α-Phosphoryl sulfoxides. Part XII. The question of sulfinyl oxygen participation in the alkaline hydrolysis of α-phosphoryl sulfoxides†

Marian Mikołajczyk,[a] Wanda H. Midura,[a] Reinhard Schmutzler,[b] Hans-Martin Schiebel[b] and Peter Schulze[c]

[a] *Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland. E-mail: marmikol@bilbo.cbmm.lodz.pl; Fax: +48 42 684 71 26*
[b] *Institute of Inorganic and Analytical Chemistry, Technical University, Hagenring 30, D-38106 Braunschweig, Germany*
[c] *Institute of Organic Chemistry, University Bremen, Leobenerstrasse, D-28334 Bremen, Germany*

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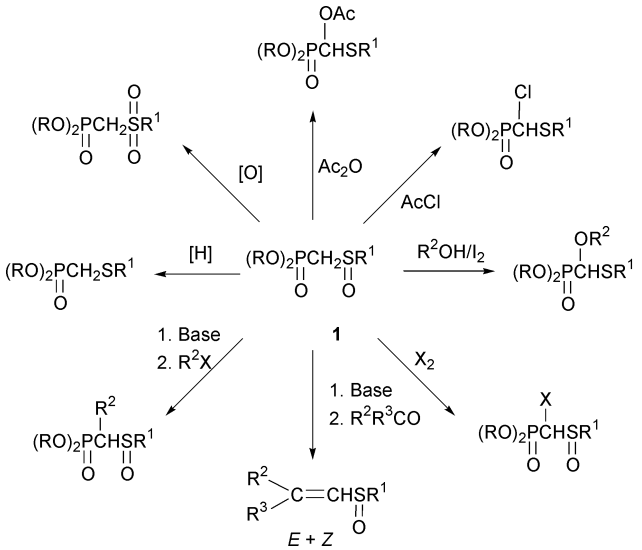
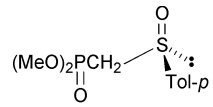
The course of the alkaline hydrolysis of (diphenoxyphosphoryl)methyl *p*-tolyl sulfoxide (**8**) has been elucidated by a combination of ^{18}O isotopic labelling and mass spectrometric analysis of the hydrolysis products. The hydrolysis of the sulfoxide **8** containing ^{18}O in the sulfinyl group afforded the corresponding phosphonic acid **9**, which, upon methylation with diazomethane, was converted into [methoxy(phenoxy)phosphoryl]methyl *p*-tolyl sulfoxide (**10**) also containing ^{18}O in the sulfinyl group, as demonstrated by the EI- and CI-mass spectra. The hydrolysis of **8** in ^{18}O-enriched water followed by methylation with diazomethane gave the sulfoxide **10** in which ^{18}O was incorporated into the phosphonic ester moiety. These results do not support a two-step mechanism for the hydrolysis of α-phosphoryl sulfoxides involving participation of the neighbouring sulfinyl group and formation of a cyclic oxathiaphosphetane intermediate. The latter is most probably formed in the mass spectrometric fragmentation process of α-phosphoryl sulfoxides.

α-Phosphoryl sulfoxides **1**, first synthesised in racemic[2] and enantiomeric forms[3] in our laboratory, are useful synthetic reagents and interesting compounds for mechanistic and stereochemical studies. They exhibit the typical reactivity characteristic of sulfoxides and phosphonic esters.[4] Among many transformations of α-phosphoryl sulfoxides **1** shown in Scheme 1, the most important is the Horner–Wadsworth–Emmons reaction affording α,β-unsaturated sulfoxides.[5] The optically active (dimethoxyphosphoryl)methyl *p*-tolyl sulfoxide **2** has become a reagent of choice for the synthesis of differently substituted chiral vinyl sulfoxides.[3]



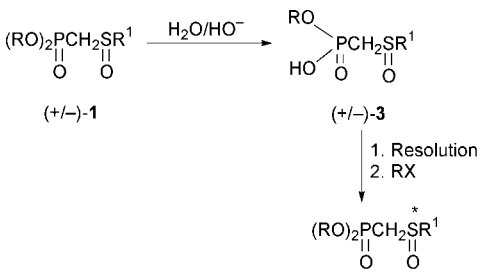
Scheme 1 Reactions of α-phosphoryl sulfoxides **1**.



