Phosphorolytic Reactivity of *o*-Iodosylcarboxylates and Related Nucleophiles

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Received January 17, 2002

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I. Introduction and Scope

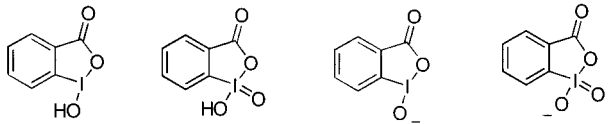
The discovery of the acute toxicity of various pentavalent organophosphorus compounds toward living species led to the development, industrial production, and widespread use of phosphoric, thiophosphoric, and phosphonothioic acid derivatives as biocides for animal and crop protection.[1] Parallel to insecticide development, appreciation of their potential lethality also led to consideration of their use as weapons of mass destruction.[2−4] Although modern chemical weapons have been used in limited circumstances (e.g., Iraq) and by terrorists in Tokyo, widescale use of these horrible materials has not thus far occurred. Nevertheless, large quantities of agents such as the fluorophosphonates sarin and soman, the phosphoroamidocyanidate tabun, and the more toxic and persistent methylphosphonothioates VX and Russian-VX (see Chart 1) are still stockpiled in a number of countries around the world, and their destruction requires the use of environmentally friendly processes.[2]

Both nerve agents and insecticides act as phosphorylating agents, reacting with the serine moiety of the enzyme acetylcholinesterase. They inhibit its regulation of the *in vivo* concentration of the neurotransmitter acetylcholine, with major effects on the nervous system.[3]

Although the use of organophosphorus compounds as pesticides is important to the agricultural industry, their extensive use can also lead to poisoning due to the occupational or incidental exposure of large numbers of people worldwide.[5] Moreover, their accumulation in the environment is a recognized ecological threat with harmful effects on human beings or other mammalian species due to possible long-term exposure to sublethal doses.[6]

Despite intense research during the second half of the last century, the decontamination and demilitarization of organophosphorus poisons is still, unfortunately, an urgent and topical problem. The recent terrorist use of sarin in Japan has raised public concern that many of these agents could be at the disposal of other groups, given their relatively simple manufacture, thus increasing the importance and need for rapid detection and efficient decontamination procedures.[7]

Though known for over 100 years, hypervalent iodine compounds such as *o*-iodosyl- (**1**) and *o*-iodylbenzoic acid (**2**) have been mainly used as oxidants in biochemical and analytical applications,[8] and their many synthetic uses are still being revealed.[9] In the early 1980s, the conjugate base of *o*-iodosylbenzoic acid (**3**, IBA) was discovered to be a potent oxygen nucleophile for the cleavage of reactive organophosphorus substrates such as *p*-nitrophenyl diphenyl phosphate (PNPDPP) when solubilized in aqueous micellar solutions of cetyltrimethylammonium chloride (CTACl) (Scheme 1).[10] A similar report on the nucleophilic reactivity of its higher valence derivative, *o*-iodylbenzoate (**4**, IBX), immediately followed.[11] Since then, iodosyl- and iodylcarboxylate derivatives have been the subject of numerous studies to explore the chemical features that elicit their nucleophilic reactivity. At the same time, a variety of related reagents and delivery forms have been developed which focus on increasing their native phosphorolytic reactivity as well as broadening the scope of their application.



1 **2** **3** (IBA) **4** (IBX)

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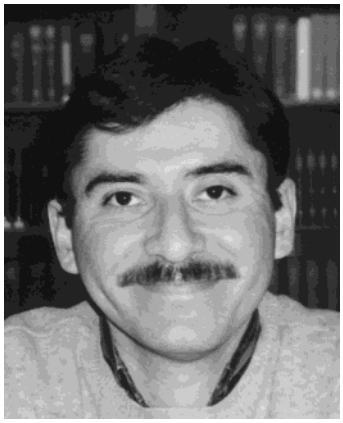
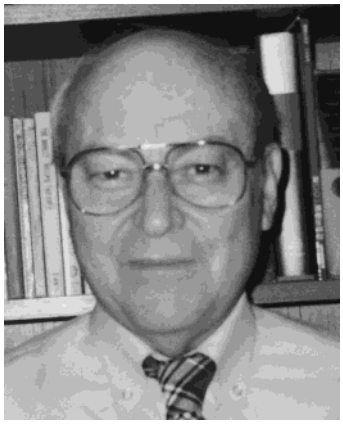
10.1021/cr9405462 CCC: $39.75
Published on Web 06/05/2002



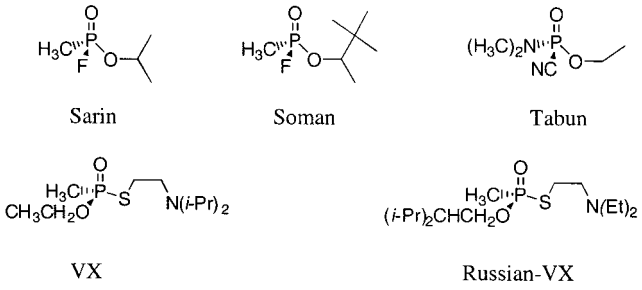
Hugo Morales-Rojas was born in México City and raised in Chiapas, México. He received his B.Sc. degree in Chemistry (1994) and M.Sc. degree in Inorganic Chemistry (1996) under the guidance of Professor Anatoly K. Yatsimirsky at the National Autonomous University of México (U.N.A.M.). As a Fulbright-CONACyT fellow he studied in the laboratories of Professor Robert A. Moss at Rutgers, The State University of New Jersey, and obtained his Ph.D. degree in 2001. His Ph.D. work focused on the hydrolysis of phosphates, phosphonates, and phosphonoformate esters mediated by *o*-iodosylcarboxylates and high-valent metal species. He is currently conducting postdoctoral studies in the laboratories of Professor Eric T. Kool at Stanford University, working on the biophysical and biochemical properties of synthetically modified DNAs and RNAs.



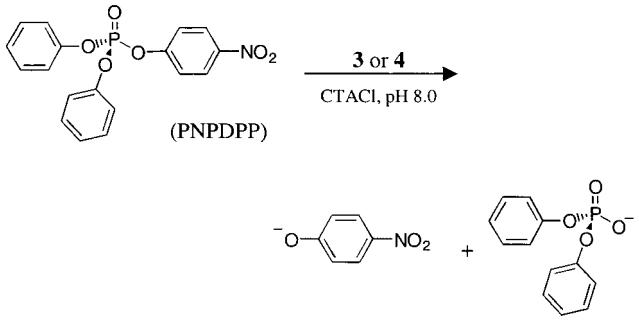
Robert A. Moss is the Louis P. Hammett Professor of Chemistry in the Department of Chemistry at Rutgers, The State University of New Jersey, New Brunswick, NJ. He was born in Brooklyn, NY, and educated at Stuyvesant High School, Brooklyn College (B.S. degree 1960), and the University of Chicago (M.S. degree 1962, Ph.D. degree 1963). After obtaining his doctoral degree with Professor Gerhard L. Closs at Chicago, Dr. Moss was a NAS–NRC Postdoctoral Fellow with Professor Ronald Breslow (1963–1964) at Columbia University. He joined the faculty at Rutgers University in 1964. Over the years, Professor Moss has held visiting appointments at M.I.T., the University of Oxford, The Weizmann Institute of Science (Israel), The Politechnika (Warsaw, Poland), The National Research Council (Canada), The University of Groningen (Netherlands), and the Hebrew University of Jerusalem (Israel). His research interests focus on chemical reactivity in aggregates, such as micelles and liposomes, the hydrolysis of phosphates and phosphonates (especially as related to the decontamination of chemical warfare agents), and the physical organic chemistry of reactive organic intermediates, particularly carbenes and carbocations. His nonscientific publications include articles on Sherlock Holmes and the literature of baseball. Professor Moss is married to Dr. Sandra Moss, M.D. They have two sons, Kenneth and Daniel.

Several previous reviews have touched upon general aspects of the nucleophilic reactivity of hypervalent iodine carboxylates.[2,12−14] The purpose of the present review is to describe in detail efforts to understand and improve the reactivity of *o*-iodosyl- and *o*-iodylcarboxylate derivatives for the degradation of organophosphorus substrates. To broaden our perspective, we also include other widely used nucleophiles and biological catalysts for the degradation of organophosphorus compounds.

Chart 1



Scheme 1

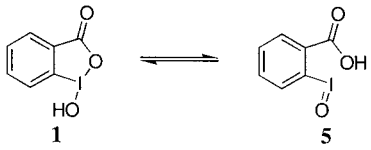


II. Structure, Bonding, and Nucleophilic Reactivity of o-Iodosylcarboxylates

o-Iodosylbenzoate (**3**, IBA) and *o*-iodylbenzoate (**4**, IBX) are examples of heterocyclic iodanes, generally called benziodoxoles, which contain hypervalent iodine and oxygen incorporated in a five-membered ring fused to benzene. The structural features of benziodoxoles have been thoroughly described by Koser[15] and Varvoglis,[13] and their chemical reactivity and synthetic utility has been recently reviewed.[14,16]

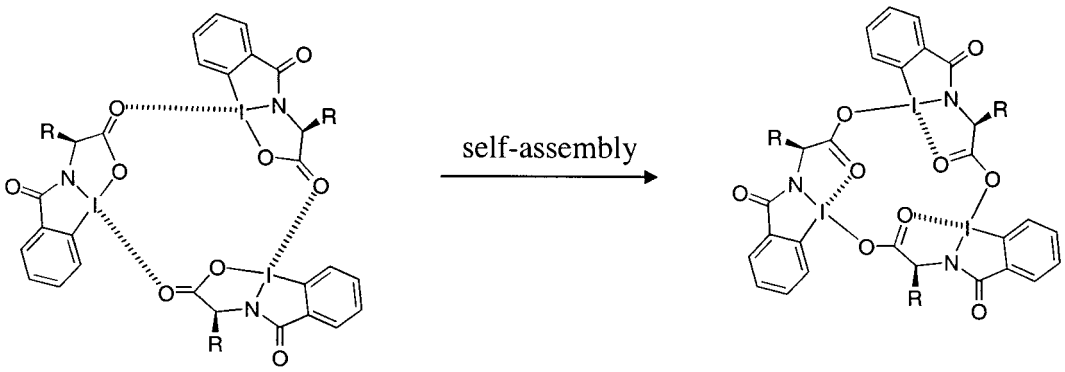
On occasion, the cyclic form of *o*-iodosylbenzoic acid (**1**) has been represented in a valence tautomeric equilibrium with the open form, **5**, Scheme 2. Evidence in favor of the closed structure was adduced long ago, based on its unusually low acidity (pK_a = 7.25, compared to 2.85 for *o*-iodobenzoic acid). The closed structure was later confirmed by X-ray structure analysis of crystalline IBA and some of its derivatives (see below).[15]

Scheme 2

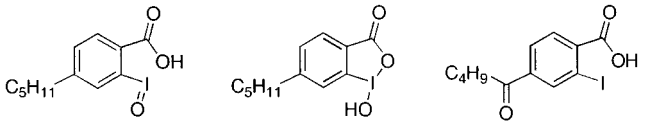


Nevertheless, representation of the tautomeric equilibrium was furthered by a report of the isolation of both structural forms of 4-alkyl-2-iodosylbenzoic acid (e.g., **6**, **7**).[17] A reinvestigation of 4-pentyl-2-iodosylbenzoic acid led to the identification of the

Scheme 3

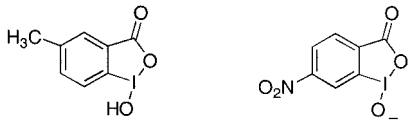


purported "open" form (**6**) as 4-pentanoyl-2-iodobenzoic acid (**8**) and the conclusion that only the cyclic form (**7**) could be isolated.[18] In consequence, it has been suggested that the use of valence tautomeric forms be avoided in representing cyclic iodoxolones. The structural features can be better described by specifying the endocyclic O−I separation determined from X-ray or computational methods.



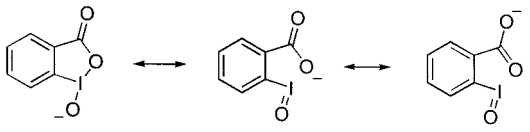
6 **7** **8**

Data derived from X-ray structural studies[15,19,20] and from ab initio molecular orbital calculations[21−23] agree that benziodoxoles generally present a planar and highly distorted five-membered ring with approximately T-shaped geometry at iodine. For instance, the O−I−O bond angle for IBA and its 5-methyl derivative **9** (in their acid form) is ∼170°.[15,20] They also present an endocyclic I−O bond length (2.30−2.35 Å) that is considerably longer than the single bond predicted from the sum of their covalent radii (∼2.07 Å).



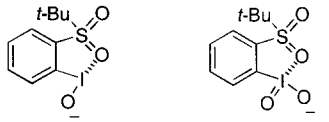
9 **10**

The related anionic *o*-iodosyl (**10**) and *o*-iodyl 4-nitrobenzoic acid sodium salts show even larger endocyclic I−O bond lengths with values of 2.44 and 2.48 Å, respectively.[20] On the basis of these observations, the structure of the benziodoxole ring has been regarded as a resonance hybrid of the closed (major contributor) and open forms, as depicted in **11a**−**c**.



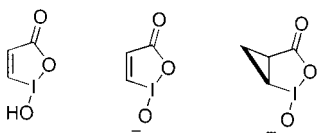
11a **11b** **11c**

The higher stability of the cyclic forms has been attributed to conjugative overlap of a p-orbital lone pair on iodine with the π-orbitals of the aromatic ring.[15] A closed, cyclic structure is needed to permit this interaction. A particularly detailed discussion of bonding and electronic structure in IBA and its analogues has been presented.[21] Moreover, even in cases where formal covalent bonds do not exist, hypervalent iodine is prone to interact in a noncovalent fashion forming cyclic structures via secondary interactions.[24] This is represented by the dashed bonds shown for the soluble iodosyl- and iodylbenzene derivatives **12** and **13**, for which X-ray diffraction studies reveal structural features resembling benziodoxoles.[25] Similar interactions (dashed bonds) also direct the self-assembly in acetone solution of the chiral hypervalent iodine macrocycles depicted in Scheme 3.[26]



12 **13**

Ab initio molecular orbital calculations performed on iodoxol-3(1*H*)-one, both in its acid (**14**) and deprotonated (**15**) forms, confirmed the trends and observations derived from the X-ray data, with computed endocyclic I−O distances of 2.1 and 2.63 Å for **14** and **15**, respectively.[21] Interestingly, the computed exocyclic I−O bond length of the anionic form **15** (1.92 Å) is closer to a single I−O bond (∼2.07 Å) with a large computed negative charge on its oxygen atom (−1.12). The computed C−O distances in the lactone unit are clearly differentiated in the acid form **14** (1.23 Å, C═O, vs 1.35 Å, C−O) but become very similar after deprotonation (1.26 Å, C═O, vs 1.29 Å, C−O in **15**), which indicates that the lactone units in iodosylcarboxylates relax toward the carboxylate-like hybrid form (**11c**).[21] Thus, the 3-center-4-electron O−I−O triad transmits negative charge toward the carboxylate group, which contributes to the observed



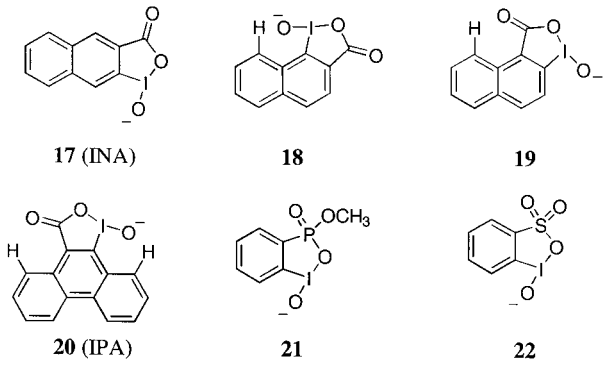
14 **15** **16**

Table 1. Structural Features and Reactivities of 1-Oxidoiodoxol-3(1*H*)-ones

property	3	15	16
I−O_{exo}, Å[a]	2.603	2.632	2.713
I−O_{endo}, Å[a]	1.908	1.917	1.925
O_{exo}, net atm chg[b]	−1.14	−1.12	−1.10
k_{ψ}^{max}, s^{-1}[c]	0.064	0.010	0.0044
k_{dis}, $M^{-1}\,s^{-1}$[d]	0.000019	0.000695	0.027

[a] Calculated bond lengths; see ref 22. [b] Calculated net atomic charges; see ref 22. [c] Maximum pseudo-first-order rate constant for PNPDPP cleavage taken from rate constant/[CTACl] profile; standard conditions pH 8.0 phosphate buffer, $\mu = 0.08$ (NaCl), 25 °C, [PNPDPP] = 0.01 mM, [catalyst] = 0.1 mM. [d] Second-order rate constants for disproportionation in water at pH 8.0; see ref 22.

