHCH_2$ | 4 h | 2 min | 40 min | 2 min |
| $(CH_3)_2CHCH_2$ | c-$C_5H_9$ | 7.5 h | 3 min | 1.5 h | 3 min |
| $(CH_3)_2CHCH_2$ | $(CH_3)_3C$ | 45 h | 2 h | 50 h | 1 h |
| c-$C_5H_9$ | $(CH_3)_2CHCH_2$ | 9 h[c] | 5 min[d] | 9 h[d] | 15 min[d] |
| c-$C_5H_9$ | c-$C_5H_9$ | 28 h | 15 min | 30 h | 40 min |
| c-$C_5H_9$ | $(CH_3)_3C$ | 75 h | 8 h | 80 h | 14 h |
| $(CH_3)_2CHCH_2$ | $(CH_3)_3CCH_2$ | 5 h | 2 min | 1.5 h | 2 min |
| $(CH_3)(C_2H_5)CH$ | c-$C_5H_9$ | 34 h | 20 min | 36 h | 35 min |
| $(CH_3)_3CCH_2$ | $(CH_3)_3C$ | 80 h | 3 h | 110 h | 7 h |
| $C_6H_5CH_2$ | c-$C_5H_9$ | 2.5 h[c] | 1.5 min[d] | 15 min[d] | 1 min[d] |
| $(CH_3)_2CHCH_2$ | $[(CH_3)_2CH]_2CH$ | 22 h | 10 min | 15 h | 20 min |
| c-$C_5H_9$ | $[(CH_3)_2CH]_2CH$ | 70 h | 1.5 h | >3 d | 8 h |
| $(CH_3)_2CHCH_2$ | $BrCH_2CH_2$ | 50 min[c] | <30 s[d] | 4 min[d] | <30 s[d] |

[a] Equimolar amounts of reagents and amine. The disappearance of $X{=}P(O)OR^1$ and the appearance of $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$ were followed by $^1H$ NMR spectrometry; the figures are the times at which the concentrations of both species became equal. Symmetrical phosphotriesters were not observed (<2%) except as indicated. [b] $pK_B$: quinuclidine, 2.9; triethylamine, 3.0; imidazole, 6.9. [c] Symmetrical dialkyl (1-methylacetonyl) phosphates were formed as by-products in 6–8%. [d] Amount of symmetrical triester reduced to <3%.

Table IV. Half-Times of the Reaction of Cyclic Phosphotriesters with Alcohols in 0.2 M $CD_3CN$ at 25 °C:[a] $R^2OH + X{=}P(O)OR^1 \rightarrow (R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$

| Reaction | | Catalyst | | | |
|---|---|---|---|---|---|
| $R^2$ | $R^1$ | None | Imidazole | Triethylamine | Quinuclidine |
| $(CH_3)_2CHCH_2$ | $(CH_3)_2CHCH_2$ | 7 h | 12 min | 1 h | 3 min |
| $(CH_3)_2CHCH_2$ | c-$C_5H_9$ | 12 h | 25 min | 2.5 h | 6 min |
| c-$C_5H_9$ | c-$C_5H_9$ | 32 h | 2 h | 17 h | 1 h |
| $(CH_3)_2CHCH_2$ | $(CH_3)_3CCH_2$ | 8.5 h | 20 min | 2 h | 4 min |
| $(CH_3)(C_2H_5)CH$ | c-$C_5H_9$ | 40 h | 3 h | 18 h | 55 min |
| $(CH_3)_2CHCH_2$ | $[(CH_3)_2CH]_2CH$ | 22 h | 2 h | 12 h | 35 min |

[a] Equimolar amounts of reagents and amine. The figures are the times at which $[X{=}P(O)OR^1] = [(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3]$ by $^1H$ NMR spectrometry. Symmetrical phosphotriesters were not observed (<2%).

Table V. Imidazole Catalysis of the Reaction of Isobutyl Alcohol with Cyclopentyl (1,2-Dimethylethenylene) Phosphate in Various Solvents[a]

| Solvent | $t_{1/2}$ | | |
|---|---|---|---|
| | No catalyst | Imidazole | 1-Methylimidazole |
| Dioxane | 6.5 h | 3 min | 4 h |
| Deuteriochloroform | 7.5 h | 3 min | 7 h |
| Acetonitrile-$d_3$ | 12 h | 25 min | 6 h |
| Pyridine-$d_5$ | 20 h | 50 min | 12 h |
| Dimethylformamide-$d_7$ | 9 days | 4 h | |

[a] Equimolar reagents and imidazole, in 0.2 M solution at 25 °C. The disappearance of X=P(O)O-c-$C_5H_9$ and the appearance of the acylic triester were followed by $^1$H NMR spectrometry; $t_{1/2}$ is the time at which the concentration of both species became equal.

$R^1$ in X=P(O)O$R^1$.

The data in Tables IV and V show that the reaction rates decrease with an increase in solvent polarity in the imidazole-catalyzed reactions. This solvent effect is not as significant in the reactions catalyzed by triethylamine or quinuclidine or in the uncatalyzed reactions. It is apparent that the amine catalysis makes it possible to carry out the syntheses in solvents such as acetonitrile and dimethylformamide, which widens their scope significantly, since some complex alcohols, e.g. the nucleosides, have limited solubility in dichloromethane. Quinuclidine becomes slightly more effective than imidazole in acetonitrile.

It is noteworthy that *N*-methylimidazole has only a slight catalytic effect, since Reese, Van Boom, and co-workers[28] have noted catalysis of the phosphorylation of alcohols by diphenyl phosphorochloridate using 5-chloro-1-methylimidazole in acetonitrile solution.

Table VI explores in more detail the ability of triethylamine to catalyze phosphorylations of primary, but not secondary alcohols. The relatively bulky tertiary amine discriminates between primary OH and secondary OH functions in separate molecules as well as in the same molecule.

