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Unexpected Double ^{18}O Labeling of a Phosphonothioate

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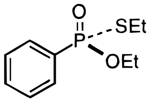
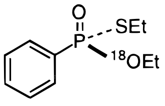
We have a continuing scientific and practical interest in the development of chemical methods for the remediation of phosphorus-based neurotoxins and other hazardous agents. We have used *O,S*-diethyl phenylphosphonothioate (**1**)[1] as a mimic for certain agents. To follow the several chemical changes that this mimic undergoes through the remediation process, we needed the ^{18}O-labeled material. We now report that the preparation of **2** from ^{18}O-labeled ethanol led also to a significant amount of the doubly ^{18}O-labeled phenylphosphonothioate **3**.



1



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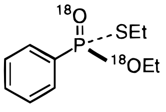
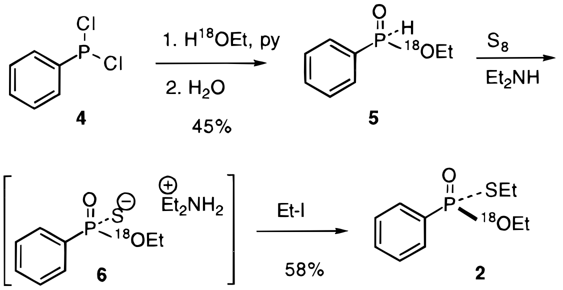


3

Following a modification of the procedure of DeBruin,[1] we reacted dichlorophenylphosphine (**4**) (Scheme 1) with ^{18}O-labeled ethanol,[2] followed by the addition of water to give **5**. Oxidation with elemental sulfur in the presence of diethylamine then gave the salt of the *O*-ethyl phenylphosphonothioate, which was alkylated with ethyl iodide to give the ^{18}O-labeled *O,S*-diethyl phenylphosphonothioate (**2**).

We noted that the mass spectrum of **2**, in addition to showing the expected molecular ion at *m/z* 232, showed a peak (16% intensity relative to 232) at *m/z* 234. This was more intense than would be accounted for by the 4.2% natural abundance of ^{34}S. There was also a peak at *m/z* 230 (2.8% intensity relative to 232). Inspection of the ^{31}P spectrum[3] of **2** confirmed that there were in fact three species present, at δ 44.508, 44.478, and 44.429, comprising 4.6, 85.5, and 9.9%, respectively, of the mixture. Given the known[4] effect of ^{18}O labeling on ^{31}P chemical shifts, we can conclude that these are the ^{16}O/^{16}O, ^{16}O/^{18}O, and ^{18}O/^{18}O species.

Scheme 1



The presence of the ^{16}O/^{16}O material was not surprising, since the ^{18}O-labeled ethanol used in the preparation was less than 100% ^{18}O-labeled. The significant proportion of ^{18}O/^{18}O material was more of a surprise. We speculate that this product was formed from the reaction of the starting dichlorophosphine **4** with ^{18}O-labeled ethanol, followed by partial hydrolysis of that product with traces of ^{18}O-labeled water that had been formed concurrently by dehydration of the ^{18}O-labeled ethanol. It is also possible, though perhaps less likely, that the commercial ^{18}O-labeled ethanol we used was contaminated with ^{18}O-labeled water.

On reinspection, we observed that the ^{1}H spectrum of **5** showed three signals for the P−H, at δ 7.55, 7.63, and 7.71, in the same proportions as observed in the ^{31}P spectrum. So far as we have been able to determine, there has been no previous report of the ^{1}H NMR of an ^{18}O-labeled phosphinate. If these minor peaks do indeed prove to be due to the ^{16}O/^{18}O-labeled phosphinates, this incremental chemical shift change may prove to be a useful probe for following the ^{18}O labeling of phosphinates.

The ^{18}O-labeled *O,S*-diethyl phenylphosphonothioate (**2**) prepared as outlined here is still suitable for the studies we have envisioned. Nevertheless, this work underscores the importance of careful analysis of all products prepared by isotope incorporation.

Experimental Section[5]

Synthesis of ^{18}O-Labeled Ethyl Phenylphosphinate (5). Following a modification of the method of DeBruin,[1] ^{18}O-labeled ethanol (1.00 g, 20.8 mmol) was added to a mixture of dichlorophenylphosphine (3.94 g, 21.0 mmol) and pyridine (2.05 g, 26.0 mmol) in toluene (26 mL) while it was being stirred in an ice/water bath. After 1 h, the reaction mixture was partitioned between half-saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic extract was dried (K_2CO_3) and concentrated, and the residue was distilled bulb-to-bulb [bp$_{0.5mm}$ (bath) = 100−105 °C] to give 1.62 g of **5** (9.4 mmol, 45% yield from the labeled ethanol) as a colorless oil: ^{1}H NMR δ 1.38 (t, J = 7.0 Hz, 3H), 4.16 (m, 2H), 7.54 (m, 3H), 7.63 (d, J = 563 Hz, 1H), 7.80 (m, 2H); ^{13}C NMR δ u 130.0, 62.1 (d); d 132.9 (m), 130.9 (m), 128.6 (m), 16.3 (t).

Synthesis of ^{18}O-Labeled *O,S*-Diethyl Phenylphosphonothioate (6). Following a modification of the method of DeBruin,[1] the distilled product from above (1.62 g, 9.42 mmol) was taken up in Et_2O (10 mL) and diethylamine (803 mg, 11 mmol) in a 25 mL Erlenmeyer flask. Sulfur (352 mg, 11 mmol) was added in small portions over 15 min while the mixture was being stirred. An exothermic reaction was observed. The flask was stoppered, and stirring was continued for 4 h. The resulting

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[1] DeBruin, K. E.; Tang, C.-l. W.; Johnson, D. M.; Wilde, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 5871.

[2] The ^{18}O-labeled ethanol used in this study was purchased from Cambridge Isotopes, Inc.

[3] These ^{31}P spectra were acquired in CD_3CN at 243 mHz on a Varian INOVA 600 FTNMR spectrometer.

[4] For leading references on the influence of ^{18}O on NMR chemical shifts, see the following. (a) ^{31}P: Cohn, M.; Hu, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 200. (b) ^{13}C: Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 252. (c) ^{1}H: Sergeyev, N. M.; Sergeyeva, N. D.; Strelenko, Y. A.; Raynes, W. T. *Chem. Phys. Lett.* **1997**, *277*, 142 and references therein.

[5] For a summary of general experimental procedures, see: Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

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white precipitate was filtered, and the filtrate was reduced in volume to give a second crop, which was also filtered. The combined crude solid was taken up in 10 mL of toluene, and ethyl iodide (3 g, 21 mmol, freshly distilled from Cu powder) was added. The reaction mixture was stirred overnight and then partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The combined organic extract was dried (K_2CO_3) and concentrated. The residue was filtered through silica gel with 5% acetone/CH_2Cl_2 to give the phenylphosphonothioate as a colorless oil (1.26 g, 26% yield from labeled ethanol): TLC R_f (15% acetone/CH_2Cl_2) = 0.61; ^{1}H NMR δ 1.22 (t, $J = 7.5$ Hz, 3H), 1.37 (t, $J = 7.1$ Hz, 3H), 2.73 (m, 2H), 4.23 (m, 2H), 7.5 (m, 3H), 7.9 (m, 2H); ^{13}C NMR δ u 131.6, 62.0 (d), 24.8 (d); d 132.4 (d), 131.1 (d), 128.4 (d), 16.3 (d), 16.1 (d).

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Supporting Information Available: ^{1}H, ^{13}C, and ^{31}P spectra for all new compounds (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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