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Bis(dialkylamide)hydrogen Dibromobromate Precursors of Hypobromite Ion in Reactions with Nerve and Blister Agent Simulants

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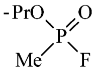
Hypobromite ion, BrO^-, is an effective α-nucleophile that reacts rapidly with activated phosphorus(V) and sulfonate esters. The parent acid rapidly oxidizes organic sulfides and aryloxide ions. At pH 10−11 BrO^- and HOBr coexist in water and are potentially useful as decontaminants of chlorosulfide blister agents and the phosphonyl nerve agents. Bis(dialkylamide)hydrogen dibromobromates are well characterized, stable, solids which rapidly form $HOBr-BrO^-$ in mildly alkaline water. Reactions of 4-nitrophenyl diethyl phosphate and phosphonate, which are simulants of the phosphonofluoridate nerve agents, and of 4-nitrophenyl tosylate, with BrO^- are rapid ($t_{1/2} = 60-700$ s) with 0.1 M BrO^-, under conditions in which oxidations of organic sulfides are too fast to be followed by conventional methods.

Introduction

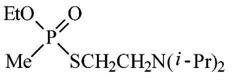
Current methods for the decontamination of chemical agents generally involve very aggressive reagents, e.g., concentrated NaOH in organic solvents reacts with HD, Mustard, in an E2 reaction, and nucleophilically with the phosphonyl nerve agents, e.g., GB (Sarin) or VX.[1] Concentrated hypochlorite, Bleach, oxidizes the sulfur compounds and reacts nucleophilically with the fluoridates.[1−3] Other, and milder, reagents, e.g., HSO_5^-, as OXONE, are excellent oxidants,[1] but ineffective nucleophiles, or are good nucleophiles, e.g., iodoso- or iodoxybenzoates,[4] or oximates, but are of limited value as oxidants. Another approach is to activate H_2O_2 as an oxidant, e.g., by forming peroxocarbonate ion,[5] or a peroxomolybdate,[6] at a pH such that nucleophilic HO_2^- is present.

$(ClCH_2CH_2)_2S$

HD



GB



VX

Hypobromite ion is a potentially useful decontaminant because it readily oxidizes sulfides and is an effective α-nucleophile. It forms in mildly alkaline bromine water, but then is unstable and not practically useful as a decontaminant, although it is convenient for use in a laboratory. However, a number of relatively stable derivatives have been examined which rapidly form BrO^- in mildly alkaline water. Structures of many crystalline derivatives are known.[7−9] Counterions in these tribromide, or dibromobromate salts in the IUPAC nomenclature, can be bulky, hydrophobic, quaternary ammonium ions which can form association colloids, micelles or microemulsions, and may be useful as decontaminants. A variety of relatively stable carriers of bromine in various states of oxidation are known and some are useful in syntheses.

In the present work we use bis(dialkylamide)hydrogen dibromobromates as sources of BrO^-, and show that rates of dephosphorylation are similar with BrO^- generated from these complexes or from Br_2-H_2O. These complexes are crystalline solids, and stable indefinitely while dry. Short time contact with dry skin causes no problems and the relatively low volatility means that mucous surfaces are not attacked.

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(1) (a) Yang, Y.-C.; Baker, J. A.; Ward, J. R. *Chem. Rev.* **1992**, *92*, 1729−1743. (b) Dagani, R. *Chem. Eng. News* **1999**, *77* (27), 20−32.

(2) Epstein, J.; Bauer, V. E.; Saxe, M.; Demek, M. M. *J. Am. Chem. Soc.* **1956**, *78*, 4068−4071.

(3) (a) Menger, F. M.; Rourk, M. J. *Langmuir* **1999**, *15*, 309−313. (b) Gonzaga, F.; Perez, E.; Rico-Lattes, L.; Lattes, A. *New J. Chem.* **2001**, *25*, 151−155.

(4) Morales-Rojas, H.; Moss, R. A. *Chem. Rev*. **2002,** *102*, 249−2521 and references cited therein.

(5) Richardson, D. E.; Yao, H.; Frank, K. M.; Bennett, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1729−1739 and references cited therein.

(6) (a) Wagner, G. W.; Procell, L. R.; Yang, Y.-C.; Bunton, C. A. *Langmuir* **2001**, *17*, 4809−4811. (b) Chiarini, M.; Gillitt, N. D.; Bunton, C. A. *Langmuir* **2002**, *18*, 3836−3842.

(7) (a) Fournier, M.; Fournier, F.; Berthelot, J. *Bull. Soc. Chim. Belg.* **1984**, *93*, 157−158. (b) Okamoto, T.; Kakinami, T.; Fujimoto, M.; Kajigayeshi, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2566−2568.