Chart 2



long endocyclic I−O bond and reduces the charge and nucleophilicity at I−O^-.[21]

This analysis leads to the idea that the inclusion of appropriate structural factors might force the 1-oxido-iodoxolone anions to remain more *closed*, which could increase the negative charge and therefore enhance the nucleophilicity at O^-.[21,22] Computational studies on the anionic forms of compound **15**, its cyclopropyl analogue **16**, and IBA (**3**) find that in the sequence **3**, **15**, **16** the endocyclic I−O bond length increases from 2.603 to 2.632 to 2.713 Å whereas the net atomic charge on the oxygen at the exocyclic I−O bond slightly decreases from −1.14 to −1.12 to −1.10, respectively.[22] Similarly to IBA, derivatives **15** and **16** display *O*-nucleophilicity toward reactive phosphate simulants such as *p*-nitrophenyl diphenyl phosphate (PNPDPP) in cationic CTACl micellar solutions (Scheme 1). Table 1 reproduces some structural and reactivity features of anionic IBA (**3**) in comparison to those of **15** and **16**.

We see that **3** (IBA), which is the most reactive nucleophile toward PNPDPP, has the largest computed electron density on its exocyclic oxygen and the shortest endocyclic I−O bond length.[22] Indeed, the observed reactivity sequence (**3** > **15** > **16**) tracks the computed charge density on the exocyclic oxygen atom, as anticipated, with the cyclopropanated iodosylcarboxylate **16** bearing the lowest negative charge on the exocyclic oxygen and displaying the lowest nucleophilic reactivity toward PNPDPP. The stability in aqueous solutions of these iodosyl derivatives, as measured by the rate of disproportionation (k_{dis}) to yield the iodo and iodyl species, correlates with the endocyclic I−O bond length, i.e., the most open structure **16** is least stable toward disproportionation.[21]

Catalyst design next focused on exploiting possible correlations between the length of the endocyclic O−I bond of 1-oxido-iodoxolones with both the calculated negative charge on the exocyclic I−O^- and the nucleophilic reactivity toward PNPDPP. Various analogues of IBA (**3**) were synthesized, such as iodosylnaphthoates **17**, **18**, and **19**,[27] iodosylphenanthroate **20**,[19] and iodosylcarboxylate analogues **21** (a cyclic phosphonate) and benziodoxathiol **22** (a cyclic sulfonate), Chart 2.[23]

Iodosylnaphthoates **18** and **19** are expected to display steric interactions between the adjacent 8-*peri*-H atoms and the oxygen of **18** or the carbonyl oxygen of **19**, where the separations indicated by models (∼1.8 Å) are shorter that the sum of the van der Waals radii (∼2.6 Å). Indeed, calculations afford endocyclic I−O bond lengths in the order **14** > **3** > **19** and the reverse order for their negative (I−O^-) net charges, suggesting that steric interactions may be relieved by a shorter I−O endocyclic bond, leading to an enhanced negative charge at I−O^-.[27] In similar fashion, iodosylphenanthroate (**20**, IPA) is expected to present high reactivity due to the enforced structural modification of the iodosylcarboxylate ring which includes both of the *peri*-H/O interactions present in compounds **18** and **19**.[19] X-ray structural studies of IPA reveal an O−I−O bond angle of 170.5°, exhibiting T-shaped coordination geometry at iodine, as well as a shortening of the endocyclic I−O bond (2.175 Å) (Figure 1). However, much of the strain caused by the *peri*-H/O steric repulsions is relieved by bond angle distortions resulting in marked deviation from planarity in both the iodoxolone and phenanthrene rings (Figure 1).[19]

Moreover, the structural modifications of **18**, **19**, and **20** translate only into marginally enhanced reactivity. Iodosylnaphthoates **18** and **19** are 5−6 times more reactive toward PNPDPP than IBA but only ∼25% more reactive than INA (**17**), in which the steric interactions are absent (see Table 2 in section III for kinetic data). The significant rate enhancements relative to IBA can be explained as a result of the additional aromatic ring present in the iodosylnaphthoates, which affords higher hydrophobicity and better binding to the cationic micelles in which the reactions occur. Surprisingly, IPA is only a little more reactive than the iodosylnaphthoates despite both the enhanced negative charge at I−O^-, promoted by steric constraints, and higher hydrophobicity. Perhaps steric congestion at the IPA nucleophilic site (I−O^-) prevents especially efficient attack on substrates such as PNPDPP.[19]

Iodosylcarboxylate analogues **21** and **22** are less reactive than IBA under comparable conditions.[23] Here, computational studies indicated a systematic decrease of the charge at I−O^- in the order IBA > **21** > **22** which correlates with the observed decrease in nucleophilic reactivity.[23]

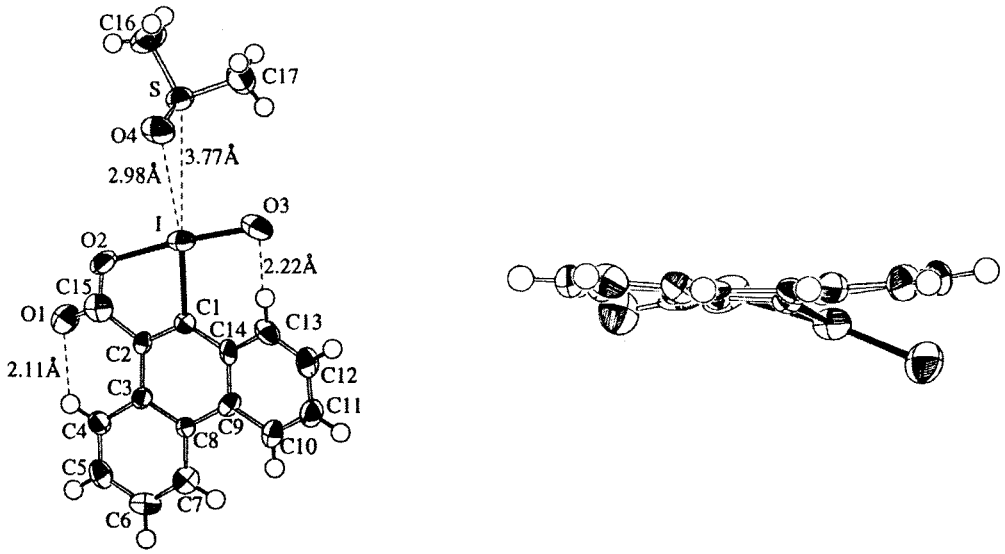


Figure 1. (left) ORTEP diagram of the crystal structure of IPA (**20**) showing nearest-neighbor DMSO and iodosyl molecules. (right) Edge on view of IPA (**20**), approximately along the C_2-O_2 vector. The thermal ellipsoids are plotted at the 50% probability level; H atoms are drawn as open spheres of arbitrary radii. (Reprinted with permission from ref 19. Copyright 1995 American Chemical Society.)

Table 2. Comparison of Kinetics Parameters for the Micellar Cleavage of PNPDPP by IBA and Analogues[a]

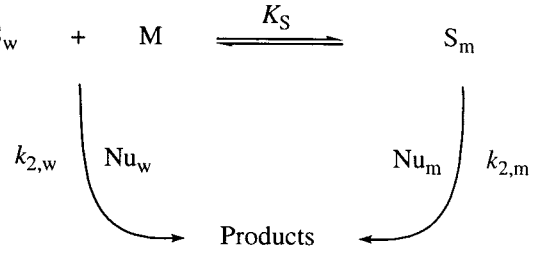
catalyst	pK_a[b]	k_ψ^{max} (s^{-1})[c]	10^3 [CTACl] (M)[d]	k_{cat}[e] (M^{-1} s^{-1})	k_{turn}[f] (s^{-1})	ref
15	7.78	0.010	3.0	160	*g*	21
16	7.55	0.0044	10.0	44	*g*	22
3 (IBA)	7.25	0.064	1.0	759	0.024	10
25	7.20	1.04	0.2	14400	0.90	11
26	6.45	1.14	0.2	28500	0.17	34
27	7.35	0.34	0.5	4150	0.13	35
17 (INA)	7.10	0.26	0.5	2950	0.16	27
18	7.20	0.36	0.5	4190	0.23	27
19	7.70	0.31	0.5	4660	0.10	27
20 (IPA)	7.40	0.38	0.35	4750	0.091	19
21	6.80	0.0016	10.0	17	*g*	23
22	6.50	0.0013	1.0	13	*g*	23
28	7.20[h]	0.055	1.0	635	0.038	36
29	6.73	0.062	0.5	648	0.035	36
30	7.44	0.0096	1.0	123	0.0058	36
31	7.40[i]	0.0073	1.5	91	0.0042	36
32	7.75	0.0028	1.0	44	0.0020	21
33	>11	0.001[j]	1.0		*g*	21
34[k]	4.85	0.18[l]	0.1	1770	0.05	37
35[m]	7.20	0.014		75	0.0012	38

[a] Standard conditions: 0.02 M pH 8.0 phosphate buffer, μ = 0.08 (NaCl), 25 °C, [PNPDPP] = 0.01 mM, [catalyst] = 0.1 mM. [b] Determined from pH vs rate constant profiles for the cleavage of PNPDPP in micellar CTACl. [c] Maximum pseudo-first-order rate constant for PNPDPP cleavage taken from rate constant/[CTACl] profile. [d] Concentration of CTACl at which k_ψ^{max} was observed. [e] $k_{cat} = k_\psi^{max}$/[catalyst], corrected for 100% ionization to IO^-. [f] Turnover rate constant for cleavage of 2-fold excess PNPDPP in 1 mM CTACl. [g] Not available. [h] Assumed to be identical to the pK_a of **25**. [i] Estimated value.[36] [j] In pH 10 phosphate buffer. [k] R = *n*-$C_{16}H_{33}$. [l] Kinetics determined in pH 8 Tris buffer. [m] Surfactant **35** was studied as a 1:2 covesicular blend with (*n*-$C_{16}H_{33})_2N^+Me_2$, Br^- in pH 8 Tris buffer.

III. Reactivity in Surfactant Systems

Reactivity in association colloids has been thoroughly studied during the past several decades.[28−30] It is now widely accepted that the rate enhancements observed in these aggregated systems are largely the result of increases in the concentrations of reactants in the small interfacial volumes in which the reactions occur.[30,31] Quantitative treatments of reactivity in association colloids frequently use the pseudophase model.[31,32] One of its basic assumptions is that the aggregate constitutes a pseudophase, separated from the bulk solution where it is dispersed, so that reagents partition between the bulk phase and the aggregate pseudophase. Thus, bimolecular nucleophilic reactions can be described as illustrated in Scheme 4, where S and Nu are the substrate and the nucleophile in water (subscript w) or in the micellar pseudophase (subscript m), $k_{2,w}$ and $k_{2,m}$ are the second-order rate constants for substrate/nucleophile reactions in the aqueous phase and in the micellar pseudophase, respectively, and K_S is the binding constant of the substrate to the micelles based on the concentration of micellized surfactant, defined as the difference in the total concentration of surfactant and the critical micelle concentration (cmc), i.e., [M] = $[surfactant]_{total}$ − cmc.[31,32]

Scheme 4



The second-order rate constant $k_{2,m}$ is written in terms of the *local* concentration of the nucleophile in units of moles per liter of reaction volume within the micellar pseudophase (Nu_m), which cannot be measured directly. The concentration of the nucleophile can also be taken as a mole fraction of the bound reactive anion to the micellized surfactant, defined as $Nu_m = [Nu_m]/[M]V_m = \beta/V_m$, where β is the degree of counterion binding to the micelle and V_m is the molar volume of the reactive region in the aggregate. V_m also relates the apparent, measurable,

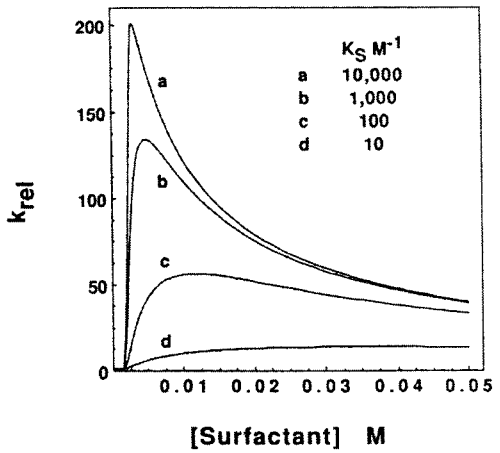


Figure 2. Effect of increasing substrate hydrophobicity on the rate constant (relative to that in water) as a function of surfactant concentration. Parameters are cmc = 0.002 M, [Nu] = 0.01 M, $K_N^X = 4$, $k_{2,m}/k_{2,w} = 1$, $\beta = 0.7$, and $V_m = 0.15$ M^{-1}. K_s values are listed in the figure. (Reprinted with permission from ref 31a. Copyright 1991 American Chemical Society.)

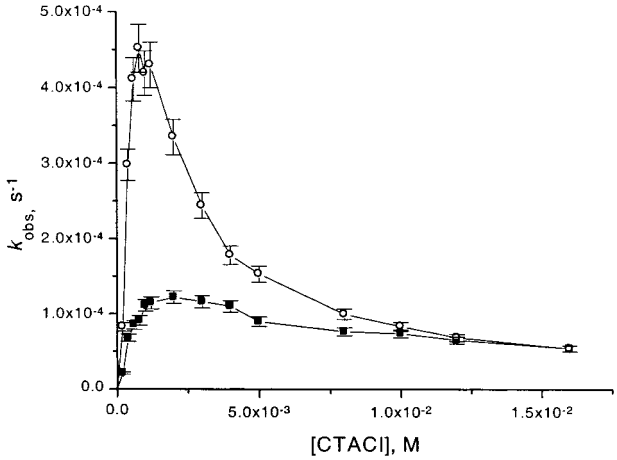


Figure 3. Pseudo-first-order rate constants, k_{obs} (s^{-1}), for the cleavage of 1×10^{-5} M parathion (**24**) by 1×10^{-4} M IBA (■) or INA (○) as a function of CTACl (M) at pH 8.0 and 25 °C. (Reprinted with permission from ref 33. Copyright 2000 American Chemical Society.)

micellar rate constant, k_m, to $k_{2,m}$, (i.e., $k_m = k_{2,m}/V_m$). Thus, formulation of the kinetics of bimolecular reactions under pseudo-first-order conditions ([Nu]≫[S]) gives eq 1.[31] The value of V_m is unknown, so that in order to estimate $k_{2,m}$ from k_m, one assumes a value for V_m; typical estimates range from 0.14 M^{-1} (the volume of the micellar Stern layer) to 0.37 M^{-1} (the volume of the micelles).[31]

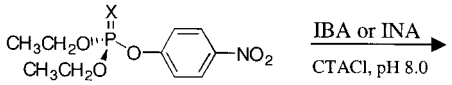
$$k_\psi = \frac{k'_w[Nu_w] + k_m K_S[M]}{1 + K_S[M]} = \frac{k'_w + (k_{2,m}/V_m)\beta K_S[M]}{1 + K_S[M]} \quad (1)$$

$$X^-_m + Nu_w \overset{K_X^{Nu}}{\rightleftharpoons} Nu_m + X^-_w \quad (2)$$

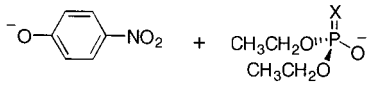
The micellar surface also behaves as a selective ion exchanger, and competition between reactive (Nu) and inert (X) counterions can be expressed as in eq 2, in which an empirical ion exchange constant, K_X^{Nu}, accounts both for ionic and hydrophobic contributions to the binding.[28d,31] This extension of the pseudophase model has been called the pseudophase ion exchange model or PIE and successfully fits the kinetics of many bimolecular reactions in micellar solutions.[32e] In the PIE model, β (the degree of counterion association to the micellar surface) is assumed to be constant and insensitive to surfactant and salt concentrations.[28d,31] However, this assumption generally fails for very hydrophilic anions such as OH^-, F^-, or OOH^-, for which the degree of association appears to increase gradually with increasing surfactant concentration.[31]

