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Oxyonium phosphobetaines – unusually stable nucleophilic catalyst–phosphate complexes formed from *H*-phosphonates and *N*-oxides†‡

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Aryl *H*-phosphonates react with *N*-oxides to form previously unknown stable zwitterionic oxyonium phosphates comprising an $^-\text{O}-\text{P}-\text{O}-\text{N}^+\text{Z}$ atom system. Their structures were confirmed *i.e.* by X-ray crystal structure analysis, and some mechanisms were proposed for their formation. Stability during storage and reactivity toward nucleophiles points to their possible synthetic applications.

Condensation reactions leading to phosphoester bond formation are usually assisted by nucleophilic catalysts. While aromatic nitrogen heterocycles are typically used for this purpose, some heteroaromatic *O*-nucleophiles surpass them in terms of catalytic efficacy.¹ Until now, in phosphorus chemistry the use of *N*-oxides as nucleophilic catalysts was reported for P^{V} species only and was limited to heteroaromatic *N*-oxides.¹ The postulated reactive intermediates contain a $\text{P}-\text{N}^+\text{Ar}$ (for *N*-nucleophilic catalysts) or $\text{P}-\text{O}-\text{N}^+\text{Ar}$ (for *O*-nucleophilic ones) system (NAr = heteroaromatic group); however, such species were never isolated and remain elusive.

Since nucleophilic catalysis is also commonly exploited in condensations of *H*-phosphonates,² we undertook investigations on usefulness of *N*-oxides in these reactions. Apart from heteroaromatic *N*-oxides, we investigated also aliphatic *N*-oxides, since their favourable catalytic activity in *H*-phosphonate chemistry cannot be excluded *a priori*. Most apparent problems that could affect application of *N*-oxides in the *H*-phosphonate chemistry could be: a competing oxidation of *H*-phosphonates, improper balance between nucleophilicity and

nucleofugicity of some *N*-oxide catalysts, and possible reactions of *N*-oxides with condensing agents.

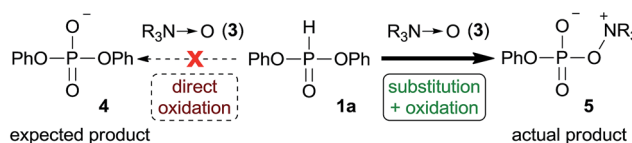
During initial experiments on the resistance of *H*-phosphonates to oxidation by *N*-oxides, we observed that diphenyl *H*-phosphonate (DPP) reacted rapidly with *N*-methylmorpholine *N*-oxide with evolution of heat, to produce virtually one product without the P–H bond and with one of the phenyl groups plausibly replaced with the *N*-oxide moiety (Scheme 1). These surprisingly stable compounds have been obtained with a number of *N*-oxides, and extensive literature search indicated that so far they have been not reported. The assumed presence of an oxyonium moiety derived from the *N*-oxide, which is in principle a good leaving group, made them promising candidates for phosphorylating agents. Novelty of the chemistry and potential applications prompted us to study this class of compounds in more detail. In particular, we were interested in susceptibility of other *H*-phosphonates to analogous reactions with *N*-oxides, development of other routes for the preparation of the new compounds (if possible), as well as structural and mechanistic studies.

Susceptibility of *H*-phosphonates to oxidation with *N*-oxides was not reported so far (in contrast to a number of phosphites and other trivalent phosphorus compounds, which are known to be readily oxidized by *N*-oxides^{3,4}). For undertaken experiments on this topic we chose four *H*-phosphonate esters [(PhO)₂P(H)O, **1a** (DPP); (EtO)₂P(H)O, **1b**; PhOP(H)O₂[−], **2a** (MPP); EtOP(H)O₂[−], **2b**], which were known to differ significantly in charge distribution and reactivity.^{5–7} As potential oxidants, 4-methoxypyridine *N*-oxide (**3a**) and *N*-methylmorpholine *N*-oxide (**3b**), were

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‡ Electronic supplementary information (ESI) available: Experimental procedures, MS and NMR spectra, X-ray crystallographic data. CCDC 1425902 for **5b** and 1425903 for **5e**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra27465f



Scheme 1 In reactions of DPP (**1a**) with *N*-oxides (**3**) phosphobetaines of type **5** are formed instead of the product of simple oxidation, diphenyl phosphate (**4**).

used as representatives of aromatic and aliphatic *N*-oxides, respectively (Scheme 2). All reactions were performed at room temperature in dichloromethane (DCM), acetonitrile or pyridine as a solvent.