(8) Rodygin, M. Y.; Mikhailov, V. A.; Savelova, V. A.; Chernovol, P. A. *J. Org. Chem. U.S.S.R.* (*Engl. Transl.*) **1992**, *28*, 1543−1544.

(9) Mikhailov, V. A.; Yufit, D. S.; Struchkov, Yu. T. *J. Gen. Chem. U.S.S.R.* (*Engl. Transl.*) **1992**, *62*, 322−327.

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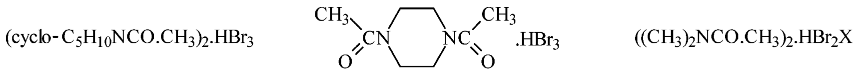
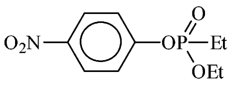
CHART 1

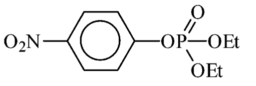


1 **2** **3, X=Br; 4, X=Cl**

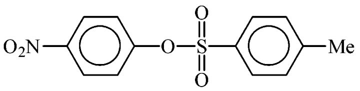
Structures of the dibromobromates (**1**−**3**) and a mixed bromochlorobromate (**4**) are shown in Chart 1. The 4-nitrophenyl esters used as simulants of phosphonofluoridates are



NPDEPN



NPDEP



NPOTos

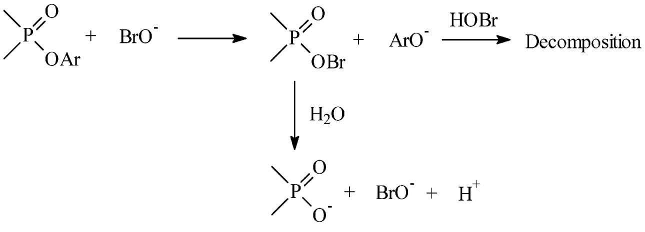
Results and Discussion

Compounds **1**, **2**, and **3** are known to form as red oils when the amide is added to cooled Br_2−HBr.[9] Crystals which form from the oil were separated and air-dried. The crude product is suitable for preparative work but can be recrystallized from MeOH. The bromochlorobromate, **4**, was prepared similarly, but with a mixture of HCl and Br_2. Details and properties are in the Experimental Section.

Kinetics. Reactions were followed spectrophotometrically from the increasing absorbance at 400−440 nm at 25.0 °C in water, with ca. 3×10^{-5} M substrate and a large excess of nucleophile. The pH was controlled with phosphate buffer, but, except as noted, pH control is not critical. Reaction was started by adding the substrate in dioxane (0.5 vol %) and the ionic strength was maintained with 1.0 M KCl.

Overall Reaction. Nucleophilic substitutions at phosphorus(V) and sulfonyl centers by ClO^- [2,10] and BrO^- are turnover reactions at higher pH (Scheme 1, for a phosphorus(V) center)

SCHEME 1



Decompositions of aryloxide ions, or organic sulfides, by the hypohalite or the intermediate phosphorylated hypohalite[1,10] deplete the hypohalite and turnover will not be observed in some practical conditions. Oxidations of organic sulfides (diethyl sulfide and thianisole) in solutions of the dibromobromate complexes are too fast to be followed by conventional spectrophotometry at the pH used in the present work.

Effect of pH. The pK_a of HOBr is 8.69[11] and reactions were generally followed at pH ca. 11, which gave extensive or complete dissociation of HOBr. However, as the pH is decreased, decomposition of the phenoxide ion cannot by neglected and absorbance at 420 nm goes through maxima with time (Figure 1). There is also a contribution of reaction with OH^- at higher pH.

The maximum absorbance and its positions on plots of absorbance against time depend on pH and on the concentration and reactivity of the substrate toward BrO^-, as shown by comparison of time scales for reactions of NPDEPN and the less reactive NPDEP. At relatively low pH 4-nitrophenoxide ion is decomposed as rapidly as it is formed from the ester, as for the relatively unreactive NPDEP (Figure 1B). For reaction with 7.5×10^{-5} M NPDEPN (Figure 1A) the initial formation of 4-nitrophenoxide ion is sufficiently fast for the absorbance to increase sharply within the time required for the initial measurement, and then to decrease as 4-nitrophenoxide ion is decomposed. We did not see this behavior with more dilute NPDEPN, or with NPDEP, which is significantly less reactive toward BrO^- than NPDEPN.[10]

The observed first-order rate constants, k_{obs}, for conditions in which oxidation is unimportant are given in Tables S1−S4 (Supporting Information) and fit eq 1

$$k_{obs} = k_{H_2O} + k_{OH}[OH^-] + k_{BrO}[BrO^-] \qquad (1)$$

In eq 1 k_{H_2O} is very small relative to the other terms, but the reaction with OH^- cannot be neglected at high pH and the correction is based on the following second-order rate constants: k_{OH} (M^{-1} s^{-1}) = 0.15 (NPDEPN), 0.009 (NPDEP), and 0.0087 (NPOTos). (The concentration of OH^- was calculated from the pH.) The corrected first-order rate constant, k'_{obs}, equals $k_{BrO}[BrO^-]$.