Usually, reactivity in surfactant systems is evaluated through full rate constant vs surfactant concentration profiles. Figure 2 shows theoretical rate constant profiles (given as relative rates) as a function of surfactant concentration calculated from eq 1. If the concentrations of the reactants, e.g., IBA and PNPDPP, are held constant under pseudo-first-order conditions ([IBA] ≫ [PNPDPP]) while the concentration of surfactant ([M]) is gradually increased, the rate constant vs [M] profile will go through a maximum that corresponds to the balance point between a rate increase caused by the transfer of the nucleophile into the micellar pseudophase and a rate decrease due to dilution of the nucleophile as the surfactant concentration continues to increase. The shape of this profile will depend on the substrate's hydrophobicity (represented by the binding constant, K_S) and the affinity of the ionic reactive nucleophile for the charged interfacial region in the presence of inert counterions (eq 2). The expected change in reactivity with hydrophobicity of the substrate for a given nucleophile is depicted in Figure 2.[28d,31]

Scheme 5



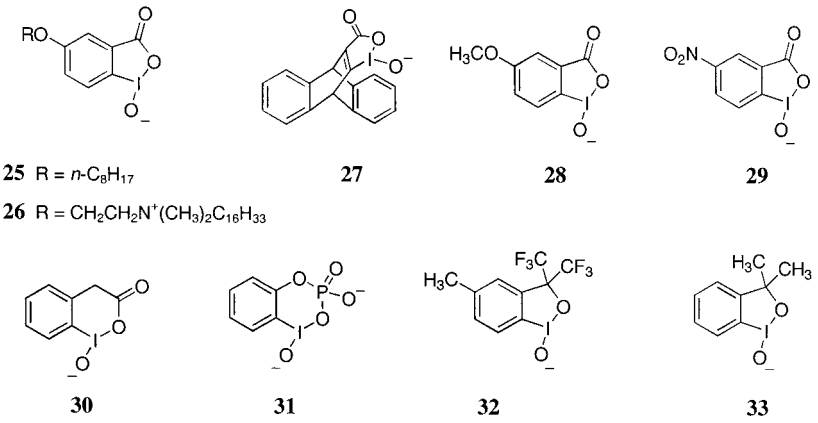
23 (X = O, paraoxon)
24 (X = S, parathion)



Since the discovery of the nucleophilic reactivity of IBA, its potency has been increased by the use of aqueous cationic micellar solutions under conditions where the anionic (deprotonated) form of IBA (**3**) predominates. Typical reaction conditions include micellar aqueous CTACl, 0.02 M pH 8.0 phosphate buffer, and 0.08 M NaCl. These reaction conditions have become "standard" to test the phosphorolytic reactivity of various IBA derivatives toward nerve agent simulants such as PNPDPP and insecticides such as paraoxon (**23**) or parathion (**24**), where the release of the *p*-nitrophenylate anion can be readily followed by UV−vis spectrophotometry, cf. Schemes 1 and 5.

The binding of the nucleophile to the micelle also influences the observed reactivity. Figure 3 shows experimental rate constants as a function of CTACl concentration for the cleavage of the thiophosphate insecticide parathion (**24**) in the presence of IBA and

Chart 3



25 R = *n*-C_8H_{17} **27** **28** **29**

26 R = $CH_2CH_2N^+(CH_3)_2C_{16}H_{33}$

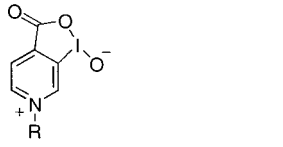
30 **31** **32** **33**

INA (**17**).[33] We note that at high concentrations of surfactant, the rates level off as predicted from the PIE model.[31] When the IBA or INA reagents are "fully bound," intrinsic differences in their hydrophobicity no longer affect the observed reaction rate constants.

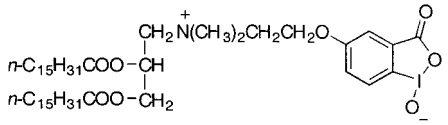
Over the years, chemists have designed many new iodosyl and iodyl derivatives, incorporating various modifications of the parent compounds, with the goal of obtaining more powerful reagents for the chemical degradation of organophosphorus substrates, see Chart 3. Strategies aimed at increasing binding to the micellar pseudophase led to more hydrophobic iodosylcarboxylates such as the *p*-octyloxy derivative **25**[11] and the functionalized surfactant **26**,[34] which displayed outstanding phosphorolytic reactivity toward PNPDPP when comicellized with CTACl (see Table 2).

Later, derivatives such as **27**, in which the planar structure of the iodoxolones was modified, also demonstrated exceptional reactivity (see Table 2). Presumably, this was driven by a higher hydrophobicity (i.e., tighter binding to the micelles) compared to the parent IBA.[35] Further modifications produced derivatives **28**−**33**, where various electronic and structural effects (ring size, substituents, heteroatoms, and replacement of the carbonyl unit) were investigated.[21,36] However, none of these reagents proved superior to **3** as a catalyst for the cleavage of PNPDPP in micellar CTACl.

For most of these examples, the phosphorolytic reactivity was examined in weakly basic micellar solutions (pH 8−9), where significant amounts of the reactive deprotonated forms of IBA ($pK_a = 7.25$) and its derivatives were present. Appropriate structural modifications led to the related iodosylpyridinium derivatives **34** which exhibited much lower pK_a values (e.g., 4.85 for R = *n*-$C_{16}H_{33}$) and displayed effective phosphorolytic reactivity under moderately acidic conditions.[37] IBA reactivity was also examined in covesicular aggregates formed from functional surfactant **35** and dihexadecyltrimethylammonium bromide.[38]



34 R = *n*-C_8H_{17}, *n*-$C_{12}H_{25}$, *n*-$C_{16}H_{33}$



35

At this point it is appropriate to compare kinetics parameters for the cleavage of PNPDPP by various iodosyl derivatives as depicted in Table 2. PNPDPP is a very hydrophobic substrate, and its binding constant to CTA^+ micelles lies in the range from 7×10^3 to 1.5×10^4 M^{-1}.[39] With the substrate at concentrations of 1×10^{-5} M, quantitative binding is reached at or above the cmc value for CTACl ($\sim 1 \times 10^{-3}$ M). The data in Table 2 reveal that the hydrophobicity of the iodosyl nucleophile greatly influences its reactivity. Higher hydrophobicity leads to increased nucleophile incorporation in the micelle, which is qualitatively reflected by a decreased concentration of CTACl at which the maximum PNPDPP cleavage rate is elicited (k_ψ^{max}). Accordingly, iodosyl derivatives with long alkyl chains, such as **25** and the functional amphiphile **26**, exhibit maximum reactivity at low CTACl concentrations. By this criterion, they are the best IBA-based catalysts synthesized to date. The effect of hydrophobicity can also be discerned in the reactivity sequence **15** < **3** < **17** < **20**, where incremental additions of aromatic (benzene) rings lead to increasing reactivity (k_ψ^{max}), although the reactivity of **20** is somewhat mitigated, probably because of steric effects (see above).

Table 2 includes kinetic data for 20 iodosylcarboxylate derivatives, and some additional comments concerning structure−reactivity relationships are in order. A convenient way to compare the reactivities of the reagents is through their k_{cat} values. k_{cat} is defined as the maximum pseudo-first-order rate constant for PNPDPP cleavage (taken from the rate constant/[CTACl] profile), divided by the concentration of the catalyst. Therefore, k_{cat} represents the molar efficiency of the iodosylcarboxylate for the cleavage of PNPDPP in micellar CTACl. The most reactive reagents ($k_{cat} > 10\,000$ M^{-1} s^{-1}) are iodosyl-

benzoate-functionalized CTA analogue **26** and octyloxybenzoate **25**, for which electronic effects favoring negative charge on the nucleophilic center (I−O⁻) and hydrophobicity (ensuring good binding to CTACl micelles) are optimized. Other effective catalysts (k_{cat} > 1000) include **20**, **27**, and **17**, where additional aromatic rings enhance reagent hydrophobicity and micellar binding at the cationic CTACl headgroups. Naphthalene derivatives **18** and **19**, in which the iodosylcarboxylate unit is bonded to naphthalene carbons 1 and 2, are slightly more reactive than their isomer **17** (iodosylcarboxylate at carbons 2 and 3). This may be a consequence of sterically determined negative charge enhancements at the I−O⁻ centers of **18** and **19** (see above, section II).

The cetylpyridinium iodosylcarboxylate surfactant, **34** (R = *n*-$C_{16}H_{33}$), which is reactive toward PNPDPP in mildly acidic micellar solutions,[37] also displays k_{cat} > 1000, a consequence of its hydrophobicity. The k_ψ^{max} values for **34** decrease sharply as the hydrophobic "tail" is shortened. Thus, k_ψ^{max} is 0.18, 0.071, or 0.0038 s^{-1}, respectively, for R = *n*-$C_{16}H_{33}$, *n*-$C_{12}H_{25}$, or *n*-C_8H_{17}.[37]

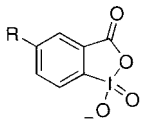
Iodosylbenzoate itself (**3**) displays k_{cat} = 759 M^{-1} s^{-1}. Its hydrophobicity and reactivity are inferior to those of its naphthalene (**17**), dibenzobarrelene (**27**), or anthracene (**20**) analogues but superior to those of the archetypal iodosylcarboxylate (**15**) or the latter's cyclopropyl modification (**16**), which are both bereft of aromatic rings. Structure−reactivity relationships for **3**, **15**, and **16** are discussed above in section II.

Attempts to enhance the reactivity of IBA by manipulating electronic factors have not been very successful thus far. Only minor reactivity effects result from the substitution of electron-donating (**28**) or electron-withdrawing (**29**) groups on the benzo ring of IBA.[36] Expanding the iodosylcarboxylate ring, as in **30**, leads to a significant reactivity decrease, with k_{cat} = 123 compared to 759 for IBA. The six-membered benziodosyl phosphate (**31**), with k_{cat} = 91, is even less reactive than **30**. Similarly, only reactivity decreases (k_{cat} < 100) result from replacement of the lactone carbonyl of IBA by phosphonyl (**21**), sulfonyl (**22**), bis-trifluoromethyl (**32**), or dimethyl (**33**) units. The lack of reactivity of **33** is due to the nonacidicity of its protonated (I−OH) form (pK_a > 11). Lacking a carbonyl group to accept negative charge (cf., **11c**), **33-OH** does not readily ionize to its anionic nucleophilic form.[21] The CF_3 groups of **32**, however, can accept negative charge inductively and do somewhat compensate for the absence of the carbonyl group.[21] Nevertheless, **32** remains approximately 20 times less reactive than IBA. Analogues **21** and **22** are also less reactive than IBA because their phosphonate or sulfonate units drain more negative charge from I−O⁻ than does the carboxylate unit of IBA; **21** and **22** are therefore weaker nucleophiles.[22]

Finally, the reactivity of the iodosylbenzoate moiety of reagent **35** is modulated by accessibility and permeability factors distinct to the liposomal environment in which it reacts. It is considerably less reactive than its more fluid, micellar analogue, **26**.

One also notes from Table 2 that the iodosylcarboxylates (in CTACl micellar solution) are true catalysts for the hydrolytic cleavage of PNPDPP, i.e., they "turn over" in the presence of excess substrate. Turnover rate constants (k_{turn}) in the presence of 2-fold excess PNPDPP appear in Table 2. Although k_{turn} is generally lower than k_ψ^{max} (determined at a 10-fold excess of catalyst), in some cases k_{turn} is rather close to k_ψ^{max}. A good example is octyloxyiodosylbenzoate, **25**. Not only is this reagent highly reactive toward PNPDPP, but k_{turn} is approximately 86% of k_ψ^{max}. It is the cleavage of phosphorylated catalyst (with rate constant k_{turn}) that will be rate-limiting in the cleavage of excess substrate. The mechanism of iodosylcarboxylate-mediated cleavage of PNPDPP is discussed in detail in section VII, below.

Following the initial report of the phosphorolytic reactivity of *o*-iodylbenzoate (**4**, IBX),[11] several IBX derivatives (**36**) were synthesized and tested against PNPDPP in CTACl solutions.[40] Although, in the original report,[11] IBX was found to be less active than IBA by a factor of 3.8 against PNPDPP, continued interest in IBX and its derivatives was based on their higher shelf stability compared to the corresponding iodosyl analogues. In most cases, however, the reactivities of the iodyl compounds were found to be nearly equivalent or slightly inferior to those of iodosyl compounds.[40]



36 R = OCH_3, OC_4H_9, OC_8H_{17}, $OC_{12}H_{25}$

OCH_2CH_2OH, $OCH_2CH_2OCH_2CH_2OCH_3$,

$OCH_2CH_2N^+(CH_2CH_3)_3$, NO_2

IV. Microemulsions, Functionalized Solid Supports, and Latexes

Most of the target organophosphorus compounds (nerve agents, insecticides, and their simulants) are sparingly soluble in water.[2] Thus, the utility of micellar surfactant systems is partly a consequence of their capacity to solubilize these organic materials in aqueous media. However, under micellar conditions, one cannot solubilize large enough quantities of substrate to achieve practical decontamination. That is why, in addition to the extensive studies of micellar IBA systems, alternative vehicles for IBA delivery have been examined. Of particular importance are microemulsions,[41−43] IBA-functionalized solid supports,[44−47] and cationic latex dispersions.[48]

A microemulsion (ME) is a thermodynamically stable and optically clear dispersion of hydrocarbon droplets suspended in water (oil-in-water or O/W) or water droplets suspended in hydrocarbon (water-in-oil or W/O).[29,28d,49] The droplets are small (60−600 Å) and form spontaneously when specific proportions of water, oil (e.g., a hydrocarbon), surfactant, and a cosurfactant (often a short-chain alcohol) are mixed. Surfactant and cosurfactant form an interface between the droplet and the continuous phase, which

Table 3. Cleavage of PNPDPP by Iodosyl Derivatives (37) in Micellar CTACl and in a Microemulsion[a]

R in **37**	$10^3\ k_\psi^{max}$ (s^{-1})[b]	10^3 CTACl (M)[c]	10^3 k_o(s^{-1})[d]	k_2 ($M^{-1}\ s^{-1}$)[e]
		Micelles[a]		
Me	3.06	5.0	0.18	30.6
Et	2.38	3.0	0.15	23.8
Bu	8.93	3.0	0.18	89.3
Oct	53.1	5.0		531.0
		Microemulsion[f]		
Me	0.87			4.3
Et	0.46			4.6
Bu	0.66			6.6
Oct	2.10			21.0

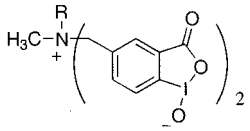
[a] Standard conditions: 0.02 M pH 8.0 phosphate buffer, μ = 0.08 (NaCl), 25 °C, [PNPDPP] = 0.01 mM, [catalyst] = 0.1 mM. [b] Maximum pseudo-first-order rate constant for PNPDPP cleavage taken from rate constant/[CTACl] profile. [c] Concentration of CTACl at which k_ψ^{max} was observed. [d] k_o is the rate constant in the absence of CTACl. [e] $k_2 = k_\psi^{max}$/[catalyst]. [f] 4.5% CTABr, 4.5% *N*-methylpyrrolidine, 90% pH 9.3, 0.03 M aqueous sodium borate, 1% toluene, [PNPDPP]= 0.01 mM, [catalyst] = 0.1 mM.

is somewhat comparable to the Stern layer of surfactant micelles. Chemical reactivity in a ME is, in many respects, similar to that in micellar surfactant systems, and so quantitative treatments are generally adaptations from the theoretical model developed for micelles in water.[28d,31]

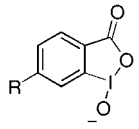
The solubility of organophosphorus compounds in an oil-in-water ME is much higher than in a micellar solution. However, one must expect lower reaction rates than those obtained in micelles as a consequence of the larger interface volumes provided by an O/W ME. Moreover, reactive anionic nucleophiles such as IBA may prefer to remain between the cationic or polar headgroups and the aqueous phase, whereas hydrophobic substrates (e.g., PNPDPP) mainly reside in the ME's oily interior. Thus, the reaction of IBA and PNPDPP will occur at the interface and will be sensitive to factors that affect the distribution of IBA between various sites in the ME.