The evidence now at hand shows that the relative amounts of unsymmetrical vs. symmetrical dialkyl (1-methylacetonyl) phosphates depend on the sequence in which the pair of alcohols is submitted to the phosphorylative coupling. Moreover, in all the cases so far examined, the amount of undesirable symmetrical triester is significantly lower in the imidazole- and triethylamine-catalyzed reactions of a given alcohol with a given alkyl cyclic triester (**4**) than in the corresponding uncatalyzed reaction.

In the uncatalyzed reactions, the formation of symmetrical triester is minimized if the relatively smaller alcohol (≡ $R^2OH$) is added to the cyclic triester which contains the bulkier alkyl group (≡ $R^1OH$), or when the more electronegative alcohol, e.g., $BrCH_2CH_2OH$, is added to the triester with the less electronegative alkyl group. Moreover, even if a significant amount of symmetrical triester (3–8%) is obtained in the uncatalyzed reaction, this amount is reduced to <2% in the presence of the amines. For example, the uncatalyzed reactions of benzyl alcohol with the cyclic triesters X=P(O)$OC_5H_9$-c, X=P(O)$OC_6H_{11}$-c, and X=P(O)$OCH(C_2H_5)_2$ produce about 4–8% of symmetrical phosphotriesters in 0.2 M $CDCl_3$ at 25 °C. The amount of symmetrical by-product is reduced to less than 2% in the imidazole- and triethylamine-catalyzed reactions under comparable conditions.

The reaction of alcohols $R^1OH$ with the phosphorylimidazole **2** is autocatalyzed by imidazole. The reaction rates for most alcohols are too rapid for the convenient demonstration of this effect; e.g., most reactions in 0.2 M $CDCl_3$ at 25 °C are complete in less than 2 min. In the case of *tert*-butyl alcohol, however, the concentrations of reactant and product become equal ([X=P(O)IM] = [X=P(O)O$R^1$]) in about 3 min (complete reaction in ca. 15 min) without amine; those figures become 30 s and 3–5 min, respectively, when 1 mol equiv of imidazole is added initially. The uncatalyzed reaction of *tert*-butyl alcohol with the pyrophosphate **1** appears to be somewhat slower ($t_{1/2} \sim 22$ min, 0.2 M $CDCl_3$, equimolar reactants, at 25 °C) than that of the phosphorylimidazole **2**.

## Discussion

The behavior of alcohols $R^2OH$ toward the cyclic enediol phosphates, X=P(O)O$R^1$, in particular (a) the variations in the relative amounts of unsymmetrical and symmetrical dialkyl(1-methylacetonyl) phosphates depending on the structure of the alkyl groups $R^1$ and $R^2$; and (b) the catalysis of the reactions by imidazole, certain tertiary amines, and phenoxide ions[6] are difficult to explain unless one postulates the formation of oxyphosphoranes as reaction intermediates.[29-34] Likewise, the reactions of alcohols (and water) with the pyrophosphate **1**, the phosphorylimidazole, **2**, and the aryl cyclic triesters[6] X=P(O)OAr are strongly suggestive of the formation of oxyphosphorane intermediates. The question is how to account for the occurrence of the relatively rapid substitutions at the four-coordinate cyclic phosphorus by 1 mol equiv of the alcohol (or water) *in aprotic solvents* of low polarity, with results that range from nearly 100% ring retention[35,36] to nearly 100% ring opening, without the incorporation into the products of imidazole or phenol in the imidazole- and phenoxide-catalyzed[6] reactions of the alkyl cyclic triesters.

In the oxyphosphorane-intermediate hypothesis, the reaction of imidazole with the pyrophosphate **1** proceeds via the phosphorane **8** (X=P(O)O in place of Y). A permutational isomerization of **8**, possibly by the turnstile rotation mechanism[37,38] with the ring as the ligand pair, generates isomer **9**, which collapses to the phosphorylimidazole **2** by apical departure of the cyclic phosphate (Y).

The uncatalyzed reaction of alcohol $R^1OH$ with the phos-

Table VI. Enhancement of Primary OH vs. Secondary OH Phosphorylation Selectivity by Triethylamine:[a]
$RCH_2OH + R'R''CHOH + X{=}P(O)O\text{-c-}C_5H_9 \rightarrow (\text{c-}C_5H_9O)(RCH_2O)P(O)OCH(CH_3 + (\text{c-}C_5H_9O)(R'R''CHO)P(O)OCH(CH_3)COCH_3$

| Primary alcohol | Secondary alcohol | Catalyst | % phosphorylation | |
|---|---|---|---|---|
| | | | Primary OH | Secondary OH |
| $(CH_3)_2CHCH_2OH$ | c-$C_5H_9OH$ | None | 75 | 25 |
| | | $(C_2H_5)_3N$ | 90 | 10 |
| $(CH_3)_2CHCH_2OH$ | $(CH_3)_2CHOH$ | None | 75 | 25 |
| | | $(C_2H_5)_3N$ | 90 | 10 |
| $(CH_3)_2CHCH_2OH$ | $(CH_3)(C_2H_5)CHOH$ | None | 83 | 17 |
| | | $(C_2H_5)_3N$ | 94 | 6 |
| *trans*-2-Hydroxymethylcyclopentanol | | None | 90 | 10 |
| | | $(C_2H_5)_3N$ | 98 | 2 |
| | | Imidazole | 80 | 20 |

[a] Equimolar amounts of reagents and amine in 0.2 M $CDCl_3$ at 25 °C. Total reaction times: 2 days (no amine); 15 h (amine). Product composition by $^1$H NMR spectrometry.

$$[X{=}P(O)]_2O + 2IMH \longrightarrow X{=}P(O)IM + X{=}P(O)\bar{O}I\overset{+}{M}H_2$$

