Mechanism in Organophosphorus Chemistry. II.[1] Reaction of Trialkyl Phosphite Esters with *N*-Methylol Carboxamides and Sulfonamides. Trapping of an Intermediate

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N-Methylol carboxamides and sulfonamides react uniquely with trialkyl phosphite esters to produce dialkylphosphonomethyl derivatives **2** and **7**, respectively. Although the product functionality observed is the same for both substrates, the contrasting reaction conditions observed suggests a difference in mechanistic behavior. Prior investigations offer convincing evidence for a transesterification–rearrangement sequence for the carboxamide system. The present study reports evidence for the sulfonamide substrate proceeding via an elimination–addition sequence. Trapping of a zwitterion intermediate, manifested as a 4-alkyl(aryl)sulfonyl-2,2,2-trialkoxy-1,4,2-oxazaphospholane, is demonstrative.

In general, trialkyl phosphite and triaryl phosphite esters react with aliphatic alcohols at temperatures in excess of 100°C to give transesterified esters and mixed esters in accordance with eq 1.[2,3]

$$P(OR)_3 + R'OH \rightleftharpoons P(OR)_2OR' + ROH$$
$$P(OR)_2OR + R'OH \rightleftharpoons P(OR')_2OR + ROH \quad (1)$$
$$P(OR')_2OR + R'OH \rightleftharpoons P(OR')_3 + ROH$$

However, for *N*-methylol carboxamide systems, reaction with trialkyl phosphites (eq 2)[4] takes a uniquely different

$$\underset{\mathbf{1}}{R'CNHCH_2OH} + P(OR)_3 \xrightarrow{>100°C} R'CNHCH_2P(OR)_2 + ROH \quad (2)$$
$$\mathbf{2}$$

course, realizing dialkylphosphonomethyl carboxamides (**2**) and no detectable mixed esters.

An investigation of the reaction mechanism by Ivanovet al.[4,5] offers strong support for a transesterification–rearrangement pathway (Scheme I, sequence a) and rules out the alternate Michales–Arbusov type displacement[6] consideration (Scheme I, sequence b). The evidence for these conclusions is as follows.

(a) Alkoxymethyl analogues of **1** (i.e., structures **3** where R′ = CH_3, C_2H_5, n-C_3H_7) show inert activity to conditions

$$\underset{\mathbf{3}}{RCNHCH_2OR'}$$

of eq 2.[7] Since an alkoxy group has similar leaving group ability to hydroxide,[8] a displacement mechanism (b) would dictate similar behavior of substrates **1** and **3**.

(b) Reaction of **1** with diethyl phosphorochloridite (**4**) at ambient temperature (eq 3) realizes no detectable quantity

$$RCNHCH_2OH + Cl—P(OC_2H_5)_2 \xrightarrow[Et_3N:]{20-25°} \left[RCNHCH_2—OP(OC_2H_5)_2\right] \longrightarrow RCNHCH_2P(OC_2H_5)_2 \quad (3)$$
$$\mathbf{5}$$

of the undoubtedly formed mixed ester **5**. Only product **2** (R′ = C_2H_5) supportive of a rearrangement mechanism was isolated.

The present investigation reports the behavior observed for the reaction of *N*-hydroxymethyl sulfonamide substrates with trialkyl phosphites. By contrast to the carboxamide systems **1**, the sulfonamide analogues **6** react under extremely mild conditions, producing the expected dialkylphosphonomethyl products **7** in excellent yields (Table I).

Particular note is made of the base-accelerating and acid-retarding influence on the reaction. In general, these catalytic conditions have little effect on the carboxamide substrates,[4] i.e., no significant reaction at ambient temperature and no change in reaction time, temperature, or yields at elevated temperatures (Table II).

Further, reasonable reactivity under neutral and base catalysis and pronounced acid retardation to preclusion of reaction was observed for the alkoxymethylsulfonamide system (Table III). The fully functionalized *N*,*N*-bis(methoxymethyl)methanesulfonamide (**8**), on the other hand, was found to be inert to the reaction conditions of Tables I and III. Only under extremes of temperature (110°C) with acid catalysis and prolonged reaction times did reaction occur (eq 4).

Scheme I

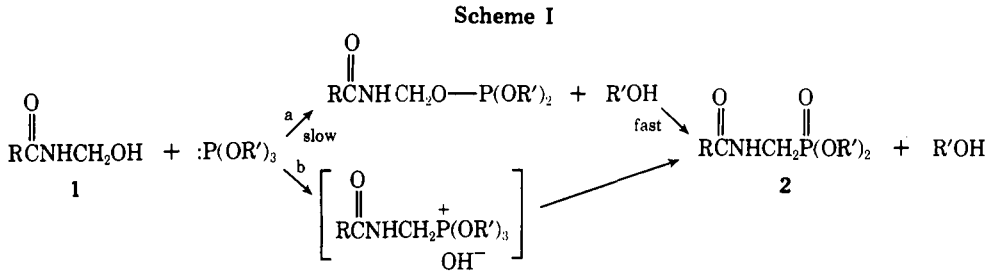


Table I[a]
Reaction of *N*-(Hydroxymethyl) sulfonamides with Trialkyl Phosphite Esters

$$\underset{6}{RSO_2NHCH_2OH} + :P(OR'')_3 \longrightarrow \underset{7}{RSO_2NHCH_2P(=O)(OR'')_2} + R''OH$$

R	R''	Catalyst[b]	Temp, °C	Solvent[c]	Time, hr	% yield[d]
CH_3	CH_3		25	CH_3OH	12	95%
CH_3	CH_3		50	CH_3OH	2.0	93
CH_3	C_2H_5		25	C_2H_5OH	15.5	72
CH_3	CH_3	$NaOCH_3$	25	CH_3OH	0.5	90
CH_3	CH_3	NaOH	25	CH_3OH	0.5	94
CH_3	CH_3	AcOH	25	CH_3OH	24	<10[e]
p-Ts[f]	CH_3		25	CH_3OH	13.5	78
p-Ts	CH_3		50	CH_3OH	2.0	75
p-Ts	CH_3	$NaOCH_3$	25	CH_3OH	1.0	75
p-Ts	C_2H_5		25	C_2H_5OH	15.0	65

[a] Reactions run on 0.1-mol scale with 10% excess $P(OR'')_3$. [b] pH adjustment to 8.0 with $NaOCH_3$ and to 6.0 with AcOH. [c] 50 ml. [d] Adjusted yields based on purity of starting material (see Experimental Section). [e] >90% starting material recovered. [f] *p*-Ts = *p*-$CH_3C_6H_4SO_2$.

