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Toward a Broad Spectrum Decontaminant for Reactive Toxic Phosphates/Phosphonates: N-Alkyl-3-Iodosopyridinium-4-Carboxylates

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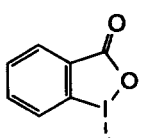
Abstract: N-n-hexadecyl-3-iodosopyridinium-4-carboxylate has pK_a<5.0, and, in comicellar aqueous cetyltrimethylammonium chloride, rapidly cleaves p-nitrophenyldiphenyl phosphate in acidic solution.

O-Iodosobenzoate, in its closed 1-oxido-1,2-benziodoxolin-3-one valence tautomeric form (**1**), is a potent O-nucleophile for the cleavage and decontamination of reactive phosphates (e.g., p-nitrophenyldiphenyl phosphate, PNPDPP, **2**)[1] and phosphonate nerve agents such as soman (**3**).[2] Expression of the nucleophilicity of **1** (and its analogues)[3] requires their deprotonated, conjugate base forms. As their pK_a's in cationic micellar solution are generally greater than 7.1,[1,3] it follows that their nucleophilicity will be suppressed upon protonation in acidic solution. More specifically, **1** will be inactive under the acidic conditions required for the oxidative decontamination of the nerve agent VX (**4**),[4,5] so that multiple nerve agents (e.g., **3** and **4**) could not be simultaneously decontaminated by a mixture of **1** and oxidants that are effective against VX (e.g., m-chloroperbenzoic acid in aqueous t-butanol [4,5]).

Now we report the preparation and anti-PNPDPP kinetic properties of N-alkyliodosopyridinium carboxylates that feature pK_a's<5, and express remarkable nucleophilic reactivity in acidic aqueous solutions.

Three pyridinium iodosocarboxylates were synthesized as illustrated in the reaction scheme. Thus, 3-iodo-4-picolinic acid, **8**, was prepared from 3,4-pyridinedicarboxylic acid (**5**, Aldrich) by dehydration to the anhydride and conversion to imide **6**,[6,7] Hofmann degradation of **6** to 3-amino-4-picolinic acid (**7**), [6-8] and diazotization and reaction with KI.[6] Alkylations of **8** were then carried out with n-hexadecyl, n-dodecyl, or n-octyl iodides in THF, affording the appropriate pyridinium iodides (**9a**) as bright yellow solids.[9] These were ion exchanged to the corresponding chloride salts (**9b**) with Dowex 1-X8 (Cl^- form, aq. EtOH, 25°C, 12 h, 3x, HCl precipitation). The N-alkylpyridinium chlorides (**9b**) were each fully characterized by IR and NMR spectroscopy, and elemental analysis (C, H, I). Finally, they were oxidized to the desired N-alkyl-3-iodosopyridinium-4-carboxylates (**10a-c**) by fuming HNO_3 in trifluoroacetic anhydride,[10] followed by hydrolysis with saturated aqueous $NaHCO_3$. Compounds **10a-c** were isolated as yellow solids from the bicarbonate solution, and are most reasonably formulated as zwitterions; they gave appropriate NMR spectra (DMSO-d_6) and 103-105% of iodoso activity by iodometric titration.[11]



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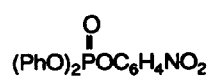

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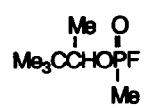

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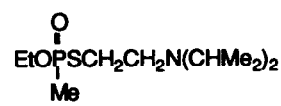

