Diastereomers (R_C,S_P)- and (R_C,R_P)-S-methyl P-(3-azidopropyl)-N-[(1R)-1-phenylethyl]phosphonamidothioate

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Diastereoisomers of the title organophosphorus compound, $C_{12}H_{19}N_4OPS$, denoted R_CS_P, (I), and R_CR_P, (II), were structurally characterized and compared. Asymmetric phosphorus compounds are of interest with regard to the use of these systems as possible protein probes *via* the stereoselective delivery of an azide group tethered to the P atom into key protein regions. The diastereomers were produced in a 1:1 mixture and isolated by chromatography. Although both isomers crystallize in the same space group with superficially similar cell constants, conformational and packing differences are pronounced. Despite the conformational differences, strong intermolecular hydrogen bonding links both isomers into chains parallel to the *a* axis [N···O = 2.8609 (18) and 2.966 (3) Å in (I) and (II), respectively], with C—H···π interchain interactions of *ca* 3.5 Å.

Comment

Organophosphates (OPs) are a well known class of compounds with particular utility as insecticides and increasing involvement in protein mechanisms as inhibitors, substrates, transition state analogs and isosteres (Rye & Baell, 2005). One of the key structural features of OPs is the potential to bear a stereogenic center at phosphorus. This important variable allows researchers to investigate the role of stereoisomerism in studies with biological targets. For example, asymmetric phosphorus esters interact stereospecifically with enzymes, receptors and transporters (Thompson *et al.*, 1992, 1993; Berkman *et al.*, 1993). Numerous routes to asymmetric OP compounds are known but few have been structurally assigned. Our current interest in asymmetric phosphorus compounds resides in their possible application as probes of proteins in which an azide group tethered to the P atom can be stereoselectively delivered into key protein regions, *e.g.* the

'gorge' in acetylcholinesterases (Sussman *et al.*, 1991; Ordentlich *et al.*, 1993).

Our goal was to prepare the stereoisomeric forms of azide-tethered OPs [structures R_CS_P, (I), and R_CP_P, (II)] for use as photoaffinity probes. Pure phosphonamide diastereomers were produced by the reaction of (R)-(+)-α-methylbenzyl-amine with a racemic mixture of O-methyl 3-azidopropyl thiophosphonyl chloride followed by S-to-O isomerization to afford the corresponding diastereomers in a 1:1 ratio. Attempts at isolation by crystallization result in small quantities of noncrystalline precipitate in a diethyl ether/minimal methanol mix. This material was difficult to isolate and clean well enough to identify whether it was a single diastereomer or a mixture. Separation by chromatography was clean and more predictable than direct separation by crystallization/cocrystallization and was used to isolate each isomer. This method, used previously to isolate stereoisomers (Bortoluzzi *et al.*, 2004), provided good yields of both (I) and (II), which readily crystallized from diethyl ether and methanol/diethyl ether solutions.
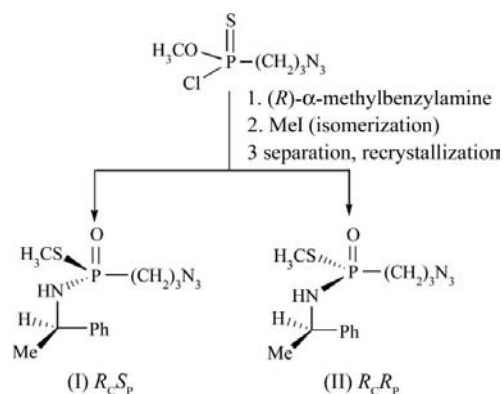
Both compounds crystallize in the space group $P2_12_12_1$, and the chirality was determined by refinement of the Flack (1983) parameter in conjunction with the known chiral carbon center. The cell parameters are similar for each compound, but with significant differences evident in the *a* and *c* axial lengths (differences of *ca* 0.26 and 1.37 Å, respectively), with compound (I), the R_CS_P isomer, having the larger cell.

The molecular species are shown in Fig. 1 and selected geometric parameters are given in Table 1. The bonding patterns within the two systems are very similar around each stereocenter, the largest difference of *ca* 0.02 Å being in the P1—N8 and N8—C9 bonds. Conformational differences are much more pronounced and are reflected in the differences in the torsion angles between the two compounds. Compound (I), the R_CS_P isomer, shown in Fig. 1(*a*), is in a more 'relaxed' conformation, with the aliphatic chain forming a straight backbone with respect to the N8—C9 vector. The azide, –SMe and C10 groups are on the same side of this chain, and the phenyl group and the oxide occupy the other side. Compound (II), the R_CR_P isomer, shown in Fig. 1(*b*), is twisted, with the azide curling back towards the phenyl group. The phenyl, –SMe and azide groups are on the same side of the chain, with

the sulfur in the –SMe group *ca* 3.2 Å from the phenyl ring plane. The conformational differences – relaxed and twisted forms – have also been seen previously in other stereoisomers (Bortoluzzi *et al.*, 2004).