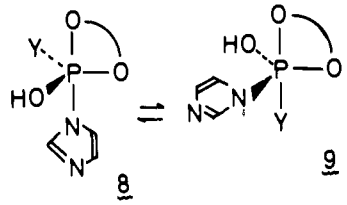
$$[X{=}P(O)]_2O + R^1OH + Et_3N \longrightarrow X{=}P(O)OR^1 + X{=}P(O)\bar{O}\overset{+}{E}t_3NH$$

$$X{=}P(O)IM + R^1OH \longrightarrow X{=}P(O)OR^1 + IMH$$

$$X{=}P(O)OAr + R^1OH \longrightarrow X{=}P(OR^1) + ArOH^6$$

$$X{=}P(O)OR^1 + R^2OH \begin{cases} \longrightarrow X{=}P(O)OR^2 + R^1OH \\ \longrightarrow (R^1O)(R^2)P(O)OCH(CH_3)COCH_3 \end{cases}$$

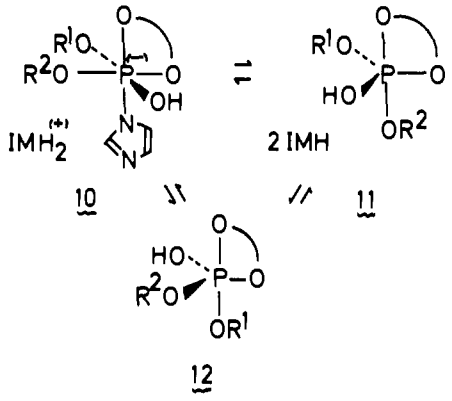
Uncatalyzed or catalyzed by $ArO^-$, IMH, or $R_3N$



8 ⇌ 9

phorylimidazole **2** proceeds via phosphorane **9** ($R^1O$ in place of Y). Permutational isomerization of **9** generates **8,** which collapses to the alkyl cyclic phosphate **4** by apical departure of imidazole.

The first step of the imidazole-catalyzed reaction of alcohol $R^2OH$ with $X{=}P(O)OR^1$ (**4**) involves the formation of the phosphorane **8** ($R^1O$ in place of Y). Now, **8** can add the second alcohol $R^2OH$ in the presence of the base to give an intermediate with hexacoordinate phosphorus **10.** Compounds analogous to **10** have actually been isolated.[39-44] Several investigators have postulated the intermediacy of P(6) structures in nucleophilic displacements of relatively stable, *isolated* oxyphosphoranes.[45-50]

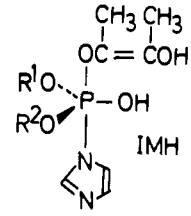


10 ⇌ 2 IMH ⇌ 11



12

The P(6) intermediate, **10,** could collapse[51] to one or both isomeric phosphoranes **11** and **12** which, moreover, can equilibrate by the TR mechanism.[37] Isomer **11** is generated directly by apical addition of $R^2OH$ to the cyclic ester, $X{=}P(O)OR^1$, in the uncatalyzed reaction. Ring opening of **11** (prior to equilibration with isomer **12**) would yield the unsymmetrical acyclic triester **5** exclusively. Equilibration of **11** and **12,** followed by apical departure of the $R^1O$ ligand from **12,** yields $X{=}P(O)OR^2$ and corresponds to a transesterification, which eventually results in the formation of symmetrical acyclic triesters. The fact that different relative amounts of unsymmetrical and symmetrical triesters are produced in the uncatalyzed phosphorylative couplings *depending on the order in which the two alcohols are allowed to react* implies that ring opening is competitive with the equilibration of isomers **11** and **12** by permutational isomerization. The decrease in the amount of symmetrical triesters in the amine-catalyzed couplings could reflect a new mechanism for ring opening, for example by collapse of the P(6) intermediate **10** to the acyclic phosphorane **13,** followed by ejection of imidazole from the latter.

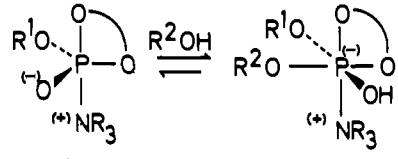


13

A phosphorane with a relatively small ligand at the apex and a bulkier ligand in the equator should be favored over its isomer with the reverse ligand distribution.[31] Likewise, the phosphorane with the more apicophilic,[37] electronegative ligand (e.g., $BrCH_2CH_2O$), at the apex should be favored over its isomer. If the thermodynamically favored P(5) isomer is initially formed by apical attack of $R^2OH$ on $X{=}P(O)OR^1$, the tendency for isomerization should be lower, and this would facilitate ring opening, resulting in less transesterification and a smaller amount of undesirable symmetrical triester in the above picture.

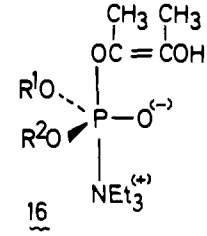
We speculate further that the addition of a nucleophile to the P(4) substrate to form the phosphorane intermediate is rate controlling, and the amine catalysis results from the higher nucleophilicity of the amine vs. the alcohol $R^2OH$. The P(5) ⇌ P(6) step is assumed to be relatively rapid. The various ways in which the P(5) and P(6) intermediates can collapse, and the possibility of permutational isomerization of P(5) provide for product control in this picture. The observations of solvent effect on reaction rates are consistent with these hypotheses. The stable oxyphosphoranes[31a] are remarkably soluble in solvents such as hexane, benzene, and dichloromethane; the transition states involved in the conversion of phosphates into unstable oxyphosphorane intermediates may be regarded as less polar in character than the corresponding ground states (i.e., the phosphate + alcohol or the phosphate + IMH). Hence, decrease in reaction rate with increase in solvent polarity is reasonable in this picture.