Table II
Reaction of *N*-Hydroxymethylacetamide with Trimethyl Phosphite[a]

$$CH_3C(=O)NHCH_2OH + P(OCH_3)_3 \longrightarrow CH_3CNHCH_2P(=O)(OCH_3)_2$$

Catalyst[b]	Temp, °C	Solvent	Time, hr	% yield
	25	CH_3OH	48	0
	70	CH_3OH	48	<10
$NaOCH_3$[c]	25	CH_3OH	48	<10
$NaOCH_3$[c]	70	CH_3OH	48	30
	105		1.5	73
$NaOCH_3$	105		1.5	75
AcOH	105		1.5	70

[a] The methyl ether derivative found unreactive to all conditions except acetic acid at elevated temperature (see ref 5). [b] pH adjustment to 8.0 for NaOCH, 6.0 for AcOH. [c] Notable retrograding to acetamide.

$$\text{no rxn} \xleftarrow[\text{room temp; 1. no cat. or 2. } NaOCH_3 \text{ or 3. AcOH}]{P(OR)_3} \underset{\mathbf{8}}{CH_3SO_2N(CH_2OCH_3)_2} \xrightarrow[110^\circ C,\ AcOH,\ 4\ days]{P(OCH_3)_3} CH_3SO_2N[CH_2P(=O)(OCH_3)_2]_2 \quad (4)$$

Discussion

The differences in behavior observed for the sulfonamide substrates (6) when compared with the carboxamide analogues (1) is an apparent consequence of the acidity inherent in the N–H proton of the respective systems. The pK_a (acidity constants)[9] for N-substituted sulfonamides (pK_a = 9–10) contrasted with that of carboxamides (pK_a = 16–18) offers support for N–H proton removal by alkoxide and hydroxide (pK_a = 14–15 for conjugate acids) in the former but not likely in the latter as a suspected part of the reaction mechanism.

If a direct displacement Arbusov-type reaction were operative for the sulfonamide systems at ambient temperature, reaction should be facilitated by acid protolysis on the hydroxy or alkoxy group rendering better leaving group ability; base would be expected to exert no enhanced rate over the uncatalyzed reaction. Further, a direct displacement mechanism would not be expected to be influenced by the N,N-bis substitution demonstrated in eq 4. Here again, the expected observations would be acid acceleration and no significant effect by base.

In keeping with all observed data, the following mechanism is suggested (Scheme II).

Table III[a]
Reaction of *N*-(Methoxymethyl)methanesulfonamide with Trimethyl Phosphite

$$CH_3SO_2NHCH_2OCH_3 + P(OCH_3)_3 \longrightarrow CH_3SO_2NHCH_2P(=O)(OCH_3)_2$$

Catalyst[b]	Temp, °C	Solvent	Time, hr	% yield
	25	CH_3OH	72	75
	50	CH_3OH	24	90
$NaOCH_3$	25	CH_3OH	1.0	93
$NaOCH_3$[c]	25		1.0	40
AcOH[d]	25	CH_3OH	168.0	0
AcOH	50	CH_3OH	164.0	20

[a] Reactions run on 0.1-mol scale with 10% excess $P(OCH_3)_3$. [b] pH 8.0 for $NaOCH_3$, 6.0 for AcOH. [c] Predominant product (50–60%) $CH_3SO_2N(CH_3)CH_2P(=O)(OCH_3)_2$. [d] Quantitative recovery of starting material.

Scheme II

$$RSO_2NHCH_2OR' \longrightarrow \underset{\mathbf{9}}{[RSO_2N{=}CH_2]} + R'OH$$

R = aryl, alkyl; R' = H, alkyl; R'' = alkyl

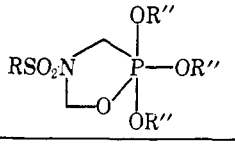
$$[RSO_2NCH_2P(OR'')_3] \quad \mathbf{10}$$

added R''OH, solvent: $RSO_2NHCH_2P(OR'')_4$ → $R''OR'' + RSO_2NHCH_2P(=O)(OR'')_2$ (**7**)

no added R''OH, R'' = CH_3: $RSO_2NCH_2P(=O)(OCH_3)_2$ (CH_3) — **11** + **7** — major product

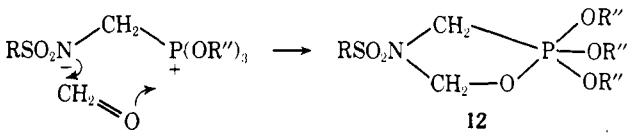
Support for this proposal was obtained from a trapping experiment in which an added equivalent of formaldehyde was placed in contact with the hydroxymethyl or alkoxymethyl sulfonamide system(s) before treatment with trialkyl phosphite. Monitoring the course of reaction by ^1H NMR (benzene as an internal standard and R = CH_3) revealed the formation of a component bearing P–OR functionality but differing significantly in overall structure from phosphonate **7**. This component was found to increase directly at the expense of starting material. At total conversion, the reaction mixture was stripped, realizing the newly produced material isolated in 70–75% purity. Although most derivatives prepared (four in number) could not be purified owing to extreme hydrolytic sensitivity, the system where R = *p*-Ts and R'' = C_2H_5 was stable enough to recrystallization to enable full unequivocal characterization as a cyclic phosphorane **12**. This adduct, produced via suggested formal 1,3-dipolar addition[10] of transient intermedi-

