

Silica Functionalized With Iodosobenzoate for the Catalytic Cleavage of Reactive Phosphates

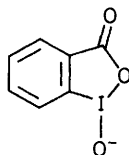
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Silica-bound iodosobenzoate derivatives have been prepared and found to be phosphorolytically active against both *p*-nitrophenyldiphenyl phosphate and the nerve agent, soman.

o-Iodosobenzoate, in its valence tautomeric 1-oxido-1,2-benziodoxol-3(1*H*)-one form (**1**), is a strong α -nucleophile capable of rapidly cleaving reactive phosphates with true catalytic turnover.¹ These properties have important applications in the decontamination of areas affected by toxic

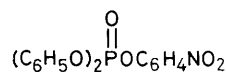


(1)

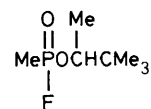
phosphate insecticides and nerve agents, so efforts are being made to develop appropriately efficient vehicles for delivery of the catalytic moiety. Accordingly, (**1**) has been covalently bonded to a surfactant;² it has been derivatized with water-solubilizing substituents;³ and it has been solubilized in aqueous micellar solutions,^{1,3} microemulsions,⁴ or liquid crystals.⁵

Solid decontaminants should offer several attractive properties for use against small 'spills' of toxic agents. They would be easy to handle and use and, if properly constructed, they could be fast, efficient, and catalytic. As initial attempts in this direction, we synthesized polystyrene and polyacrylate

polymers, functionalized with (**1**) which was covalently bonded to the polymer backbones *via* quaternary ammonium ion 'extender' units.⁶ These materials did catalyse the cleavages of both the test phosphate simulant, *p*-nitrophenyl diphenyl phosphate (**2**) (PNPDPP), and the nerve agent soman (**3**). However, the polymers were not easy to prepare and they were not very 'wetable' under the aqueous conditions required for phosphate destruction.



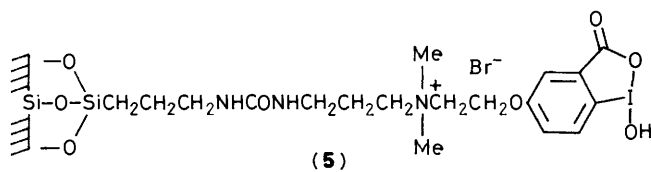
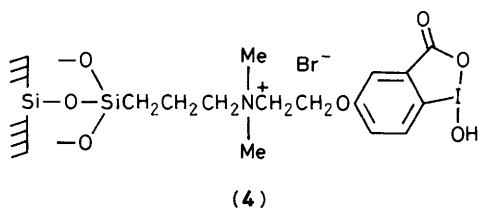
(2)



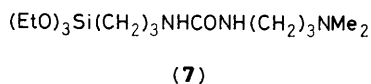
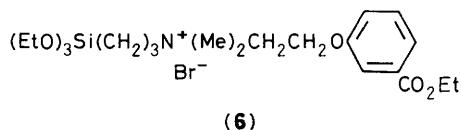
(3)

In contrast, silica-based iodosobenzoate catalysts should be more polar and wettable, cheaper, and easier to prepare by silylation of silica's surface hydroxy groups.⁷ This approach has been previously used to prepare phosphonium salt-modified silica gels as catalysts for phase-transfer reactions.⁸ More to the point, amine- and imidazole-functionalized silica reagents were used to accelerate the hydrolysis of di-isopropyl fluorophosphate.⁹ Here, we report the preparation and kinetic evaluation of two *o*-iodosobenzoate-functionalized silica reagents for the catalytic cleavage of reactive phosphates.

Silica reagents (**4**) and (**5**) were prepared as follows.



3-Dimethylaminopropyltrimethoxysilane (Petrarch) was refluxed with ethyl 3-(2-bromoethoxy)-2-iodobenzoate² (EtOH, 3 days) to give the quaternary salt (6) (m.p. 133–135 °C)* in 72% yield after recrystallization from EtOH–Et₂O. Ethoxy for methoxy exchange occurred at silicon during the reaction. Triethoxysilane (6) (1 mmol) was then coupled to activated¹⁰ silica (1 g; 350 m²/g; Strem) during a 60 h reflux period in dry toluene, with water removal *via* a Dean–Stark trap. The coupled



material was filtered, washed sequentially with toluene, ethanol, hexane, and ether, and then dried (68 °C, 3 h, 0.1 Torr). The loading on silica of residues derived from (6) was 0.40–0.45 mmol/g, determined either by titration for the Br[−] counterions or by elemental analysis for iodine. Preparation of (4) was completed by direct conversion of the *o*-iodobenzoate ester groups into *o*-iodosobenzoate moieties either by chlorination in CHCl₃ followed by hydrolysis in 10% aqueous NaHCO₃ solution, or by oxidation with 30% peracetic acid.¹¹ Reagent (4) was washed sequentially with water, ethanol, hexane, and ether, and then dried. Titration for iodosobenzoate² gave its loading on the silica as 0.10 mequiv./g, corresponding to 22–25% conversion of iodo- to iodoso-benzoate in the chlorination/hydrolysis sequence; conversion was higher (0.18 mequiv./g) in the peracetic acid oxidation.