Both aromatic and aliphatic *H*-phosphonate monoesters **2** appeared to be resistant to oxidation by *N*-oxides, obviously due to the negative charge. Reactivities of *H*-phosphonate diesters **1a** and **1b** were decidedly different. While diethyl ester (**1b**) did not react with *N*-oxide **3a**, and was oxidized only very slowly by **3b** (ca. 20%/3 days), diphenyl *H*-phosphonate (**1a**)⁸ reacted rapidly (the reactions were completed before the first ³¹P NMR spectrum was recorded, *i.e.*, <1 min) with both *N*-oxides. However, instead of the expected diphenyl phosphate (**4**, $\delta_{\text{P}} -11$ ppm) as the product of oxidation, other compounds were formed, showing ³¹P NMR resonances at $\delta_{\text{P}} -6.0$ ppm (the reaction of DPP with *N*-oxide **3a**) and $\delta_{\text{P}} -8.9$ ppm (the reaction of **3b**).[§] According to the lack of a one-bond P–H coupling and the region of their chemical shifts in ³¹P NMR spectra, they were tentatively assigned as phosphate esters. In follow-up experiments we observed formation of analogous (but not the same) compounds in the reaction of DPP with other *N*-oxides (4-methylpyridine *N*-oxide **3c**, 4-(*N,N*-dimethylamino)pyridine **3d**, and trimethylamine *N*-oxide **3e**), indicating that the *N*-oxide moieties were incorporated into these products. Interestingly, their signals in ³¹P NMR spectra were grouped around -9 ppm for derivatives of aliphatic *N*-oxides, and around -6 ppm for aromatic ones, *i.e.*, oppositely to the general rule that the chemical shifts of aliphatic phosphates are located downfield to those of aromatic phosphates.

The products of the reactions of aliphatic *N*-oxides had limited solubility in organic solvents and when the reaction mixtures were allowed to stand for several minutes, they precipitated spontaneously as white, microcrystalline solids. The derivatives of aromatic *N*-oxides were better soluble and their isolation required precipitation from DCM/Et₂O system.[¶] The products were analyzed by ¹H, ³¹P, and ¹³C NMR, and MS techniques (see ESI[†]), revealing the presence of one phenyl ring, one *N*-oxide moiety, and lack of counter-ions, even in the presence of pyridine or Et₃N in the reaction mixtures. According to these data, we assigned tentatively their structure as phosphobetaines of type **5** (Fig. 1).

For two betaines, **5b** and **5e**, monocystals suitable for X-ray analysis were obtained when the reaction was performed in higher dilution and the solvent was allowed to evaporate slowly (see ESI[†]). Their X-ray structures (Fig. S1 and S2[†]) confirmed unequivocally correctness of our initial assignments.[‡]

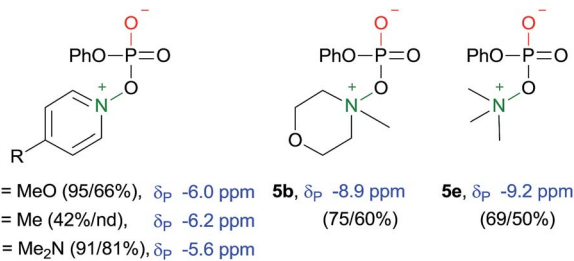
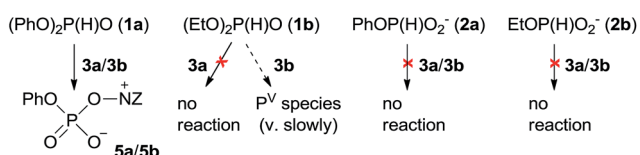


Fig. 1 Structures of betaines **5**, their ³¹P NMR/isolated yields (in parentheses) and ³¹P NMR chemical shifts in DCM solutions.