Table IV
^{31}P amd ^{1}H NMR Parameters for 1,4,2-Oxazaphospholanes (12)



R	R''	% yield[a]	^{31}P ($CDCl_3$)	^{1}H (δ_{CDCl_3})[b] P–CH_2N	P–OCH
CH_3	CH_3	70	+30.8	3.38 ($J_{P\text{-}CH}$ = 13 Hz, 2H)	4.72 ($J_{P\text{-}OCH}$ = 17 Hz, 2 H)
CH_3	C_2H_5	80	+32.6	3.35 ($J_{P\text{-}CH}$ = 12 Hz, 2 H)	4.65 ($J_{P\text{-}OCH}$ = 17 Hz, 2 H)
p-Ts	CH_3	90	+30.3	3.25 ($J_{P\text{-}CH}$ = 13 Hz, 2 H)	4.70 ($J_{P\text{-}OCH}$ = 17 Hz, 2 H)
p-Ts	C_2H_5	95	+33.6	3.26 ($J_{P\text{-}CH}$ = 13 Hz, 2 H)	4.68 ($J_{P\text{-}OCH}$ = 17 Hz, 2 H)

[a] The remainder of the product mix consists of hydrolysis product 13 and 7 from reaction before trapping. [b] For ^{1}H NMR support of chemical shifts and coupling constants, see ref 14–16.



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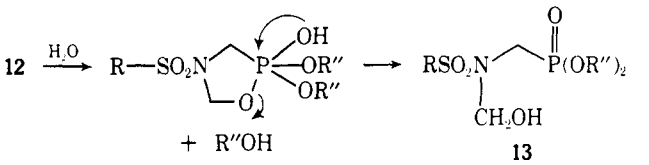
ate 10 across the carbon–oxygen double bond of formaldehyde, was characterized as follows. In accordance with five-membered phosphorane ring systems prepared and rigorously studied by Ramirez et al.,[11,12] ^{31}P NMR proves diagnostic for the C–P–O–C (30.0–35.0 ppm) relationship within the ring; that is, the chemical shift for this atomic relationship is distinct from others (e.g., O–P–O, 48–55 ppm).[13] ^{1}H NMR shows further consistency with the proposed structures, in that the ring methylene protons are clearly distinguished and manifest the expected chemical shifts.[14–16] For structures 12 where R = CH_3 and *p*-Ts, the P–CH_2N proton chemical shift was obscured by the P–OCH_3 resonance. Determination of this shift was made from preparation of the perdeuteriomethoxyl system (R'' = CD_3), the ^{1}H NMR spectrum of which clearly revealed these protons. Pertinent data are reported in Table IV.

Additional support for structures 12 was obtained from identification of the hydrolysis product from treatment with 1 equiv of water. Compounds 13 were isolated in near quantitative yield based on purity of 12. These products



+ R''OH

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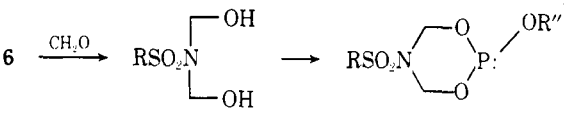
are in keeping with the hydrolysis behavior that was observed for the 1,4,2-dioxophospholanes studied by Ramirez.[12] Appropriate identification parameters are found in the Experimental Section.

In summary, a difference in mechanism for the reaction of *N*-hydroxymethyl sulfonamide systems vs. carboxamide analogues with phosphite esters is suggested. An elimination–addition pathway is in keeping with the former and a transesterification–rearrangement consistent with the latter. Although the transesterification route may prevail to some degree for the sulfonamides as indicated by the slightly greater reactivity of the *N*-hydroxymethyl vs. the *N*-alkoxymethyl derivatives, the major pathway is undoubtedly as described for the following reasons.

(a) In general, heat >90–100°C is required for facile transesterification of alkyl phosphite esters by alcohols.[2,3] At ambient temperature, reaction is too slow to compare with observations made in this investigation.

(b) Formation of 1,4,2-oxazaphospholanes (12) from trapping experiment. If transesterification was the accepted pathway, six-membered 1,3,5-dioxazaphosphorinanes (14) would be the expected products (not observed) from the reaction with excess formaldehyde.



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(c) Transesterification processes show some response to catalytic activity by acid[2] (retardation observed in sulfonamide systems 6).

(d) For the system where R'' = CH_3 in Scheme II, N-methylation (11) of substrate occurs in the absence of excess R''OH. This process is not amenable to a transesterification process.

One further comment regards the minor response of *N*-(hydroxymethyl)carboxamides to base catalysis at low temperature (Table II). Since the alkoxymethyl analogue (3) exhibits no similar response, an elimination–addition mechanism in accordance with Scheme II is unlikely. A better explanation, emphasized by noted retrograding to amide substrate, is conversion of 1 to alkoxide 15 which fa-

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cilitates the transesterification rearrangement reaction with phosphite ester. Further evidence against the carboxamide systems engaging in elimination–addition reactions is the inability to trap phospholane intermediates similar to the sulfonamides.

Experimental Section

Materials. Methanesulfonamide (mp 91–93°) and *p*-toluenesulfonamide (mp 136–138°) were purchased from Eastman Organic Chemicals and were used without further purification. Trimethyl phosphite (bp 111–112°) and triethyl phosphite (bp 156°) were purchased from Aldrich Chemical Co., Inc., and were fractionally distilled through a 12-in. glass helices (0.125 in.) column several times before use. Column chromatography was conducted on Baker Analyzed Reagent silica gel, powder, 60–200 mesh.

General Information. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on Varian Models T-60 and HA-100 MHz spectrometers. Infrared spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. In vacuo strippings were carried out on a Buchler Instruments Flash-Evaporator.