The group at the U.S. Army Edgewood Research, Development and Engineering Center intensively examined ME's as media for the IBA-catalyzed hydrolysis of PNPDPP.[41] Variations in ME composition and IBA structure led to optimized substrate solubilization and hydrolytic rate.[41a,b] Although, in several instances, the reactivity in ME was much lower in comparison to micellar systems, the incorporation of *N*-methylpyrrolidinone as a cosurfactant in the ME formulations permitted significant penetration to agents adsorbed in polymers such as polystyrene and poly(methyl methacrylate). These ME's could be used for the decontamination of *polymer-thickened* nerve agents that are resistant to simple aqueous decontaminants.[41d]

IBA reagents with adjustable hydrophobicity were also applied in ME systems, optimizing the phase distribution of IBA.[17,42] Kinetic data for the reactivity of the duplex−IBA catalyst **37** are collected in Table 3 for both micellar and ME formulations. Catalyst **37** exhibited the expected octyl > butyl > ethyl ≈ methyl kinetics sequence in both types of organized media, and the reactivity of the catalyst with the longest chain was most strongly amplified by the CTACl micelles.[42]



37 R = CH_3, C_2H_5, *n*-C_4H_9, *n*-C_8H_{17}



38 R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_5H_{11}, *n*-C_8H_{17}

For derivatives of **38**, the rate constants decreased as R increased, with a rate maximum at R = Et.[17] However, this result was probably erroneous because inactive *iodo* compounds were present instead of iodosyl derivatives (see the discussion of the 5-pentyl derivative, **38** R = *n*-C_5H_{11}, in section II above).[18]

Immobilized iodosylcarboxylates have been prepared as alternatives to the fluid decontaminant systems, i.e., micelles and microemulsions. Solid supported decontaminants offer the attractive properties of easy handling and applicability in flow-through treatment of contaminated water or in the clean up of small "spills" of toxic agents. The solid supports to which IBA has been covalently attached include polymers,[44] silica gel,[45] ion-exchange resins,[46] titania, and nylon.[47]

The first report concerning these materials demonstrated that IBA-functionalized polystyrene or polyacrylate reagents (e.g., **39**, see Chart 4) catalytically cleaved both PNPDPP and the nerve agent soman, but high IBA loading was difficult to achieve, and the polymeric supports were not compatible with aqueous environments.[44] This "wetability" problem was overcome by the use of a silica-bound IBA (**40**), which displayed higher reactivity than its polymer analogues against PNPDPP and soman, but was still ~16 times less reactive than IBA in micellar solutions (see Table 4).[45] Good catalysts for the cleavage of PNPDPP were found when titania or nylon (**41**) were used as supports.[47] In many cases, dilute CTACl aqueous solutions (in place of water) potentiated the reactivity of the supported IBA reagents (Table 4).

Remarkably, materials that cleaved PNPDPP under heterogeneous conditions with rate constants and turnover comparable to those of the micellar systems were prepared from the cross-linked, macroreticular, acrylic anion-exchange resin IRA-35, functionalized with IBA and an auxiliary residue, **42** (e.g., R = $C_{16}H_{33}$).[46] Advantages of these materials include higher loading and good wetting properties. In principle, one could prepare a family of related doubly functionalized resin catalysts with adjustable hydrophilicity.

Phosphorolytic reactivity in other aggregated systems, for example, cationic latex dispersions, has been extensively investigated.[48] In the simplest de-

Chart 4

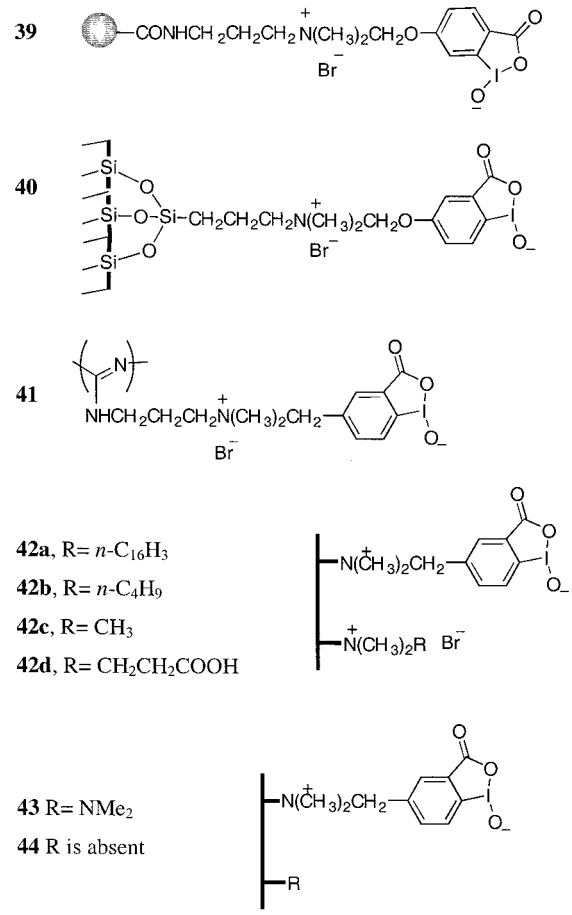


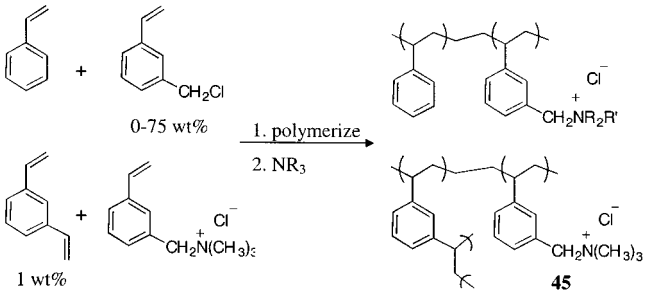
Table 4. Cleavage of PNPDPP by Supported Iodosylbenzoates[a]

		no CTACl		0.5 mM CTACl	
catalyst	10^3 Mequiv[b]	$10^3\ k_\psi^{max}$ (s^{-1})[c]	k_2 ($M^{-1}\ s^{-1}$)[d]	$10^3\ k_\psi^{max}$ (s^{-1})[c]	k_2 ($M^{-1}\ s^{-1}$)[d]
42a[e]	9.2	67	22	*f*	*f*
42b[e]	12	16	4.0	9.1	2.3
42c[e]	13	7.4	1.7	3.4	0.8
42d[e]	12	1.9	0.48	51	13
43[e]	9.2	5.2	0.17	71	23
44[e]	15	17	3.4	49	9.9
39[g]	3.2	11	17	*h*	*h*
40[i]	1.0	18	40	*h*	*h*
41[j]	2.5	12	14	67	~80

[a] Conditions: 0.02 M pH 8.0 phosphate buffer, μ = 0.08 (NaCl), 25 °C, [PNPDPP] = 0.01 mM, [catalyst] = 0.033 mM. [b] Mequiv of iodosylbenzoate in 10 mg of solid catalyst in 3 mL of buffer solution. [c] Pseudo-first-order rate constant for PNPDPP cleavage. [d] $k_2 = k_\psi^{max}$/[catalyst], treating the catalyst as if it were soluble. [e] Reference 46. [f] Too fast to be followed by methodology employed. [g] Reference 44. [h] Not available. [i] Reference 45. [j] Reference 47.

scription, latexes are colloidal anion-exchange resins of 200−300 nm diameter, which do not exhibit diffusional limitations to the overall reaction rates that are commonly observed with large polymer particles.[48] The kinetics of bimolecular nucleophilic reactions in these latexes have been successfully described by the PIE model.[48c] A family of monodisperse cross-linked polystyrene latexes containing various poly(styrylmethyl)trialkylammonium chloride repeat units (**45**, Scheme 6) greatly accelerated

Scheme 6



the IBA-catalyzed hydrolysis of PNPDPP. Hydrolytic rates increased with increasing radius of the quaternary ammonium ion (trimethyl < triethyl < tripropyl < tributyl), affording hydrolytic rates comparable to those of micellar systems and with half-lives of 10 s or less.[48c,d]

An interesting phase-dependent reactivity has been observed in lyotropic nematic liquid crystals of myristyltrimethylammonium bromide in 1-decanol, ammonium bromide, and water.[50] The solubility of organic molecules in these systems is about 100 times greater than that in the dilute micellar phase of the same surfactant; the rate of PNPDPP cleavage by IBA occurring in the rodlike nematic phase is more than 10^3-fold higher than in the disklike phase, where the solute is mainly in the hydrocarbon region. In the rodlike phase, the substrate is believed to reside at the aqueous interface.

V. Modeling Nerve Agents

A successful test of the phosphorolytic potential of iodosylcarboxylate derivatives in aqueous CTACl solution was the efficient *catalytic* cleavage of the fluorophosphonate G-type nerve agents sarin and soman as well as the toxic phosphoroamidocyanate tabun (see Chart 1).[51] Experiments with nerve agents can only be conducted in a limited number of controlled laboratories; therefore, most research with potential phosphorolytic decontaminants uses model compounds or *simulants* to avoid the risk involved in the use of highly toxic substrates. In this regard, *p*-nitrophenyl diphenyl phosphate (PNPDPP) and the insecticide paraoxon (**23**) are widely used simulants.

During the past decade, studies of simulant design have modeled different decontamination and demilitarization scenarios. PNPDPP and paraoxon present important intrinsic differences as simulants of the G-agents. For instance, PNPDPP is more hydrophobic and more reactive toward IBA than the G-agents, whereas paraoxon, whose hydrophobicity is similar to that of the G-agents, is much less reactive toward IBA.[51,52] The interplay between the hydrophobic−hydrophilic balance of these commonly used simulants, their structural differences, and their suscep-

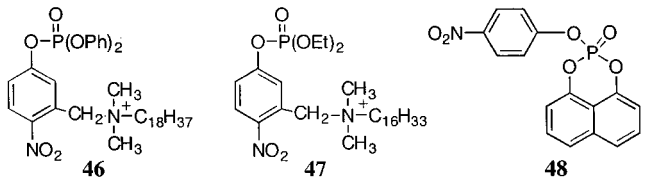


Table 5. Kinetics Data for the Cleavage of Phosphotriesters by IBA and INA[a]

substrate	cat.	k_ψ^{max} (s^{-1})[b]	10^3 [CTACl] (M)[c]	k_{INA}/k_{IBA}[d]	k_ψ^{max} ratio[e]
PNPDPP	IBA	0.064	1.0	4.0	(**46**/PNPDPP) 10.3
23 (paraoxon)	IBA	0.000135	5.0	1.8	(**47**/**23**) 7.0
46	IBA	0.66	1.0	7.9	(**46**/**47**) 701.0
47	IBA	0.000941	1.0	9.5	
48	IBA	2.82	1.0	1.7	(**48**/PNPDPP) 44.0
(PNPDPP)	INA	0.26	0.5		(**46**/PNPDPP) 20.1
23 (paraoxon)	INA	0.00024	2.5		(**47**/**23**) 37.2
46	INA	5.24	0.5		(**46**/**47**) 586.0
47	INA	0.00893	0.5		
48	INA	4.83	0.5		(**48**/PNPDPP) 18.5

[a] In most cases standard conditions were used: 0.02 M pH 8.0 phosphate buffer, $\mu = 0.08$ (NaCl), 25 °C, [substrate] = 0.01 mM, [catalyst] = 0.1 mM. [b] Maximum pseudo-first-order rate constant for PNPDPP cleavage taken from rate constant/[CTACl] profile. [c] Concentration of CTACl at which k_ψ^{max} was observed. [d] Ratio of k_ψ^{max} of INA and IBA for a given substrate. [e] Ratio of k_ψ^{max} for the indicated substrates using the same catalyst (IBA or INA).

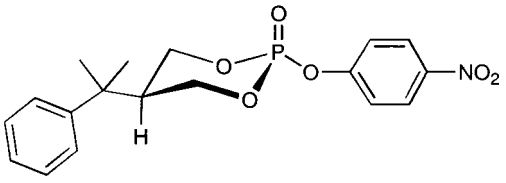
tibility to nucleophiles when bound to association colloids was not obvious. To better compare the reactivity differences, surfactant-bound phosphotriesters **46** (derived from PNPDPP) and **47** (derived from paraoxon) were synthesized and expected to be fully bound in CTACl comicelles.[52,53]

The reactivity of **46** and **47** was studied in the presence of iodosylcarboxylates IBA and INA in CTACl micelles.[52,53] In a similar fashion, they examined the reactivity consequences of fusing the phenyl residues of PNPDPP into a naphthyl moiety as in phosphotriester **48** (PNPNP).[54] Table 5 summarizes kinetics data obtained with substrates **46**, **47**, and **48** and offers some comparisons with the parent PNPDPP and paraoxon.

Interesting trends emerged from these studies. Generally, it was observed that the differential reactivities of the various substrates reflected both their innate reactivity as well as differences in their binding to the micellar pseudophase.[52] For instance, surfactant-bound substrates were more reactive than small nonsurfactant analogues by factors of 7−10 in the presence of IBA and 20−37 with the more hydrophobic nucleophile INA (see the comparisons **46**/PNPDPP or **47**/**23** (paraoxon) for IBA and INA in Table 5). Additionally, diphenyl derivatives (PNPDPP and **46**) were more reactive than their corresponding diethyl analogues (**23** and **47**) either in native or surfactant form, a clear indication of their innate reactivity differences. On the other hand, the naphthyl phosphotriester **48** was 18- to 44-fold more reactive than PNPDPP toward iodosylcarboxylates INA and IBA, respectively. The reactivity of **48** is a special case, where less hindered access for nucleophilic attack at the phosphorus center is probably the main source of its kinetic sensitivity.[54]

Further examinations of simulants have also included the diastereomeric dialkyl *p*-nitrophenyl phosphotriesters **49** and **50**. These substrates, related to the insecticide paraoxon, were found to undergo rapid cleavage in the presence of IBA and INA in micellar solutions with modest diastereoselectivity favoring the axial substrate **50**.[55]

The V-agents are more persistent and more toxic than the G-agents (Chart 1) and generally present more complex chemistry due to intramolecular reactions of the amino group.[2c] Their solubility in basic aqueous solutions is limited, and in very dilute solutions they slowly react with OH^- (e.g., $t_{1/2} = 31$ min for 0.01 M VX in 0.1 M NaOH at 22 °C).[2c] A major problem in the hydrolytic detoxification of V



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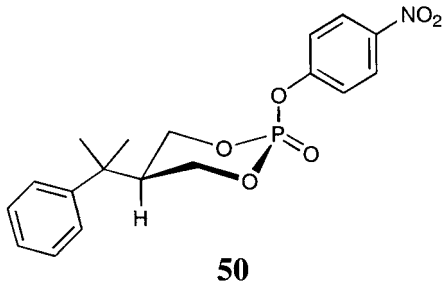


50

agents is the requirement for regiospecific P−S cleavage to fragment **51**. Simple basic hydrolysis of VX produces both the desired P−S cleavage (87%) and the undesired P−O cleavage (13%), which produces fragment **52**, Scheme 7. Fragment **52** has similar anticholinesterase activity to VX, so that basic hydrolysis alone is useless for decontamination purposes.