Since these are the first X-ray structures of *O*-substituted aliphatic *N*-oxides, some of their features deserve comments. Betaine **5b** crystallized in the orthorhombic space group *Pbca* with one molecule in the asymmetric unit. Compound **5e** gave monoclinic crystals in space group *P2*₁ and also with one molecule in the asymmetric unit. Only weak C–H⋯O interactions are present in the crystal scaffold, without any close contacts of molecules, *e.g.*, due to electrostatic interactions of the positive and negative charges or stacking of the aromatic rings. Conformation of the morpholine ring in **5b** is similar to that of the free *N*-oxide **3b**.⁹

The P–O₂ and N–O bonds lengths in **5b** ($d_{\text{P-O}} = 1.690$ Å and $d_{\text{N-O}} = 1.457$ Å, respectively) and in **5e** ($d_{\text{P-O}} = 1.682$ Å and $d_{\text{N-O}} = 1.445$ Å) are rather close; nevertheless, slightly longer distances in **5b** coincide with its moderately higher reactivity. Two structures of compounds with a P–O–N bonding system resembling that of the betaines **5** are known, *i.e.*, (EtO)₂P(O)–O–[N-(1,2,3-benzotriazin-4(3*H*)-one)]¹⁰ with $d_{\text{P-O}} = 1.635$ Å and $d_{\text{N-O}} = 1.360$ Å, and (NMe₂)₃P⁺–O–[N-(benzotriazole)]¹¹ with $d_{\text{P-O}} = 1.651$ Å and $d_{\text{N-O}} = 1.381$ Å. The N–O bonds in **5b/5e** are longer by ca. 0.1 Å, pointing to their possible higher lability.

As an extension of the studies on phenyl phosphobetaines **5a–e**, we investigated mixed alkyl aryl *H*-phosphonates, which were expected to react with *N*-oxides to yield corresponding aliphatic phosphobetaines. To this end, we prepared 5'-dimethoxytritylthymidin-3'-yl phenyl *H*-phosphonate (**6a**, see ESI, Scheme S1[†])⁵ and treated it *in situ* with *N*-oxide **3b** (DMF–Py 7 : 3 solvent system gave the best results). In ³¹P NMR spectra we observed an immediate disappearance of the signal of the starting material and formation of a new one at $\delta_{\text{P}} -4.2$ ppm ($^3J_{\text{PH}} = 6.4$ Hz; see ESI, Fig. S8a/b[†]). The same compound was obtained from analogous *p*-chlorophenyl and *p*-nitrophenyl 5'-*O*-DMTr-thymidin-3'-yl *H*-phosphonates (**6b/6c**),¹² indicating that in every case the aryl group was substituted with the *N*-oxide. This product was isolated by precipitation with Et₂O and its mass, ¹H and ¹³C NMR spectra confirmed the formation of the expected *N*-methylmorpholino-4-ium derivative of 5'-*O*-DMTr-thymidin-3'-yl phosphate (**5f**). We consider these results as particularly important, since they show that not only phenyl but also a variety of other phosphate esters can be obtained in the form of betaines similar to compounds **5**. In the context of possible application of the studied oxonium phosphobetaines it is worth noting that while all of them were rather inert in the presence of water and alcohols, they were found to react rapidly

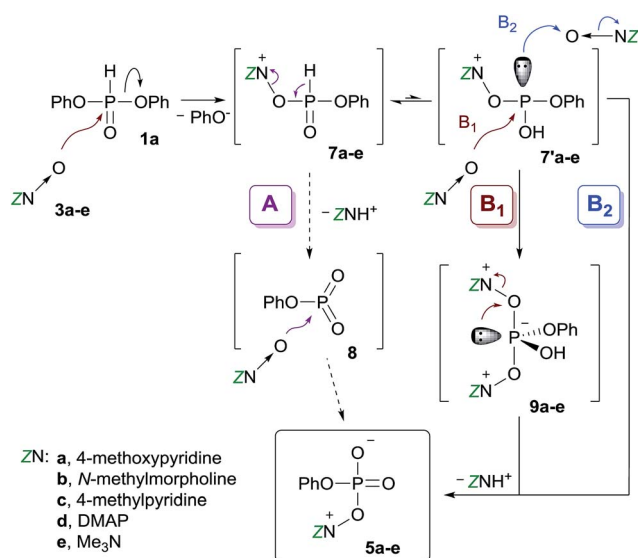


Scheme 2 Reactivities of *H*-phosphonates **1a/b** and **2a/b** with 4-methoxypyridine *N*-oxide (**3a**) and *N*-methylmorpholine *N*-oxide (**3b**).