***N*-(Hydroxymethyl)methanesulfonamide.** To a solution of 9.5 g (0.10 mol) of methanesulfonamide in 100 ml of anhydrous methanol was added 3.3 g (0.11 mol) of paraformaldehyde. The suspension was adjusted to pH 8–9 with sodium methoxide (Matheson Coleman and Bell) and then heated to 45–50°C for 2 hr. After cooling to room temperature, the reaction solution was neutralized to pH 7 with acetic acid (glacial) followed by stripping in vacuo to constant weight as an amber oil, weight of crude product 12.3 g (98.4%).

In general, the *N*-methylol sulfonamides proved too unstable to conventional purification by recrystallization, distillation, and column chromatography. Retrograding to starting sulfonamides was observed. Proof of structure was made on the basis of consistent spectral properties (infrared and ^{1}H NMR) and additional support for hydroxyl absorption through H–D exchange (D_2O treatment of NMR samples in $CDCl_3$). The degree of purity of *N*-(hydroxymethyl)methanesulfonamide was further assessed by degree of conversion to its methyl ether derivative (see below): ir ν_{max} (film) 3550 (OH), 3280 (NH), 1450, 1330 (SO_2), 1145 (SO_2), 1055, 965, 920, 830, 790 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 3.08 (3 H, CH_3SO_2–), 4.20 (broad singlet, 1 H, –OH), 4.95 (broad singlet, 2 H, NCH_2O), 6.60–7.20 (baseline integration for 1 H, NH). NMR signals at δ 4.20 and 6.60–7.20 disappear upon treating the sample with several drops of D_2O.

***N*-(Methoxymethyl)methanesulfonamide.** To a fresh solution of 6.25 g (0.05 mol) of *N*-(hydroxymethyl)methanesulfonamide in 100 ml of anhydrous methanol was added 8 drops of concentrated HCl (aqueous). Stirring at room temperature for 5 hr was followed by careful neutralization to pH 7 with sodium methoxide and stripping in vacuo. The clear, colorless oil (6.9 g, >99%) was chromatographed on silica gel ($CHCl_3$ as elution solvent): ir ν_{max} (film) 3275 (NH), 1340, 1150, 1075, 940, 790 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 3.08 (singlet, 3 H, CH_3SO_2–), 3.38 (singlet, 3 H, –OCH_3), 4.60 (doublet, J = 7 Hz, 2 H, NCH_2O), 6.18 (broad triplet, J = 7 Hz, 1 H, NH).

Anal. Calcd for $C_3H_9NO_3S$: C, 25.90; H, 6.47; N, 10.07. Found: C, 25.67; H, 6.31; N, 9.92.

***N*-(Hydroxymethyl)-*p*-toluenesulfonamide.** The procedure for preparing *N*-(hydroxymethyl)methanesulfonamide was utilized. From 17.10 g (0.1 mol) of *p*-toluenesulfonamide and 4 g (0.13 mol) of paraformaldehyde, 20.0 g (99.5%) of crude product was obtained from exhaustive stripping in vacuo. The clear, colorless, glassy solid exhibited the same instability to purification as noted for the methanesulfonamide system. Structure identification and degree of purity was determined by ^{1}H NMR (90%): ir ν_{max} (film) 3500 (OH), 3250 (NH, broad doublet), 1590, 1450, 1330, 1155, 1070, 900, 820, 740, 665 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) inter alia (trace amounts of methyl ether) 2.4 (singlet, 3 H, aromatic methyl), 4.78 (broad singlet, ca. 2 H, NCH_2O), 5.40 (singlet, 1 H, OH), 7.50 (AB quartet, J = 8 Hz, 5 H, four aromatic protons, one proton due to N–H broad peak under the resonance). The N–H and O–H signals disappeared upon treatment of the sample with several drops of D_2O.

General Procedure for Preparing *N*-(Dialkylphosphonomethyl)sulfonamides. Method A. To a solution of 0.10 mol of *N*-(hydroxymethyl)methane(*p*-toluene)sulfonamide in 50 ml of anhydrous methanol (ethanol for triethyl phosphite runs) was added 0.11–0.13 mol of trialkyl phosphite. Stirring and external heat was applied. When the temperature reached 35–45°C, exotherming was noted and moderating was accomplished with an ice–water bath. Temperature was maintained at 50°C for 1–2 additional hr followed by cooling to room temperature and stripping in vacuo to remove all volatiles. The residue was dissolved in a small portion of chloroform and chromatographed on silica gel ($CHCl_3$ as elution solvent). See characterization data below.

Method B. The above procedure can be conducted in one flask starting with parent sulfonamide substrates and preparing *N*-hydroxymethyl derivatives in situ.

Methanesulfonamide (9.5 g, 0.10 mol) was dissolved in 50 ml of anhydrous methanol. The pH was adjusted to 8–9 with sodium methoxide and 3.3 g (0.11 mol) of paraformaldehyde was added. Upon heating to 50°C, solution was obtained. After 1 hr the reaction flask was cooled to room temperature, at which time 13.6 g (0.11 mol) of trimethyl phosphite was added. Heat was applied; exotherming set in at 35°C. Reaction was maintained at 50°C for 1 hr followed by stripping in vacuo on a rotary evaporator (50°C, 0.5 mm). The crude *N*-(dimethylphosphonomethyl)methanesulfonamide (21.6 g, 99.5%) was shown to be of high purity (>95%) by ^{1}H NMR analysis. Part of this material was chromatographed on silica gel ($CHCl_3$) and recovered as a water-white oil. Attempted distillation led to decomposition. Characterization data for all systems prepared is given in the following.

***N*-(Dimethylphosphonomethyl)methanesulfonamide:** ir ν_{max} (film) 3200 (NH), 1320 (SO_2), 1240 (P=O), 1150 (SO_2), 1030 (P–O), 830 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) –24.7; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 3.03 (singlet, 3 H, CH_3SO_2), 3.55 (doublet of doublets, J_{P-CH_2} = 12, J_{NH-CH_2} = 6 Hz, 2 H, NCH_2P=O), 3.82 (doublet, J = 12 Hz, 6 H, $POCH_3$'s), 6.42 (broad triplet, J = 6 Hz, 1 H, NH).

