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Immobilized Iodosobenzoate Catalysts for the Cleavage of Reactive Phosphates

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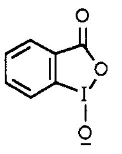
Titanium dioxide and nylon covalently supported iodosobenzoate reagents **11** and **19** have been prepared by the procedures outlined in Schemes I and II. Both **11** and **19** are good catalysts for the cleavage of *p*-nitrophenyl diphenyl phosphate (PNPDPP) under heterogeneous aqueous conditions at pH 8. The kinetics of the cleavage reactions have been characterized in the presence of excess substrate (turnover conditions), and in the presence of dilute cetyltrimethylammonium chloride, which enhances both PNPDPP cleavage and catalyst turnover.

o-Iodosobenzoate, cyclized as 1-oxido-1,2-benziodoxol-3(1*H*)-one (**1**) is a strong O-nucleophile that rapidly cleaves reactive esters or phosphates with true catalytic turnover.[1] The nucleophilic properties of **1** depend, in part, on its α-nucleophilic structure,[1e] and they are particularly well expressed in cationic aggregates, such as micelles[1a-c] or vesicles,[1g] where the catalyst and substrate are brought into close proximity. Various structural relatives of **1**,[1d,h] including *cis*-iodosocyclopropanecarboxylic acid (**2**)[1i] also manifest O-nucleophilicity, and theoretical analysis suggests that the strength of this property sensitively reflects the degree of closure of the iodoxole ring.[1h] The catalytic (turnover) properties of **1** apparently depend on the susceptibility of its iodine atom to direct attack by OH$^-$, so that the O-acylated or O-phosphorylated intermediates, formed from **1** during its cleavage of esters or phosphates, are unstable in basic media.[1f]



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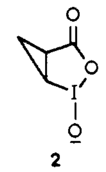

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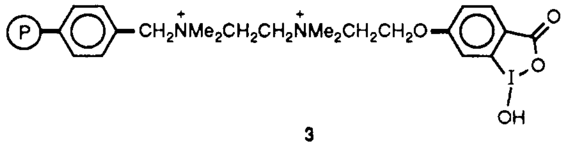
The need to decontaminate areas affected by phosphate toxins, such as nerve agents and insecticides,[2] has fostered sustained interest in the effective utilization of iodosobenzoate reagents. Notable developments include covalent bonding of **1** to surfactants,[1c,g] derivatization with water solubilizing substituents,[3] and solubilization in aqueous micellar solutions,[1,3] microemulsions,[4] and liquid crystals.[5]

We became interested in the preparation of immobilized iodosobenzoates as alternatives to the fluid decontaminant systems.[1,3-5] Solid decontaminants offer several attractive properties. They are easy to handle, potentially fast and efficient, and lend themselves to continuous recycling procedures (e.g., for the decontamination of water). Initially, we prepared polystyrene and polyacrylate polymers, functionalized with **1** that was covalently bonded to the polymer backbones via quaternary ammonium ion extender groups, cf., **3**.[6] These polymers did indeed catalyze cleavages of both the test "simulant" substrate, *p*-nitrophenyl diphenyl phosphate (**4**, PNPDPP), as well as the nerve agent, soman (**5**),[6] but the polymeric catalysts were not easy to prepare and not very compatible with the aqueous conditions required for phosphate decontamination.



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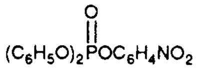
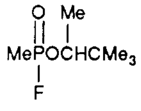


$(C_6H_5O)_2\overset{O}{\overset{\|}{P}}OC_6H_4NO_2$

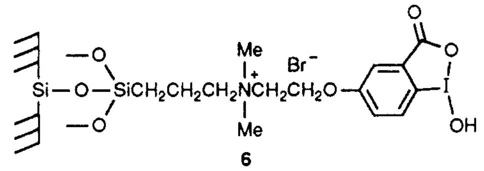
4 (PNPDPP)



$\mathrm{Me}\underset{F}{\overset{O}{\overset{\|}{P}}}\mathrm{O}\overset{\mathrm{Me}}{\overset{|}{\mathrm{C}}}\mathrm{HCMe_3}$

5

We therefore prepared silica-bound iodosobenzoate derivatives, e.g., **6**,[7] where the silylation of silica's surface OH groups provided easy synthetic access.[8,9] We expected that the polar and wettable silica surface would provide catalytically effective, immobilized iodosobenzoate reagents. Indeed, amine- and imidazole-functionalized silica reagents had already been shown to potentiate the hydrolysis of diisopropyl fluorophosphate.[10] Silica reagent **6** was, in fact, found to be phosphorolytically active against both substrates **4** and **5**.[7]



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In this paper, we describe the preparations and kinetic properties of iodosobenzoate reagents immobilized on titanium dioxide, an important constituent of various paints, and on nylon, a principal element of synthetic fabrics. It is possible that these reagents or their analogues could find use in "self-decontaminating" materials that would be

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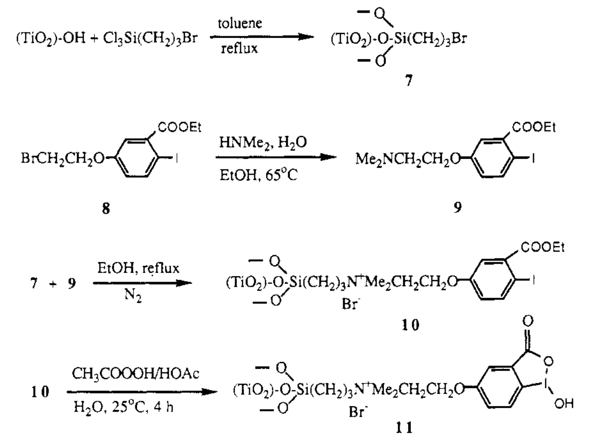
Scheme I



protective against several toxic phosphates or phosphonates. Further, we compare the phosphorolytic proclivities of the new reagents with those of iodosobenzoate 1 itself, and we show that significant enhancement of their phosphorolytic potency toward PNPDPP can be obtained in dilute aqueous solutions of cetyltrimethylammonium chloride (CTACl).