(+)-(*S*)-**2**

As expected, the alkaline hydrolysis of **1** affords the corresponding phosphonic acids **3**.[3] The presence of the phosphonic acid moiety in **3** allows them to resolve *via* diastereoisomeric salts formed with alkaloid bases and enables enantiomeric **1** to be obtained on subsequent alkylation.

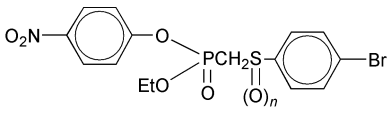
A more detailed kinetic study by Cevasco *et al.*[6] on the alkaline hydrolysis of [ethoxy(*p*-nitrophenoxy)phosphoryl]-methyl *p*-bromophenyl sulfoxide **4** and its sulfide **5** and sulfone **6** analogues revealed that the sulfoxide **4** undergoes hydrolysis faster than **5** and **6**. The rate enhancement observed in the hydrolysis of **4** was interpreted in terms of intramolecular assistance by the sulfinyl oxygen to nucleophilic substitution at the tetrahedral phosphorus and the formation of a



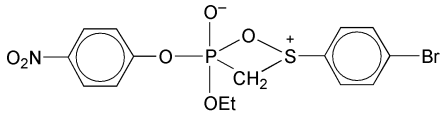
(1)

† For part XI, see: ref. 1.

four-membered cyclic oxathiaphosphetane intermediate **7**, which undergoes attack by the hydroxy anion.



4, $n = 1$
5, $n = 0$
6, $n = 2$



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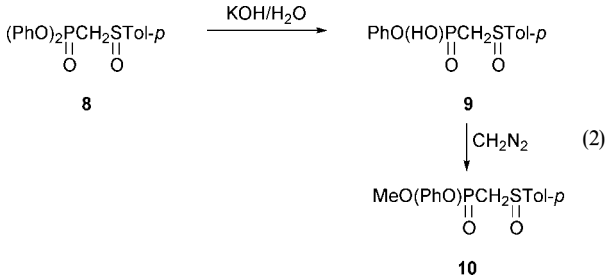
Although the participation of the sulfinyl oxygen as a neighbouring group in some reactions occurring at carbon is well documented in the chemical literature,[7] the intervention of the adjacent sulfinyl group in the hydrolysis of α-phosphoryl sulfoxides, suggested by Cevasco *et al.* based only on kinetic studies, required, in our opinion, more convincing evidence. We report herein the results of our investigation of this problem using ^{18}O-labelled compounds and mass spectrometry as an analytical tool.

Results and discussion

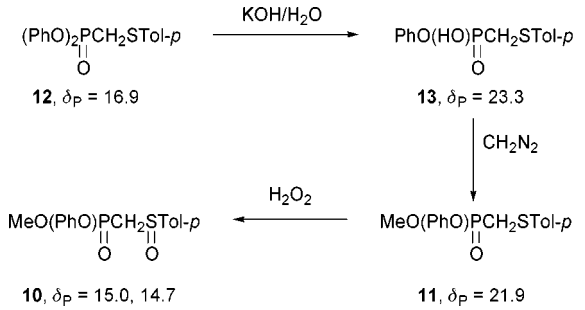
In this work, (diphenoxyphosphoryl)methyl *p*-tolyl sulfoxide **8** was chosen for studies of the mechanism of alkaline hydrolysis. The phosphonic acid **9** obtained in this reaction was methylated with diazomethane to give [methoxy(phenoxy)phosphoryl]methyl *p*-tolyl sulfoxide **10** [eqn. (2)].



8 **9** **10** (2)

To answer the question of whether the sulfinyl oxygen does or does not participate as a neighbouring group, forming the oxathiaphosphetane intermediate in the hydrolysis of **8**, two experiments were carried out. The first was the alkaline hydrolysis of the sulfoxide **8** labelled with ^{18}O in the sulfinyl group, while the second involved hydrolysis of the non-labelled sulfoxide **8** in ^{18}O-enriched water. The content and position of ^{18}O in the sulfoxide **10** obtained after methylation was determined by mass spectrometry.