Anal. Calcd for $C_4H_{12}NO_5PS$: C, 22.10; H, 5.53; N, 6.46; P, 14.29. Found: C, 21.80; H, 5.91; N, 6.13; P, 14.50.

***N*-(Diethylphosphonomethyl)methanesulfonamide** was chromatographed on silica gel ($CHCl_3$): ir ν_{max} (film) 3140 (NH), 1325 (SO_2), 1240 (P=O), 1155 (SO_2), 1020–1050 (P–O), 970, 800 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) –21.3; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.35 (triplet, J = 7 Hz, 6 H, ethyl ester CH_3's), 3.02 (singlet, 3 H, CH_3SO_2), 3.48 (doublet of doublets, J_{P-CH_2} = 12, J_{NH-CH_2} = 6 Hz, 2 H, NCH_2P=O), 4.15 (quintet, J = 7 Hz, 4 H, ethyl ester CH_2's), 6.45 (broad triplet, J = 6 Hz, 1 H, NH).

Anal. Calcd for $C_6H_{16}NO_5PS$: C, 29.39; H, 6.53; N, 5.71; P, 12.65. Found: C, 29.19; H, 6.47; N, 5.64; P, 12.80.

***N*-(Dimethylphosphonomethyl)-*p*-toluenesulfonamide** was recrystallized from $CHCl_3$–hexane: mp 117–119°C; ir ν_{max} (Nujol) 3100 (NH), 1330 (SO_2), 1250 (P=O), 1162 (SO_2), 1030–1050 (doublet, P–O), 880, 828, 805 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) –23.6; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.40 (singlet, 3 H, aromatic CH_3), 3.25 (doublet of doublets, J_{P-CH_2} = 12, J_{NH-CH_2} = 6 Hz, 2 H, NCH_2P=O), 3.72 (doublet, J_{P-OCH_3} = 11 Hz, 6 H, $POCH_3$'s), 6.70 (broad triplet, J = 6 Hz, 1 H, NH), 7.53 (AB quartet, J = 8 Hz, 4 H, aromatic protons).

Anal. Calcd for $C_{10}H_{16}NO_5PS$: C, 40.96; H, 5.46; N, 4.77; P, 10.60. Found: C, 40.60; H, 5.70; N, 4.60; P, 10.52.

***N*-(Diethylphosphonomethyl)-*p*-toluenesulfonamide.** Crude product was recrystallized from $CHCl_3$–hexane: mp 83–85°C; ir ν_{max} (Nujol) 3100 (NH), 1332 (SO_2), 1300 (doublet), 1245 (P=O), 1205, 1160 (SO_2), 1100, 1025 (P–O), 978, 925, 800 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) –20.2; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 1.30 (triplet, J = 7 Hz, 6 H, ethyl CH_3's), 2.23 (singlet, aromatic CH_3), 3.25 (doublet of doublets, J_{P-CH_2} = 14, J_{NH-CH_2} = 6 Hz, 2 H, NCH_2P=O), 4.18 (quintet, J = 7 Hz, 4 H, ethyl CH_2's), 6.0 (broad triplet, J = 6 Hz, 1 H, NH), 7.50 (AB quartet, J = 8 Hz, 4 H, aromatic protons).

Anal. Calcd for $C_{12}H_{20}NO_5PS$: C, 44.86; H, 6.23; N, 4.36; P, 9.66. Found: C, 44.77; H, 6.18; N, 4.14; P, 9.80.

***N*-(Hydroxymethyl)acetamide.** A solution of 5.9 g (0.1 mol) of acetamide in 8.1 g of 37% aqueous formalin was treated with 5% aqueous sodium hydroxide to a pH 8–9. A slight exotherm to 30°C was observed. After stirring at room temperature for several hours, reaction was neutralized to pH 6 with dilute aqueous HCl followed by stripping in vacuo to a colorless oil which solidified on standing. Recrystallization from dioxane realized 8.0 g of *N*-(hydroxymethyl)acetamide representing an 89% yield: mp 50–52° (lit.[17] 50–52°); ir ν_{max} (Nujol) 3300 (broad OH, NH), 1660 (C=O), 1540, 1285, 1090, 1030 cm^{-1}; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.00 (singlet, 3 H, CH_3CO), 4.65 (doublet, J = 7 Hz, 2 H, NCH_2O), 5.50 (singlet, 1 H, OH), 8.10 (broad triplet, J = 7 Hz, 1 H, NH).

***N*-(Dimethylphosphonomethyl)acetamide.** To 25 g (0.20 mol) of trimethyl phosphite (TMP) preheated to 105°C was added 13.3 g (0.15 mol) of *N*-(hydroxymethyl)acetamide portionwise over 15 min. Exotherm to 110° was noted during the addition. The reaction was then held at 105°C for 1.5 hr, followed by cooling to room temperature and stripping in vacuo. The oily residue was chromatographed on silica gel employing benzene as eluent, yield 13.2 g, as a colorless oil, representing a 73% yield: ir ν_{max} (film) 3290 (NH), 1685 (C=O), 1460, 1250 (P=O), 1040 (P–O), 890, 820 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) –25.6; ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.02 (singlet, 3 H, CH_3C=O), 3.65 (doublet, J_{P-CH_2} = 12 Hz, 2 H, NCH_2P), 3.78 (doublet, J_{P-OCH_3} = 11 Hz, 6 H, $POCH_3$'s), 7.60 (broad, 1 H, NH).

Anal. Calcd for $C_5H_{12}NO_4P$: C, 33.15; H, 6.63; N, 7.73; P, 17.13. Found: C, 32.91; H, 6.42; N, 7.81; P, 17.10.