Results and Discussion

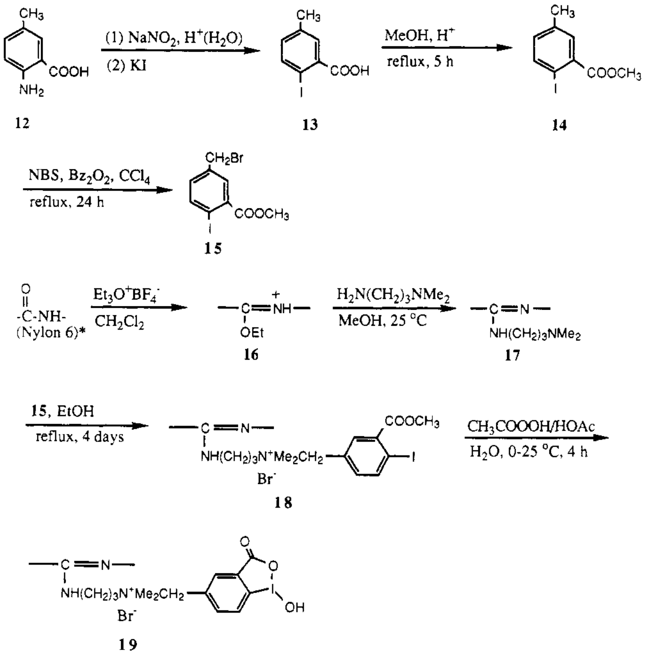
Synthesis. Titanium Dioxide Reagent. The synthetic sequence for the titanium dioxide–iodosobenzoate reagent (**11**) is described in Scheme I. Titanium(IV) oxide was ground in a mortar, dried at 110 °C, and refluxed with 1-(trichlorosilyl)-3-bromopropane in toluene to give the silylated titanium dioxide derivative **7**.[8a,11] From its Br elemental analysis, **7** was found to carry 0.59 mmol/g of the bromopropylsilyl residue. Separately, the known[1c] 5-(bromoethoxy)-2-iodobenzoate ester, **8**, was converted to the corresponding tertiary amine by heating with dimethylamine in absolute ethanol (sealed tube), affording 79% of **9** after chromatography on silica gel.

The titanium derivative **7** and excess amine **9** were then coupled by quaternization in refluxing anhydrous ethanol. The iodotitanium oxide reagent thus obtained (**10**) had an organic residue loading (mmol/g) of 0.38 by weight gain, 0.41 by titration for ionic bromide with $AgNO_3$, or 0.53 from elemental analysis for bromine. We take the average value, 0.44 mmol/g, as the organic residue loading of **10**, which represents about a 74% conversion of **7** to **10**.

Finally, iodobenzoate **10** was directly oxidized to the titanium iodosobenzoate reagent **11** with peracetic acid.[12,13] The *effective* loading of *redox-active iodosobenzoate* moieties was found to be 0.13 mequiv/g by $KI/Na_2S_2O_3$ iodometric titration,[14] corresponding to ~30% conversion of **10** to **11**. Iodo to iodoso conversions of this magnitude appear to be typical on solid supports.[6,7] Dynamic light scattering in water showed the particles of **11** to have a mean diameter of 43 nm with a unimodal distribution (standard deviation = 11.8 nm).

Nylon Reagent. The synthetic sequence for preparation of nylon iodosobenzoate reagent **19** is based on the nylon imidate activation procedure for nylon immobilized enzymes[15,16] and is outlined in Scheme II. In this case, we also introduce a new iodosobenzoate synthon, **15** (compare with **8**), that can be prepared in three steps from commercially available **12**. Thus, methylanthranilic acid **12** was converted to the corresponding iodide, **13**, by diazotization, followed by treatment with KI at 80 °C for 1 h.[17,18] Esterification to methyl ester **14** was followed by NBS bromination, affording methyl 5-(bromomethyl)-2-iodobenzoate (**15**) in 41% yield after recrystallization.

Scheme II



*The Nylon-6 repeat unit is $[C(O)NH(CH_2)_5]_n$.

Nylon 6 pellets were converted to powder by dissolution in $CaCl_2$/MeOH, followed by precipitation in water.[19] The nylon powder was then "activated" by partial conversion to imidate salt **16** through reaction with triethyloxonium tetrafluoroborate (−23 °C).[15,16] The activated nylon **16** was treated with excess *N*,*N*-dimethyl-1,3-propanediamine, affording aminonylon derivative **17**,[20] which, without further characterization, was quaternized with iodobenzoate **15**, leading to the quaternary ammonium iodobenzoate nylon derivative, **18**.

The iodobenzoate residue loading (mmol/g) of scrupulously dried **18** (see the Experimental Section) was found to be 1.05 by weight gain in the **17** → **18** conversion, 0.87 by bromide titration, and 0.90 from an elemental analysis for bromine (7.23%). The three results are in reasonable agreement, and afford an average value for the loading of 0.94 mmol/g, about twice the loading of titanium derivative **10**.

Finally, nylon iodobenzoate **18** was oxidized to nylon iodosobenzoate reagent **19** with peracetic acid.[12,13] Iodometric titration[14] with $KI/Na_2S_2O_3$ indicated an *effective* iodosobenzoate loading of 0.25 mequiv/g, corresponding

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(11) For relevant discussions, see: Weetall, H. H. *Meth. Enzymol.* **1976**, *44*, 134.