Scheme 7

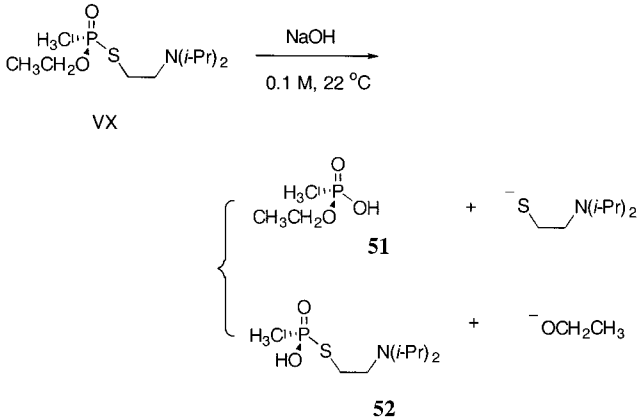
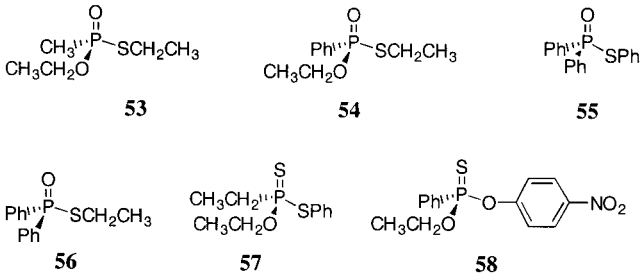


Chart 5



Remarkably, it has been observed that **52** decomposes at elevated temperatures in highly basic solutions with moderate rates ($t_{1/2}$ = 35 min in 2.0 M NaOH and 75 °C). This finding is the basis for a VX neutralization−demilitarization technology explored by U.S. Army laboratories.[2c] In a related report, VX or Russian-VX undergo autocatalysis with equimolar water in which the agents are fully hydrolyzed over 1−2 months.[56]

Due to the risk involved in using the actual nerve agent, significant information has been obtained from simulants. Phosphonothioates (**53** and **54**), thiophosphinates (**55** and **56**), and several insecticides such as parathion (**24**), fonofos (**57**), or EPN (**58**) have been frequently used to model the substitution reactions at phosphorus of VX, Chart 5.[2c]

O,S-Alkyl phosphonothioates **53** and **54** are excellent models to examine effects due to the VX amino group; they produce a product distribution similar to VX in basic solutions.[2c,57] Detailed studies on VX (and simulant **53**) showed that the P−S/P−O cleavage ratio is constant (87/13, P−S vs P−O for VX) from 0.01 to 0.5 M NaOH at 22 °C. This ratio decreased at higher NaOH (e.g., 73/27 in 4 M NaOH for VX).[2c] It was demonstrated that nucleophilic attack occurs at phosphorus and that variations in the ionic strength, the nature of the cations and anions present, and the solvent had little effect on the product selectivity. Thus, the reason P−O cleavage increased at higher base concentrations was not evident.[2c]

Several *O,S*-dialkyl phenylphosphonothioates were examined as simulants of VX reactivity.[57] Among these, *O,S*-diethyl phenylphosphonothioate (**54**) was a useful mimic for the phosphoryl chemistry of VX. The P−S/P−O partition (81/19) in 0.1 M aqueous NaOH most nearly simulates the behavior of VX, although **54** is slightly more reactive ($t_{1/2} \approx$ 18 min at 22 °C). In addition, simulant **54** is more convenient than the previously studied methyl analogue (**53**), which is considered highly toxic.[4,57]

Further examination of simulant **54** showed that excess IBA in micellar CTACl rapidly cleaved this substrate.[57] Kinetics were monitored by ^{31}P NMR spectroscopy with 0.02 M **54** and 0.063 M NaIBA at pH 9.5 (Tris buffer) in D_2O at various CTACl concentrations. This afforded $k_\psi^{max} = 0.115$ min^{-1} ($t_{1/2} \approx$ 6 min) at a CTACl concentration of 0.05 M. Most importantly, *only* the P−S cleavage product (**59**) was observed (Scheme 8).[57]

Although IBA is a true turnover catalyst for the hydrolysis of phosphotriesters and fluorophosphonates, its reaction with **54** is not catalytic: reaction of equimolar **54** and IBA in 0.1 M CTACl at pH 9.5 affords incomplete hydrolysis, and efficient cleavage is observed only with an excess of IBA.[57,58]

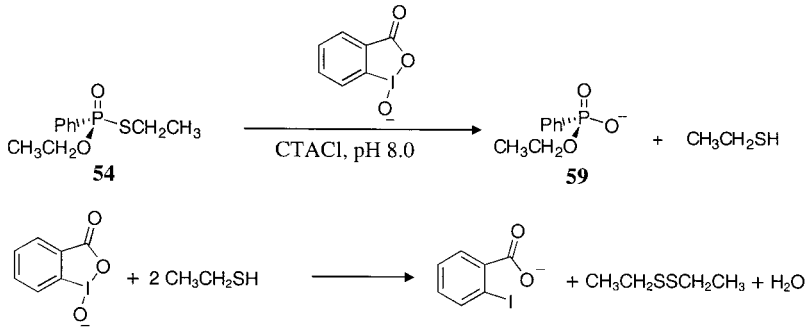
Reduction of IBA by the ethane thiol released from **54** is responsible for the *noncatalytic* behavior of IBA.[58] The direct reaction of EtSH with IBA in the micellar aqueous solution occurs rapidly (k_2 = 250 M^{-1} s^{-1}), consuming two molecules of thiol per IBA to produce iodobenzoate (IB) and diethyl disulfide (Scheme 8). Accordingly, the overall IBA/**54** reaction can be written as the sum of two processes: a mediated cleavage of **54** that releases the thiol and the subsequent reduction of IBA.[58]

In Hammond et al.'s study of nerve agent cleavage by iodosylcarboxylates,[51] IBA was found to cleave VX agent very slowly in aqueous micellar CTACl. These experiments, however, were carried out at pH 7.5, where VX (p$K_a \approx$ 8.6) would be protonated and largely excluded from the cationic micelles. Nevertheless, the high chemoselectivity observed for IBA cleavage of the P−S bond of VX simulant **54** encourages further studies of this system and suggests a reexamination of the cleavage of VX with IBA at higher pH.

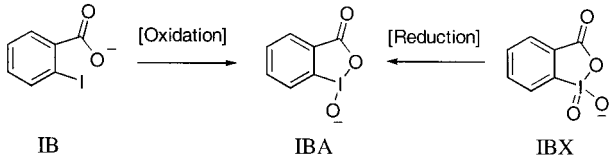
To convert the IBA/**54** reaction into a catalytic process, potential sacrificial oxidants were tested. However, Co(II) phthalocyaninetetrasulfonate, which is known to catalyze the autoxidation of thiols by molecular oxygen, as well as 2,6-dichloroindophenol and acrylonitrile, otherwise excellent reagents for the oxidation or capture of thiols in basic solutions, failed to block the IBA−EtSH redox process.[58]

On the other hand, although the reaction of IBX with simulant **54** proceeds very slowly and with incomplete cleavage, IBX reacts with thiols at a rate similar to that of IBA: there are stepwise reductions

Scheme 8



Scheme 9



that first produce IBA, which is further reduced to IB. Thus, (IBX + IBA) mixtures efficiently cleave **54**. In this reaction, IBX partially protects IBA from reduction by EtSH. However, IBX is not just a sacrificial oxidant; at least some of its effect accrues from its own conversion to IBA when it oxidizes EtSH.[58]

Bunton and co-workers examined a similar approach to making the reaction of IBA with phosphonothioates a catalytic process.[59] In this study, reduction of IBA to IB by 4-methoxybenzenethiol was partially reversed by oxidants such as oxone (HSO_5^-) or magnesium peroxyphthalate (MPPA). Both oxidants reacted with 4-methoxybenzenethiol, in the same fashion as IBA, initially affording the corresponding disulfide. The regeneration of IBA by the oxidation of IB was not selective and depended on the concentration of the oxidants. For instance, at equimolar concentrations of IB and oxidant (HSO_5^- or MPPA) about 60−70% of IBA and 20−24% of IBX was formed. However, with an excess of the oxidants, both IBX formation and its further decomposition were enhanced.[59]

IBX, oxone, or peroxyphthalate oxidants work by replenishing the active IBA via reduction of IBX or oxidation of IB, respectively (Scheme 9). Accordingly, the overall process remains stoichiometric rather than catalytic. Given the rapidity of the IBA/EtSH reaction, it is difficult to find a sacrificial oxidant that can compete efficiently for the thiol.

Thiophosphinates **55** and **56** reacted with IBA similarly to phosphonothioate **54**; they produced diphenyl phosphinic acid as well as products expected from the redox reaction between the released thiol and IBA, i.e., IB and the corresponding disulfide. Diphenylthiophosphinate substrates **55** and **56** have also been reacted with hydroxide,[60] oxone,[61] and hydroperoxide. Thus, it is interesting to compare the rate constants for the cleavages of substrates **54**, **55**, and **56** by potential decontaminants such as hydroxide, oxone, hydroperoxide, and IBA (Table 6).[58]

Generally, nucleophilic cleavage (IBA or HOO^-) occurs more rapidly than the oxidative reaction (HSO_5^-). IBA is faster than OH^- or HSO_5^- in the destruction of all three VX simulants, at least under the investigated conditions. Only hydroperoxide appears to function more rapidly than IBA, but it usually requires strongly basic solutions. However, because the reactions are stoichiometric rather than catalytic, hydroperoxide is potentially a cheaper decontaminant than IBA for these phosphorus thioesters.

Table 6. Comparative Reactivities of VX Simulants and Decontaminants

	rate constants			
simulant	OH^-	HSO_5^- (oxone)	OOH^-	IBA
54	0.00064[a]	0.008[b]	very fast[c]	0.032[d]
55	0.6[e]	0.0071[b]		fast[f]
56	0.05[g]	0.0054[b]	6.9[h]	0.135[i]

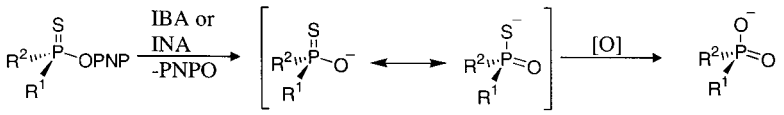
[a] k_Ψ, s^{-1}, 0.1 M aq NaOH, 22 °C; the reaction occurs with 81% P−S and 19% P−O cleavage. [b] k_2, $M^{-1}\ s^{-1}$, 99.6 wt % H_2O, 0.4 wt % MeCN (96.6 wt % H_2O, 3.4 wt % MeCN for **55**), 25 °C. [c] 0.9 M H_2O_2, 0.1 M OH^- (~0.1 M OOH^-), P−S cleavage only, 22−25 °C. [d] k_2, $M^{-1}\ s^{-1}$, 0.1 M aq CTACl, pH 9.5, 20.5 °C, P−S cleavage only. [e] k_Ψ, s^{-1}, 0.01 M aq OH^-, 2×10^{-3} M CTA mesylate, 25 °C; estimated from data in Figure 5 of ref 60. [f] $t_{1/2} < 1$ min in 0.05 M CTACl, pH 9.5, 25 °C. [g] k_Ψ, s^{-1}, 0.03 M aq OH^-, 3×10^{-3} M CTABr, 25 °C; estimated from data in Figure 4 of ref 60. [h] k_2, $M^{-1}\ s^{-1}$, 25 °C, aq H_2O_2/OH^-. [i] k_2, $M^{-1}\ s^{-1}$, 0.05 M aq CTACl, pH 9.5, 25 °C.

The phosphorolytic cleavage of *O*-alkyl (or *O*-aryl) thiophosphates and phosphonothioates is of practical interest because they are commonly used pesticides, e.g., parathion (**24**), fonofos (**57**), or EPN (**58**). In nature, insecticides containing P=S bonds are bioactivated to their oxygen analogues (P=O) by microsomal P_{450} enzymes that convert (e.g.) parathion into paraoxon via desulfuration.[5,62]

IBA or INA in aqueous CTACl micelles at pH 8.0 were effective reagents for the cleavage of EPN, its *O*-methyl analogue (**60**) (Scheme 10), and the thiophosphate insecticide parathion.[33] In contrast, IBX was much less reactive toward substrate **60** or parathion. The reactions of micellar *o*-iodosyl and *o*-iodylcarboxylates with the phosphonothioate ester **60** followed a successive hydrolysis−oxidation pathway, illustrated in Scheme 10, where accumulation of the sulfur fragment **61** was observed. Similarly, parathion was first hydrolyzed to **62** and then oxidized to **64** rather than first being oxidized to paraoxon.[33]

Because the sulfur-containing fragments **61** or **62**, released in the initial cleavages, reduce the iodosyl reagents to iodo species, the iodosylcarboxylate nucleophiles do not turn over in the cleavages of **60** or parathion. The reactions of the sulfur-containing fragments **61** or **62** with IBA and IBX resemble the reactions of thiols (R−SH), which produce the corresponding disulfides (cf., IBA cleavage of **54**). Oxida-

Scheme 10

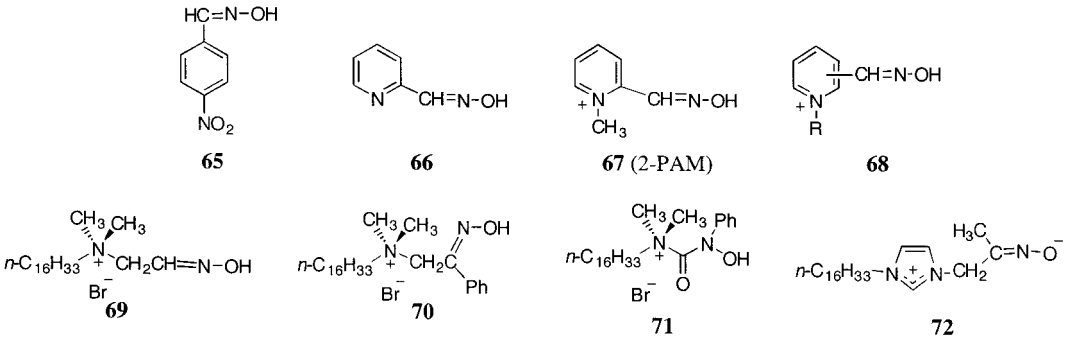


60 R^1 = Ph, R^2 = OMe **61** R^1 = Ph, R^2 = OMe **63** R^1 = Ph, R^2 = OMe

24 parathion ($R^1 = R^2$ = OEt) **62** ($R^1 = R^2$ = OEt) **64** ($R^1 = R^2$ = OEt)

(PNP = *p*-nitrophenyl)

Chart 6



tion of **62** by CTACl micellar IBA (or IBX), however, produces a complex mixture of products in which the disulfide is not present. This is in marked contrast to the oxidation of **61** by IBA or IBX which produces only *O*-methyl phenylphosphonic acid **63**.[33]

Recently, the cleavages of paraoxon and parathion were examined with holomicellar cetyltrimethylammonium iodosobenzoate, (CTA)IBA. With excess reagent in Bis-Tris buffer at pH 9, the half-times for paraoxon and parathion cleavages were 50 s and 3.8 min, respectively, suggesting that practical decontamination protocols could be developed for these persistent, toxic materials using (CTA)IBA.[63]

VI. Related Nucleophiles

Given the practical importance of the decontamination and demilitarization of organophosphorus toxins, the search for efficient nucleophilic systems has been extensive. Various methods have been investigated, including photolysis, oxidation, combustion, and microbial degradation.[2,4] Here, however, we consider only those processes that feature nucleophilic reagents. Apart from iodosyl- and iodylcarboxylate derivatives, the other nucleophiles examined include fluoride, alkoxides, oximes, peroxyanions, and metal complexes, either in association colloids (i.e., micelles, microemulsions, or vesicles) or as functional reagents. Alternatively, biologically related systems such as catalytic antibodies or enzymes have proven to be effective in the degradation of organophosphorus compounds.[64]

In this section we will discuss the reactivity of these nucleophiles toward standard organophosphorus triesters such as PNPDPP or insecticides such as paraoxon or parathion. For clarity, the presentation has been organized according to the *nature* of the nucleophile, i.e., α-effect nucleophiles, metal ions, or biological systems.

A. α-Effect Nucleophiles

Oximates, hydroxamates, peroxyanions, and iodosylcarboxylates often display an enhanced nucleophilic reactivity when compared with other nucleophiles of similar basicity (e.g., substituted phenolates). Although the causes of this phenomenon are not completely understood, the operational criterion defines what is commonly called an α-effect nucleophile.[65,66]

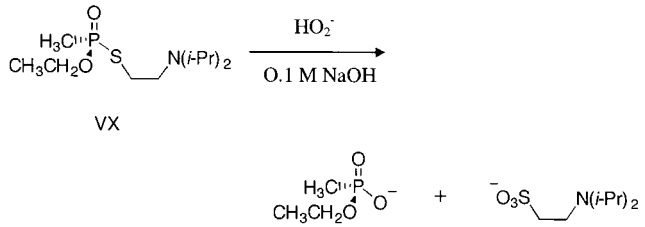
As indicated above for hypervalent iodine carboxylates (section III), the overall rates of phosphorolysis of (e.g.) PNPDPP by oximate anions are also increased in cationic micelles. Micellar effects on phosphorolytic reactions mediated by benzaldoximes (**65**) and pyridinealdoximes (**66**) were studied in the presence of surfactants with inert counterions such as CTACl or CTABr.[67]

Neutral oximes, such as benzaldoximes or pyridinealdoximes, usually possess pK_a values in the range 9.5−12, so that the fraction of reactive oximate anions present under neutral or slightly basic conditions is small. However, pyridiniumcarbaldehyde oximes bonded to positively charged moieties exhibit a markedly decreased pK_a while maintaining the high nucleophilic character of the oximate anion.[68−70] Several examples of substituted pyridiniumcarbaldehyde oximes, such as 2-PAM (**67**), find therapeutic use as acetylcholinesterase reactivators or antidotes in association with atropine in cases of nerve agent intoxication, Chart 6.[1,69]

The micellar effects are strongly amplified with long chain *N*-alkyl pyridinealdoxime amphiphiles (**68**, R = hexyl to hexadecyl), which cleave PNPDPP and paraoxon.[68,70] Effective phosphorolytic reactions of PNPDPP were also achieved with amphiphilic oximes **69** and **70** or hydroxamic acid **71**, comicellized with inert surfactants.[68,71,72] Usually these long chain functional surfactants are not very soluble in water, so that the addition of an inert surfactant is needed to solubilize them. Remarkably, zwitterionic imidazolium oximate surfactant **72** is fully soluble in water with a cmc value of 2.5×10^{-4} M at pH 12.9.[73] Surfactant **72** efficiently cleaves PNPDPP with a micellar rate constant $k_m = 0.0165\ s^{-1}$ and $K_s = 280\ M^{-1}$. In general, oximate surfactants (e.g., **69**) are better reagents than hydroxamates; they afford faster initial attack on PNPDPP and more rapid turnover of the phosphorylated oxime, whereas, with the phosphorylated hydroxamate, turnover competes with reconversion to reactants.

