Use of an ^{18}O-labelled phosphonamidic-sulfonic anhydride to learn more about the mechanism by which *O*-sulfonyl-*N*-phosphinoylhydroxylamines rearrange

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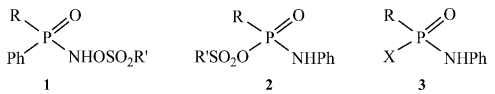
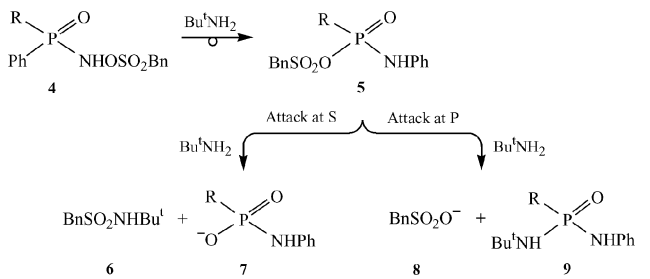
With Bu^tNH_2 the anhydride R(PhNH)P(O)OS$^{18}O_2$Bn 5 (R = Bu^t), like the hydroxylamine derivative R(Ph)P(O)NH-OS$^{18}O_2$Bn 4 (R = PhMeCH), gives $Bu^tNHS^{18}O_2Bn$ containing only a part (76–78%) of the available ^{18}O label; this is a result of partial scrambling of the label in 5 ($OS^{18}O_2 \rightleftharpoons {}^{18}OSO_2$) while it is reacting; there is no need to postulate scrambling in the rearrangement of 4 to 5 (R = PhMeCH) or to exclude a concerted mechanism.

The *O*-sulfonyl derivatives **1** (R = alkyl or phenyl) of *N*-phosphinoylhydroxylamines react with alkoxides or aliphatic amines to give products **3** (X = OMe, $NHBu^t$, *etc.*) in which a phenyl group has migrated from phosphorus to nitrogen.[1] It now seems that this migration is just one half of a transposition reaction, the other half being migration of the sulfonate group from nitrogen to phosphorus.[2] The result is a phosphonamidic-sulfonic anhydride **2** which reacts rapidly with the nucleophile (HX) to give the product **3**.



1 **2** **3**

In principle, the anhydride intermediate could be attacked at sulfur instead of phosphorus but in only one case (Scheme 1, R = PhMeCH) has appreciable competition been seen.[3] That observation opened the way to an investigation of the transposition mechanism using the hydroxylamine derivative **4** (R = PhMeCH) labelled specifically with ^{18}O in the sulfonyl (SO_2) group. By measuring the distribution of the label between the products **6** and **7** resulting from attack at sulfur, the distribution of ^{18}O (SO_2 *vs.* SOP) in the anhydride intermediate **5** could, we supposed, be deduced.[3] The results, however, were not consistent



4 **5** **6** **7** **8** **9**

Scheme 1

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with any straightforward transposition mechanism. Our concern now is with the possibility that the distribution of the label in the anhydride intermediate might not be the same when it reacts as when it is formed.

Ideally we would have used the anhydride **5** (R = PhMeCH) labelled with ^{18}O specifically in the bridging (SOP) or the non-bridging (SO_2) position but it could not be obtained. Phosphonylation[4] of labelled sulfonate ($BnS^{18}O_3^-$) cannot possibly give a product with ^{18}O in just one position, and sulfonylation of phosphonate generally fails because the phosphonate displaces sulfonate from the anhydride as it is formed, giving largely pyrophosphonate.[5] This pyrophosphonate formation involves nucleophilic attack at the P atom of the anhydride; we thought it might usefully be suppressed (steric hindrance) if the alkyl group on phosphorus (R = PhMeCH) were changed to one even more bulky (R = Bu^t).

The *tert*-butylphosphonamidic chloride **3** (R = Bu^t, X = Cl) (δ_P 53.5; M^+ 231,233) was prepared from $Bu^tP(O)Cl_2$ and LiNHPh in THF at −40 °C and was hydrolysed using aqueous NaOH or $H_2{}^{18}O$–Et_3N.† The resulting phosphonamidate **7** (R = Bu^t) could be sulfonylated without much pyrophosphonate formation by addition of $BnSO_2Cl$ [unlabelled or labelled (57.5 mol% one ^{18}O atom)[3]] to a suspension of the Et_3NH^+ salt in diethyl ether.‡ Samples of the anhydride **5** (R = Bu^t) were thus obtained containing no label [mp 142–143 °C; *m*/*z* (FAB) 367 (M^+) and 368 (MH^+)] and with ^{18}O in the SO_2 group (sample A) [57.5 mol% one ^{18}O (FAB MS); δ_P 36.4 only (no high field P–^{18}O peak)] or in the phosphonate group (sample B) [95.5 mol% one ^{18}O; δ_P 36.3 (*ca.* 5%) with much larger peaks at higher field, $\Delta\delta_P$ 0.034 (P–^{18}O) and 0.047 ppm (P=^{18}O), ratio *ca.* 1 : 1].