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(20) This reaction is analogous to previous reactions of **16** with (e.g.) 1,6-diaminohexane[16] or adipic acid dihydrazide.[15] We write **17–19** as imines, not iminium ions,[15] because the iminium proton of **16** should be lost to the excess amine reagent.

to ~26% conversion of the iodobenzoate to iodosobenzoate. This is similar to the conversion obtained in the titanium dioxide system (**11**), although the redox available iodosobenzoate in the nylon reagent **19** (0.25 mequiv/g) is nearly twice that of titanium reagent **11** (0.13 mequiv/g). Dynamic light scattering (in water) showed the particles of **19** to have diameters ranging from 400 to 1500 nm. The mean diameter was 724 nm, and ~90% of the particles were 500–1000 nm in size.

Kinetic Studies. General Procedure. For reactions in which the catalyst was in excess over the substrate, the cleavages of 3.3×10^{-5} M (0.10 μmol) of PNPDPP by 10 mg of supported iodosobenzoate reagents (i.e., the effective iodosobenzoate quantities were 2.5 μmol for nylon reagent **19** and 1.3 μmol for titanium reagent **11**) were followed in 3-mL aliquots of 0.02 M pH 8 phosphate buffer ($\mu = 0.08$, KCl) at 25 °C by monitoring the absorbance of the released *p*-nitrophenylate ($PNPO^-$) ions at 400 nm as a function of time. The solid reagents were wetted by vigorous stirring for 10 min before the addition of the PNPDPP (20 μL of 5×10^{-3} M PNPDPP in CH_3CN). Subsequent to substrate addition, vigorous magnetic stirring continued and the kinetics were followed by the 1 vial/1 point method, with each reaction solution quenched by filtration at time *t*. Filtered catalyst was washed twice (2×1 mL) with 0.1 M aqueous $NaClO_4$ solution; the final $PNPO^-$ absorbance was determined on the combined reaction and wash solutions. Reactions were followed to completion, and good infinity titers of $PNPO^-$ were obtained. Rate constants were calculated from at least five points and were accompanied by good correlation coefficients ($r > 0.99$) for pseudo-first-order kinetics.

Rate constants were also determined in phosphate buffer solutions containing CTACl at various concentrations. The procedure was identical with that described above, except that the filtered catalysts were washed with aqueous solutions of CTACl rather than $NaClO_4$ (which precipitates CTACl).

For "turnover" experiments, where substrate PNPDPP was in excess over catalyst, 2–6 mg of catalyst in 5 mL of the usual phosphate buffer was reacted with 0.5 μmol of substrate, in the absence or presence of CTACl, in the usual way. In these experiments, "burst kinetics" were observed.[21] The *available* iodosobenzoate participating in these reactions was considerably *less* than expected based on the iodosobenzoate loadings indicated by the $KI/Na_2S_2O_3$ redox titrations. We will return to this point below.

pK_a Determinations. The apparent pK_a's of the IOH groups of titanium oxide reagent **11** and nylon reagent **19** were determined from pH–rate constant profiles, where **11** or **19** cleaved PNPDPP under standard, excess catalyst, kinetic conditions. Phosphate buffers were used at six different pH conditions between pH 7.0 and 8.5. Plots of lot k_ψ vs pH (Figure 1) revealed sharp discontinuities at pH 7.4 for both reagents that were taken as the pK_a values for conversion of IOH to the nucleophilic, anionic IO^- form. pK_a values of this magnitude are typical of *o*-iodosobenzoates that are either bonded to quaternary ammonium ions or solubilized in aqueous cationic micellar solutions.[1a,b] Silica reagent **6**, for example, showed pK_a 7.36 under comparable conditions,[7] and *o*-iodosobenzoate itself has pK_a 7.25 in micellar CTACl.[1a]

These data indicate that **11** and **19** will be >80% ionized to their reactive IO^- forms under pH 8 kinetic conditions. Note, however, that the ionization converts the cationic, unreactive, IOH bound reagent to a zwitterionic (N^+, IO^-) iodosobenzoate. The charge type may well affect the reactivity;[1g] see below.

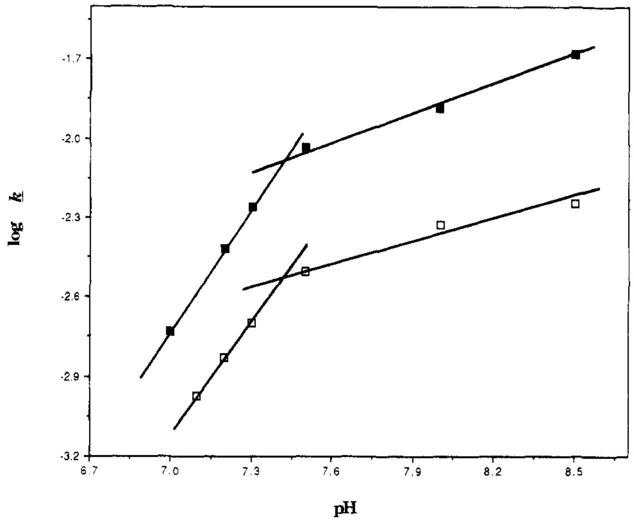

Figure 1. pH–rate constant profile for the cleavage of PNPDPP by **11** (□) or **19** (■) in phosphate buffers; log k_ψ (s^{-1}) vs pH. The discontinuities at pH 7.4 are taken as the systemic pK_a's. See text for a description of the kinetic methods and conditions.