The catalysis of the reaction $R^2OH + X{=}P(O)OR^1$ by triethylamine can be explained by the dipolar phosphorane intermediate, **14,** which then adds the second alcohol to form the P(6) intermediate **15.** A compound entirely analogous to **15** has been isolated from a tertiary amine and a stable phosphorane.[39] An intermediate similar to **14** has also been postulated to explain the rapid stereomutation at phosphorus of five-membered cyclic acyl phosphates by tertiary amines.[52]



14 ⇌ 15

The fate of the P(6) intermediate **15** should be similar to that of **10,** with the appropriate differences in charge type, e.g. **16**



16

vs. **13.** The differences in the charge distribution and the steric features of phosphoranes **8** and **14** could account for the ob-

servations in Tables III–VI. In both $CDCl_3$ and $CD_3CN$, triethylamine is less efficient as a catalyst and more selective for primary vs. secondary alcohol phosphorylations with X=P(O)OR[1] than imidazole. However, this lower efficiency and higher selectivity become less noticeable in the more polar solvent $CD_3CN$; in the latter, triethylamine shows a slight catalytic effect for secondary-alcohol phosphorylation. The more crowded phosphorane derived from a tertiary amine, **14**, should display a higher tendency to discriminate between a primary vs. a secondary alcohol in forming the P(6) intermediate **15** than the less crowded phosphorane derived from imidazole, **8** → **10**. The interesting thing is that this difference between tertiary amines and imidazole seems to be sensitive to both the steric effects of the tertiary amine and to the polarity of the medium. Quinuclidine resembles imidazole rather than triethylamine in catalytic efficiency and in selectivity; moreover, quinuclidine becomes slightly more effective than imidazole in the more polar solvent $CD_3CN$. Evidently, for synthetic purposes, the amine and the solvent must be chosen with the particular objective in mind: triethylamine in $CH_2Cl_2$ or $CDCl_3$ provides the maximum selectivity among the systems studied so far.

The imidazole autocatalysis of the reaction of alcohols with the phosphorylimidazole **2** can proceed via **8** (imidazolyl in place of Y).

The experimental facts presented in this paper, and the hypotheses offered to interpret them, could be applicable to the behavior of some of the enzymes that are involved in biological phosphoryl-group transfer.[53-57] It is apparent that imidazole and other amines are capable of exerting a particularly strong phosphate activation *in aprotic solvents of low polarity*. Moreover, it has been shown that considerable enhancement of primary OH vs. secondary OH selectivity in phosphorylations can be achieved through amine catalysis of the reactions. It is conceivable that these effects are mechanistically related to those operating in enzymes in which histidine and lysine[56,57] residues are involved in the catalytic activity. This suggestion complements a recent one[6] to the effect that the demonstrated phenoxide ion catalysis of the phosphorylation of alcohols by the cyclic triesters[6] **4** may be related to the mechanism of the action of enzymes in which tyrosine,[54] histidine, and lysine residues are involved in the catalytic activity. The possible intervention of six-coordinate, as well as five-coordinate phosphorus species in these reactions is an attractive hypothesis that should be considered in future interpretation of the enzymatic mechanisms.

## Experimental Section

The physical constants of the new compounds are given in Table I. Additional $^1H$ NMR data are summarized in Table VII. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Derivatives of the group X=P(O)– are very sensitive to moisture. Solvents were purified and stored over molecular sieves. A dry $N_2$ atmosphere is advisable in all reactions.

**Reaction of Di(1,2-dimethylethenylene) Pyrophosphate (1) with Imidazole.** Imidazole (6.42 g; 94.4 mmol) was added to a stirred solution of the pyrophosphate (**1**; 13.30 g; 47.2 mmol) in $CH_2Cl_2$ (100 ml) at 0 °C. After 30 min at 0° and 30 min at 20°, the solvent was evaporated (at 30 °C (20 mm, then 0.2 mm)). The residue was extracted with diethyl ether (5 × 50 ml), the combined ether extract was evaporated in vacuum, and the residue (9.07 g) was recrystallized from benzene–hexane to give *N*-(1,2-dimethylethenylenedioxyphosphoryl)imidazole (**2**; 8.41 g; 90% of the theory).

**Reactions of *N*-(1,2-Dimethylethenylenedioxyphosphoryl)imidazole (2) with 1 and 2 Mol Equiv of an Alcohol.** The alcohol (0.9 mol equiv) was added to a 0.6 M $CDCl_3$ solution of the X=P(O)IM **2** in an NMR tube at 25°. The $^1H$ NMR spectrum was recorded immediately, and at 2 min time intervals, until no further changes were noted. More of the same alcohol was introduced in ca. 0.1 mol equiv increments up to a total of 2 mol equiv relative to X=P(O)IM **2**. The $^1H$ NMR spectra were recorded after each increment, and until no further changes were noted on each successive addition. Several of the alcohols employed in the syntheses (Table II) were tested in this manner. The first step, ROH + X=P(O)IM → X=P(O)OR + IMH, was much faster than the second, X=P(O)OR + ROH → $(RO)_2P(O)$-$OCH(CH_3)COCH_3$.

Table VII. Main $^1H$ NMR Signals of the Alkyl Groups $R^1$ and $R^2$ in Dialkyl (1-Methylacetonyl) Phosphates

| Alkyl group | $\tau$, ppm ($J$, Hz) |
|---|---|
| $CH_3CH_2$ | 5.8; 8.65 (7) |
| $(CH_3)_2CHCH_2$ | ~6.1–6.2; 8.0; 9.08 (6) |
| $(CH_3)_3CCH_2$ | 6.2–6.3; 9.03 |
| $CH_2=C(CH_3)CH_2CH_2$ | 5.15; 5.58; 7.55; 8.25 |
| $(CH_3)_2C=CHCH_2$ | 4.64; 5.40 (10); 8.14 (3) |
| $C_6H_5CH_2$ | 2.68; 4.93 (8) |
| $BrCH_2CH_2$ | 5.70; 6.47 |
| $CCl_3CH_2$ | 5.5–5.6 |
| $(CH_3)_2CH$ | 5.4; 8.63 (6) |
| $(CH_3)(CH_3CH_2)CH$ | 5.46; 8.39 (7); 8.61 (6.5); 9.04 (7) |
| $(CH_3CH_2)_2CH$ | 5.70 (7); ~8.3; 9.07 (6) |
| $[(CH_3)_2CH]_2CH$ | 2.70; 4.96 (8); 5.00 (8); 5.32; 5.94; 8.04; 9.10 |
| c-$C_5H_9$ | 5.1; 8.2 |
| c-$C_6H_{11}$ | 5.4; 8.3 |
| (±)-3-*p*-Menthanyl | 5.80; 9.20 (m) |
| $(CH_3)_3C$ | 8.50 |

