## A Phosphorylated Iodosobenzoate: The Intermediate in the Iodosobenzoate Cleavage of a Reactive Phosphate

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During the past decade,1 iodosobenzoic acid (IBA), 1, has become the premier reagent for the rapid, catalytic cleavage of reactive esters and phosphates.<sup>2</sup> Its easy availability, utility in



dilute aqueous micellar base, and demonstrated activity against several nerve agents<sup>3</sup> have stimulated studies of IBA analogues,<sup>4</sup> as well as varied modalities for IBA delivery, including micelles, 1,2,5 liquid crystals,6 cationic latex dispersions,7 microemulsions,8 and IBA immobilized on solid supports.9

Despite intensive development, key mechanistic details of IBA's catalytic and hydrolytic function remain obscure. A likely scenario for the cleavage of a typical substrate, p-nitrophenyl diphenyl phosphate (PNPDPP), is shown in eq 1.5a No evidence

$$\begin{array}{c} & \bigcap_{i=1}^{O} & \bigcap_{i=1}^{O} & PNPO' \\ 1 & O_{i} & (PNPDPP) \end{array} \xrightarrow{PNPO'} & O_{i} & O_{i} & O_{i} & O_{i} \\ 2 & O_{i} & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} & O_{i} & O_{i} & O_{i} \\ 0 & O_{i} \\ 0 & O_{i} & O_{i} \\ 0$$

for the existence of the putative phosphorylated IBA intermediate, 2, has yet been obtained. In the parallel cleavage of p-nitrophenyl acetate by IBA in DMSO, the formation and decay of the acetyl analogue, 3, can be visualized by <sup>1</sup>H NMR.<sup>10</sup> Although



acetoxyiodinane 3 can be directly prepared by the reaction of

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## Scheme 1



IBA and acetic anhydride,<sup>10,11</sup> previous attempts to prepare 2 have provided only 4,<sup>11</sup> the anhydride of IBA<sup>5a</sup> (see below).

Here, we describe the first successful generation of (phosphoryloxy)iodinane 2 and its ready derivatization by phosphate displacement at iodine with a variety of O-nucleophiles. The extraordinary ease of these reactions explains our inability to visualize 2 in previous attempts.<sup>5a</sup>

Reaction of 1-chloro-1,2-benziodoxolin-3-one<sup>12</sup> with silver diphenyl phosphate,<sup>13</sup> each 0.084 M in 1 mL of DMSO- $d_6$ , afforded AgCl and a solution that revealed comparably intense <sup>31</sup>P NMR singlets at  $\delta$  -10.04 and -10.9 to -11.1;<sup>14</sup> see eq 2. The

$$\begin{array}{c} & & & \\ &$$

signal at  $\sim \delta - 11$  is due to diphenyl phosphate-diphenyl phosphoric acid [HOP(O)(OPh)<sub>2</sub>], as demonstrated by NMR spiking experiments,<sup>15</sup> whereas the resonance at  $\delta$  –10.04 is assigned to the desired iodosobenzoate-diphenyl phosphate ester, 2, on the basis of chemical quenching experiments (see below).

Iodoso phosphate 2 is extremely sensitive to adventitious water, and diphenyl phosphate always accompanies its preparation; deliberate addition of traces of  $D_2O$  to DMSO- $d_6$  preparations of 2 increases diphenyl phosphoric acid ( $\delta$  -10.9 to -11.1) at the expense of 2 ( $\delta$  -10.04). In the absence of added water, 2 is reasonably stable in DMSO; the intensity of its NMR signal decreases about 12% in 30 min and about 67% in 5 h, so that reactions between 2 and added nucleophiles can be readily monitored. A series of such reactions appears in Scheme 1.

For each freshly prepared DMSO- $d_6$  solution of 2, addition of excess nucleophile completely destroyed the phosphate ester (<sup>31</sup>P NMR), with the simultaneous formation of the appropriate product (1, 3-6) and diphenyl phosphate (diphenyl phosphoric acid).16

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(14) <sup>31</sup>P NMR spectra were determined at 81 MHz and are reported relative to an external standard of 85% H<sub>3</sub>PO<sub>4</sub> in DMSO-d<sub>6</sub>. Samples were prepared in a drybox. Unless otherwise noted, all chemical shifts refer to <sup>31</sup>P.

(15) Pure silver diphenyl phosphate in DMSO- $d_6$  exhibits  $\delta$  -9.22, while  $(PhO)_2 P(O)OH$  is found at  $\delta - 11.22$ . Mixtures afford composition-dependent, averaged single signals between these limits.