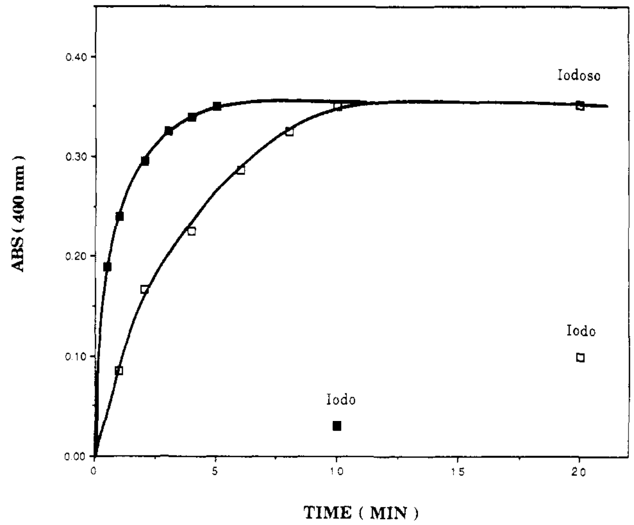

Figure 2. Absorbance of released $PNPO^-$ vs time (min) for cleavages of PNPDPP by excess **11** (□) or **19** (■) in 0.02 M phosphate buffer at pH 8, 25 °C; see text for other conditions. Points labeled "iodo" refer to runs with *iodo precursors* **10** (□) or **18** (■) of **11** or **19**, respectively.

Kinetic Studies. Excess Catalyst. Cleavages of PNPDPP by excess **11** or **19** in 0.02 M pH 8 phosphate buffer typically gave the results illustrated in Figure 2 for the absorbance of released $PNPO^-$ vs time. The nylon reagent appeared to be more reactive, with rate constants (k_ψ) = $(1.2 \pm 0.1) \times 10^{-2}$ s^{-1} for **19**, and $(4.3 \pm 0.4) \times 10^{-3}$ s^{-1} for **11**, in duplicate runs. Importantly, *iodo* precursors (**18** and **10**) of **19** and **11** were essentially unreactive toward PNPDPP (see Figure 2). In related control experiments, we found that the nylon and titania supports (even after treatment with peracetic acid) were also unreactive toward PNPDPP.

For comparison, silica reagent **6** cleaves PNPDPP with $k_\psi = 1.8 \times 10^{-2}$ s^{-1} under comparable conditions.[7] On a second order basis, corrected for mequiv of *titratable* iodosobenzoate per milliliter of buffer, reagents **6**, **11**, and **19** afford $k_2 \sim 40$, 10, and 14 M^{-1} s^{-1}, respectively. All three supported iodosobenzoate reagents are significantly less reactive than iodosobenzoate itself, solubilized in *micellar* CTACl, where $k_2 = 645$ M^{-1} s^{-1}.[1a,b]

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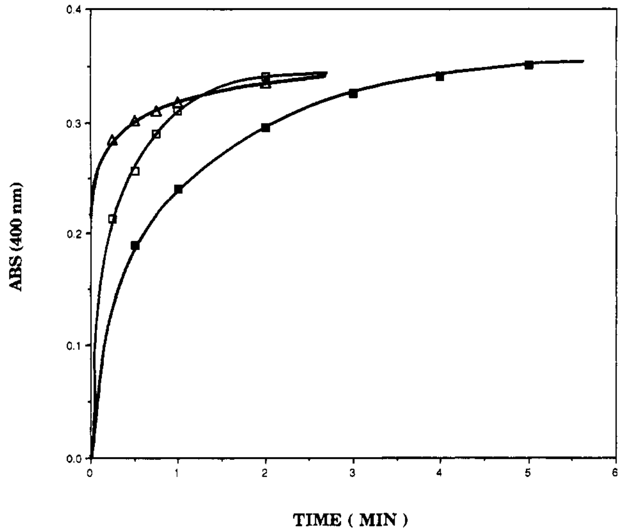

Figure 3. Absorbance of released PNPO$^-$ vs time (min) for cleavages of PNPDPP by excess **19** in 0.02 M pH 8 phosphate buffer alone (■), or with 5 × 10^{-5} M (□), or 1 × 10^{-4} M (△) added CTACl. See text for rate constants.

Importantly, however, the reactivities of the supported iodosobenzoates could be significantly enhanced in the presence of CTACl. Thus, kinetic runs carried out with nylon reagent **19** gave the results shown in Figure 3, where k_ψ increased from 0.012 s^{-1}, in pH 8 phosphate buffer alone, to 0.030 s^{-1} with 5 × 10^{-5} M CTACl, and to 0.067 s^{-1} in 1 × 10^{-4} M CTACl, 0.02 M pH 8 phosphate (μ = 0.08, KCl). The latter rate constant is equivalent to $k_2 \sim 80$ M^{-1} s^{-1}, based on titratable iodosobenzoate in **19**. At [CTACl] ≥ 2.5 × 10^{-4} M, k_ψ became too fast to measure by the 1 vial/1 point method. Under the 1 × 10^{-4} M CTACl, pH 8 conditions, reagent **19** approaches the reactivity of iodosobenzoate (**1**), for which k_ψ = 0.064 s^{-1} and k_2 = 645 M^{-1} s^{-1} in 1 × 10^{-3} M CTACl/phosphate buffer solution.[1b]

Enhancements in k_ψ were also observed for titanium regent **11**, where k_ψ reached 0.039 s^{-1} at [CTACl] = 2.5 × 10^{-4} M, and for a silica reagent related to **6** (reagent **5** in ref 7). Control experiments indicated that CTACl *alone* was not very reactive toward PNPDPP and was not responsible for the rate enhancements. Rather, it appears that CTACl potentiates the reactivity of the supported iodosobenzoate reagents. The CTACl might act as a kind of solid–liquid phase-transfer agent, facilitating substrate–iodosobenzoate interaction at the solid support's surface. Alternatively, the cationic surfactant could affect the "availability" of the iodosobenzoate moieties of reagents **11** and **19**. We noted above that the functional iodosobenzoate residues of both reagents are mainly zwitterionic at pH 8 (viz., a quaternary ammonium ion covalently linked to an iodosobenzoate anion). Electrostatic interactions may normally cause the iodosobenzoate moieties to reside near the support's surface, in close proximity to the ammonium ion centers, and, consequently, with less availability to the substrate in solution. Such a problem apparently affects the reactivity of zwitterionic, iodosobenzoate-functionalized vesicles.[1g] A cationic surfactant like CTACl could bind at the solid surface, modify the microenvironment, disrupt IO$^-$/N$^+$ interactions, and enhance the availability of the catalytic units. Such an effect is observed in the vesicular case.[1g]