Relative Rate Studies. All experiments were carried out on a 0.10-mol basis and conducted in accordance with the conditions indicated in Tables I–III. Reactions were monitored to exhaustive conversion (no further change) at varying intervals; i.e., 2–4 hr for long-term conversions, 15 min for short-term conversions. Aliquots were withdrawn at these times, stripped in vacuo, and qualitatively analyzed by ^{1}H NMR integration of P–OR″ and P–CH_2N resonances of product vs. diminution of –CH_2OH(–CH_2OCH_3) resonances of starting material.

***N,N*-Bis(methoxymethyl)methanesulfonamide.** A solution of 9.5 g (0.10 mol) of methanesulfonamide and 32.4 g (0.40 mol) of 37% aqueous formalin in 100 ml of distilled water was treated with

10% aqueous NaOH to pH 9 and allowed to stir at room temperature for 15 hr. The aqueous solvent was stripped in vacuo (20 mm, 50°C) and the residue redissolved in 200 ml of anhydrous methanol. Several drops (8–10) of concentrated hydrochloric acid were added followed by stirring at room temperature for an overnight period. The reaction was neutralized with sodium methoxide and stripped of methanol solvent. Chromatography on silica gel with chloroform as eluent realized 9.2 g of a colorless oil representing a 50% yield of product: ir ν_{max} (film) 1345 (SO_2), 1150 (SO_2), 1075, 930, 790 cm^{-1}; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 3.07 (singlet, 3 H, CH_3SO_2), 3.40 (singlet, 6 H, OCH_3's), 4.80 (singlet, 4 H, NCH_2O's).

Anal. Calcd for $C_5H_{13}NO_4S$: C, 32.75; H, 7.10; N, 7.66. Found: C, 32.68; H, 7.08; N, 7.54.

***N,N*-Bis(dimethylphosphonomethyl)methanesulfonamide.** To 50 g of trimethyl phosphite (TMP) were added 5 g (0.027 mol) of *N,N*-bis(methoxymethyl)methanesulfonamide and 1 ml of glacial acetic acid. External heat was applied and the flask contents taken to reflux. Reaction was monitored by ^1H NMR analysis of stripped aliquots taken twice daily. Owing to eventual consumption of AcOH through reaction with TMP, 1 additional ml of AcOH was added each day. After 4 days, reaction progressed no further. The flask contents were stripped in vacuo (1 mm, 50°C) followed by chromatography on silica gel ($CHCl_3$): yield of colorless oil 3.6 g (40%); ir ν_{max} (film) 1320 (SO_2), 1240 (P=O), 1145 (SO_2), 1030 (P–O), 800 cm^{-1}; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 3.03 (singlet, 3 H, CH_3SO_2), 3.58 (doublet, J_{P-CH_2} = 11 Hz, 4 H, NCH_2's), 3.75 (doublet, J_{P-OCH_3} = 12 Hz, 12 H, $POCH_3$'s).

Anal. Calcd for $C_7H_{19}NO_8PS$: C, 27.27; H, 6.17; N, 4.55; P, 10.06. Found: C, 27.13; H, 5.92; N, 4.43; P, 10.14.

General Procedure for Trapping Zwitterion Intermediates (10). Preparation of 4-Alkyl(aryl)sulfonyl-2,2,2-trialkoxy-1,4,2-oxazaphospholanes. A solution of 0.1 mol of *N*-(hydroxymethyl)methanesulfonamide or the *p*-toluenesulfonamide analogue in 100 ml of anhydrous methanol was treated with 1 equiv of paraformaldehyde (pH 8) at room temperature. When solution was obtained, the methanol solvent was stripped at 25° with a water aspirator. The residue was dissolved in excess trialkyl phosphite (ca. 100 ml total) and was agitated at room temperature. Reaction was monitored by ^1H NMR analysis of stripped aliquots withdrawn at 30-min intervals and was complete in 1–2 hr. All completed reactions were stripped exhaustively of excess phosphite ester at 30–35° (0.5 mm).

For those systems (R″ = CH_3) where ring proton NMR resonance was obscured by P–OCH_3 resonance, perdeuteriotrimethyl phosphite[18] was employed for complete characterization. Additional data not contained in Table IV in support of the oxazaphospholanes are given as follows.

4-Methanesulfonyl-2,2,2-trimethoxy-1,4,2-oxazaphospholane. Crude material was isolated as a colorless oil: estimated purity ca. 60–70%; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.83 (singlet, 3 H, CH_3SO_2), 3.38 (doublet, *J* = 13 Hz, 2 H, PCH_2N), 3.60 (doublet, *J* = 12 Hz, 9 H, $POCH_3$'s), 4.72 (doublet, *J* = 17 Hz, 2 H, $POCH_2$).

4-Methanesulfonyl-2,2,2-triethoxy-1,4,2-oxazaphospholane. Crude material was isolated as a colorless oil: purity: ca. 75–80%; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 1.20 (triplet, *J* = 8 Hz, 9 H, Et methyls), 2.80 (singlet, 3 H, CH_2SO_2), 3.35 (doublet, *J* = 12 Hz, 2 H, PCH_2N), 3.90 (pentuplet, *J* = 8 Hz, 6 H, Et methylenes), 4.65 (doublet, *J* = 17 Hz, 2 H, $POCH_2$ ring protons).

4-*p*-Toluenesulfonyl-2,2,2-trimethoxy-1,4,2-oxazaphospholane. Crude material was isolated as a white solid in estimated purity of >90%; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.43 (singlet, 3 H, aromatic CH_3), 3.30 (doublet, *J* = 12 Hz, 9 H, $POCH_3$'s), 3.25 (doublet, *J* = 13 Hz, 2 H, PCH_2N), 4.70 (doublet, *J* = 17 Hz, 2 H, $POCH_2$ ring protons), 7.50 (AB quartet, *J* = 8 Hz, 4 H, aromatic protons).