Since the mass spectrometric behaviour of α-phosphoryl sulfoxides has not been studied in detail, the fragmentation patterns of the sulfoxide **10** and its parent sulfide **11** were first investigated. Both compounds were prepared as shown in Scheme 2.



12, $\delta_P = 16.9$ **13**, $\delta_P = 23.3$ **10**, $\delta_P = 15.0, 14.7$ **11**, $\delta_P = 21.9$

Scheme 2 Synthesis of [methoxy(phenoxy)phosphoryl]methyl *p*-tolyl sulfoxide **10**.

(Diphenoxyphosphoryl)methyl *p*-tolyl sulfide **12** was hydrolysed under alkaline conditions to give the corresponding phosphonic acid **13**, which, upon subsequent methylation with diazomethane, afforded [methoxy(phenoxy)phosphoryl]methyl *p*-tolyl sulfide **11**. Its oxidation with hydrogen peroxide resulted in the formation of the desired sulfoxide **10** as a mixture of two diastereoisomers in an almost equal ratio.

The electron impact mass spectrum of the sulfide **11** [Fig. 1(a)] is dominated by an ion at *m/z* 137 (elemental composition C_8H_9S) obtained by loss of the complete phosphonic acid ester residue. Simultaneously, the ion at *m/z* 213 with the composition $C_{14}H_{13}S$ is observed. This can be rationalised by loss of a methyl metaphosphate fragment from the molecular ion of **11** by an unexpected rearrangement process involving migration of the phenyl group (Scheme 3).

The transformation of the sulfide **11** into the sulfoxide **10** is connected with a distinct change in the fragmentation pattern. The base peak of the EI-mass spectrum of **10** [Fig. 1(b)] is an ion at *m/z* 231 (elemental composition $C_9H_{12}O_3PS$) obtained by loss of the phenoxy residue. This fragmentation process is only of minor importance for the sulfide **11**. It indicates, however, neighbouring group participation of the sulfinyl oxygen in the fragmentation of the sulfoxide **10**. The loss of the phenoxy radical can induce attack of the sulfinyl oxygen on the tetracoordinate phosphorus, forming a stable four-membered cyclic oxathiaphosphetane cation **14** as the most probable structure for the ion at *m/z* 231. A common fragment for both compounds and base peak in the spectrum of **11** [Fig. 1(a)] is the ion at *m/z* 137. In the case of the sulfoxide **10**,

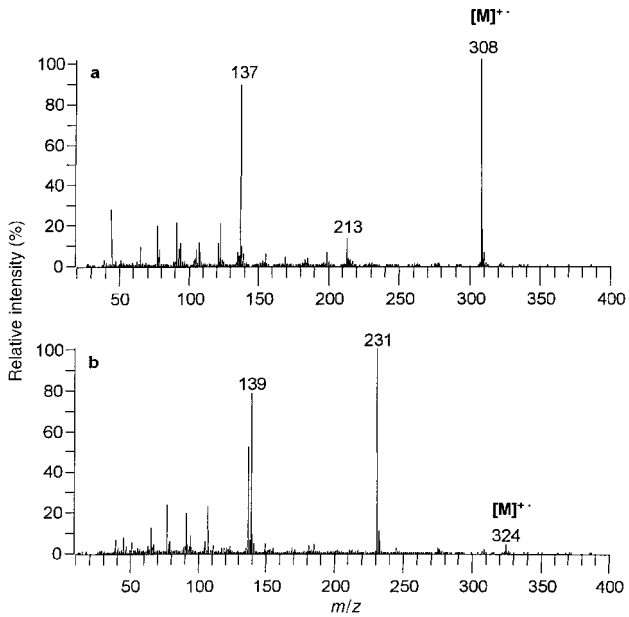
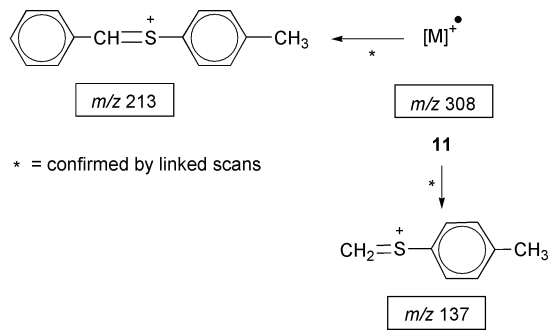
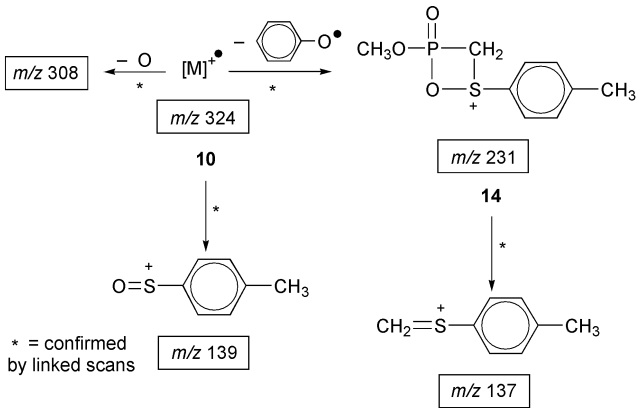