Turnover Experiments. When the nominal molar ratio of substrate PNPDPP to nylon catalyst **19** was increased to 1:1, "burst kinetics"[21] were observed; see Figure 4. Thus, rapid phosphorylation of the *available* iodosobenzoate moieties in a 2-mg sample (0.5 μmol) of *titratable* catalyst **19** by 0.5 μmol of PNPDPP in 0.02 M pH 8 phosphate buffer led to a rapid release (burst) of PNPO$^-$, followed by a steady, linear (with time) release. The linear portion of the reaction represents the OH$^-$ mediated, rate-limiting cleavage of phosphorylated iodosobenzoate; the regenerated IO$^-$ is rapidly rephosphorylated by excess substrate.[1c,22] In this situation, the slope of the linear portion, divided by [catalyst], affords the turnover rate constant (k_{turn}), and the Y intercept of the linear portion gives the absorbance of the PNPO$^-$ that is stoichiometrically equivalent to the iodosobenzoate that was phosphorylated in the initial burst.

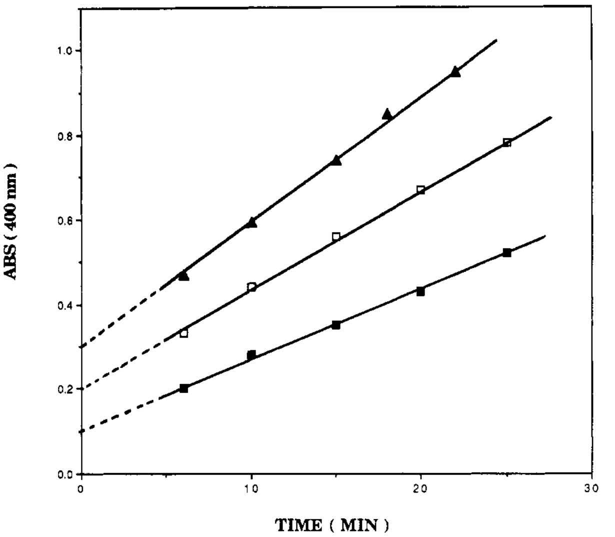

Figure 4. Burst kinetics for the cleavage of "excess" PNPDPP by catalyst **19**; see text for conditions. Plotted is the absorbance of released PNPO$^-$ vs time (min) for the cleavages of 1 × 10^{-4} M PNPDPP by 2 mg (■), 4 mg (□), or 6 mg (▲) of **19** in pH 8 phosphate buffer. The values of [PNPO$^-$] at zero time are extrapolated from the data points.

In fact, the intercepts of the PNPO$^-$ absorbance vs time correlations of Figure 4 indicate that only ~8.3% of the titratable IO$^-$ of catalyst **19** actually participates in PNPDPP cleavage. Thus, in the first set of reactions, rapid cleavage of 0.5 μmol of PNPDPP, equivalent to the 0.5 μmol of titratable iodosobenzoate moieties carried by 2 mg of **19**, should afford an absorbance of 1.2. The observed absorbance intercept of 0.1 indicates, however, that only about $^1/_{12}$ of the redox active iodosobenzoates are catalytically available to the substrate. Clearly, most of the iodosobenzoate moieties, though available to I$^-$ in redox titrations, are unavailable to the PNPDPP substrate, possibly because they are weakly bound at the nylon surface by electrostatic interactions; see above.

The slopes of the linear correlations in Figure 4, corrected for the *available* iodosobenzoate, give turnover rate constants of 2.3 × 10^{-3}, 1.9 × 10^{-3}, and 1.7 × 10^{-3} s^{-1}, for 2, 4, or 6 mg of **19**, respectively. As expected, the slopes increase with increasing catalyst, but k_{turn} is reasonably constant at an average value of ~2 × 10^{-3} s^{-1}. This is ~10 times less than k_ψ for PNPDPP cleavage by *excess* **19**, so that turnover is rate-limiting when excess *substrate* is present. Note (Figure 4) that the Abs intercept increases as expected with increasing **19**. In all three cases, however, the intercept remains only 8–10% of the value anticipated if all of the redox-active iodosobenzoate moieties had been phosphorylated in the burst. Similar experiments with titanium reagent **11** gave k_{turn} = 3.1 × 10^{-3} s^{-1}, about the same as k_ψ (4.3 × 10^{-3} s^{-1}) for this reagent.

Most importantly, addition of CTACl to the pH 8 phosphate buffer enhances turnover, just as it enhanced

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[22] The mechanism of this reaction most probably involves hydroxide attack at *iodine*, not phosphorous; see ref 1f.