Reaction of the labelled anhydride **5** (R = Bu^t) (sample A or B) with Bu^tNH_2 (50 equiv.; 2.0 mol dm^{-3} in CH_2Cl_2) at 30 °C was complete inside 0.5 h (^{31}P NMR). The dominant products were the phosphonic amide **9** (R = Bu^t) (δ_P 30.7) and the sulfonate **8** (δ_H 4.05) resulting from attack at phosphorus (*ca.* 90%), but minor amounts of the sulfonamide **6** (δ_H 4.25) and the phosphonamidate **7** (R = Bu^t) (δ_P 26.5) were also formed as a result of attack at sulfur. The salts (**7** + **8**) were removed by aqueous extraction and esterified (CH_2N_2) and both the esters and the amides (**6** + **9**) were analysed by GC–MS to determine their ^{18}O content (Table 1).§

The results for the sulfonate and phosphonic amide (attack at P) are as expected, reflecting (within experimental error) the content and distribution of ^{18}O in the anhydride, but the results for the sulfonamide and phosphonamidate (attack at S) are not. A faithful reflection of the labelling in the anhydride would give sulfonamide **6** with 57.5 mol% one ^{18}O from sample A, not 45 mol%, and with no ^{18}O from sample B, not 20.5 mol%. Also, the phosphonamidate from sample A would not contain any ^{18}O. There must, it seems,

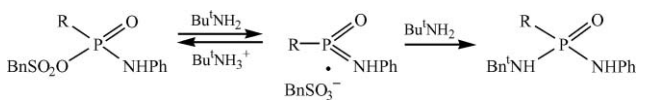
Table 1 ^{18}O Content (mol% one ^{18}O atom) of products from reaction of ^{18}O-labelled phosphonamidic-sulfonic anhydride **5** (R = Bu^t) (sample A or B) with Bu^{t}NH$_2$ (2 mol dm^{-3}) in CH_2Cl_2 [a]

	Sample A	Sample B
Sulfonamide **6**	45	20.5
Phosphonamidate **7** (R = Bu^t)	9.5[b]	70[b]
Sulfonate **8**	57.5	49
Phosphonic amide **9** (R = Bu^t)	0	47

[a] Sample A, label (57.5 mol% one ^{18}O) in SO_2; sample B, label (95.5 mol% one ^{18}O) shared equally between P–O and P=O; products **7** and **8** analysed as methyl esters. [b] Lower-than-expected ^{18}O content of **7** is attributable to traces of moisture [**7** is only a minor product from **5** + Bu^{t}NH$_2$ (attack at S) but a major product from **5** + H_2O (attack at P; cleavage of the P–^{18}O bond)].

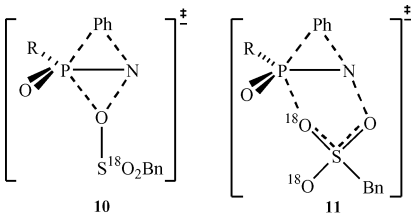
be some scrambling of the label between the bridging (SOP) and non-bridging (SO_2) positions of the anhydride while it is reacting.

Scrambling could easily be explained if the sulfonate anion released during the reaction were to displace the sulfonate leaving group from the anhydride yet to react. Such simple exchange seems not to occur, however, since labelled anhydride (sample B) suffers no change when dissolved in $CDCl_3$ containing unlabelled sulfonate (Bu^{t}NH$_3^+$ salt; 1 equiv.) (^{31}P NMR: size of P–^{18}O peak unchanged after 25 h at 30 °C). Any scrambling clearly occurs only when the amine is present and must, we think, be coupled with the product-forming reactions of the anhydride. For substitution at phosphorus, the structure of the anhydride (bulky alkyl group, acidic NH group) and the nature of the nucleophile (Bu^{t}NH$_2$) will hinder $S_N2(P)$ but will assist an elimination–addition mechanism (Scheme 2). In this, a reactive three-coordinate metaphosphonimidate is generated by the amine acting as a base and is trapped by the amine acting as a nucleophile.[6,7] If sulfonate anion competes with amine for the metaphosphonimidate so that some of it returns, any ^{18}O in the sulfonate anion will be shared between the bridging and non-bridging positions of the resulting anhydride. The sulfonate anion (1 equiv. at most) is unlikely to compete effectively in the bulk solution where the amine (50 equiv.) is in large excess; more likely is some direct recombination of the metaphosphonimidate and the sulfonate leaving group before they diffuse apart.