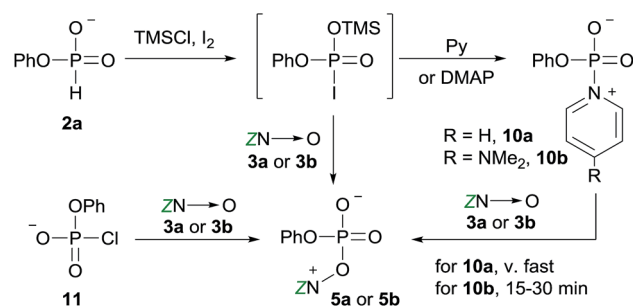
and practically quantitatively with a variety of *N*-nucleophiles, *e.g.*, BuNH₂, *i*PrNH₂, PhNH₂, NH₂NH₂, PHNHNH₂, or LiN₃ toward the respective P–N species. With phosphates they form pyrophosphates, although the yields are lower (*ca.* 80–90%). In contrast, they do not react with *H*-phosphonates.

As it was mentioned in the introduction, heteroaromatic *N*-oxides are known to be very effective nucleophilic catalysts for the conversion of phosphate diesters into triesters, in which reactive intermediates of (RO)(R'O)P(O)–O–N⁺Ar type are presumably involved.^{1c} Oxyonium betaines **5** contain the same P–O–N⁺Ar motif but they lack one of the ester groups. Plausibly, the presence of a negative charge is responsible for decreased electrophilicity at the phosphorus atom and the resulting pronounced stability. It is worth noting that while analogous phosphopyridinium zwitterionic intermediates of [–]O–P–N⁺Ar type (**9**, Scheme 4) were observed by ³¹P NMR,¹³ to the best of our knowledge the oxyonium phosphobetaines **5** reported here are the first isolated and fully characterized phosphorus species containing a residue of an assumed nucleophilic catalyst.

For the formation of betaines **5**, two mechanisms may be considered: oxidation of DPP followed by substitution or substitution followed by oxidation. The first scenario could be, however, excluded since in separate experiments we found that diphenyl phosphate **4**, *i.e.*, the postulated product of direct oxidation of DPP, did not react with *N*-oxides, and thus, could not be an intermediate in this reaction. In the second sequence of reactions (Scheme 3) the rapid initial formation of intermediate **7** is congruent with the known susceptibility of DPP to substitution,¹² and its subsequent fast oxidation toward betaine **5** can be plausibly rationalized by one of the pathways shown in Scheme 3. In the first one (**A**), oxidation takes place by a concerted breaking of P–H and O–N bonds in intermediate **7**, and formation of an extremely reactive metaphosphate monoester **8**, which is expected to react immediately with a second molecule of an *N*-oxide yielding product **5**. Alternatively,



Scheme 3 Possible mechanisms for the reaction of DPP (**2b**) with *N*-oxides.



Scheme 4 Reactions of reactive derivatives of phosphate esters with *N*-oxides.

H-phosphonate **7** may tautomerize to a trivalent form **7'**, which upon addition of a second molecule of *N*-oxide (path **B**₁) forms dication-anion **9** of a trigonal bipyramid (tbp) geometry. In a final step, the last intermediate collapses to betaine **5** and an amine (since **9** may be a transition state, not an intermediate, the path **B**₁ could be a one-stage process as well).^{||} It is also possible that the free electron pair of the phosphorus atom in phosphite **7'** attacks an *N*-oxide, and the oxygen atom is directly transferred from the nitrogen to the phosphorus atom *via* a linear P–O–N transition state (path **B**₂).¹⁴

Due to high rates of all transformations, we were unable to perform kinetic studies, and neither of the intermediates **7–9** could be detected in ³¹P NMR spectra of the reaction mixtures. In order to get some insight into the mechanism, reactions of DPP and *N*-oxides were repeated in the presence of an excess of poorly nucleophilic *t*BuOH. Formation of *t*-butyl phenyl phosphate would indicate involvement of metaphosphate **7**, since it was unlikely that intermediates **7'** or **9** could react with *t*BuOH. Since *tert*-butyl esters were not detected, the metaphosphate route **A** was rendered rather unlikely.