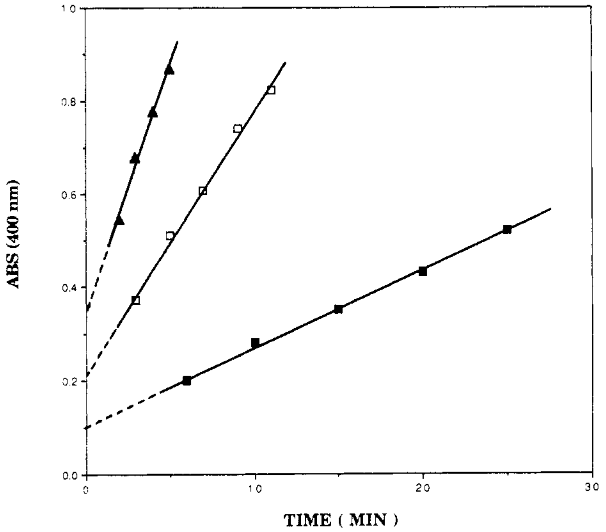

Figure 5. Burst kinetics for the cleavage of "excess" PNPDPP by catalyst **19** in the presence of CTACl; see caption to Figure 4 and text. The [CTACl] are 0 (■), 5 × 10^{-5} M (□), and 7.5 × 10^{-5} M (▲).

k_ψ (see above). The results with nylon reagent **19** are illustrated in Figure 5. The lowest line represents turnover of 2 mg of **19** in the presence of 0.5 μmol of PNPDPP in 0.02 M pH 8 phosphate buffer with *no* added CTACl. (This is the lowest line shown in Figure 4.) Addition of 5 × 10^{-5} or 7.5 × 10^{-5} M CTACl enhances turnover, with k_{turn} increasing from 2 × 10^{-3} s^{-1}, in the absence of CTACl, to 4.8 × 10^{-3} or 5.4 × 10^{-3} s^{-1} with the additions of CTACl. At [CTACl] ≥ 1 × 10^{-4} M, k_{turn} becomes too fast to follow by the 1 point/1 vial method.

Not only does CTACl enhance turnover, but it *activates* additional iodosobenzoate groups on the nylon surface. In the absence of CTACl, the Abs intercept is only 8–10% of its expected value (see above). The same reactant concentrations produce Abs intercepts of 0.20 or 0.34 in the presence of 5 × 10^{-5} or 7.5 × 10^{-5} M CTACl, 17% or 28%, respectively, of the anticipated $PNPO^-$ absorbance for complete burst phosphorylation of the redox titratable iodosobenzoate in the 2-mg sample of **19**.

This behavior strongly implicates interaction of the CTACl with the nylon surface or its pendant groups. The cationic CTACl may bind at the nylon surface, enhance the local [OH^-], augment OH^- attack on the phosphorylated iodosobenzoate, and raise k_{turn}. At the same time, the CTACl could mitigate N^+/IO^- electrostatic interactions, "free" iodosobenzoate groups, and make them available for nucleophilic attack on the substrate. Something very like this seems to happen upon covesicallization of zwitterionic iodosobenzoate-functionalized ammonium ion vesicles with dihexadecyldimethylammonium bromide.[1g]

CTACl enhancement of turnover was also observed with titanium reagent **11**, where k_{turn} increased from 3 × 10^{-3} s^{-1}, in the absence of CTACl, to 4.6 × 10^{-3} s^{-1} or 1.2 × 10^{-2} s^{-1} in the presence of 5 × 10^{-5} or 1 × 10^{-4} M CTACl, respectively. A brief reinvestigation of our previously studied silica iodosobenzoate reagents[7] revealed similar CTACl enhancements of turnover.[23]

In control experiments, we observed that the nylon and titanium dioxide iodosobenzoate catalysts could be filtered, washed with buffer, dried, and then recycled at least four times, under turnover conditions, with little or no loss in their activity against PNPDPP.

Conclusions

Nylon and titanium dioxide bound iodosobenzoate reagenst **19** and **11**, like silica reagent **6**, are good catalysts for the cleavage of the active phosphate substrate PNPDPP. Under heterogeneous conditions, in pH 8 phosphate buffer, excess **11** or **19** cleave PNPDPP with "second order" rate constants of ~10 or ~14 M^{-1} s^{-1}, based on titratable iodosobenzoate. Corrected for catalytically available iodosobenzoate,[24] k_2 for nylon reagent **19** is ~170 M^{-1} s^{-1}, only ~4 times less than k_2 = 645 M^{-1} s^{-1} for 1 × 10^{-3} M aqueous micellar CTACl solutions of iodosobenzoate itself.[1a,b] Both **11** and **19** are true catalysts, turning over in the presence of excess PNPDPP by rate-limiting OH^- attack on the phosphorylated iodosobenzoate moieties, with k_{turn} = 3.1 × 10^{-3} and 2.0 × 10^{-3} s^{-1}, respectively, based on available iodosobenzoate. Addition of modest amounts of CTACl to the pH 8 phosphate buffer enhances *both* the rates of PNPDPP cleavage in the presence of excess catalyst *and* that of catalyst turnover in the presence of excess substrate. Additionally, more of the redox titratable, bound iodosobenzoate groups come into catalytic action in the presence of CTACl.

Ease of preparation and practical simplicity make solid reagents **11** and **19** candidate solid decontaminants in applications against toxic phosphates. Evaluations of their reactivities toward representative phosphate nerve agents are in progress.

Experimental Section

General. Melting points are uncorrected. NMR spectra were measured with a Varian VXR-200 instrument and chemical shifts are reported in δ units (signal locked to $CDCl_3$). Microanalyses were performed by Robertson Laboratory, Madison, NJ.

Titanium Dioxide Reagent 11 (See Scheme I). Titanium dioxide (2.0 g, 25 mmol, Aldrich, 99.99%) was ground in a mortar, dried in an oven (110 °C, 3 h), and then stirred and refluxed under N_2 for 30 h with 3.0 g (12 mmol) of 1-(trichlorosilyl)-3-bromopropane (Petrarch) in 50 mL of toluene (dried over CaH_2). HCl gas evolution was detected with Hydrion paper. After cooling, the suspension was filtered through a 30-mL medium-grade sintered-glass funnel, and the solid was washed sequentially with 20 mL of toluene, 20 mL of hexane, and 2 × 20 mL of ether and then dried under vacuum (0.1 Torr) for 3 h. We obtained 2.05 g of slightly tan (((bromopropyl)silyl)oxy)titania (**7**). From the Br elemental analysis (4.73% Br), the loading of (bromopropyl)silyl residue was calculated to be 0.59 mmol/g of support.