Bunton and co-workers also examined the dephosphorylation of PNPDPP with *tert*-butyl hydroperoxide, *m*-chloroperbenzoic acid, peroxyphthalate dianions, or hydroperoxide in the presence of cationic micelles and microemulsions.[74] In particular, hydroperoxide (HO_2^-), in the presence of cationic micelles, displayed excellent reactivity ($t_{1/2} < 10$ s) toward PNPDPP. Most importantly, hydroperoxide (HO_2^-) also showed outstanding reactivity against VX and related simulants; for instance, VX reacted with 0.1 M HO_2^- with $t_{1/2} = 45$ s at 23 °C.[75] Not only was the reaction rapid (40 times faster than with OH^-), but

Scheme 11

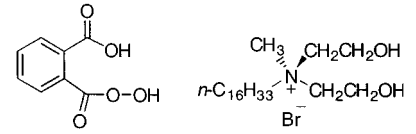


VX

it gave exclusive P−S cleavage with the formation of nontoxic products. Moreover, the resulting thiol fragment was further oxidized to the disulfide (RSSR) and eventually to the sulfonate (RSO_3^-), Scheme 11.[75]

However, the pK_a of H_2O_2 is ≥11, so that the generation of hydroperoxide usually requires strongly basic conditions.[75] In this regard, monoperoxyphthalate (**73**) has been proposed as a better choice.[76,77] Deprotonation of peroxy acid **73** in cationic micelles occurs at a much lower pH (pK_a ≈ 8), producing a reactive nucleophilic species under milder conditions. Lion and co-workers studied the cleavages of paraoxon and parathion with **73** and some of its ester derivatives in the presence of cationic surfactants.[76] Half-times as short as 3 and 9 s were reported for the cleavage of paraoxon and parathion with **73** in the presence of surfactant **74** under basic conditions (pH 10−11.3).[76b] Later, kinetics and mechanistic studies showed that **73** rapidly cleaved PNPDPP at pH 8.5 and 25 °C with turnover in micelles, microemulsions, and vesicles containing cationic surfactants.[77] Moreover, spectroscopic evidence for an intermediate phosphorylated monoperoxyphthalate was also found.[77]

Screening potential decontamination systems has also included potent nucleophiles such as alkoxides. The phosphorolytic reactivity of alkoxides has been extensively studied,[78] but the need for strong bases and nonaqueous solvents hampered many applications. Although the pK_as of alcohols usually are 15 or higher, the presence of positively charged groups, such as quaternary ammonium ions, in close proximity to the OH group greatly increases an alcohol's acidity. This property has been exploited with functionalized surfactant **75** (pK_a ≈ 12.4), which acts as an effective nucleophile in PNPDPP hydrolysis under milder conditions.[79] However, regeneration of the nucleophile from the *O*-phosphorylated intermediate formed from **75** is difficult.[79] Recently, the related hydroxyethylammonium surfactants **76**, in which the quaternary ammonium group of **75** is replaced by secondary or tertiary hydroxyethylamine units, were shown to efficiently cleave PNPDPP under mild conditions with polyols such as glycerol or poly(ethylene glycol) as cosolvents.[80] Derivative **76a** displayed turnover behavior due to the ability of the β-amino group to act as an internal nucleophile to displace phosphate from the *O*-phosphorylated intermediate and regenerate the catalyst.[80]



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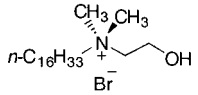

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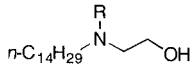
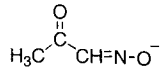


76 (**a**) R = H, (**b**) R = CH_3

Surfactants with long alkyl chains and reactive headgroups are fully incorporated in the micellar phase, thus simplifying the problem of quantifying the equilibrium transfer of the nucleophile between the bulk and micellar pseudophase for the kinetics analysis. Their concentration is taken as their mole fraction within the comicellar blend with the inert surfactant or the concentration of the surfactant itself (e.g., **72**). Unlike the maxima seen in the rate profiles of Figure 2 (section III), the reactivity of functionalized surfactants usually shows saturation of the observed rate constant when the substrate is fully bound (k_m).

Within the framework of the pseudophase ion-exchange (PIE) model, competition takes place at the micellar interface between reactive nucleophiles and inert counterions, leading to inhibition of the observed reactivity in the presence of a high concentration of inert salts. Using surfactants containing reactive counterions, however, inhibition due to unreactive ions is avoided and the observed reactivity is optimized. Examples include cetyltrimethylammonium surfactants with fluoride (CTAF),[81] hydroxide (CTAOH),[82] hydroperoxide (CTAOOH),[83] *anti*-pyruvaldehyde 1-oximate (**77**, CTAOx),[84] and *o*-iodosylbenzoate (CTAIBA)[85,86] counterions.



77

Nucleophilic cleavage of PNPDPP by fluoride anions is particularly effective when fluoride is the only counterion. For example, in the presence of 0.01 M CTA^+F^- cleavage occurred with $k_\psi = 0.12\ s^{-1}$, whereas 0.01 M NaF in 2 mM CTABr gave $k_\psi = 0.0027\ s^{-1}$.[81] Similarly, in situ preparation of the surfactant cetyltrimethylammonium hydroperoxide ($CTA^+HO_2^-$) by mixing CTAOH and hydrogen peroxide produced a reagent that rapidly catalyzed the cleavage of paraoxon.[83]

In 1989, Bunton et al. prepared a cetyltrimethylammonium surfactant with *o*-iodosylbenzoate as the counterion (CTAIBA) and examined its reactivity toward PNPDPP.[85] Further evaluation of CTAIBA phosphorolytic reactivity demonstrated the broad spectrum of its applicability.[86] In aqueous solutions at pH 9, excess CTAIBA cleaved persistent insecticides such as paraoxon or parathion with half-lives of 50 s or 3.8 min, respectively.[86] Recently, the properties of a surfactant containing *anti*-pyruvaldehyde 1-oximate (**77**) as a reactive anion were described.[84] Cleavages of PNPDPP and paraoxon were strongly accelerated by CTAOx (Ox = **77**) micelles, with half-lives on the order of 2 min for

Table 7. Micellar Rate Constants for Cetyltrimethylammonium Surfactants (CTA^+) with Reactive Counterions or Reactive Headgroups ($R-Nu^-$) in the Cleavage of Phosphate Triesters

		k_m (s^{-1})[a]	
surfactant	pK_a	PNPDPP ($K_s = 0.7-1 \times 10^4$ M^{-1})[b]	Paraoxon ($K_s = 79-200$ M^{-1})[b]
CTAOH[c]	15.7	0.78	
CTAOx[d]	8.4	1.9	0.0125
CTAIBA[e]	7.2	4.5	0.016
CTAOOH[f]	11.6		>0.45
R−OH (**75**)[g]	12.4	5.6	
R−Ox (**69**)[h]	9.59	3.4	
R−Ox (**72**)[i]	8.4	0.0165	0.00032
R−IBA(**26**)[j]	6.45	6.0	0.00034

[a] k_m (s^{-1}) is the micellar rate constant at fully bound substrate (also written as $k_{2,m}/V_m$). [b] In parentheses are the calculated binding constants K_s (M^{-1}) of the substrates to the micellized CTA^+ surfactant. [c] Reference 82. [d] Reference 84. [e] Reference 86. [f] Reference 83. [g] Reference 79a. [h] Reference 71. [i] Reference 73. [j] Reference 34.

paraoxon. Table 7 summarizes the micellar rate constants for cleavage of phosphate triesters such as PNPDPP or paraoxon and offers some reactivity comparisons between surfactants with reactive headgroups and CTA^+ surfactants with a reactive nucleophile as the sole counterion.

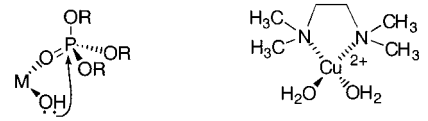
Interestingly, the *micellar* rate constant ($k_m \approx 4.5$ s^{-1}) for CTAIBA is similar to the value for the functionalized surfactant **26** (~6 s^{-1}, see section III). With oximates as the reactive nucleophiles, the *micellar* rate constant of the functionalized amphiphile **72** and CTAOx also display very similar rate constants, i.e., $k_m = 0.016$ vs 0.0125 s^{-1}, respectively. These comparisons show that reactive counterions paired with inert surfactants are just as efficient at phosphotriester cleavage as the more synthetically demanding functional surfactants with reactive headgroups. From Table 7, we conclude that IBA surfactants are the most effective phosphorolytic reagents under mild conditions (pH 8−9). In stronger base, hydroperoxy surfactants are very reactive.

B. Metal Complexes and Metallomicelles

Hydrolysis of phosphate triesters has also been achieved using transition- or lanthanide-metal cations and their complexes.[87−91] In principle, metal ions may simultaneously act as electrophilic catalysts (Lewis acids) by first binding the phosphoryl group and as nucleophiles by then providing a metal−hydroxide to perform an intramolecular attack (**78**).[92] The bifunctional role of the metal ions has only been unambiguously demonstrated in studies of kinetically inert Co(III) complexes.[93] Kinetically labile metals such as copper(II), zinc(II), or trivalent lanthanides display very effective catalysis although their mechanism of hydrolysis is less certain.[93e]

Early reports established the ability of Cu(II) ions to promote the degradation of the G-agent simulant diisopropyl phosphorofluoridate[94] and the hydrolysis of thiono (P=S) insecticides such as parathion (**24**) and EPN (**58**).[95] Interestingly, Cu(II) ions catalyzed the hydrolysis of thiono esters but not that of their corresponding oxygen analogues.[95] Similarly, mercuric cations provided enhancements of 2 or 3 orders of magnitude in the hydrolysis of several thiono insecticides.[96]

The tetramethylethylenediamine copper(II) complex (**79**) was one of the first metal complexes used for the hydrolysis of sarin.[97] More recent kinetics and mechanistic studies indicated both electrophilic activation and metal−hydroxide attack with catalytic turnover in the hydrolysis of sarin.[98] These remarkable features of **79** have led to its incorporation into porous silicon thin films used for the detection of fluorophosphonate nerve agents.[99] The stability of uncomplexed metal cations in aqueous solution is always a concern, especially for highly charged species such as trivalent lanthanides. In this regard, macrocyclic (**80**)[90] or cryptate (**81**)[91] lanthanide complexes were effective turnover catalysts of activated substrates such as 2,4-dinitrophenyl diethyl phosphate or PNPDPP, respectively. Among the metal complexes, however, those with amphiphilic character have proven most effective against neutral lipophilic substrates such as PNPDPP.



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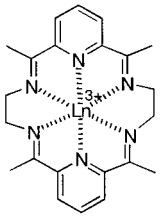

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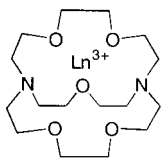


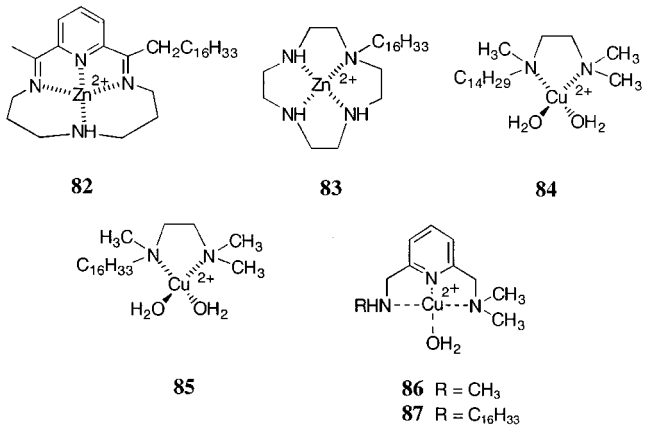
81

Ln = lanthanides

Early examples of these functionalized surfactants with metal complex headgroups (also called metallomicelles) came from Gellman and Breslow,[100] who synthesized a macrocyclic Zn(II) complex with a pendant long alkyl chain (**82**) that effectively cleaved PNPDPP. A long alkyl chain cyclen−Zn^{2+} compound (**83**) was also reported to cleave tris(*p*-nitrophenyl) phosphate.[101] A significant advance was the introduction of the Cu(II) metallomicellar system, **84**.[102] This long chain Cu(II) chelate, whose critical micelle concentration was 1.8×10^{-4} M, displayed potent reactivity in cleavage of PNPDPP, with $k_{obs} = 0.041$ s^{-1} with 1.5 mM **84** at pH 6 and 25 °C, representing a rate enhancement of $>10^5$ for micellized **84** over the background reaction.[102]

Further examples of Cu(II) metallomicellar systems include compounds **85** and **87**.[103] Metallomicelles **85** and **87** (as well as their short chain versions **79** and **86**) are designed to elucidate the source of the extraordinary acceleration displayed by the long alkyl chain metallomicelles (**85**, **87**). Analysis of the rate of cleavage of PNPDPP using the PIE model demonstrates that electrophilic assistance only operates with the small (nonaggregated) complexes,

Chart 7



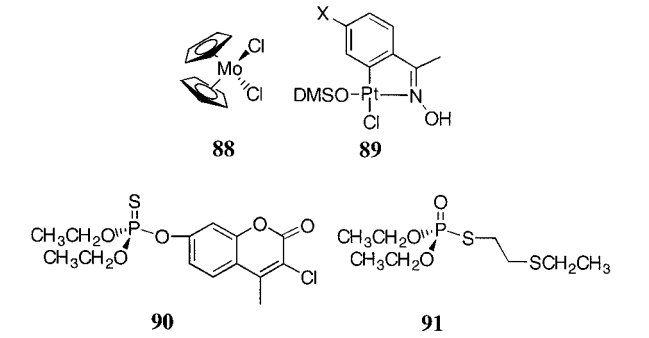
82 **83** **84**

85 **86** R = CH_3 **87** R = $C_{16}H_{33}$

whereas the main source of the observed rate accelerations in the aggregates (comicellized with $CTANO_3$) comes from the enhanced concentration of the reactants at the micelle-water interfaces, Chart 7.[103]

The reactivity of Cu(II) complexes **79** and **85** was examined not only toward PNPDPP, but against several other phosphate triesters and monoanionic diesters.[104] As in the iodosylcarboxylate studies (section V), the survey also included surfactant substrate analogues of PNPDPP (**46**) and paraoxon (**47**), and when possible, comparisons were made with iodosylcarboxylate reagents.[104] Small substrates, like PNPDPP and paraoxon, showed similar rate accelerations in the presence of metallomicelle **85** and its nonaggregated relative **79**, even though they exhibited intrinsic differences in reactivity. On the other hand, the cleavages of surfactant phosphotriesters were only accelerated when they were comicellized with metallomicelles **85**. Comparisons with iodosylcarboxylate catalysts showed that metallomicelles **85** were better catalysts than iodosyl-based catalysts toward phosphate diesters but less reactive with phosphate triesters. This disadvantage was substrate dependent and tended to disappear as the phosphate triester became intrinsically less reactive.[104]

Recently, an organometallic bis(η^5-cyclopentadienyl)molybdenum(IV) dichloride complex (**88**) was shown to promote the hydrolysis of paraoxon and parathion in aqueous solutions.[105] Although this complex afforded only modest rate accelerations, kinetics studies with paraoxon demonstrated that the metal center in **88** functioned only as a Lewis acid that activated the substrate for intermolecular hydroxide attack. Moreover, labeling studies using parathion proved that the cleavage involved mainly C−O scission, contrary to the more commonly observed attack at the phosphorus center.[105]



88 **89**

90 **91**

Another interesting nonmicellar approach to nucleophilic dephosphorylation of phosphate triesters makes use of *ortho*-metalated (Pt^{II} or Pd^{II}) aryl oximes **89**.[106] In these complexes, metal electrophilic assistance is coupled to the nucleophilicity of the coordinated oximate anions (whose basicity is substantially lowered due to coordination with the metal), providing outstanding reactivity toward thiophosphate triester insecticides such as parathion (**24**), coumaphos (**90**), and demeton-S (**91**). The proposed mechanism of hydrolysis is depicted in Scheme 12; initial coordination to the metal activates the ester toward intramolecular nucleophilic attack of the oximate, providing rate enhancements of 10^9-fold over the hydroxide-catalyzed reaction. Moreover, rapid decomposion of the phosphorylated oxime intermediate (**92**), in analogy to the very fast deacylation step characteristic of ester hydrolysis,[107] must account for the observed turnover.