Precursors of BrO^-. Second-order rate constants, k_{BrO}, were estimated for reactions in solutions of BrO^-

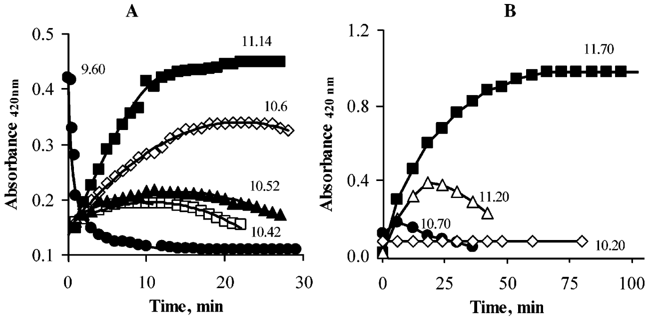


FIGURE 1. Variations of absorbance with time as a function of pH for reactions of NPDEPN (A) with 0.01 M BrO^-−HOBr and of NPDEP (B) with 0.02 M BrO^-−HOBr. In part A, [NPDEPN] = 7.5×10^{-5} M at pH 9.6 and 2.5×10^{-5} M at other pH values, and in part B [NPDEP] = 3.75×10^{-5} M. The pH is shown with each plot.

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[10] Simanenko, Y. S.; Popov, A. F.; Prokop'eva, T. M.; Karpichev, E. A.; Savelova, V. A.; Suprun, I. V.; Bunton, C. A. *Russ. J. Org. Chem.* (*Engl. Transl.*) **2002**, *38*, 1286−1298.

[11] Weast, R. C.; Astle, M. J., Eds. *Handbook of Chemistry and Physics*; CRC Press: Boca Raton, FL, 1983.

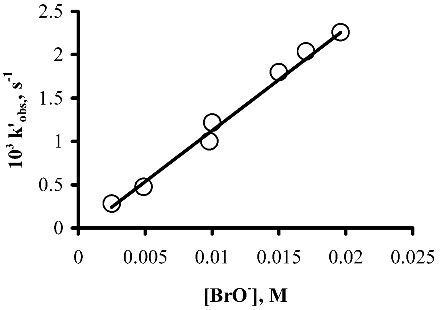

FIGURE 2. Variation of k'_{obs} for the reaction of NPDEPN with [BrO$^-$] from **1** at pH 11.35.

TABLE 1. Second-Order Rate Constants (k_{BrO^-}, M^{-1} s^{-1}) for Reaction of Hypobromite Ion at 25 °C in 1 M KCl

	reagents				
substrate	Br_2-H_2O	1	2	3	4
NPDEPN	0.16[a]	0.13[a]	0.12[b]	0.12[a]	0.12[a]
NPDEP	0.010[a]	0.010[c]		0.011[c]	0.011[c]
NPOTos	0.017[d]	0.015[e]		0.015[f]	0.015[f]

[a] pH 11.3. [b] pH 11.2. [c] pH 11.7. [d] pH 11.7 or 12.3. [e] pH 11.6. [f] pH 12.1.

generated from bromine water and from **1**−**4** as precursors. Figure 2 shows a plot of the first-order rate constants, k'_{obs} (s^{-1}), against [BrO$^-$] for the reaction of NPDEPN in solutions of **1**, with correction for the contribution of reaction with OH$^-$. Similar linear fits of k'_{obs} as a function of [BrO$^-$] were obtained for reactions of the other substrates with all the BrO$^-$ precursors. Rate constants of the reaction of BrO$^-$ formed from various precursors, and monitored at pH where decomposition could be neglected, are shown in Table 1. There are contributions from reaction with OH$^-$, especially at high pH and with dilute BrO$^-$.