2-Iodo-5-(β-(dimethylamino)ethoxy)benzoic Acid Ethyl Ester (9). This compound was prepared from the corresponding, known[1c] bromoethoxy compound, **8**. Thus, 1.6 g (4.0 mmol) of **8** and 10 mL (56 mmol) of 33% dimethylamine in ethanol (Fluka) were sealed in a 1 in. × 9 in. screw-top Carius tube, and stirred and warmed in an oil bath at 65 °C for 10 h. Ethanol was removed on the rotary evaporator, and the product was extracted with 2 × 30 mL of ether. The ethereal extract was washed with 30 mL of 10% $NaHCO_3$ solution, then with 20 mL of water, and dried over $MgSO_4$. Removal of dessicant and solvent gave 1.2 g of brown oil that was purified by chromatography over 230–400-mesh silica gel, eluted with 4:1 $CHCl_3$–MeOH. We obtained 1.15 g (3.16 mmol, 79%) of dimethylamino compound **9**, R_f 0.68 (silica gel on polyester TLC, 4:1 $CHCl_3$–MeOH). NMR ($CDCl_3$): 1.33 (t, J = 7 Hz, 3 H, CH_3), 2.23 (s, 6 H, Me_2N), 2.61 (t, J = 7 Hz, 2 H, CH_2N), 3.97 (t, J = 7 Hz, 2 H, CH_2CH_2O), 4.30 (q, J = 7 Hz, 2 H, CH_2CH_2O), 4.30 (q, J = 7 Hz, $COOCH_2$), 6.70, 7.20, 7.70 (m, m, d, 1 H each, aromatic).

Anal. Calcd for $C_{13}H_{18}INO_3$: C, 42.9; H, 5.00; N, 3.86. Found: C, 42.6; H, 4.96; N, 3.77.

Iodobenzoate Reagent 10. The (((bromopropyl)silyl)oxy)-titanium reagent **7** (2.0 g, 1.18 mmol of Br) and 900 mg (2.48 mmol)

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[23] Details of these experiments will appear in the Ph.D. Dissertation of Y.-C. Chung.

[24] This correction is based on the turnover experiments; see above.

of amine **9** were stirred and refluxed for 3 days under N_2 in 40 mL of anhydrous (CaH_2) ethanol. The slurry was filtered on a 30-mL medium-grade sintered-glass funnel, and the solid was washed sequentially with 2 × 20 mL of ethanol and 2 × 20 mL of ether and then dried under vacuum (0.1 Torr) over P_2O_5 for 12 h. We obtained 2.3 g of **10**, which had an organic residue loading of 0.38 mmol/g by weight gain, and 0.53 mmol/g by elemental analysis for Br (4.24%). The loading was 0.41 mmol/g by bromide ion titration.[25]

Iodosobenzoate Reagent 11. Iodo reagent **10** (1.7 g, ~0.75 mmol of I) was slurried with 10 mL of acetic acid and cooled in an ice bath. Next, 2 mL of 35% peracetic acid (FMC)[26] was added dropwise, with stirring, over 10 min. The mixture was stirred for an additional 4 h at room temperature, and then neutralized by the addition of 10% aqueous Na_2CO_3. The solid **11** was filtered on the sintered-glass funnel, washed with 2 × 30 mL of water, 20 mL of methanol, and 2 × 20 mL of ether, and dried at 0.1 Torr over P_2O_5 for 12 h. We obtained 1.4 g of **11** that carried 0.13 mequiv/g of iodoso residue by iodometric titration.[14,27]

Nylon Reagent 19 (See Scheme II). 2-Iodo-5-methylbenzoic Acid (13). 2-Amino-5-methylbenzoic acid, **12** (10 g, 66 mmol, Aldrich), was dissolved in a mixture of 30 mL of concentrated sulfuric acid and 300 mL of water and cooled to <5 °C in an ice bath. Then, 6.2 g (90 mmol) of $NaNO_2$ in 30 mL of chilled water was added, with stirring, at such a rate that the temperature did not exceed 5 °C. A solution of 15 g (90 mmol) of KI in 30 mL of chilled water was added (nitrogen was evolved), and the mixture was then heated to 80 °C for 1 h and cooled. Activated charcoal (3 g) was added, and the solution was heated to 80 °C, filtered while hot, and then cooled in ice to afford 14.3 g (54.5 mmol, 83%) of light brown crystals of **13**, mp 115–117 °C (lit.[17,18] mp 118–119 °C). The NMR spectrum agreed with the literature description.[18]

Acid **13** was esterified by refluxing 11.0 g (42.0 mmol) in 50 mL of methanol and 5 mL of concentrated sulfuric acid for 5 h. The reaction mixture was poured over 50 g of crushed ice and neutralized with aqueous $NaHCO_3$ solution. Extraction with 100 and 50-mL portions of EtOAc afforded an organic solution that was washed with dilute $Na_2S_2O_3$ solution, then with water, and dried over sodium sulfate. Removal of dessicant and solvent, and chromatography over 70–230-mesh silica gel (4:1 hexane–EtOAc), gave 11.0 g (39.9 mmol, 95%) of ester **14** as a light brown oil, R_f 0.64 (TLC on silica gel, 4:1 hexane–EtOAc). The NMR spectrum (δ, $CDCl_3$) showed 3 H singlets at 2.28 and 3.85 ($ArCH_3$ and OCH_3, respectively), as well as 1 H aromatic signals at 6.90 (d, J = 8 Hz), 7.55 (s), and 7.78 (d, J = 8 Hz).