Changes in conformation are reflected in the packing of each system. Each phosphine oxide acts as a hydrogen-bond acceptor for the amine group (N8; see Table 2), which generates a strong intermolecular hydrogen bond linking the molecules into chains parallel to the *a* axis. The twofold axis in both (I) and (II) dictates the placement of the azide group; however, the conformational differences between the structures result in the azide groups wrapping around each other in (I) and facing each other in (II), both in alternating patterns (see Fig. 2). The intermolecular distances between the terminal azide N atoms in (I) and (II) are *ca* 3.5 and 3.2 Å, respectively. In both (I) and (II) there is also a close intermolecular contact between atom C7 (thiomethyl) and an adjacent phenyl group, with a C—H···π plane distance of *ca* 3.5 Å.

Two closely related phosphonamidothioates, both $S_C S_P$, namely *S*-(9-anthracenylmethyl) *N*-(1-phenylethyl)(ethoxyvinyl)thiophosphonamidate (Lee *et al.*, 1992) and (S_P,S_C)-*S*-[2-(4-nitrophenyl)]-2-oxoethyl *N*,*P*-dimethyl-*N*-(1-phenylethyl)-

(a)

(b)

Figure 2
The packing of (*a*) (I) and (*b*) (II), viewed approximately parallel to the *a* axis in each case. Cell axes are labeled and H atoms have been omitted for clarity. Hydrogen bonds are drawn with dashed lines.

phosphonamidothioate (McQueney *et al.*, 1991), have been reported. These molecules have similar bonding patterns to (I) and (II) but have very different intermolecular interactions. The former compound displays a similar hydrogen-bonding synthon (*e.g.* N···O = *ca* 2.96 Å) and the S atom is *ca.* 3.5 Å from the phenyl ring substituent, as seen in (I) and (II). The latter compound is much more complex with many hydrogen-bonding interactions, unlike (I) or (II).
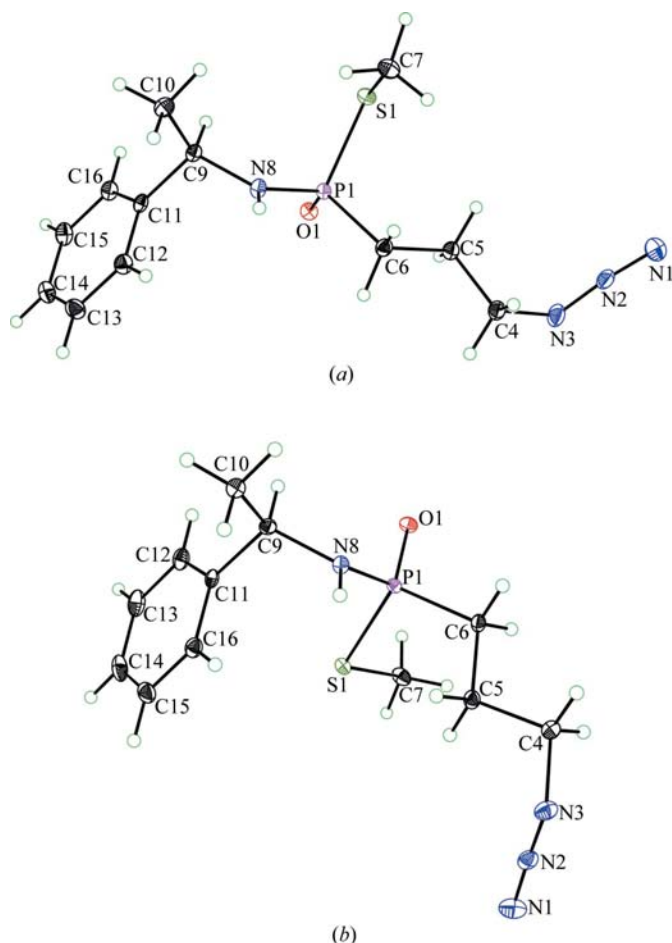
Experimental

(a)

(b)