Fig. 1 EI-mass spectra of (a) the sulfide **11** and (b) the sulfoxide **10**.



Scheme 3 Electron impact fragmentation of the sulfide **11**.



Scheme 4 Electron impact fragmentation of the sulfoxide **10**.

it is formed by a two-step mechanism (Scheme 4). In addition to the peak at *m/z* 137, the spectrum of sulfoxide **10** displays a second prominent peak at *m/z* 139 with an elemental composition of C_7H_7OS [Fig. 1(b), Scheme 4]. Together with the fragment at *m/z* 231, this ion represents a key fragment as it has diagnostic value in determining the mechanistic details of the alkaline hydrolysis of the sulfoxide **10** using ^{18}O-labelling. The loss of oxygen results in the formation of an ion at *m/z* 308, which corresponds to the molecular ion of the parent sulfide **11**.

In the negative chemical ionization mass spectra of **10** and **11**, only one highly abundant fragment can be observed: the *p*-tolylsulfanyl ion $[CH_3(C_6H_4)S]^-$ at *m/z* 123 for the sulfide **11** and the phosphonic ester moiety $[MeO(PhO)P(O)CH_2]^-$ at *m/z* 185 for the sulfoxide **10** (Fig. 2). The formation of the latter by chemical ionization provides additional and complementary proof in determining the course of hydrolysis (Scheme 5).

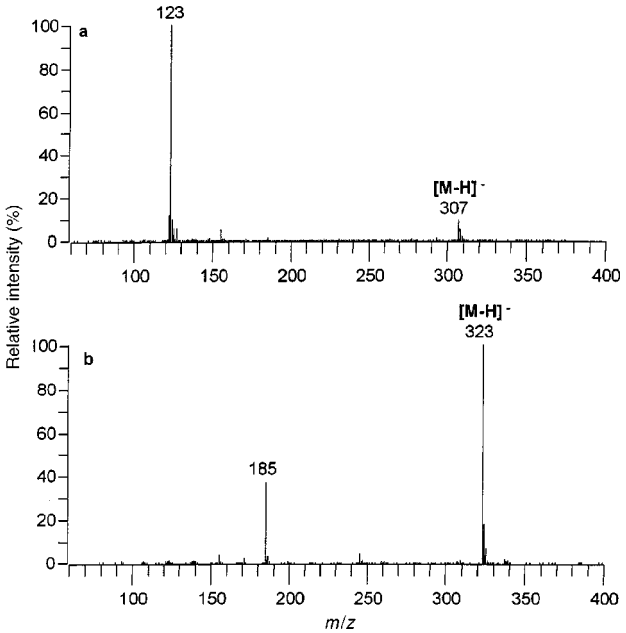
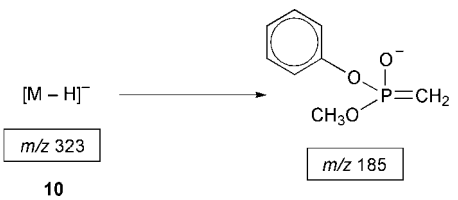


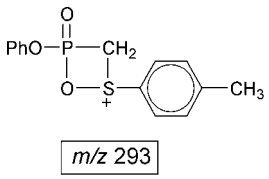
Fig. 2 Negative CI-mass spectra of (a) the sulfide **11** and (b) the sulfoxide **10**.