**Stepwise Preparation of Dialkyl (1-Methylacetonyl) Phosphates (5) via Isolated Alkyl (1,2-Dimethylethenylene) Phosphates (4).** Several known[5] and new (cf. Table I) cyclic triesters **4** were prepared from the alcohol $R^1OH$ and the pyrophosphate (**1**) in dichloromethane solution, using 1 mol equiv of γ-collidine or nicotinamide as the base, following the published procedure.[5] The isolated cyclic triesters **4** were allowed to react with alcohol $R^2OH$ in dichloromethane solution in the absence of catalyst and in the presence of imidazole or triethylamine to verify the formation of the acyclic triesters **5** in the "one-flask" syntheses.

The cyclic triesters **4** are also generated from the alcohol $R^1OH$ and the phosphorylimidazole **2**, but the separation of the by-product imidazole from the triester is impractical.

**Procedure 1. One-Flask Synthesis of Unsymmetrical Phosphodiesters from *N*-(1,2-Dimethylethenylenedioxyphosphoryl)imidazole (2).** An acetonitrile solution of $R^1OH$ is added (5–10 min) to a stirred solution of the phosphorylimidazole (**2**; 1 mol equiv) in the same solvent, and the mixture is stirred for 45 min (20 °C, 0.6–0.8 M). An acetonitrile solution of $R^2OH$ (1 mol equiv) is introduced (2–3 min), and the solution (0.4–0.6 M) is stirred at 20 °C for periods which vary with the structure of the alcohols (cf. Table II); reaction times are conveniently ascertained by $^1H$ NMR spectrometry. The solution is diluted with acetonitrile, mixed with twice its volume of water (final molarity ~0.1), treated with 2 mol equiv of triethylamine or diisopropylethylamine, and stirred at 70 °C for ca. 10 hr. The acetonitrile is evaporated under reduced pressure and the aqueous solution is treated with sodium carbonate (ca. 5 mol equiv), extracted with dichloromethane[58] (three times) to remove by-products, acidified (e.g., with 5% HCl), and reextracted with dichloromethane (four times). The organic extract is dried ($Na_2SO_4$) and evaporated to give the dialkyl phosphate $(R^1O)(R^2O)P(O)OH$ (**6**) in high degree of purity, according to the $^1H$ NMR spectrum (Table I). The acid is converted into a crystalline amine salt, **6a** (Table I), for characterization. Suitable amines are dicyclohexylamine or cyclohexylamine and appropriate solvents are ethyl acetate, diethyl ether, or hexane. The salts **6a** are isolated in 75–80% yield based on $R^1OH$.

A simpler workup applicable to many phosphodiesters involves the removal of by-products by diethyl ether extraction (three times) of the aqueous solution containing the trialkylammonium salt of the phosphate (without addition of sodium carbonate). This is followed by acidification and extraction of the organic acid into dichloromethane as before. Attention should be paid to the relatively high solubility of some dialkyl hydrogen phosphates in water.

If $R^1OH$ is relatively hindered, e.g., 2,4-dimethyl-3-pentanol, it may be necessary to increase reaction time (ca. 2 h) in the first step (i.e., reaction with **2**).

**Procedure 2. One-Flask Synthesis of Unsymmetrical Dialkyl (1-Methylacetonyl) Phosphotriesters from *N*-(1,2-Dimethylethenylenedioxyphosphoryl)imidazole (2). 2A. From Preformed Phosphoryli-**

**midazole.** A dichloromethane solution of $R^1OH$ is added (5–10 min) to a stirred solution of the phosphorylimidazole (**2**; 1 mol equiv) in the same solvent, and the mixture is stirred for 20–30 min (20 °C; 0.6–0.8 M). A dichloromethane solution of $R^2OH$ (1 mol equiv) is introduced (2–3 min) and the solution (0.4–0.6 M) is stirred at 20° for periods which vary with the structure of the alcohols (cf. Table II). The solution is diluted with dichloromethane (~0.1 M) and extracted with 5% HCl (twice) to remove imidazole. The organic solution is dried ($Na_2SO_4$) and evaporated to give the virtually pure dialkyl (1-methylacetonyl) phosphate (**5**) in 92–96% yield based on $R^1OH$; see Table I.

The triesters **5** are hydrolyzed[59,60] to the diesters **6** with or without an intervening purification step (by short-path distillation under reduced pressure or other suitable technique). The hydrolysis can be performed by one of these methods. (a) In 2:1 v/v water:acetonitrile with 2 mol equiv of triethylamine or diisopropylamine (70 °C; 10 h); the workup is as in procedure 1 above. (b) In 1:1 v/v water:pyridine with 2 mol equiv of the tertiary amine (70 °C; 10 h). The solution is evaporated in vacuum, the residue is dissolved in water, and the solution is extracted with dichloromethane to remove by-products. The aqueous solution is acidified (5% HCl) and extracted with dichloromethane to retrieve the phosphodiester. (c) In 2:1 v/v water:acetonitrile with 2 mol equiv of $Na_2CO_3$ instead of the tertiary amine. The $Na_2CO_3$ procedure is indicated for $(BrCH_2CH_2O)(RO)P(O)OCH(CH_3)COCH_3$ to avoid side reactions of the tertiary amine with the 2-bromoethyl group.

**2B. From Phosphorylimidazole (2) Made in Situ.** A dichloromethane solution of imidazole (2 mol equiv) is added to di(1,2-dimethylethenylene) pyrophosphate[5] (**1**; 1 mol equiv) and the solution is stirred for 15 min (20 °C) to generate the phosphorylimidazole **2.** The alcohols $R^1OH$ and $R^2OH$ (1 mol equiv of each) are introduced as in procedure 2A. The solution is diluted with dichloromethane (~0.1 M) and extracted with 5% sodium carbonate (three times) to remove the $X{=}P(O)O^{(-)}$ present as by-product and 5% HCl (twice) and water (once) to remove the imidazole. The dialkyl (1-methylacetonyl) phosphates (**5**) are isolated as in procedure 2A, and are obtained in 92–96% yield based on $R^1OH$.

