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Hydroxylamine as an oxygen nucleophile. Chemical evidence from its reaction with a phosphate triester†

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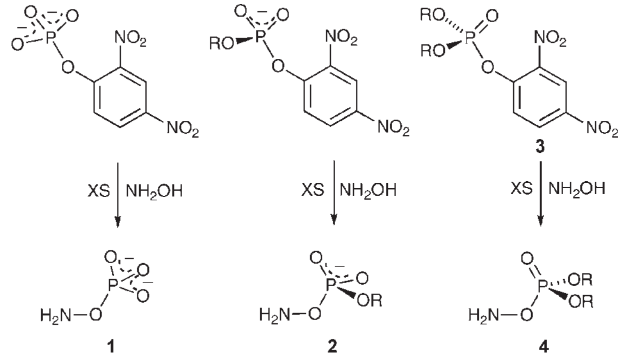
The reaction of hydroxylamine with 2,4-dinitrophenyl diethyl phosphate gives the *O*-phosphorylated product, which is rapidly converted to hydrazine and nitrogen gas in the presence of the excess of hydroxylamine.

We have been interested in recent years in the reactions of phosphate esters with α-effect nucleophiles, and particularly with hydroxylamine. Hydroxylamine is a unique, ambident α-effect nucleophile, readily alkylated on nitrogen but often acylated[1,2] and generally phosphorylated[3] on oxygen, with reaction through oxygen favored for harder electrophiles. *N*-Alkylated hydroxylamines show similar enhanced reactivity, but NH_2OMe, which cannot react through oxygen, is typically less reactive toward phosphorus.[4,5] The products of phosphorylation by reactive phosphate mono- and diesters are presumed to be the hydroxylamine-*O*-phosphates **1** and **2** (Scheme 1), though often these structures are based on little more than argument by analogy. Following the reaction by ^{31}P NMR shows clearly that hydroxylamine is phosphorylated,[3,6] but not obviously whether phosphorylation is on N or O: chemical shift arguments are typically inconclusive.

The question of product structure came to a head in our recent work on the reactions of NH_2OH, typically in large excess in aqueous solution, with activated phosphate triesters **3**. We use the reaction with 2,4-dinitrophenyl diethyl phosphate (**3**, R = Et) as a simple example. As expected, the reaction with the triester is faster than those with the mono- and diesters, but the only phosphorus-containing product detected by ^{31}P NMR turned out to be not the hydroxylamine-*O*-phosphate **4** (R = Et) but diethyl phosphate (Scheme 2). Careful analysis showed that nitrogen was evolved during the reaction, and hydrazine was detected as a second nitrogen-containing product by its reaction with *p*-(dimethylamino)benzaldehyde to give the hydrazone (see ESI†). This is the product combination expected from the disproportionation of diazene (diimide) **5**,[7] suggesting that the *O*-phosphorylated derivative **4** derived from the triester has reacted with the hydroxylamine free base present in solution, as shown in Scheme 2.

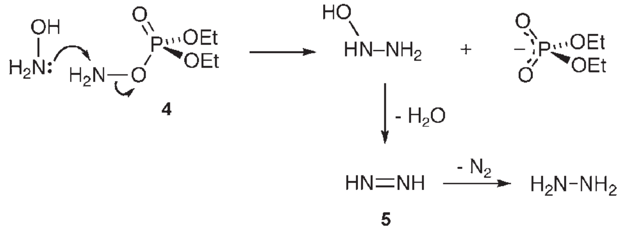


Scheme 1 Hydroxylamines are generally phosphorylated on oxygen. Mono-, di- and triesters are expected to give the hydroxylamine-*O*-phosphate esters **1**, **2** and **4**, respectively.

A standard test for the identification of diimide as an intermediate is its powerful reducing potential.[9,10] When the reaction of hydroxylamine with the triester described above is carried out under the same conditions, but in the presence of fumaric acid, we find that hydrazine is no longer produced, the yield of nitrogen essentially doubles, and fumarate is reduced quantitatively to succinate (see ESI†).

The higher reactivity of **4** (Scheme 2) compared with that of the *O*-phosphorylated products **1** and **2** from the reactions with mono- and diesters is simply explained, since leaving group ability (as measured by the pK_a of the conjugate acid) increases significantly in the series **1** → **2** → **4**.

This sequence of reactions provides clear evidence that the reaction of hydroxylamine with this representative triester gives initially the *O*-phosphorylated derivative **4**, consistent



Scheme 2 Suggested mechanism for the decomposition of **4** in the presence of an excess of hydroxylamine. Diimide **5** is known to be generated from other derivatives of hydroxylamine with good leaving groups, including the *O*-sulfate.[8]

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with our previous suggestion[11] that ammonia oxide ($NH_3^+–O^−$) is a serious candidate for the active nucleophile in these reactions.

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