Scheme 5 Formation of the ion at *m/z* 185 from the sulfoxide **10** by negative chemical ionization.

Having established the main fragmentation pathways of the sulfoxide **10**, we could perform the hydrolysis experiments mentioned above. The sulfoxide **8** containing ^{18}O in the sulfinyl group was prepared by oxidation of the sulfide **12** using bromine, ^{18}O-water and pyridine, according to a literature procedure.[8] However, due to the prolonged reaction time, a mixture of the ^{18}O-sulfoxide **8** and the corresponding sulfone as an over-oxidation product was obtained. The former was isolated in a pure state by column chromatography.

The EI-mass spectrum of ^{18}O-**8** was found to be similar to that of the sulfoxide **10**, showing additional peaks due to oxygen isotopic substitution. Thus, two peaks at *m/z* 386 and 388 are due to the molecular ions of ^{16}O-**8** and ^{18}O-**8**. The base peak in the spectrum of this sulfoxide is an ion at *m/z* 137. As in the case of **10**, the loss of the phenoxy radical results in the formation of the oxathiaphosphetane cation **15** at *m/z* 293, accompanied by its ^{18}O-analogue at *m/z* 295.



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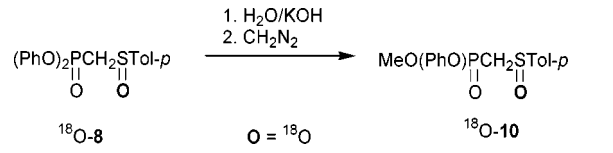
The fragmentation involving cleavage of the carbon–sulfur bond generates two ions at *m/z* 247 and 139. The former is the phosphonic ester residue $[(PhO)_2P(O)CH_2]^+$, while the second is the *p*-tolylsulfinyl fragment at *m/z* 139 accompanied by its oxygen isotopomer at *m/z* 141. As expected, the loss of oxygen gives rise to an ion at *m/z* 370, that is the molecular ion of the sulfide **12**.

The alkaline hydrolysis of the sulfoxide ^{18}O-**8** afforded the phosphonic acid ^{18}O-**9**, which, without purification, was converted by treatment with diazomethane into the sulfoxide ^{18}O-**10**, as a mixture of two diastereoisomers in a 1.2 : 1 ratio) [eqn. (3)]. Mass spectrometric analysis of this sulfoxide revealed unequivocally that it contains ^{18}O located in the sulfinyl group (Fig. 3). First of all, in the EI-mass spectrum, two molecular ions $[M]^{\cdot+}$ are seen at *m/z* 324 and 326, which correspond to the non-labelled sulfoxide ^{16}O-**10** and its labelled analogue ^{18}O-**10**, respectively [Fig. 3(a)]. Similarly, the negative CI-mass spectrum of this sulfoxide shows two peaks corresponding to $[M - H]^-$ ions at *m/z* 323 and 325 [Fig. 3(b)]. Since two peaks at *m/z* 139 and 141 due to the *p*-tolylsulfinyl fragments ^{16}O=STol and ^{18}O=STol are visible in the EI-mass spectrum, and in the negative CI-mass spectrum, only one fragment of the phosphonic ester moiety at *m/z* 185, $[MeO(PhO)P(O)CH_2]^-$, is observed, it can be concluded that during the hydrolytic conversion of **8** into **10** the position of the ^{18}O was not changed (Fig. 3).

In the second experiment, the sulfoxide **8** was hydrolysed using heavy water to give, after methylation, the sulfoxide **10′**



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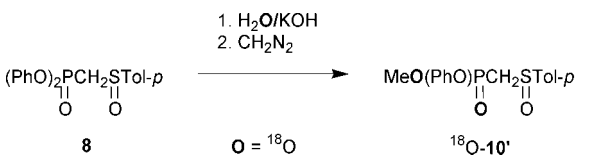