**Procedure 3. One-Flask Synthesis of Unsymmetrical Dialkyl (1-Methylacetonyl) Phosphotriesters from Di(1,2-dimethylethenylene) Pyrophosphate (1).** A dichloromethane solution of $R^1OH$ containing 1 mol equiv of triethylamine is added to a solution of the pyrophosphate[5] (**1**; 1 mol equiv) in the same solvent and the mixture is stirred for 30 min (20 °C, 0.6–0.8 M). A dichloromethane solution of $R^2OH$ (1 mol equiv) containing 1 mol equiv of triethylamine is introduced and the mixture is stirred for the appropriate period of time (Table II; usually 10 h at 20 °C in 0.5 M solutions, when $R^1$ = secondary alkyl, and $R^2$ = primary alkyl; significantly shorter if $R^1$ = primary alkyl, and longer if $R^2$ = secondary alkyl). The solution is diluted with dichloromethane (~0.1 M) and worked up as in procedure 2B (successive extractions with dilute $Na_2CO_3$ and HCl). The dialkyl (1-methylacetonyl) phosphates (**5**) are isolated in 92–96% yields based on $R^1OH$.

When $R^1OH = BrCH_2CH_2OH$, it is added to the pyrophosphate **1** in the absence of amine, then 2 mol equiv of triethylamine is introduced, followed by $R^2OH$. Another variation, when $R^1OH$ is complex and may be sensitive to triethylamine, consists of placing the first mole equivalent of the amine in solution with the pyrophosphate **1.**

## References and Notes


(1) This work was supported by Public Health Service Grant GM 20672 from the National Institute of General Medical Sciences. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (Grant 7136). Preliminary Communication: F. Ramirez, J. F. Marecek, and H. Okazaki, *J. Am. Chem. Soc.*, **97**, 7181 (1975).

(2) X = 1,2-dimethylethenylenedioxy in subsequent formulas. Another systematic nomenclature for these compounds is based on the 1,3,2-dioxaphosphole ring: X=P(O)–, 2-oxo-4,5-dimethyl-1,3,2-dioxaphospholyl; =P(O)OR, 2-alkoxy-2-oxo-4,5-dimethyl-1,3,2-dioxaphosphole; X–P(O)IM, 2-(1′-imidazolyl)-2-oxo-4,5-dimethyl-1,3,2-dioxaphosphole. The pyrophosphate can also be named oxybis(1,2-dimethylethenylenedioxyphosphoryl); a descriptive name for it is acetoin enediol cyclopyrophosphate.

(3) (a) F. Ramirez, O. P. Madan, and C. P. Smith, *J. Am. Chem. Soc.*, **87**, 670 (1965); (b) D. Swank, C. N. Caughlan, F. Ramirez, O. P. Madan, and C. P. Smith, *ibid.*, **89**, 6503 (1967).

(4) F. Ramirez, J. F. Marecek, S. L. Glaser, and P. Stern, *Phosphorus*, **4**, 65 (1974).

(5) F. Ramirez, J. F. Marecek, and I. Ugi, *J. Am. Chem. Soc.*, **97**, 3809 (1975).

(6) F. Ramirez and J. F. Marecek, *J. Org. Chem.*, **40**, 2849 (1975).

(7) F. Ramirez and I. Ugi, *Phosphorus*, in press.

(8) For other recent syntheses of phosphodiesters, see ref 9–11 and literature cited therein.

(9) (a) C. B. Reeese, *Colloq. Int. C.N.R.S.*, **182**, 319 (1970); (b) T. A. Khwaja, C. B. Reese, and J. C. M. Stewart, *J. Chem. Soc. C*, 2092 (1970).

(10) (a) Y. Mushika, T. Hata, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **44**, 232 (1971); (b) T. Mukaiyama and M. Hashimoto, *J. Am. Chem. Soc.*, **94**, 8528 (1972).

(11) (a) T. Koizumi, Y. Yoshida, Y. Watanabe, and E. Yoshii, *Chem. Pharm. Bull.*, **23**, 1381 (1975); (b) M. Rubinstein and A. Patchornik, *Tetrahedron*, **31**, 2107 (1975).

(12) Several unstable *N*-phosphorylimidazoles have been reported; see ref 13–17.

(13) (a) T. Wagner-Jauregg and B. E. Hockley, Jr., *J. Am. Chem. Soc.*, **75**, 2125 (1953); (b) B. Atkinson and A. L. Green, *Trans. Faraday Soc.*, **53**, 1334 (1957).

(14) (a) J. Baddiley, J. G. Buchanan, and R. Letters, *J. Chem. Soc.*, 2812 (1956); (b) H. Hellman, F. Lingens, and H. Burkhardt, *Chem. Ber.*, **91**, 2290 (1958).

(15) D. Theodoropoulos, J. Gazopoulos, and I. Sauchleris, *J. Chem. Soc.*, 5257, (1960).

(16) F. Cramer, H. Schaller, and H. Stabb, *Chem. Ber.*, **94**, 1612 (1961).

(17) R. Blakeley, F. Kerst, and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 112 (1966).

(18) Preliminary report of preparation: F. Ramirez, H. Okazaki, and J. F. Marecek, *Synthesis*, 637 (1975).

(19) J. S. Ricci, B. R. Davis, F. Ramirez, and J. Marecek, *J. Am. Chem. Soc.*, **97**, 5457 (1975).

(20) The free acid 1,2-dimethylethenylene phosphate, X=P(O)OH, reacts with alcohols at a significant rate. Therefore, salts of this acid with relatively weak bases, e.g., pyridine ($pK_B$ 8.7) show some reactivity toward alcohols, attritbutable to the formation of some free acid by dissociation. Quaternary ammonium salts, e.g., the *N*-methyl pyridinium salt $X{=}P(O)O^{(-)}{-}CH_3N^{(+)}C_5H_5$ display negligible reactivity toward alcohols under comparable conditions.