Scheme 2

In our earlier study the ^{18}O label was confined to the SO_2 group of the hydroxylamine derivative **4** (R = PhMeCH) but was shared in the product between the sulfonamide **6** (76% of the available ^{18}O) and the phosphonamidate **7** (R = PhMeCH).[3] ¶ We inferred that the label in the anhydride intermediate **5** (R = PhMeCH) was shared in the same way between the SO_2 group and the bridging O atom but then struggled to relate the labelling pattern to a reasonable mechanism for the rearrangement of **4** to **5**. In the present study the similar anhydride **5** (R = Bu^t) (sample A) gives products in which the label is shared between **6** (78% of the ^{18}O in the anhydride) and **7** (R = Bu^t) in much the same way *even though the label is all in the SO_2 group of the anhydride to begin with*. It therefore seems likely that our earlier inference was wrong and that the anhydride intermediate **5** (R = PhMeCH) is actually *formed* with all the label in the SO_2 group. If that is so, the transposition reaction **4** → **5** (conjugate bases) must surely be concerted with a transition state resembling **10**. The alternative transition state **11** can be discounted, as can a non-concerted mechanism in which the three sulfonate O atoms become equivalent; in neither case could the resulting anhydride produce sulfonamide containing more than two-thirds of the available label.



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Notes and references

† Two equivalents of LiNHPh are required because the phosphonamidic chloride is acidic (NH) and cooling must be continued until the reaction has been quenched (CF_3CO_2H) because the conjugate base (NLi) is of limited stability (elimination of LiCl). The phosphonamidic chloride (0.4 mmol) can be hydrolysed in $CHCl_3$ (1.5 ml) by addition of $H_2{}^{18}O$ (2 equiv.) and then Et_3N (0.8 ml), with vigorous stirring for 4 h at 30 °C; in this way pyrophosphonate formation is largely avoided without the need of a large excess of $H_2{}^{18}O$.

‡ A small excess of $BnSO_2Cl$ (1.2 equiv.) was used and a little Et_3N (0.4 equiv.) was added after 3–4 min. Because chloride ion (from $BnSO_2Cl$) tends to displace sulfonate from the anhydride (attack at P), diethyl ether was used as the solvent (Et_3NHCl precipitates out) and the reaction was quenched (slightly acidic ice-cold water) after just 5 min. The product (a foam, initially) was purified by washing with warm light petroleum and diethyl ether and crystallisation from CH_2Cl_2–diethyl ether (1 : 8); $\delta_H(CDCl_3)$ 7.5–7.0 (10 H), 5.40 (d, J_{PH} = 10 Hz, NH), 4.67 (AB quartet, δ_A 4.71, δ_B 4.63, J_{AB} = 14 Hz, CH_2Ph) and 1.23 (d, J_{PH} = 19 Hz, Bu^t); $\delta_C(CDCl_3)$ 140–120, 60.1 (s), 35.0 (d, J_{PC} = 125 Hz) and 24.3 (s).

§ Mass spectra were recorded in EI mode. The proportion of molecules containing the ^{18}O label was determined from the abundance of $(M + 2)^+$ ions (relative to M^+) corrected for the contribution of ions containing ^{16}O and natural abundance ^{18}O, ^{34}S or ^{13}C (2 atoms). The molecular ion was of very low abundance in the case of sulfonamide **6** and (M^+ − Me) was used.

¶ A similar study using **4** (R = Bu^t) is not possible because the requisite *N*-phosphinoylhydroxylamine [Bu^{t}PhP(O)NHOH] cannot be prepared (steric hindrance).

1 M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2699; M. J. P. Harger and A. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1987, 683.
2 M. J. P. Harger and A. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2507; M. J. P. Harger and R. Sreedharan-Menon, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3261.
3 M. J. P. Harger, *Org. Biomol. Chem.*, 2003, **1**, 3390.
4 J. Wasiak and J. Michalski, *Tetrahedron Lett.*, 1994, **35**, 9473.
5 W. Dabkowski, J. Michalski, C. Radziejewski and Z. Skrzypczynski, *Chem. Ber.*, 1982, **115**, 1636; J. Michalski, W. Dabkowski and J. Wasiak, *Pol. J. Chem.*, 1992, **66**, 879.
6 P. S. Traylor and F. H. Westheimer, *J. Am. Chem. Soc.*, 1965, **87**, 553.
7 M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2127; S. Freeman and M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 2*, 1988, 81.