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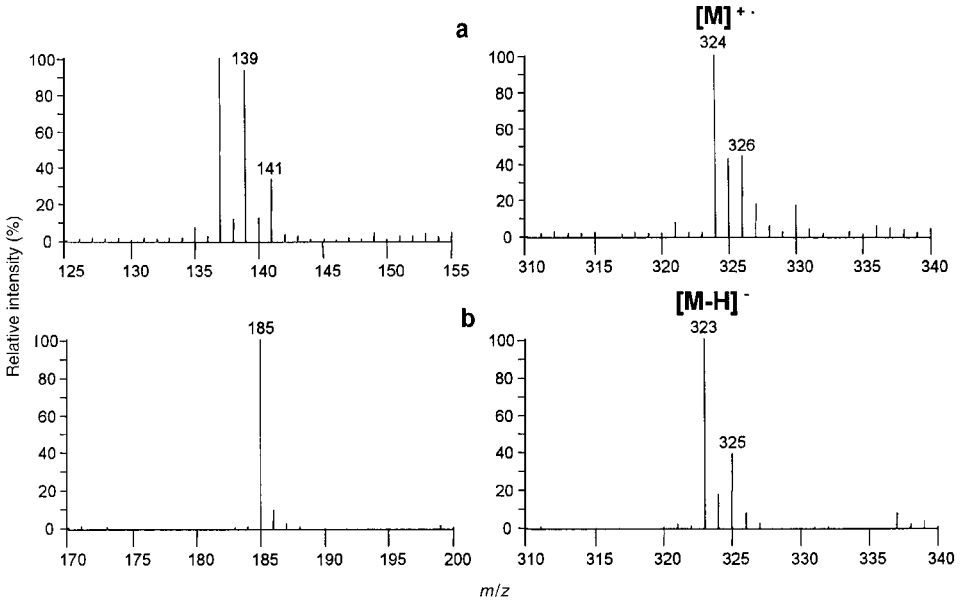
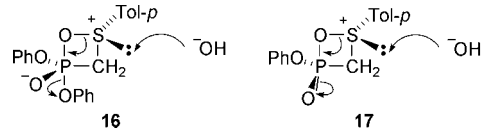


Fig. 3 Partial mass spectra of the sulfoxide ^{18}O-**10**: (a) El-spectrum, (b) negative Cl-spectrum. Intensities are normalised to the most intense peak of the corresponding mass range.

containing ^{18}O [eqn. (4)]. However, in this case the EI- and CI-mass spectra clearly indicate that ^{18}O is present in the phosphonic ester moiety (Fig. 4). Thus, in the negative CI-mass spectrum of this product, two peaks at *m*/*z* 185 and 187 are observed, while the EI-mass spectrum shows only one peak at *m*/*z* 139 for the *p*-tolylsulfinyl fragment (Fig. 4).

In light of the results presented above it is doubtful that the alkaline hydrolysis of the sulfoxide **8** proceeds through a cyclic intermediate **16**, the structure of which is analogous to that proposed by Cevasco *et al.* for the hydrolysis of the sulfoxide **4**, or *via* the transient oxathiaphosphetane cation **17**. In both cases, the nucleophilic attack of hydroxy anion should be at least partially, if not exclusively, directed at sulfur, which bears a full positive charge. Consequently, the alkaline hydrolysis of **8** in ^{18}O-enriched water should lead to isotopic exchange at the sulfinyl group and that of ^{18}O-**8** should result in transfer of the ^{18}O from the SO group to the phosphonate moiety. However, this was not found to be the case. Therefore, our results suggest direct attack of hydroxy anion on the tetracoordinate phosphorus atom. In this context, it is interesting to note that, in contrast to hydrolysis, under mass spectrometric conditions the sulfinyl group most probably does participate in the fragmentation process of α-phosphoryl sulfoxides, forming the highly abundant fragments having oxathiaphosphetane structures like **14** and **15**.



16 **17**

Experimental

General

^{1}H and ^{31}P NMR spectra were recordered on a Bruker AC200 Spectrometer at 200 and 81 MHz, respectively, using deuterochloroform as solvent. Electron ionization (EI) and