(21) The required cyclic triesters, $X{=}P(O)OR^1$ were made from the alcohols $R^1OH$ and the pyrophosphate (**1**) in the presence of γ-collidine or nicotinamide, as previously described (ref 5).

(22) (a) G. DiSabato and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4393, 4400 (1961).

(23) (a) P. Haake and G. W. Allen, *Proc. Natl. Acad. Sci., U.S.A.*, **68**, 2691 (1971); (b) *J. Am. Chem. Soc.*, **95**, 8080 (1973).

(24) T. C. Bruice and J. J. Benkovic, "Bioorganic Mechanisms", W. A. Benjamin, New York, N.Y., 1966; Vol. 1, p 46; Vol. 2, p 29, 80.

(25) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969.

(26) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Wiley Interscience, New York, N.Y., 1971.

(27) (a) W. P. Jencks and J. Regenstein, "Handbook of Biochemistry" 3rd ed, H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1970, p J-187; (b) H. Walba and R. W. Isensee, *J. Org. Chem.*, **26**, 2789 (1961).

(28) (a) J. H. Van Boom, P. M. J. Bargess, G. R. Owen, C. B. Reese, and R. Saffhill, *Chem. Commun.*, 869 (1971); (b) J. H. Van Boom, J. F. M. deRooy and C. B. Reese, *J. Chem. Soc., Perkin Trans. 1*, 2513 (1973).

(29) The formation of *intermediates* with five-coordinate phosphorus has been postulated by a number of investigators to explain their observations on nucleophilic displacements of a variety of compounds with four-coordinate phosphorus. For leading references see the review articles of ref 30–34.

(30) (a) W. E. McEwen, *Top Phosphorus Chem.*, **2**, 1 (1965); (b) W. E. McEwen and K. D. Berlin, Ed., "Organophosphorus Stereochemistry", Dowden, Hutchinson and Ross, Stroudsburg, Pa., 1975.

(31) (a) F. Ramirez, *Acc. Chem. Res.*, 1, 168 (1968); (b) P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, *Angew. Chem., Int. Ed. Engl.*, **12**, 91 (1973).

(32) F. H. Westheimer, *Acc. Chem. Res.*, 1, 70 (1968).

(33) K. Mislow, *Acc. Chem. Res.*, **3**, 321 (1970).

(34) R. F. Hudson and C. Brown, *Acc. Chem. Res.*, **5**, 204 (1972).

(35) Exclusive ring retention has been observed in the reaction of five-membered cyclic saturated phosphotriesters with 1 mol equiv of water *in aprotic solvents;* ref 36.

(36) F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson, and E. M. Banas, *J. Am. Chem. Soc.*, **85**, 2681 (1963).

(37) (a) P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **10**, 687 (1971); (b) I. Ugi and F. Ramirez, *Chem. Br.*, **8**, 198 (1972).

(38) The new oxyphosphorane can also be generated by the pseudorotation mechanism (R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960)).

(39) F. Ramirez, V. A. V. Prasad, and J. Marecek, *J. Am. Chem. Soc.*, **96**, 7269 (1974).

(40) (a) H. R. Allcock, *J. Am. Chem. Soc.*, **86**, 2591 (1964); (b) H. R. Allcock and E. C. Bissell, *J. Chem. Soc., Chem. Commun.*, 676 (1972).

(41) (a) L. Lopez, M. T. Baisdon, and J. Barrans, *C. R. Acad. Sci., Ser. C*, **275**, 295 (1972); (b) L. Lopez and J. Barrans, *ibid.*, **276**, 1211 (1973).

(42) R. Burgada, D. Bernard, and C. Laurenco, *C. R. Acad. Sci., Ser. C*, **276**, 297 (1973).

(43) (a) M. Koenig, A. Munoz, D. Houalla, and R. Wolf, *J. Chem. Soc., Chem. Commun.*, 182 (1974); (b) A. Munoz, G. Gence, M. Koenig, and R. Wolf, *C. R. Acad. Sci., Ser. C*, 395 (1975).

(44) D. Hellwinkel in "Organophosphorus Compounds" Vol. 3, G. M. Kosolapoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1972, p 185.

(45) F. Ramirez, K. Tasaka, N. B. Desai, and C. P. Smith, *J. Am. Chem. Soc.*, **90**, 751 (1968).