5-(Bromomethyl)-2-iodobenzoic Acid Methyl Ester (15). Methyl ester **14** (10 g, 36.2 mmol), 6.12 g of *N*-bromosuccinimide (Fisher, 34.4 mmol), and 34 mg of benzoyl peroxide were added to 100 mL of dry CCl_4, and the mixture was stirred and refluxed for 24 h under nitrogen. The reaction mixture was cooled, succinimide was filtered, and the filtrate was successively washed with $Na_2S_2O_3$ solution, water, and brine. It was then dried over Na_2SO_4. Removal of dessicant and solvent gave a solid that was recrystallized from EtOAc, affording 5.32 g (15.0 mmol, 41%) of white crystalline **15**, mp 71–72 °C, R_f 0.46 (4:1 hexane–EtOAc). NMR (δ, $CDCl_3$): 3.92 (s, 3 H, OCH_3), 4.43 (s, 2 H, CH_2Br), 7.18 (dd, J = 2, 9.5 Hz, 1 H, H para to COOMe), 7.84 (d, J = 2 Hz, 1 H, H ortho to COOMe), 7.95 (d, J = 9.5 Hz, 1 H, H meta to COOMe).

Anal. Calcd for $C_9H_8BrIO_2$: C, 30.4; H, 2.27; I, 35.8. Found: C, 30.6; H, 2.13; I, 36.0.

The nylon support was activated by the following procedures.[15,16,19,20] Nylon 6 pellets (20 g, Aldrich) were dissolved in a mixture of 80 g of $CaCl_2$ in 300 mL of MeOH by stirring for 12 h. The viscous solution was then added dropwise, with vigorous mechanical stirring, to 4 L of distilled water. The nylon powder precipitate was filtered on a Büchner funnel and washed with 500 mL of water. The *entire procedure* was repeated a second time, and the final nylon powder was washed with 1 L of water, 200 mL of ethanol, and 2 × 200 mL of ether, and then dried at 0.1 Torr. We recovered 20 g of nylon powder.

In a three-neck, 100-mL flask was placed 3 g of nylon powder, in 40 mL of dry CH_2Cl_2, under a nitrogen atmosphere. The flask was cooled to −23 °C, and its contents were stirred, while 20 mL of 1 M triethyloxonium tetrafluoroborate in CH_2Cl_2 (20 mmol, Aldrich) was slowly added by syringe over 30 min. After the addition was complete, the temperature was allowed to rise to 25 °C, and stirring was continued for 2 h. The sticky nylon aggregate was filtered on a 30-mL medium-grade sintered-glass funnel, washed quickly under suction with dry MeOH, covered with a rubber sheet, and dried under suction for 1 h. This afforded nylon iminium ether **16**.

The powdered **16** was added to a solution of 3 g (30 mmol, Aldrich) of *N*,*N*-dimethyl-1,3-propanediamine in 40 mL of dry methanol. The mixture was then stirred for 10 h at 25 °C and filtered. The solid was washed with 2 × 20 mL of methanol and dried, affording 2.8 g of aminonylon **17**.

Finally, aminonylon **17** was coupled with (bromomethyl)iodobenzoic ester **15** by quaternization. Thus, 2.2 g of powdered **17** and 1.2 g (3.4 mmol) of **15** were added to 40 mL of dry ethanol and refluxed under a nitrogen blanket for 4 days. The resulting nylon-supported iodobenzoate **18** was filtered, washed with 20 mL of ethanol and 2 × 20 mL of ether, and dried over P_2O_5 at 0.1 Torr for 12 h. We obtained 3.023 g of **18** that had an organic residue loading (mmol/g) of 1.05 by weight gain, 0.87 by bromide ion titration,[25] and 0.90 by bromine elemental analysis (7.23% Br).

The nylon iodobenzoic ester was oxidized by slurrying 2.4 g of **18** with 10 mL of glacial acetic acid at 25 °C. Then 4 mL of 35% peracetic acid[26] was added dropwise over 1 h at 25 °C. A color change from dark red to pale yellow was noted during this hour. The reaction mixture was neutralized with aqueous 5% $NaHCO_3$ solution (which discharged the color) and filtered on the sintered-glass funnel to give solid **19**. This was washed with 20 mL of water, 20 mL of methanol, and 3 × 20 mL of ether and then dried for 5 h at 0.1 Torr. We obtained 2.0 g of nylon iodoso reagent **19** that was loaded with 0.25 mequiv/g of iodoso moieties by iodometric titration.[14,27]

Kinetics. Kinetic procedures are described in detail above; see Results and Discussion. Absorbances of $PNPO^-$ were determined with a Hewlett-Packard 8451A spectrometer. Reactions were followed to >90% of completion, and good (r > 0.998) first-order kinetics were observed. Rate constants were obtained from computer-generated correlations of log $(A_\infty - A_t)$ with time for the appearance of $PNPO^-$ at 400 nm. Kinetic results appear in Figures 1–5 and are discussed above.

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[25] Bromide containing reagent (100 mg) was added to 40 mL of 0.2 M aqueous $NaNO_3$, and the mixture was stirred for 20 min to extract Br^- into the solution. Then 8 mL of 0.03 M aqueous $AgNO_3$ solution was added; AgBr precipitated. The solution was then titrated for excess $AgNO_3$ using 0.03 M aqueous NaBr as the titrant. The end point was found from the titration curve of millivolts vs volume, followed with an Orion Br-selective electrode, an Orion double junction reference electrode, and a Corning Model 12 pH/mV meter. From the difference in the sample titration, and an otherwise identical blank titration, we calculated millimoles/gram of ionic bromide.

[26] FMC "35% peracetic acid" also contains 17.4% of water, 1% of sulfuric acid, 6.8% of H_2O_2, and 39.3% of acetic acid.

[27] Iodoso reagent (40 mg) in 3 mL of 6 N HCl was stirred for 5 min at 25 °C; 50 mg of KI was added. The color changed to dark yellow or red. The mixture was titrated with 0.01 N $Na_2S_2O_3$ solution (standardized against $K_2Cr_2O_7$), using starch indicator added near the end point.