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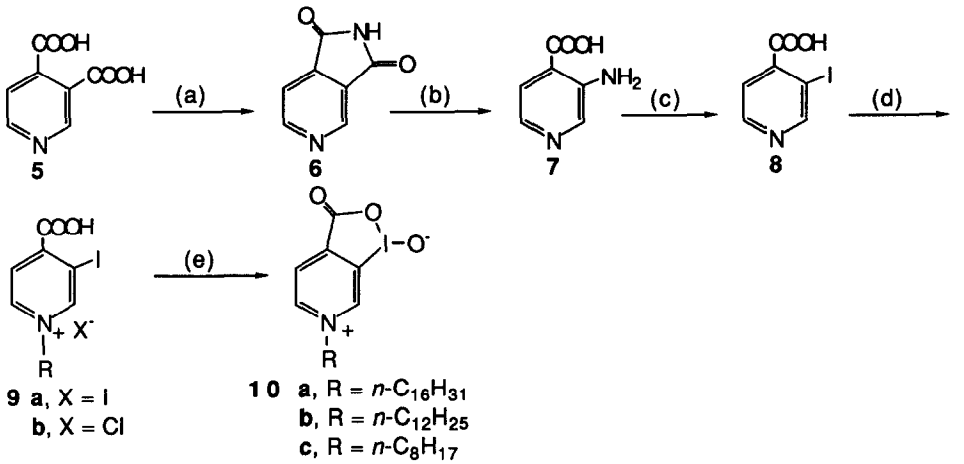

Reagents and conditions. (a) 1. Ac_2O, refl. 2. $MeCONH_2$, refl., 72%. (b) Br_2, aq. NaOH, 80°C, 69%. (c) 1. H^+, $NaNO_2$, 0°C. 2. KI, 50-60°C, 40%. (d) RI, THF, 80-90°C, 7 d, 20-30%. (e) 1. Fuming HNO_3, $(CF_3CO)_2O$, -30°C; 2 h at 25°C. 2. Satd. aq. $NaHCO_3$, 60-88%.

The pK_a's of **10a** and **10b** were determined from pH-rate constant profiles or classical titration curves. For example, pseudo-first-order rate constants were measured for the cleavage of $1x10^{-5}$ M PNPDPP by $1x10^{-4}$ M **10a** in $5x10^{-4}$ M comicellar cetyltrimethylammonium chloride (CTACl) and 0.01 M aqueous buffers at pH 4.17-5.81 (acetate), 6.11-7.02 (Bis-Tris), and 7.20-8.30 (Tris), with the release of p-nitrophenylate followed at either 400 nm (pH>6.1) or 320 nm (pH<6.1). A plot of log k_ψ vs pH (Figure 1) is quite linear above pH~5, but exhibits a sharp discontinuity at pH 4.85, which we take as the systemic pK_a of **10a** under our micellar conditions.[12] Classical NaOH titration curves for **10a** (or **10b**) gave pK_a's of 4.2-4.3 in aqueous CTACl.

The low pK_a means that at pH 8, **10a** is effectively 100% ionized to its reactive conjugate base; even at pH 5.4 (see below), it will be >78% ionized (taking $pK_a = 4.85$). The low pK_a's of reagents **10** reflect their "internal" positively charged nitrogen, and the "external" aggregate positive charge on the CTACl micelles.

Reactivities of the new iodosocarboxylates were first evaluated at pH 8.0 from full rate constant - [CTACl] profiles for the CTACl comicellar hydrolyses of $1x10^{-5}$ M PNPDPP by $1x10^{-4}$ M **10a-c** at 25°C in 0.01 M Tris buffer,[13] μ=0.01(KCl). The results appear in Figure 2, where k_ψ is plotted against [CTACl]. Typical[14] micelle-catalyzed rate enhancements are observed with maximum k_ψ values of 0.18 s^{-1} (**10a**); 0.071 s^{-1} (**10b**); and 0.0038 s^{-1} (**10c**). The latter is not shown. Reagents **10a** and **10b** reach their maxima at [CTACl] = $1x10^{-4}$ M or $5x10^{-4}$ M, respectively, and the longer chain reagent is the more potent kinetically. In the absence of CTACl, but under otherwise identical conditions, k_ψ was 0.10 s^{-1} for $1x10^{-4}$ M (micellar) **10a**. Clearly, the reactivities of **10a** and **10b** toward PNPDPP at pH 8 compare very favorably with that of **1** (k_ψ^{max} = 0.064 s^{-1}).[1b] Indeed, k_{cat} (=k_ψ/[reagent]) is ~1770 M^{-1} s^{-1} for **10a**/CTACl/Tris compared to 760 M^{-1} s^{-1} for **1**/CTACl/phosphate.