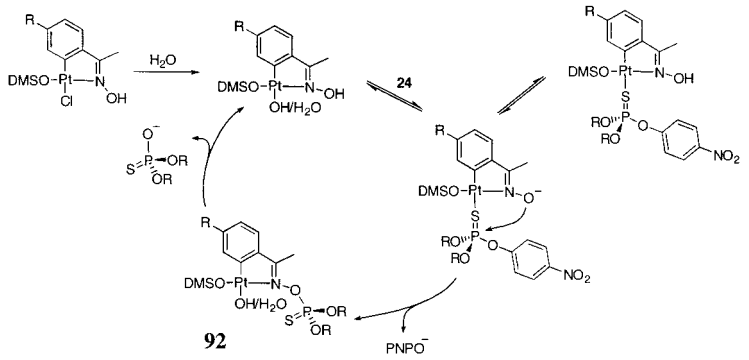
Generally, S for O substitution produces a small rate retardation (<10-fold) in the alkaline hydrolysis of phosphate, phosphonate, or phosphinate esters, presumably due to a slight reduction in the electrophilicity at the phosphorus center because S is less electronegative than O.[108] A similar trend is observed with micellar nucleophilic systems, where the rate depends on both the intrinsic reactivity of the substrate and its efficient incorporation into the micellar surface. Thus, for example, CTAIBA shows micellar rate constants of $k_m = 0.016$ and 0.0031 s^{-1} for the cleavages of paraoxon and parathion, respectively.[86] On the other hand, metal systems usually provide the opposite selectivity. For example, copper complex **85** cleaves parathion with $k_m = 1.26 \times 10^{-3}$ s^{-1}, slightly more rapidly than paraoxon under similar conditions ($k_m = 8.3 \times 10^{-4}$ s^{-1}).[33] Larger discrimination is seen with metal−aryl−oximes (**89**) which hydrolyze parathion 30 times more efficiently than paraoxon. Most likely the soft sulfur donor interacts more favorably with the soft Pd(II) or Pt(II) metal centers of these complexes than does the harder oxygen.[106]

C. Biological Catalysts

Enzymes implicated in the hydrolysis of organophosphorus triesters are generally called phosphotriesterases (PTEs). Even though their biological function is largely unknown and their natural substrates still remain to be established, a correlation has been observed between organism levels of PTEs and tolerance to the effects of organophosphates.[109] Thus, mammals, with high levels of PTEs, are more tolerant of organophosphates than, e.g., birds and insects, which are considered species lacking PTEs.[109]

Organophosphorus triesters are not naturally occurring compounds, yet their enzymatic hydrolysis is remarkably efficient. Early observations of this outstanding reactivity demonstrated the wide distribution and specificity of PTEs in biological fluids and tissues.[110,111] Several kinds of PTEs have been identified, including those showing specificity for the

Scheme 12



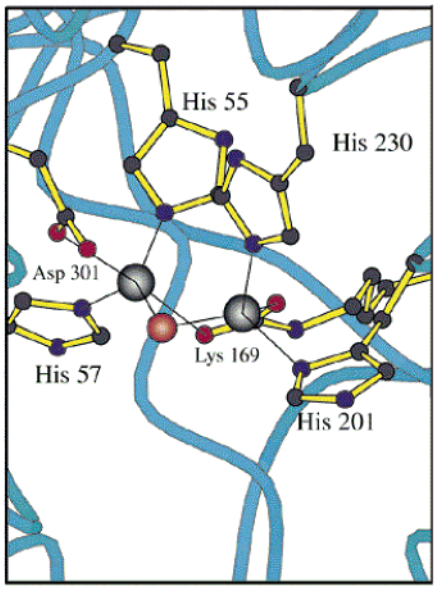


Figure 4. X-ray crystallographic structure of the metal center of the organophosphorus hydrolase (OPH) with two Zn^{2+} ions shown as large gray spheres. The position of the bridging water or hydroxide ion is indicated by the large red sphere. (Reprinted with permission from ref 118. Copyright 2001 American Chemical Society.)

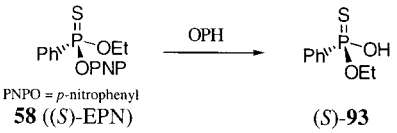
hydrolysis of alkyl fluorophosphate nerve agents (DFPase, tabunase) and paraoxon (paraoxonase).[112]

During the past decade an organophosphorus hydrolase (OPH) isolated from the soil-dwelling bacteria *Pseudomonas diminuta* has received much attention. It is able to hydrolyze a wide variety of organophosphorus compounds, including the chemical nerve agents sarin, soman, tabun, and VX, as well as the insecticides parathion, coumaphos, and paraoxon.[113–116] For instance, the enzymatic hydrolysis of paraoxon, the preferred substrate for OPH, occurs at nearly diffusion-controlled rates with $k_{cat}/K_m \approx 10^8$ M^{-1} s^{-1}.[116]

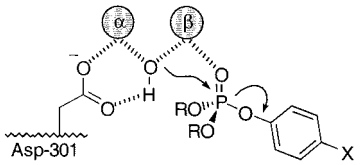
Biochemical and X-ray structural investigations of this OPH have identified the major catalytic components within the active site of the protein. The native enzyme is dimeric, composed of subunits that contain a bimetallic Zn^{2+} active center.[117] Recent high-resolution X-ray structures at 1.3 Å of different metal-substituted forms show the array depicted in Figure 4 for the binuclear metal center located at the active site.[118]

The native Zn^{2+} can be replaced by other divalent metals, including Co^{2+}, Mn^{2+}, Cd^{2+}, or Ni^{2+}, while the

Scheme 13



Scheme 14



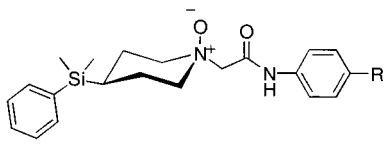
enzyme retains most of its catalytic activity toward paraoxon hydrolysis.[115] Moreover, OPH hydrolytically cleaves the insecticide (*S*)-EPN (**58**) to produce (*S*)-*O*-ethyl phenylphosphonothioic acid (**93**) with inversion of configuration, suggestive of a single *in-line* displacement by an activated water molecule directly at the phosphorus atom of **58** (Scheme 13).[119]

Mechanistically, the precise roles of the two divalent cations in the catalytic process are not entirely clear, although proposals based on the X-ray structures of various metal-substituted enzymes as well as labeling and kinetics studies on a wide variety of genetically modified PTEs point to an initial catalytic complex that adopts the binding orientation of the substrate with the binuclear metal center presented in Scheme 14. The substrate's phosphoryl bond is polarized through coordination to the more "buried" metal ion (site β), while nucleophilic attack occurs from the bridging ligand (water or hydroxide) which is apparently hydrogen bonded to Asp 301.[118] The nature of the bridging ligand and the actual position of the substrate−enzyme active complex is a matter of controversy. Dynamics simulations and quantum mechanical calculations suggest that the critical bridging ligand is a hydroxide anion rather than a water molecule.[120] Similarly, the strong polarization of the P═O and P═S bonds of phosphotriesters, suggested from OPH kinetics data, are not in accord with observations from X-ray studies in which the phosphoryl bond and the nearest metal center are separated by 3.4 Å, too far to afford strong polarization. Molecular dynamics simulations have shown that multiple orientations of, e.g., paraoxon in the dinuclear active site of zinc-substituted PTE are possible, indicating a more complex mechanism.[121]

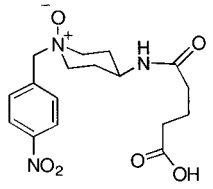
Apart from high reactivity, native OPH also features a kinetic preference to cleave the S_P enantiomer of chiral organophosphate triesters.[122] Three binding pockets (*small*, *large*, and *leaving group*) have been recognized as directly interacting with the substituents attached to the phosphorus center of phosphotriesters.[117c] Stereoselectivity is controlled to a large extent by the size of the *small* subsite, as demonstrated by engineered OPH mutants.[123] Thus, modulation of the reactivity and stereoselectivity of these modified proteins has been used in the kinetic resolution of racemic mixtures of chiral organophosphates[124] or to increase the specificity toward organophosphorothiolates.[125]

OPH is the only enzyme known to hydrolyze P−S ester bonds at a significant rate;[115,125] therefore, several studies have sought the immobilization of the enzyme on different matrices to afford a practical bioremediation reagent. OPH has been immobilized on nylon,[126] polyurethanes,[127] photopolymerized PEG-based hydrogels,[128] sol−gel silicates,[129] and nanocomposite protein−silicone polymers.[130]

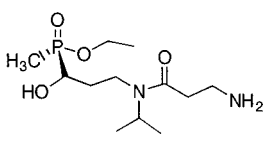
Another approach to the cleavage of phosphate triesters or nerve agent simulants employs catalytic antibodies (mAb), that is antibodies elicited against haptens that mimic the geometry and electrostatic features of a reaction transition state.[131] The mimicry of enzyme mechanisms has been extensively pursued. However, in the case of phosphotriesters, the enzymatic OPH reaction has not provided us with useful guides for hapten design. Moreover, a pentacoordinated transition state for direct nucleophilic displacement at phosphorus is difficult to mimic with regular organic functionalities, and more elaborate strategies have utilized oxotechnetium(V) and oxorhenium(V) complexes as haptens.[132] Thus, the first examples of mAb's designed to cleave phosphotriesters were elicited against haptens designed using the "bait and switch" strategy, which involves a charged hapten to elicit a complementary charged residue in the antibody. For instance, a positively charged hapten induces negatively charged residues on the antibody which can act as general bases.[133] A first generation of mAb raised against **94**, however, only showed modest reactivity and selectivity toward phosphotriesters **49** and **50** and did not hydrolyze the related substrate paraoxon.[133] Further structural modifications led to hapten **95**, which elicited a mAb that could hydrolyze paraoxon.[134]



94



95



96

Although the main source of mAb catalysis seems to be transition-state stabilization rather than general base catalysis, this study demonstrates the feasibility of generating mAb's as therapeutically active abzymes to treat insecticide poisoning. More recently, a first generation of mAb designed to cleave VX-like substrates has been reported, based upon the methyl-α-hydroxy-phosphinate hapten **96**.[135] In this work 13 mAbs were obtained that could neutralize VX under physiological conditions.

D. Reactivity Comparisons

Quantitative treatments of the reactions of nucleophilic anions in terms of pseudophase models show that the rate constants for reactions in the micellar pseudophase ($k_{2,m}$) are generally similar or inferior to the rate constants for the same reactions in water ($k_{2,w}$). Phosphorolytic reactions of oximes,[72,84] peroxyanions,[74b] metallomicelles,[103a] and IBA derivatives[85] in zwitterionic or cationic micelles follow this trend. Hence, the potency of these nucleophilic anions in association colloid systems results from concentrating both the nucleophile and the hydrophobic substrate in the small pseudophase volume.[28−32]

It is, nevertheless, instructive to compare the experimental reactivities of these nucleophiles from the practical point of view. Comparisons of kinetic parameters such as k_ψ^{max}, k_m, and half-life ($t_{1/2}$) as well as turnover capabilities, chemical stabilities, and/or accessibility of the nucleophiles with standard simulants or agents under a given set of conditions provides direct information on the nucleophiles' decontaminant efficiencies.[54,80,104]

Parathion is a toxic and persistent insecticide, and therefore, it is valuable to compare its reactivity with several different nucleophilic systems that are potential decontaminants. Table 8 collects kinetics data for the hydrolytic cleavage of parathion under various conditions.

Taking the lowest reported rate constant (entry 1) as a standard and assuming that only OH^- hydrolysis is operative in the absence of catalyst or additives at pH 8.0, relative rate constants for the other conditions are readily calculated.

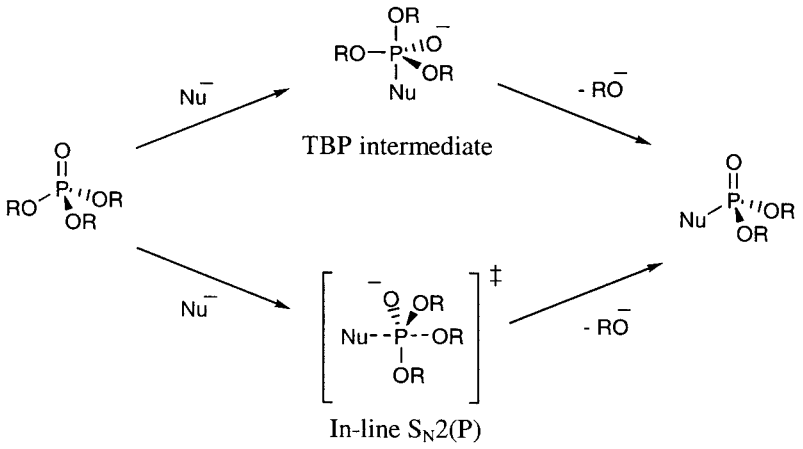
We see that CTAIBA, INA/CTACl, **85**/$CTANO_3$, 0.1 M KOH/CTABr, and 0.1 M $OH^-/(C_8H_{17})_4NBr$ all afford accelerations in the 10^6-10^7 range for the cleavage of parathion. Although micellar IBA and INA are not catalytic, they are effective decontaminants of parathion (and paraoxon) when used in excess under mild conditions at ambient temperature; however, their toxicity remains to be determined. Nevertheless, these reagents cannot compete with the extraordinary catalytic reactivities of platinum−aryloxime metallacycles or the organophosphorus hydrolase from *Pseudomonas diminuta*. Relative to the hydrolysis of parathion in buffer, rate accelerations of 10^9-10^{11} can be obtained with the Pt complex and the enzyme (entries 9 and 10). From a practical standpoint, however, the cost of the platinum complexes as well as the availability and stability of the enzyme are major considerations.

Table 8. Comparative Kinetics for the Hydrolytic Cleavages of Parathion (24)

entry	reagent	conditions	k_{obs} (s^{-1})	k_{rel}
1	OH^{-a}	from $k_2 = 9.5 \times 10^{-5}$ M^{-1} s^{-1} (0.001−1.0 M NaOH), with $[OH^-] = 10^{-6}$ M (pH 8, 25 °C)	9.5×10^{-11}	1
2	OH^{-b}	[**24**] = 1×10^{-5} M, [KOH] = 0.1 M, 85:15 H_2O:MeCN, 25 °C	5.5×10^{-5}	5.8×10^{5}
3	IBA/CTACl[c]	k_ψ^{max}, [**24**] = 1×10^{-5} M, [IBA] = 1×10^{-4} M, 0.1 M phosphate, pH 8.0, 0.01 M KCl, 25 °C	1.2×10^{-4}	1.2×10^{6}
4	$OH^-/(C_8H_{17})_4NBr^b$	as in entry 2, $[(C_8H_{17})_4NBr] = 1 \times 10^{-3}$ M	1.4×10^{-4}	1.5×10^{6}
5	OH^-/CTABr[b]	[**24**] =1×10^{-5} M, [KOH] = 0.1 M, [CTABr] = 4×10^{-3} M, 25 °C	4.1×10^{-4}	4.3×10^{6}
6	INA/CTACl[c]	k_ψ^{max}, [**24**] = 1×10^{-5} M, [IBA] = 1×10^{-4} M, 0.1 M phosphate, pH 8.0, 0.01 M KCl, 25 °C	4.5×10^{-4}	4.7×10^{6}
7	**85**/$CTANO_3$[c]	k_m, [**24**] = 1×10^{-5} M, 0.05 M Hepes buffer, pH 8.0, 25 °C	1.0×10^{-3}	1.0×10^{7}
8	CTAIBA[d]	k_m, [**24**] = 1×10^{-5} M, 0.1 M Bis-Tris buffer, pH 9.0, 25 °C	3.1×10^{-3}	3.2×10^{7}
9	Pt−aryloxime (**89**)[a]	from $k_2 = 914$ M^{-1} s^{-1} (pH 8, 25 °C) with [Pt−aryloxime] = 10^{-4} M	9.1×10^{-2}	9.6×10^{8}
10	OPH[e]	k_{cat} at pH 9.0, 25 °C ($k_o = 9.5 \times 10^{-10}$ s^{-1} from $k_2 = 9.5 \times 10^{-5}$ M^{-1} s^{-1} with $[OH^-] = 10^{-5}$ M)	600	6.3×10^{11}

[a] Reference 106. [b] Reference 136. [c] Reference 33. [d] Reference 86. [e] Reference 113.