The silica reagent (5) was prepared in a related manner. The key steps were condensation of 3-triethoxysilylpropyl cyanate (Petrarch) with 3-dimethylaminopropylamine (toluene, 12 h, 25 °C, N₂ blanket) to give the urea (7), which was immediately quaternized with ethyl 3-(2-bromoethoxy)-2-iodobenzoate² (refluxing EtOH, 4 days) affording the appropriate *o*-iodobenzoate ethyl ester quaternary ammonium bromide salt (m.p. 74–75 °C) in 54% overall yield.* This was coupled to silica (loading, 0.53 mmol/g) and converted into the *o*-iodosobenzoate reagent (5) as described above for the reagent (4). The final silica reagent (5) had a titrimetric *o*-iodosobenzoate loading of 0.10 mequiv./g, again indicative of a 20% iodo to iodoso conversion upon chlorination/hydrolysis.

The apparent p*K*_a of the I–OH group of reagent (4) was determined from a rate constant/pH profile in which (4) was used to cleave substrate (2) in aqueous solution at six different pH values in the range 6.64–8.5. A plot of log *k*_w (for the appearance of *p*-nitrophenolate ion at 400 nm) vs. pH showed a sharp discontinuity at pH 7.36 which was taken as the p*K*_a of (4).^{1,2} The value is typical of *o*-iodosobenzoates in cationic micellar solutions,^{1,2} and indicates that *ca.* 81% of the I–OH groups of (4) will be in their reactive I–O[−] form at pH 8, under our normal kinetic experimental conditions.

The cleavage of 5 × 10^{−5} M (0.15 μmol) of (2) by 15 mg (1.5 μequiv.) of silica reagents (4) and (5) in 3 ml aliquots of 0.02 M pH 8 phosphate buffer (μ = 0.08, KCl) at 25 °C was followed spectroscopically at 400 nm, using the 1 vial/1 kinetic point method. Good pseudo-first-order kinetics were observed with *k*_w = 0.018 s^{−1} (4) or 0.017 s^{−1} (5), corresponding to τ_{1/2} ~ 40 s.† Interestingly, a preparation of reagent (4) loaded at 0.16 mequiv. of I=O per g of silica onto a higher surface area silica (500 m²/g, chromatographic grade) was *less* reactive, with *k*_w ~ 0.007 s^{−1} under comparable conditions. The nonoxidized, silica-bound iodosobenzoate precursor of (4) was inactive towards substrate (2).

Reagent (4) is a true catalyst, turning over in the presence of an excess of (2). For example, when (4) (2 mg, 0.2 μequiv. of I=O) in pH 8 phosphate buffer (5 ml) was challenged with either 1.38 or 2.75-fold excesses of (2), rapid phosphorylation of (4) and release of *p*-nitrophenolate ion were observed, followed by a slower, linear increase of absorbance with time (*i.e.*, ‘burst kinetics’).¹² The later kinetic phase afforded the ‘turnover’ rate constant, *k*_{turn} = 1.8 ± 0.1 × 10^{−3} s^{−1}. Reagent (4) could be cycled through 3–4 reactions with an equimolar proportion or an excess of (2) without significant decrease in its reactivity.

The kinetic behaviour of (4) with an excess of (2) indicates that OH[−] mediated (buffer) hydrolysis of *O*-phosphorylated (4) (*k*_{turn}) is *ca.* 10 times slower at pH 8 than the initial phosphorylation of (4) by (2) (*k*_w = 1.8 × 10^{−2} s^{−1}), and is therefore rate-limiting. Similar burst kinetics and rate determining turnover were exhibited by the *o*-iodosobenzoate entity when it was bound to an alkylammonium ion surfactant, but *k*_{turn} was *ca.* 100 times greater under the more nearly homogeneous, micellar conditions.²

Initial experiments demonstrate that the silica reagent (4) is very active against the nerve agent soman (GD) (3). For example τ_{1/2} for the OH[−] mediated hydrolysis of (3) in 0.05 M pH 8 phosphate buffer alone is 67 ± 0.5 min (as followed continuously with a fluoride-sensitive electrode).⁶ This is reduced to 4.2 min when 5 μmol of (3) is cleaved by 100 mg of (4) (10 μequiv. of I=O) under comparable conditions. The silica reagent (4) is *ca.* 4 times more reactive against soman than our polymer-iodosobenzoate reagents (τ_{1/2} *ca.* 18.1 min) under comparable conditions.⁶

Silica-bound *o*-iodosobenzoate reagents (4) and (5) are good catalysts for the cleavage of the phosphates (2) or (3). Under heterogeneous conditions of (10-fold) excess catalyst, they cleave (2) with ‘second order’ rate constants of *ca.* 40 M^{−1} s^{−1} (*i.e.*, *k*_w/mequiv. I=O/ml of buffer), which is *ca.* 2–8 times faster than our polymeric iodosobenzoate catalysts,⁶ although still some 16 times slower than aqueous micellar solutions of 1 × 10^{−4} M (1) in 1 × 10^{−3} M cetyltrimethylammonium chloride (*k*₂ *ca.* 645 M^{−1} s^{−1}).¹ Their ease of preparation and handling, together with their simplicity of use and effectiveness, indicates considerable potential for silica-bound iodosobenzoate reagents as toxic phosphate decontaminants.

† Reproducibilities were ± 0.001 s^{−1} in duplicate experiments. The cited rate constants represent our most reactive preparations. Other batches of reagent (4), for example, gave *k*_w = 0.012 and 0.014 s^{−1}; the latter was used in the soman reaction described below.

* This material was characterized by an appropriate 200 MHz ¹H n.m.r. spectrum and C, H, N microanalysis.

Acknowledgements

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