Most importantly, a rate constant - [CTACl] profile (not shown) for **10a** and PNPDPP in 0.01 M acetate buffer, μ = 0.01 (KCl) at pH 5.43 (other conditions as above) gave k_ψ^{max} = 0.13 s^{-1} at [CTACl] = $2.5x10^{-4}$ M.

Correction for 78% ionization of **10a** at pH 5.4, leads to 0.17 s^{-1} at 100% ionization, comparable to the rate constant at pH 8. Thus, **10a** is an effective phosphorolytic reagent in moderately acidic solution, where the reactivity of iodosobenzoate (pK_a 7.25[1b]) is suppressed.

Moreover, **10a** is catalytic in the cleavage of PNPDPP under both basic and acidic conditions. At pH 8, $1x10^{-4}$ M **10a** in $5x10^{-4}$ M CTACl cleaves $2x10^{-4}$ M PNPDPP (PNPDPP:**10a** = 2:1) with k_ψ = 0.05 s^{-1} with turnover and without noticeable "burst kinetics." In acid, at pH 5.43, $1x10^{-4}$ M **10a** in $1x10^{-3}$ M CTACl cleaves $2x10^{-4}$ M PNPDPP with k_ψ = 0.033 s^{-1}, again with turnover.[15] Under basic conditions, OH^- ions bound to the surface of the cationic micelles are responsible for cleavage of the intermediate phosphorylated iodosocarboxylate catalysts,[16] but it is presently unclear what mechanism controls turnover in acidic media. We hope to independently prepare examples of phosphorylated **10** to elucidate this problem.

The discovery that iodosopyridinium carboxylates efficiently cleave a reactive phosphate under acidic conditions means that a mixture of these reagents and certain oxidants [4,5] might well constitute an effective, broad-spectrum decontaminant for multiple nerve agent targets, exemplified by **3** and **4**. In view of the serious decontamination problems arising from huge, unwanted stockpiles of nerve agents, here and abroad,[17] reagents **10** are of practical significance.

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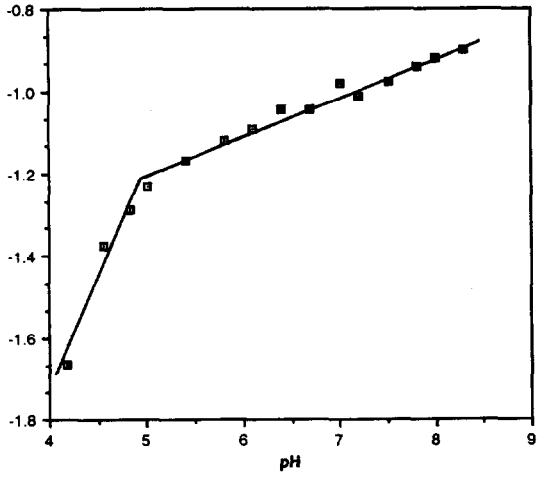

Figure 1. pH rate profile for the cleavage of PNPDPP by **10a** in CTACl; see text for conditions. The discontinuity at pH 4.85 is taken as the pK_a of **10a**.

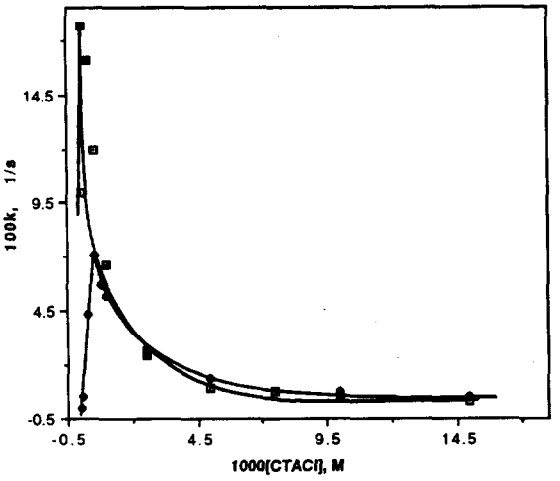

Figure 2. Pseudo-first-order rate constants (s^{-1}) for the cleavage of PNPDPP by **10a** (□) and **10b** (◆) in aq. CTACl at pH 8 as a function of [CTACl].

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