4-*p*-Toluenesulfonyl-2,2,2-triethoxy-1,4,2-oxazaphospholane. Crude material was isolated as a white solid in 95% yield and recrystallized as colorless needles from $CHCl_3$–hexane: mp 115–117°C. ir ν_{max} (Nujol) 1340 (SO_2), 1155 (SO_2), 1100, 1040–1080 (P–O), 975, 925, 834, 780, 710, 675 cm^{-1}; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 1.07 (triplet, *J* = 7 Hz, 9 H, Et CH_3's), 2.43 (singlet, 3 H, aromatic CH_3), 3.26 (doublet, *J* = 13 Hz, 2 H, PCH_2N), 3.63 (pentuplet, *J* = 7 Hz, 6 H, Et CH_2's), 4.68 (doublet, *J* = 17 Hz, 2 H, $POCH_2$ ring protons), 7.55 (AB quartet, *J* = 8 Hz, 4 H, aromatic).

Anal. Calcd for $C_{15}H_{26}NO_8PS$: C, 47.49; H, 6.86; N, 3.69; P, 8.18. Found: C, 47.12; H, 6.83; N, 3.72; P, 8.33.

Hydrolysis of 4-Alkyl(aryl)sulfonyl-2,2,2-trialkoxy-1,4,2-oxazaphospholanes. A 2-g sample of phospholane derivative was dissolved in 10 ml of tetrahydrofuran and the solution treated with 1 equiv of water. After stirring for 10–15 min at room temperature, a small portion of $MgSO_4$ was added followed by filtration and stripping in vacuo. The product (**13**) was purified by chromatography or recrystallization. The following data are germane.

***N*-(Dimethylphosphonomethyl)-*N*-(hydroxymethyl)methanesulfonamide.** Crude material isolated as a colorless oil was chromatographed on silica gel ($CHCl_3$): yield 95% based on purity of starting material; ir ν_{max} (film) 3300 (OH), 1340 (SO_2), 1230 (P=O), 1150 (SO_2), 1030 (P–O), 970, 865, 800 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −24.2; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 3.05 (singlet, 3 H, CH_3SO_2), 3.75 (doublet, *J* = 10 Hz, 2 H, NCH_2P), 3.83 (doublet, *J* = 11 Hz, 6 H, $POCH_3$'s), 4.97 (singlet, 2 H, NCH_2O), 5.25 (broad singlet, 1 H, OH).

Anal. Calcd for $C_5H_{14}NO_6PS$: C, 24.29; H, 5.67; N, 5.67; P, 12.55. Found: C, 24.12; H, 5.49; N, 5.65; P, 12.36.

***N*-(Diethylphosphonomethyl)-*N*-(hydroxymethyl)methanesulfonamide.** Crude material isolated as a colorless oil (93% pure) was chromatographed on silica gel ($CHCl_3$): ir ν_{max} (film) 3290 (OH), 1340 (SO_2), 1230 (P=O), 1150 (SO_2), 1030 (P–O), 970, 850, 780 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −21.3; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 1.38 (triplet, *J* = 7 Hz, 6 H, Et CH_3's), 3.03 (singlet, 3 H, CH_3SO_2), 3.75 (doublet, *J* = 10 Hz, 2 H, NCH_2P), 4.17 (pentuplet, *J* = 7 Hz, 4 H, Et CH_2's), 5.00 (singlet, 2 H, NCH_2O), 5.46 (broad singlet, 1 H, OH).

Anal. Calcd for $C_7H_{18}NO_6PS$: C, 30.55; H, 6.55; N, 5.09; P, 11.27. Found: C, 30.52; H, 6.33; N, 5.19; P, 10.89.

***N*-(Dimethylphosphonomethyl)-*N*-(hydroxymethyl)-*p*-toluenesulfonamide.** Crude product (98% purity) was recrystallized from toluene–hexane: mp 120–122°C; ir ν_{max} (Nujol) 3300 (OH), 1335 (SO_2), 1260 (P=O), 1165 (SO_2), 1030 (P–O), 955, 864, 810 (doublet), 740, 665 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −23.5; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 2.43 (singlet, 3 H, aromatic CH_3), 3.75 (two doublets superimposed, determined from O=P(OCD_3)$_2$ derivative: *J* = 10 Hz, 2 H, NCH_2P; *J* = 11 Hz, 6 H, $POCH_3$'s), 4.20 (singlet, 1 H, OH), 5.03 (singlet, 2 H, NCH_2O), 7.58 (AB quartet, *J* = 8 Hz, 4 H, aromatic protons).

Anal. Calcd for $C_{11}H_{18}NO_6PS$: C, 40.87; H, 5.57; N, 4.33; P, 9.60. Found: C, 41.03, H, 5.63; N, 4.27; P, 9.73.

***N*-(Diethylphosphonomethyl)-*N*-(hydroxymethyl)-*p*-toluenesulfonamide.** Crude product (>95% purity) was recrystallized from $CHCl_3$–hexane: mp 86–90°C; ir ν_{max} (Nujol) 3300 (OH), 1340 (SO_2), 1258 and 1220 (P=O), 1168 (SO_2), 1040 (P–O), 950, 857, 740, 660 cm^{-1}; ^{31}P NMR $\delta_{H_3PO_4}$ ($CDCl_3$) −20.3; ^1H NMR δ_{Me_4Si} ($CDCl_3$) 1.30 (triplet, *J* = 7 Hz, 6 H, Et CH_3's), 2.41 (singlet, 3 H, aromatic CH_3), 3.68 (doublet, *J* = 11 Hz, 2 H, NCH_2P), 4.10 (pentuplet, *J* = 7 Hz, 4 H, Et CH_2's), 4.40 (broad singlet, 1 H, OH), 5.00 (singlet, 2 H, NCH_2O), 7.50 (AB quartet, *J* = 8 Hz, 4 H, aromatic protons).

Anal. Calcd for $C_{13}H_{22}NO_6PS$: C, 44.44; H, 6.27; N, 3.99; P, 8.83. Found: C, 44.53; H, 6.37; N, 3.96; P, 8.94.