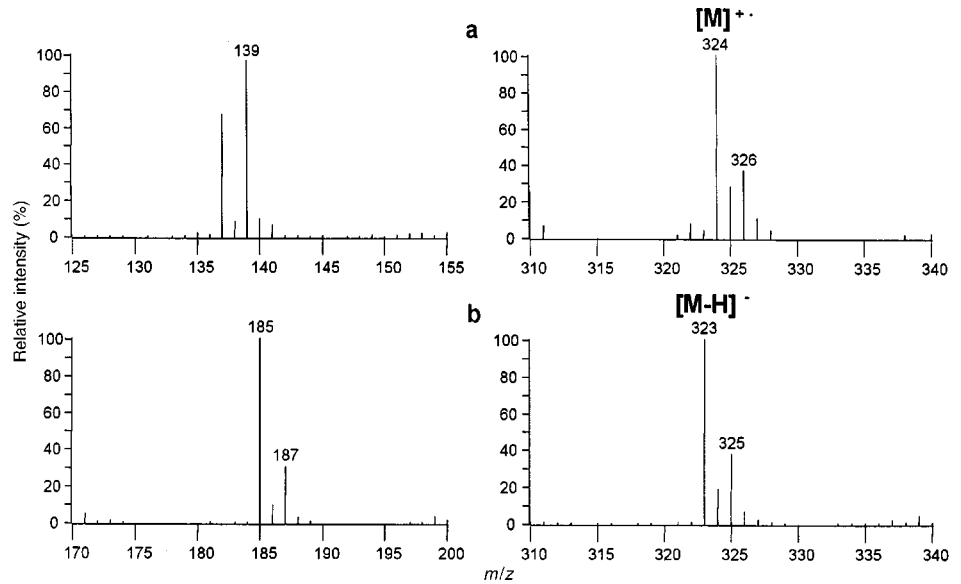


Fig. 4 Partial mass spectra of the sulfoxide ^{18}O-**10′**: (a) El-spectrum, (b) negative Cl-spectrum. Intensities are normalised to the most intense peak of the corresponding mass range.

chemical ionization (CI) mass spectra were recorded on a double focussing MAT 8220 instrument (Finnigan AT, Bremen). Ammonia served as the reagent gas for CI experiments. The high resolution EI data were obtained by peak matching at a resolution of approximately 10.000 (10% valley definition). The metastable ion spectra were recorded using linked scans (B/E constant).

TLC was carried out on silica gel plates (Merck F_{254}) and silica gel 60 (70–230 ASTM) was used for column chromatography.

Syntheses

[Methoxy(phenoxy)phosphoryl]methyl *p*-tolyl sulfide (11). To a solution of sulfide **12** (0.26 g, 0.7 mmol) in dioxane (10 mL), potassium hydroxide (0.15 g, 2.7 mmol) in water (1 mL) was added. The reaction mixture was stirred at room temperature for 1 h and then acidified and extracted with chloroform (3 × 10 mL). The extract was dried over $MgSO_4$ and concentrated to give a mixture of the corresponding phosphonic acid **13** ($\delta_p = 23.3$) and phenol. The crude acid **13** was dissolved in diethyl ether (10 mL) and treated with an excess of an ethereal solution of diazomethane. After 15 min, the solvent was removed under vacuum and the residue was purified by thin layer chromatography (benzene–acetone, 4 : 1) affording sulfide **11** as an oil (0.19 g, 88% yield). ^{1}H NMR ($CDCl_3$) δ: 2.33 (3H, s, CH_3Ph); 3.30 (2H, d, $J = 13.6$, CH_2P); 3.82 (3H, d, $J = 11.1$ Hz, CH_3OP); 7.07–7.40 (9H, m, aromatic). ^{31}P NMR ($CDCl_3$) δ: 21.9; HRMS (EI): M^+, found 308.0634; $C_{15}H_{17}O_3PS$ requires 308.0636.

[Methoxy(phenoxy)phosphoryl]methyl *p*-tolyl sulfoxide (10). To a solution of sulfide **11** (0.16 g, 0.5 mmol) in methanol (1 mL), catalyst (0.1 g) and hydrogen peroxide (2 mmol) were added with stirring. The catalyst was prepared by mixing 96% H_2SO_4 (1.38 g) and 2-propanol (30 g). After completion of the oxidation (5 h), water (10 mL) was added to the reaction mixture and the solution was extracted with chloroform (3 × 20 mL). The organic extracts were dried over $MgSO_4$ and evaporated to give, in almost quantitative yield (0.16 g, 98.8%), sulfoxide **10** (mixture of diastereoisomers) as an oil. ^{31}P NMR ($CDCl_3$) δ: 15.0 and 14.7 (1 : 1.1); ^{1}H NMR ($CDCl_3$) δ: 2.42 (3H, s, CH_3Ph); 3.29–3.64 (2H, m, CH_2P); 3.78 and 3.89 (3H, 2 d, $J = 11.5$ Hz, CH_3OP); 7.13–7.39 (7H, m, aromatic); 7.63 (2H, aromatic). HRMS (EI): M^+, found 324.0584; $C_{15}H_{17}O_4PS$ requires 324.0585.