The second-order rate constants are similar to those for reactions with OH$^-$, despite the large difference in basicities. There are many examples of nucleophilic attack on aryl, phosphoryl, or sulfonyl centers for which rate constants vary with basicities, following Bronsted relationships, but OH$^-$ and H_2O are typically much less reactive than expected from their basicities. There is extensive discussion on these deviations and the source of the so-called α-effect.[12,13]

The half-lives for decompositions with 0.1 M BrO$^-$ are approximately 60, 700, and 400 s for NPDEPN, NPDEP, and NPOTos, respectively, at 25 °C, and it will be easy to obtain rapid decomposition of agents by going to higher concentrations of the precursors.

Conclusions

The dibromobromate derivatives, **1**−**3**, and the bromochlorobromate derivative, **4**, are potentially useful sources of hypobromite ion, which is an effective α-nucleophile and reacts very rapidly with 4-nitrophenyl phosphates and phosphonates which are widely used as simulants for the phosphonofluoridate nerve agents. The active nucleophile is BrO$^-$, which forms very rapidly when **1**−**4** are dissolved in water, and reactivities are independent of the structures of the precursors. At pH ca. 10 there is nucleophilic attack on phosphorus and oxidation of phenoxide ions and organic sulfides, and these dibromobromates, or the bromochloro derivative, are stable solids which should be potentially useful in the development of relatively mild, wide-spectrum, decontaminants, and in preparative chemistry. As for reactions of ClO$^-$ with phosphonofluoridates, the corresponding reactions with BrO$^-$ are turnover processes,[2] but reactions with sulfur compounds, HD and VX, will be stoichiometric.

Experimental Section

Materials. The nitrophenyl derivatives, NPDEPN and NPOTos, were prepared from 4-nitrophenol and the acid chloride in anhydrous dioxane/Et_3N[10] and NPDEP was a commercial sample (Aldrich) or was prepared as above: NPOTos was recrystallized (EtOH) and NPDEP and NPDEPN were vacuum distilled.

The dibromobromates, **1**, **2** and **3**, have been described earlier[8] and were prepared by the general method for the preparation of **3**.[8] *N,N*-Dimethylacetamide (3.0 mol, 275 mL) was added with continuous stirring to a mixture of water-cooled bromine (1.5 mol, 241 g) and 40% HBr (1.5 mol, 220 mL). The viscous red liquid crystallized with stirring and the crystals were removed by filtration and air-dried. The product was recrystallized, MeOH, with minimum heating, and can be vacuum distilled by using a short path and a N_2 trap. Physical properties, mp 81−83 °C, and ^{1}H and ^{13}C NMR spectra agreed with the literature.[8,9] The crystal structure is available in the Cambridge Structural Database (SEGMOG, SEGMOG 01).

Bis(*N*-acetylpiperidine)hydrogen dibromobromate (**1**, mp 81−83 °C) and diacetylpiperazinehydrogen dibromobromate (**2**, mp 183−184 °C) were prepared as described above.[8]

Bis(*N,N*-dimethylacetamide)hydrogen bromochlorobromate, **4**, was prepared as described above,[8] but from bromine (54 mmol 2.8 mL), 28% HCl (54 mmol, 6.1 mL), and *N,N*-dimethylacetamide (108 mmol, 10 mL). The yellow-orange precipitate was recrystallized, MeOH (mp 80−82 °C).[8]

Inorganic materials were commercial samples of the highest purity available.

Kinetics. Reactions were followed spectrophotometrically at 400−440 nm, with freshly prepared aqueous solutions. The pH was adjusted by using 0.01−0.05 M phosphate buffer and KOH, and the ionic strength was 1.0 (KCl). Changes in [buffer] did not affect k_{obs}.

All reactions were followed at 25 °C and hypobromite concentrations were determined immediately before adding the substrates in dioxane to the reaction solution. Substrate concentrations were generally ca. 3 × 10^{-5} M and reaction solutions contained 0.5 vol % of dioxane. Integrated first-order kinetic plots were linear for up to 5 half-lives at the pH used in following the nucleophilic reactions, and deviations from first-order kinetics observed as the pH was decreased (Figure 1) are due to decomposition of 4-nitrophenoxide ion, as for reactions with hypochlorite ion.[10]

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Supporting Information Available: Tables S1 and S2 which show rate and pH data for NPDEPN and Tables S3 and S4 which show data for NPDEP and NPOTos, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962,** *84*, 16−24. (b) Colthurst, M. J.; Kanagasooriam, J. S. S.; Wong, M. S. O.; Contini, C.; Williams, A. *Can. J. Chem.* **1998**, *76*, 678−685. (c) Um, I.-H.; Buncel, E. *J. Am. Chem. Soc.* **2001**, *123*, 11111−11112.

(13) Pross, A.; Shaik, S. S. *New J. Chem.* **1989**, *13*, 427−433.