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Registry No.— 1 (R = Me), 625-51-4; 2 (R = R′ = Me), 20495-30-1; 6 (R = Me), 52089-33-5; 6 (R = *p*-Ts), 23666-91-3; 7 (R = R″ = Me), 52089-34-6; 7 (R = Me; R″ = Et), 53376-16-2; 7 (R = *p*-Ts; R″ = Me), 28447-27-0; 7 (R = *p*-Ts; R″ = Et), 57049-65-7; 8, 23069-55-8; 12 (R = R″ = Me), 57049-66-8; 12 (R = Me, R″ = Et), 57049-67-9; 12 (R = *p*-Ts; R″ = Me), 57049-68-0; 12 (R = *p*-Ts; R″ = Et), 57049-69-1; 13 (R = R″ = Me), 57049-70-4; 13 (R = Me; R″ = Et), 57049-71-5; 13 (R = *p*-Ts; R″ = Me), 57049-72-6; 13 (R = *p*-Ts, R″ = Et), 57049-73-7; methanesulfonamide, 3144-09-0; methanol, 67-56-1; *N*-(methoxymethyl)methanesulfonamide, 57049-74-8; *p*-toluenesulfonamide, 70-55-3; acetamide, 60-35-5; formalin, 50-00-3; trimethyl phosphite, 121-45-9; *N,N*-bis(dimethylphosphonomethyl)methanesulfonamide, 53376-14-0; triethyl phosphite, 122-52-1.

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Kinetic Solvent Deuterium Isotope Effects on the Micellar-Catalyzed Hydrolysis of Trisubstituted Phosphate Esters[1]

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Functional micelles of hexadecyl(2-hydroxyethyl)dimethylammonium bromide (I) are better catalysts than hexadecyltrimethylammonium bromide (CTABr) for the alkaline hydrolysis of diethyl and di-*n*-hexyl *p*-nitrophenyl phosphate (IIIa,b). The kinetic solvent deuterium isotope effects for reactions catalyzed by CTABr are very similar to those for reaction in water, but for reaction of IIIb in the presence of I the inverse isotope effect gradually disappears with increasing concentration of hydroxide ion. These results show that the inverse isotope effect is due to the ionization of I to its zwitterion II at high pH. They are consistent with nucleophilic attack by the alkoxide moiety in II but not with general acid or base catalysis.

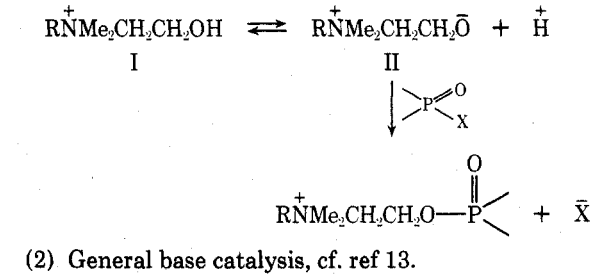
Micelles catalyze (or inhibit) many bimolecular reactions in aqueous solvents.[3] The catalysis can be explained in terms of the ability of the micelle to bring the reagents together at its surface in an environment which is favorable to reaction with stabilization of the transition state and avoidance in part of the unfavorable entropy effects caused by forming an activated complex from two or more reagents.[8] In general the catalysis is greater if one reagent is chemically incorporated into the surfactant, by analogy with the greater ease of intra- as compared with intermolecular reactions.[8] Most functional surfactants have contained amino or thiol groups and the former could act as nucleophiles or general bases,[4-6] but we have used quaternary ammonium ions derived from ethanolamine as reagents in reactions of phosphate esters[9,10] and acyl phosphates. Our evidence is consistent with the surfactant (I) generating the zwitterion (II) which reacts as a nucleophile. These micellized surfactants are effective reagents toward saturated and carbonyl carbon, and it was suggested that here they acted by increasing the nucleophilicity of hydroxide ion.[11]

Micelles of I can be regarded as models of protein bond serine, whose nucleophilicity is important in many enzymic reactions,[12] so that it is important to distinguish between the possible modes of catalysis in reactions catalyzed by micelles of I and related surfactants.

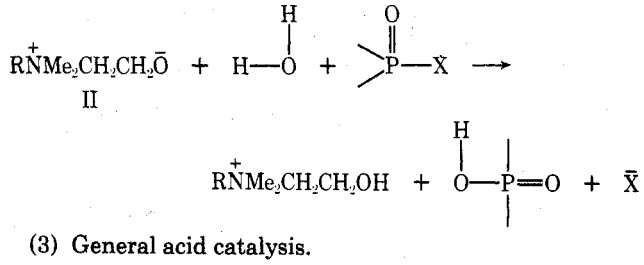
There are four reasonable mechanisms (1–4) by which micelles of I could speed reactions. They are shown for reaction at a phosphoryl group, but similar paths can be written for some of the reactions at carbon.

The fact that micelles of I are no better catalysts than micelles of cetyltrimethylammonium bromide (CTABr) for attack of fluoride ion upon *p*-nitrophenyl diphenyl phosphate[10] argues against 3 and 4, but either 1 or 2 are consistent with the evidence.

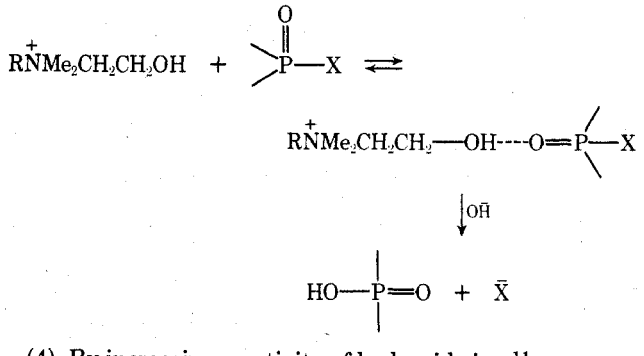
(1) Nucleophilic attack.[9,10]



(2) General base catalysis, cf. ref 13.



(3) General acid catalysis.



(4) By increasing reactivity of hydroxide ion.[11]