^{18}O-(Diphenoxyphosphoryl)methyl *p*-tolyl sulfoxide (^{18}O-8). To a magnetically stirred solution of the sulfide **12** (0.37 g, 1mmol) in methylene chloride (3 mL) was added at room temperature a solution of ^{18}O-labelled water (0.1 mL) in pyridine (0.5 mL), followed by dropwise addition of a solution of bromine (0.16 g) in methylene chloride (3 mL). Vigorous stirring was continued for 8 h and then the excess bromine was destroyed by addition of anhydrous $NaHSO_3$ (0.3 g). The organic solvent was evaporated and the residue was shaken with two portions of benzene (10 mL). The combined benzene solution was dried over $MgSO_4$ and evaporated to give a mixture of the sulfoxide ^{18}O-**8** and the corresponding sulfone in a 1 : 1 ratio. Column chromatography (petroleum ether–acetone) gave pure sulfoxide ^{18}O-**8** as an oil (0.12 g, 31% yield). ^{31}P NMR ($CDCl_3$) δ: 9.6. ^{1}H NMR ($CDCl_3$) δ: 2.41 (s, 3H, CH_3Ph): 3.56 and 3.65 (2H, AB part of an ABX system, $J_{H-H} = 14.7$, $J_{H-P} = 14.8$, $J_{H-P} = 15.1$ Hz, CH_2P); 7.1–7.35 (m, 12H, aromatic); 7.66 (2H, aromatic).

^{18}O-[Methoxy(phenoxy)phosphoryl]methyl *p*-tolyl sulfoxide (^{18}O-10). To a solution of sulfoxide ^{18}O-**8** (0.038 g, 0.1 mmol) in dioxane (3 mL), a solution of potassium hydroxide (0.02 g, 0.4 mmol) in water (0.5 mL) was added. The reaction mixture was stirred for 1 h at room temperature, acidified with trifluoroacetic acid and extracted with chloroform (3 × 10 mL). The chloroform extracts were dried over $MgSO_4$ and concentrated to afford phosphonic acid **9** [^{31}P NMR ($CDCl_3$): 6.5 ppm]. The crude acid **9**, prepared as above, was dissolved in diethyl ether (5 mL) and an excess of diazomethane dissolved in diethyl ether (5 mL) was added. After 15 min, the ether was removed, affording the crude sulfoxide ^{18}O-**10** (mixture of diastereoisomers), which was purified by thin layer chromatography (benzene–acetone, 3 : 1); 0.28 g, 86% yield. ^{31}P NMR ($CDCl_3$) δ: 15.0 and 14.6 (1.2 : 1).

Alkaline hydrolysis of sulfoxide 8. To a solution of sulfoxide (0.06 g, 0.15 mmol) in dioxane (1 mL), a solution of potassium hydroxide (0.04 g, 0.65 mmol) in ^{18}O-water (1 mL) was added. The reaction mixture was stirred for 1 h at room temperature. Then the reaction solution was acidified with trifluoroacetic acid and extracted with chloroform (3 × 10 mL). The organic extracts were dried over $MgSO_4$ and evaporated to afford phosphonic acid **9**. ^{31}P NMR ($CDCl_3$) δ: 6.5.

^{18}O-[Methoxy(phenoxy)phosphoryl]methyl *p*-tolyl sulfoxide (^{18}O-10′). The crude phosphonic acid **9**, prepared as above, was dissolved in diethyl ether (5 mL) and an excess of diazomethane in diethyl ether (5 mL) was added. After 15 min, the solvent was removed under vacuum affording the crude sulfoxide ^{18}O-**10′** as a mixture of two diastereoisomers in a 1.2 : 1 ratio [^{31}P NMR ($CDCl_3$) δ: 15.0 and 14.6]. Purification by thin layer chromatography gave 0.04 g (82% yield) of the pure title sulfoxide.

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