Scheme 15

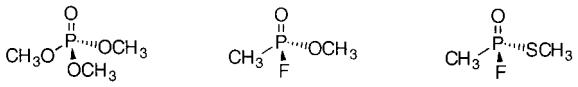


VII. Mechanism

A. $S_N2(P)$ vs Addition–Elimination

Reaction of nucleophiles with neutral phosphoryl species has long been considered to occur by a stepwise addition−elimination mechanism that transits trigonal bipyramidal (TBP) intermediates which can interconvert via pseudorotations (Scheme 15, top).[137,138] However, if the lifetime of the TBP is very short, the reaction can be considered to be essentially concerted, with the incoming nucleophile and departing group at apical positions, i.e., an in-line, direct $S_N2(P)$ displacement (Scheme 15, bottom).[137,138]

Experimental evidence, in the form of a linear Brønsted dependence in the reactions of PNPDPP with substituted phenoxide ions as nucleophiles, has been interpreted as favoring a dissociative $S_N2(P)$-like mechanism.[139] Results in the cleavage of trimethyl phosphate (**97**) by ^{18}O-labeled hydroxide are also best explained in terms of a $S_N2(P)$ transition state.[140] Similarly, mechanistic and stereochemical studies of the metallophosphotriesterase-mediated hydrolysis of a *P*-chiral phenylphosphonothioate substrate (**58**), which occurs with inversion at phosphorus, is also consistent with "in-line" direct nucleophilic attack.[119] On the other hand, semiempirical and ab initio calculations of the hydroxide-mediated hydrolysis of **97**[141] and *O*-methyl methylphosphonofluoridate[143] (**98**), as well as the hydroperoxide scission of a VX model[143] (**99**), suggest a multistep process involving TBP intermediates. Very recently, ab initio calculations were reported that support a two-step, TPB mechanism for the hydroxide-mediated cleavage of fluorophosphonate substrates (e.g., sarin, soman, diisopropyl phosphorofluoridate) but a single-step $S_N2(P)$ mechanism for the cleavage of paraoxon: substitution of the (better) *p*-nitrophenylate leaving group for fluoride alters the mechanism.[144] However, there is no experimental evidence that requires phosphorane TBP intermediates for the cleavage of acyclic triesters.



97 **98** **99**

Assuming the "in-line" displacement mechanism, different extents of bond-breaking and bond-making in the transition state (TS) can be expected depending on the nature of the leaving group, for example, in the alkaline hydrolysis of the diethyl phosphotriesters shown in Chart 8.[145]

On the basis of primary and secondary ($^{16}O/^{18}O$) isotope effects, it was concluded that diethyl phosphotriesters with good leaving groups (e.g., **24** or **100**) show a slightly associative TS, characterized by an early departure of the leaving group, Figure 5.

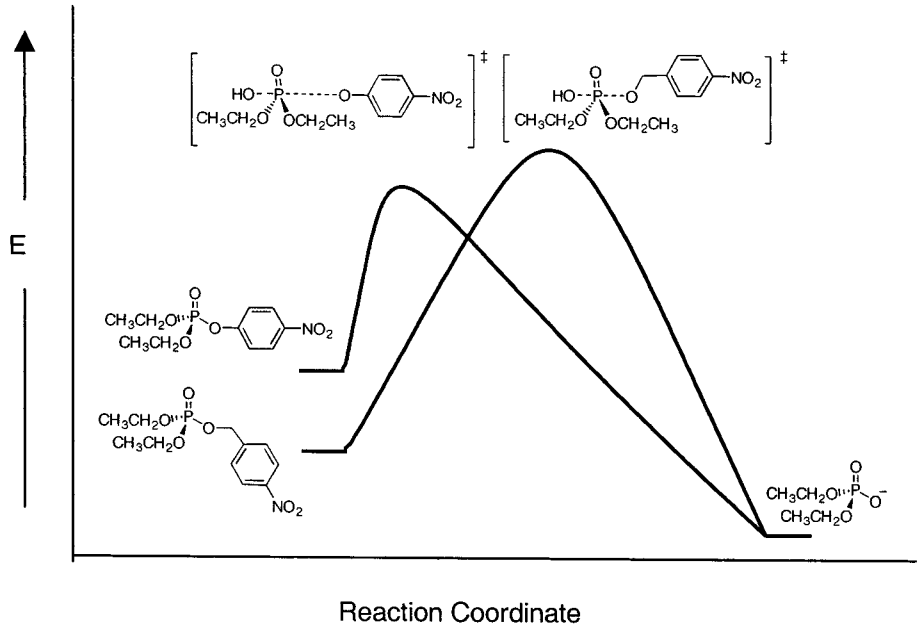
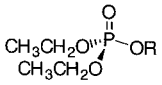


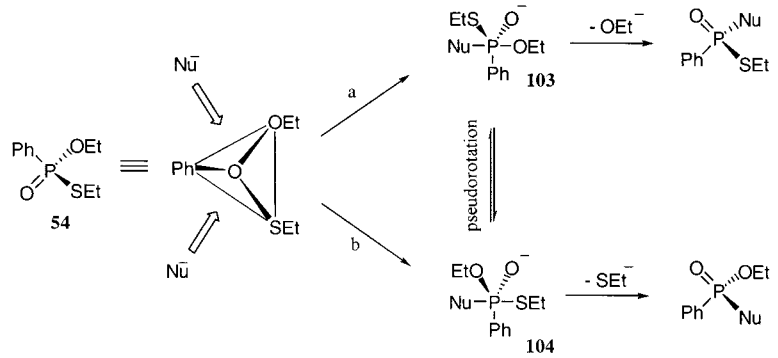
Figure 5. Reaction coordinates and transition-state structures for alkaline hydrolysis of paraoxon (**24**) or *m*-nitrobenzyl diethyl phosphate (**102**). (Reprinted with permission from ref 145a. Copyright 2001 American Chemical Society.)

Chart 8



	Leaving group (ROH)	pK_a	Transition State
24	*p*-nitrophenol	7.2	Slightly associative
100	*p*-carbamoylphenol	8.6	Associative
101	choline	13.9	Highly associative
102	*m*-nitrobenzyl alcohol	14.9	Highly associative

Scheme 16

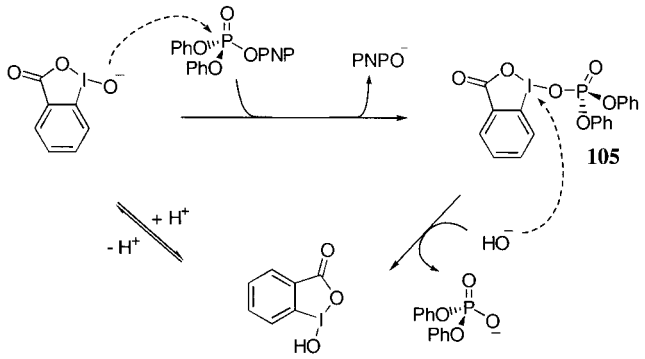


However, with poorer leaving groups (e.g., **101** or **102**) both displacements, EtO^- or RO^-, occur because the pK_a values are relatively close to that of ethanol (pK_a 16), leading to a highly associative TS, Figure 5, in which the nucleophile and the leaving group are both close to the phosphorus center and the TS is nearly symmetrical.[145]

A key feature in the utility of IBA as a (stoichiometric) decontaminant for VX simulants is the selective P−S ester cleavage.[57,58] Similar chemoselectivity is also shown by other α-effect nucleophiles, e.g., hydroperoxide (HOO^-) and butane-2,3-dione monooximate.[75a] The ability of α-effect nucleophiles to displace only thiols from phosphonothioates is in sharp contrast to the cleavage by hydroxide, which does not proceed chemospecifically.[2c,57] Bunton, Yang, and co-workers[75a] offered an extensive explanation for these results, from which we excerpt several important points.

In the formation of TPB intermediates (Scheme 15), nucleophiles preferentially enter at and depart from apical positions. Moreover, electronegative groups prefer to occupy apical positions, whereas bulky or π-donor groups tend to occupy equatorial positions.[69,70] Therefore, in nucleophilic attack on compound **54**, we expect the OEt group to prefer to reside in the apical position of the TBP intermediate (Scheme 16, **103**, Path a) rather than SEt (**104**, Path b), given the higher electronegativity of oxygen. However, the leaving group ability of SEt is higher, based on the pK_a values of thiol and alkoxide groups. For long-lived TBP intermediates, **103** can pseudoro-

Scheme 17



tate to locate the better leaving group at the apical position, as in **104**. Thus, the final products will depend on a balance between the apicophilicity and leaving group ability of the groups in the TBP intermediates.

Although this mechanism can rationalize the results obtained with hydroxide as the nucleophile, it does not clarify the P−S selectivity observed with α-effect nucleophiles. One possibility is that the TPB intermediate with the nucleophile and the alkoxide in the apical positions is a dead-end species that always reverts to reactants. [75a]

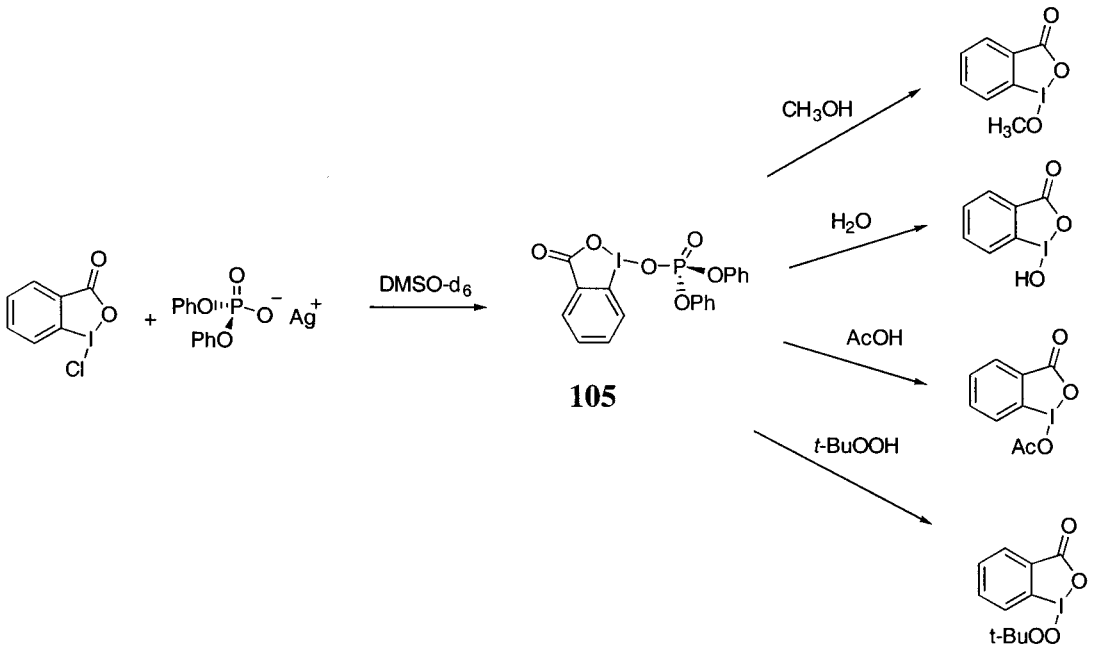
A more satisfactory explanation, however, can be given in terms of concerted $S_N2(P)$ reactions with no real intermediates. These nucleophilic displacements involve direct attack on the trigonal face of the tetrahedral phosphorus center opposite to the thiol or alkoxide leaving groups (cf., Scheme 16). Thus, reaction occurs by two distinct pathways and transition states whose structures are similar to those of the corresponding TBP intermediates, **103** or **104**. In this case, the relative basicities of the nucleophiles and the leaving groups will define the preferred pathway. Strong nucleophiles such as hydroperoxide, oximate, and iodosylcarboxylates, which are weaker bases than hydroxide, will favor displacement of the better leaving group, i.e., thiolate.

Direct stereochemical evidence that could further support these proposals still remains to be offered. In this regard, reactions with chiral phosphorus(V) substrates could provide valuable information on the stereochemical course of phosphorolysis mediated by α-effect nucleophiles. To this end, enantiomerically enriched mixtures of phosphonothioate **60** were reacted with micellar IBA.[146] However, the IBA/**60** cleavage in micellar solutions only transiently affords the hydrolytic product, *O*-methyl phenylphosphonothioic acid (**61**). It mainly produces the oxidized phosphonic acid **63** in which all stereochemical information is lost. In contrast, cleavage effected by the copper(II) metallomicelle **85** produces (after the release of *p*-nitrophenol) only **61** with ∼100% inversion of configuration.[146] This result is consistent with an in-line $S_N2(P)$ cleavage by hydroxide bound to Cu in reagent **85**.

B. Catalytic Behavior of Iodosylcarboxylates

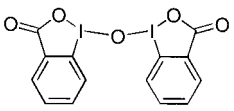
Regardless of the precise course of nucleophilic displacement at the substrate's phosphorus center, the overall mechanism of turnover and the catalytic function of IBA derivatives have already been dissected. IBA appears to function in a two-step sequence whereby its nucleophilic I−O⁻ moiety first attacks the substrate's phosphoryl group, with expulsion of the leaving group (e.g., *p*-nitrophenylate from PNPDPP or fluoride from sarin and soman) forming the phosphorylated intermediate **105** (Scheme 17). The first attempts to isolate **105** provided only the anhydride **106**. However, upon reaction of equimolar concentrations of the silver salt of diphenyl phosphate with 1-chloro-1,2-benziodoxolin-3-one (Scheme 18), the formation of **105** was observed by ^{31}P NMR.[147] The high susceptibility of **105** to *O*-nucleophiles was demonstrated by the quenching experiments illustrated in Scheme 18.[147]

Scheme 18

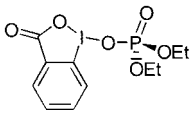


Experiments in the presence of ^{18}O-enriched water found the label mainly in the iodosyl hydroxyl, thus demonstrating that regeneration of the starting catalyst is accomplished by a rapid attack of hydroxide/water on **105** primarily at its *iodine* (Scheme 17).[148] Major involvement of the lactone unit is ruled out by ^{18}O-labeling experiments. Thus, the acetoxy derivative of **105** (see Scheme 17) reacted with 22 atom-% (^{18}O) H_2O/OH^- to give IBA with 21.6 atom-% ^{18}O at the iodosyl OH but only 2 atom-% ^{18}O at the carbonyl oxygen.[148]

Although IBA and INA are rapid *turnover* catalysts for the hydrolysis of PNPDPP and fluorophosphonates, they display slow turnover for the cleavage of paraoxon.[33] When PNPDPP is the substrate, leading to intermediate **105**, expulsion of the diphenyl phosphate from the intermediate and turnover to IBA are both rapid and the catalytic cycle is efficient. However, when paraoxon is the substrate, expulsion of the presumably poorer diethyl phosphate leaving group from intermediate **107** is considerably slower; both turnover and catalysis are impeded.



106



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VIII. Summary and Outlook

Iodosyl- and iodylcarboxylate derivatives are effective reagents for the hydrolytic cleavage of fluorophosphophosphonate nerve agents as well as certain insecticides and phosphate triester simulants. Many iodosyl- and iodylcarboxylate derivatives and various delivery systems have been prepared and tested against a variety of phosphate triesters and phosphonate diesters. True *turnover* capability under mild conditions is the most important feature of IBA-related systems in comparison with other nucleophiles that only react stoichiometrically.

However, the reactions of IBA with agent VX and other organophosphorus compounds containing sulfur fragments (**24**, **54**, or **60**) are not catalytic. In the case of simulant **54**, despite the lack of turnover, excess IBA displays outstanding reactivity and chemoselectivity, cleaving only the P−S bond. Other α-effect nucleophiles, such as oximes and hydroperoxide display similar chemoselectivity.[60a] However, IBA is the only reagent that is potentially catalytic, which should stimulate further exploration.

Given both the spectre of chemical warfare and the requirement for the destruction of stockpiled chemical weapons mandated by the international Chemical Weapons Convention, there is an urgent and continuing need for efficient chemical modalities for the detoxification, decontamination, and wholesale neutralization ("demilitarization") of the phosphorus-based nerve agents. We hope that this review helps to define the problems and inspires further progress.

IX. Acknowledgments

We are grateful to the U.S. Army Edgewood Research, Development, and Engineering Center and the U.S. Army Research Office for financial support. H.M.-R. acknowledges a Fulbright-CONACyT fellowship.

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CR9405462