(16) The corresponding <sup>31</sup>P NMR signal appeared as a singlet between  $\delta$ -10.57 and -11.29, depending on the presence of added water and cations, and the diphenyl phosphate/diphenyl phosphoric acid balance.

These reactions were complete within the requisite manipulation time of the NMR experiments ( $\sim 3$  min).

Reaction of 2 with excess MeOH gave diphenyl phosphoric acid ( $\delta$ -11.20) and the methoxyiodoxolinone 5, identified by its <sup>1</sup>H NMR singlet at  $\delta$  4.16 and by NMR spiking experiments with an authentic sample.<sup>10,11</sup>

When 2 was reacted with either water or  $5 \times 10^{-3}$  N aqueous HCl, diphenyl phosphoric acid ( $\delta$  -11.24) and IBA (1) were formed. The latter was clearly identified by the distinctive <sup>1</sup>H NMR pattern of its aromatic protons. Note that the rapid destruction of 2 under acidic conditions agrees with our observation of fast turnover for a pyridinium iodosocarboxylate analogue of 2 at pH 5.4.17

The reaction of 2 with excess glacial HOAc gave diphenyl phosphoric acid ( $\delta$  –11.20) and 1-acetoxy-1,2-benziodoxolin-3one (3), identified by its <sup>1</sup>H NMR methyl signal at  $\delta$  2.26<sup>10</sup> and by NMR spiking experiments with an authentic sample.<sup>10,11</sup>

Reaction with excess NaIBA converted 2 to anhydride 4, which was isolated by centrifugation and identified by FTIR comparison with an authentic sample.<sup>10,11</sup> In addition, the formation of diphenyl phosphate ( $\delta$  -10.57) was observed.<sup>16,18</sup>

Quenching the DMSO- $d_6$  solution of 2 with 20  $\mu$ L of (Aldrich) 5.0-6.0 M tert-butyl hydroperoxide in 2,2,4-trimethylpentane (~20-50% excess) gave diphenyl phosphoric acid ( $\delta$  -11.19) and the (tert-butyldioxy)iodinane 6. The identity of 6 followed from its <sup>1</sup>H NMR *t*-Bu resonance ( $\delta$  1.28) and TLC behavior  $(R_f = 0.60; SiO_2, 2:1 CH_2Cl_2/Et_2O)$ , both identical to those of an authentic sample.19

The <sup>31</sup>P NMR and chemical quenching results leave little doubt that the carrier of the  $\delta$  -10.04 resonance, formed as in eq 2, and rapidly destroyed by each of the reactions in Scheme 1, is indeed

(phosphoryloxy)iodinane 2.20 Note that the reactions of Scheme 1 involve nucleophilic attack at iodine.<sup>21</sup> Acyloxy and (phosphoryloxy)iodinanes such as 3 and 2 are subject to nucleophilic attack at I with the formation of hypervalent 12-I-4 intemediates,<sup>10,22</sup> e.g., 7, that subsequently lose acetate or diphenyl phosphate. The latter is the better leaving group, so that acetate 3 is less reactive and less rapidly destroyed by nucleophiles than phosphate 2.23 Therefore, 3 builds up and can be observed when IBA cleaves *p*-nitrophenyl acetate in DMSO.<sup>10</sup>

However, when NaIBA is reacted with PNPDPP under similar conditions, we find only sodium diphenyl phosphate ( $\delta$  -10.54) and iodoso anhydride 4; 2 is not observed after the manipulation time. Clearly, 2 cannot long survive in the presence of a nucleophile, in this case, IBA. IBA destroys 2 more rapidly than it cleaves PNPDPP, so that the preparation of 2 can succeed only when the reagent combination is made as non-nucleophilic as possible, as in eq 2.

With the preparation of 2, we are now in a position to study the generation of other highly reactive and labile iodinanes. These experiments are in progress.

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determining in IBA catalytic turnover.

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<sup>(18)</sup> Note that the ionization of phosphoric acid derivatives often produces downfield shifts in the <sup>31</sup>P NMR resonance; cf.: Gorenstein, D. G. Phosphorus-31 NMR Principles and Applications; Academic Press: New York, 1984; p 10 f.

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<sup>(20)</sup> Alkyl or any phosphates generally afford <sup>31</sup>P signals in the  $\delta$  0 to -50 range; the chemical shifts are a sensitive function of the O-P-O bond angles. See Gorenstein, D. G., in ref 18.

<sup>(21)</sup> The conversion of 2 to 1 could involve hydrolysis at phosphorus, but this is unlikely, on the basis of the behavior of  $3^{10}$  and the other reactions in Scheme 1