Whichever mechanism operates, the rapidity of the whole process remains surprising. The very high rate of oxidation of the assumed *H*-phosphonate intermediates **7/7'** is particularly astonishing since *H*-phosphonate esters typically require relatively strong oxidizers and were found to be *per se* resistant (in contrast to phosphite triesters) to direct oxidation by *N*-oxides. Thus, such high susceptibility to oxidation seems to be an intrinsic, unusual feature of *H*-phosphonates bearing a residue of an *N*-oxide (**7**), either due to their rapid collapse to metaphosphate **8** (Scheme 3, path **A**) or unusually high contribution of the tautomeric phosphite form **7'** (paths **B**). Computational studies might be probably helpful in the elucidation of the actual mechanism; however, these are beyond the scope of this preliminary contribution.

According to the mechanisms outlined in Scheme 3, the reaction of diaryl *H*-phosphonate **1a** with *N*-oxides consists of two or three steps in which the PhO group is at first substituted with an *N*-oxide, and the intermediate quasi-diester **7** is oxidized with a second molecule of the *N*-oxide, and this sequence of reactions was fully congruent with all experimental data. However, it was intriguing whether it is possible to obtain oxyonium betaines **5** starting from compounds in which the phosphorus atom is already in the V oxidation state. We paid our attention to pyridinium betaines **10** (Scheme 4), which have

structures and charges similar to the oxonium species **5**. Indeed, simple adaptation of the procedure for the preparation of compounds of type **10**⁷ by replacing pyridines by *N*-oxides led unambiguously to the formation of the expected betaines **5** (reactions in DCM or pyridine, ³¹P NMR analysis). Unfortunately, these were accompanied by a number of other products, and the yields did not exceed 50%, indicating incompatibility of *N*-oxides with the other reactants. However, pyridinium betaines **10a** and **10b** can be generated quantitatively *in situ*,⁷ and when *N*-oxides **3a/3b** were added to such reaction mixtures, we were satisfied to observe signals of betaines **5a/5b**, respectively, as practically sole products. In these experiments, pyridinium betaine **10a** reacted with the *N*-oxides very rapidly, while the more stable 4-(*N,N*-dimethylamino)pyridinium derivative **10b** required 15–30 min, and the progress of the reaction could be monitored with ³¹P NMR. Also phenyl phosphorochloridate **11** (prepared *in situ* by partial hydrolysis of commercial phenyl phosphorodichloridate) yielded betaines **5** in reaction with *N*-oxides, confirming the general character of this approach.

Conclusions

Concluding, neither of the *H*-phosphonates studied was oxidized directly by *N*-oxides, indicating that the last species are much poorer oxidants for *H*-phosphonate esters than *e.g.* iodine, CCl₄, or S₈. However, DPP **1a** and other *H*-phosphonate diesters bearing an aryl ligand were found to react promptly with aliphatic and aromatic *N*-oxides with formation of a new type of compounds, oxonium-type phosphobetaines **5**. A plausible mechanism involves substitution of one phenoxy group with an *N*-oxide, addition of a second molecule of the *N*-oxide, and oxidative collapse of the *tbp* intermediate. Despite this rather complex mechanism, the products were formed with surprisingly high yields, often >90%. An alternative route to the same betaines is a reaction of *N*-oxides with active derivatives of phosphate monoesters. It is worth noting that according to preliminary experiments, the obtained betaines reacted readily with amines and some other nucleophilic reagents. This fact, together with clean formation of betaines **5**, their easy isolation (if necessary) and appreciable stability during storage, make them potentially valuable intermediates in synthetic applications. Studies on this topic are in progress in this laboratory and will be reported in due course.

Acknowledgements

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Notes and references

§ The second product was MPP (**2a**), probably due to a rapid *N*-oxide-catalyzed hydrolysis of DPP by residual water (Fig. S3–S8†).

¶ Only the most reactive aromatic *N*-oxides (**3a** and **3d**) formed phosphobetaines (**5a** and **5d**, respectively) efficiently. Compound **5c** derived from 4-methylpyridine

N-oxide **3c** was observed in ³¹P NMR spectra (see ESI†) but could not be isolated. Unsubstituted pyridine *N*-oxide did not form phosphobetaines.

|| It is worth noting that the sequence 7' → 9 → 5 in route **B**₁ is in line with the mechanism postulated by Stec *et al.* for oxidation of phosphines and phosphite triesters with *N*-oxides.³ In contrast, an intramolecular: P–OBt → O=P–Bt rearrangement postulated by Sekine *et al.* for oxidation of phosphoramidite diesters with hydroxybenzotriazole (HOBt)¹⁵ cannot operate for quaternary nitrogen atoms in the oxonium intermediates formed from *H*-phosphonates and *N*-oxides.

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