(46) B. C. Chang, D. B. Denney, R. L. Powell, and D. W. White, *Chem. Commun.*,

1070 (1971).
(47) F. Ramirez, K. Tasaka, and R. Hershberg, *Phosphorus*, **2**, 41 (1972).
(48) F. Ramirez, G. V. Loewengart, E. A. Tsolis, and K. Tasaka, *J. Am. Chem. Soc.*, **94**, 3531 (1972).
(49) W. C. Archie, Jr., and F. H. Westheimer, *J. Am. Chem. Soc.*, **95**, 5955 (1973).
(50) G. Aksness and A. I. Eide, *Phosphorus*, **4**, 209 (1974).
(51) The stereochemistry of the formation (and decomposition) of octahedral six-coordinate phosphorus from (and to) trigonal bipyramidal phosphorus is not considered in this discussion.
(52) F. Ramirez, S. L. Glaser, P. Stern, I. Ugi, and P. Lemmen, *Tetrahedron*, **29**, 3741 (1973).
(53) F. H. Westheimer in *Adv. Enzymol.*, **25**, 441 (1961).
(54) (a) S. J. Benkovic and K. J. Schray, "The Enzymes", 3d ed, Vol. 7, P. D. Boyer, Ed., Academic Press, New York, N.Y., 1973; (b) D. C. Watts, *ibid.*, Vol. 8, Chapter 12; (c) V. P. Hollander, *ibid.*, Vol. 4, Chapter 19; (d) S. Fantremoli, E. Grazi, and A. Accorsi, *J. Biol. Chem.*, **242**, 61 (1967).
(55) D. A. Usher, D. I. Richardson, Jr., and D. G. Oakenfull, *J. Am. Chem. Soc.*, **92**, 4699 (1970).
(56) A. P. Mathias and B. R. Rabin, *Biochem. J.*, **103**, 62P (1967).
(57) W. Stillwell, G. Steinman, and R. L. McCarl, *Bioorg. Chem.*, **2**, 1 (1972), and references cited therein.
(58) The extraction was carried out with diethyl ether in the particular case of $[[(CH_3)_2CH]_2CHO]$ $(C_6H_5CH_2O)P(O)ONa$ to avoid the loss of some salt in the dichloromethane.
(59) F. Ramirez, B. Hansen, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 4588 (1962).
(60) (a) D. M. Brown and D. A. Usher, *J. Chem. Soc.*, 6547 (1965); (b) D. S. Frank and D. A. Usher, *J. Am. Chem. Soc.*, **89**, 6360 (1967).
(61) NOTE ADDED IN PROOF. The pyrophosphate **1** is normally prepared from *N*-methylpyridinium (1,2-dimethylethenylene) phosphate (analogous to **3**) by reaction with 0.5 mol equiv of phosgene. If this salt is allowed to react with an excess of phosgene for an extended period, the product is 1,2-dimethylethenylene phosphorochloridate[18] instead of 1. This observation facilitates the preparation of the highly reactive phosphorochloridate reagent which can be used for the preparation of **2**.

# Quenching of Aromatic Hydrocarbon Singlets and Aryl Ketone Triplets by Alkyl Disulfides

**William L. Wallace,[1a] Richard P. Van Duyne,* [1b] and Frederick D. Lewis* [1c]**

*Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201.* *Received September 19, 1975*

**Abstract:** Quenching of aromatic hydrocarbon fluorescence and aryl ketone phosphorescence by alkyl disulfides has been investigated. Two quenching mechanisms, charge-transfer stabilized exciplex formation and electronic energy transfer, have been considered. Charge transfer appears to be unimportant for the aromatic hydrocarbons and ketones studied. Endothermic singlet–singlet energy transfer is more efficient than predicted by the Arrhenius equation. Excitation of vibrationally excited ground-state disulfide molecules provides a possible explanation for efficient endothermic quenching. Low-temperature uv spectroscopy indicates that the long-wavelength absorption of disulfides consists predominately of hot-band transitions.

## Introduction

The spectroscopic[2,3] and photochemical[4-9] properties of disulfides have attracted substantial interest. The optical rotatory properties of chiral disulfides provide a probe of protein structure and environment.[3] Photochemical cleavage of the sulfur–sulfur bonds can result in inactivation of sulfur-containing proteins.[5] Since disulfides do not absorb strongly in the near ultraviolet,[2] photochemical inactivation of proteins may involve quenching of aromatic amino acid excited states by disulfide. Walling and Rabinowitz[6] demonstrated that sulfur–sulfur homolysis of alkyl disulfides can be sensitized by aromatic hydrocarbons (eq 1); however, the mechanism of

$$\mathrm{RSSR} \xrightarrow{h\nu} 2\mathrm{RS}\cdot \qquad (1)$$

sensitization was not investigated. In a recent series of papers, Hayon and co-workers[7] have established that quenching of triplet tyrosine and tryptophan by the cyclic disulfide thioctic acid in aqueous solution occurs by an electron transfer mechanism to form the disulfide radical anion (eq 2). The radical anion subsequently undergoes sulfur–sulfur cleavage (eq 3).[10]

$$^3\mathrm{Trp} \text{ or } ^3\mathrm{Tyr} + \mathrm{RSSR} \rightarrow \mathrm{Trp}\cdot^+ \text{ or } \mathrm{Tyr}\cdot^+ + \mathrm{RSSR}\cdot^- \qquad (2)$$

$$\mathrm{RSSR}\cdot^- \rightarrow \mathrm{RS}\cdot^- + \mathrm{RS}\cdot \qquad (3)$$

Quenching of aromatic ketone $^3n,\pi^*$ excited states by disulfides,[8] sulfides,[11] and thiols[12] has been postulated to involve partial charge transfer from sulfur to the half-vacant carbonyl n orbital. Kampmeier[8b] has proposed a charge-transfer stabilized exciplex mechanism for the ketone-sensitized carbon–sulfur homolysis of benzyl disulfide.

$$^3\mathrm{Ketone} + \mathrm{RSSR} \longrightarrow [^3\mathrm{Ketone}\cdots\mathrm{RSSR} \longleftrightarrow \mathrm{Ketone}\cdot^- \ \mathrm{RSSR}\cdot^+] \downarrow \mathrm{Ketone} + \mathrm{R}\cdot + \cdot\mathrm{SSR} \qquad (4)$$

The ability of disulfides to act as either electron donors or acceptors is consistent with their high electron affinities[2b,10] and low ionization potentials.[13]

Disulfides have been observed to quench the fluorescence of proteins and their constituent amino acids,[4c,6a,8] aromatic hydrocarbons, and biacetyl.[7a] Unlike the quenching of triplet tyrosine, quenching of singlet tyrosine does not result in electron transfer.[7a] A singlet–singlet energy transfer mechanism for tyrosine quenching

$$^1\mathrm{Tyr} + \mathrm{RSSR} \rightarrow \mathrm{Tyr} + {}^1\mathrm{RSSR} \qquad (5)$$

and an electron transfer mechanism (eq 2) for tryptophan quenching have been proposed by Shafferman and Stein.[5c] Fluorescence quenching of tyrosine and tryptophan containing peptides requires close approach of fluorescer and disulfide, leading Cowgill[9b] to propose vibrational dissipation of the excitation energy.

Investigations of disulfide quenching mechanisms have been hindered by the absence of information about the singlet and triplet excited states of disulfides. Neither fluorescence nor phosphorescence has been detected for disulfides. The broad,