Figure 1
The molecular structures of (*a*) (I) and (*b*) (II). Displacement ellipsoids are shown at the 30% probability level and H atoms are shown as spheres of arbitrary radii.
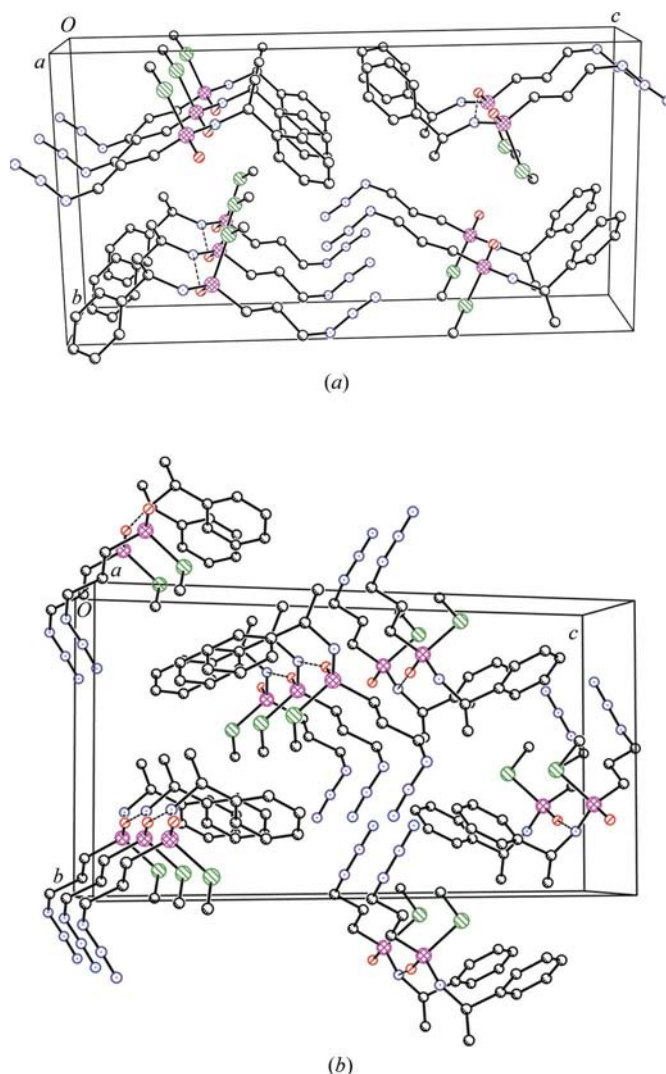
pure fractions of the two diastereomers, which were subsequently recrystallized successively prior to diffraction analysis using diethyl ether and methanol/diethyl ether, respectively.

Isomer (I) was the faster eluting fraction and was recrystallized from diethyl ether: m.p. 368.7–369.0 K; $[\alpha]_D^{20} = +23.6°$ (CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.23–7.33 (5H, m), 4.46–4.56 (1H, m), 3.31 (2H, t, $J = 6.5$ Hz), 3.16 (1H, t, $J = 10.2$ Hz), 2.17 (3H, d, $J = 12.6$ Hz), 1.90–1.97 (2H, m), 1.81–1.87 (2H, m), 1.52 (3H, d, $J = 6.7$ Hz); ^{31}P NMR (161.9 MHz, CDCl$_3$): δ 49.5 (s).

Isomer (II) was collected as the slower eluting fraction and was dissolved in a minimal amount of methanol and crystallized by the slow addition of diethyl ether: m.p. 361.7–362.0 K; $[\alpha]_D^{20} = +60.1°$ (CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.22–7.33 (5H, m), 4.46–4.56 (1H, m), 3.31 (2H, t, $J = 6.5$ Hz), 3.23 (1H, t, $J = 9.1$ Hz), 2.16 (3H, d, $J = 12.6$ Hz), 1.81–1.87 (2H, m), 1.68–1.78 (2H, m), 1.52 (3H, d, $J = 6.7$ Hz); ^{31}P NMR (161.9 MHz, CDCl$_3$): δ 50.9 (s).

Composition analysis of the racemate [(I)/(II)]: ν_{max} (KBr, cm^{-1}): 2099.25 ($-N_3$); HRMS calculated m/z 299.1095, found m/z 299.1093 $(M + H)^+$; analysis calculated for C$_{12}$H$_{19}$N$_4$OPS: C 48.31, H 6.42, N 18.78%; found: C 48.30, H 6.44, N 18.68%.

Compound (I)

Crystal data

C$_{12}$H$_{19}$N$_4$OPS	$V = 1494.56$ (9) Å^3
$M_r = 298.34$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation
$a = 5.1896$ (2) Å	$\mu = 0.32$ mm^{-1}
$b = 12.1755$ (4) Å	$T = 90$ K
$c = 23.6534$ (8) Å	$0.39 \times 0.19 \times 0.17$ mm

Data collection

Bruker SMART APEX diffractometer	22210 measured reflections
Absorption correction: multi-scan (*SADABS*; Bruker, 2007)	3437 independent reflections
	3317 reflections with $I > 2\sigma(I)$
$T_{min} = 0.885$, $T_{max} = 0.947$	$R_{int} = 0.030$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.027$	$\Delta\rho_{max} = 0.39$ e Å^{-3}
$wR(F^2) = 0.065$	$\Delta\rho_{min} = -0.17$ e Å^{-3}
$S = 0.99$	Absolute structure: Flack (1983),
3437 reflections	1418 Friedel pairs
178 parameters	Flack parameter: −0.01 (7)
H atoms treated by a mixture of independent and constrained refinement	

Compound (II)

Crystal data

C$_{12}$H$_{19}$N$_4$OPS	$V = 1469.88$ (13) Å^3
$M_r = 298.34$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation
$a = 5.4509$ (3) Å	$\mu = 0.33$ mm^{-1}
$b = 12.0987$ (6) Å	$T = 90$ K
$c = 22.2882$ (11) Å	$0.48 \times 0.08 \times 0.05$ mm

Data collection

Bruker SMART APEX diffractometer	21644 measured reflections
Absorption correction: multi-scan (*SADABS*; Bruker, 2007)	3372 independent reflections
	2858 reflections with $I > 2\sigma(I)$
$T_{min} = 0.859$, $T_{max} = 0.984$	$R_{int} = 0.074$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.041$	$\Delta\rho_{max} = 0.50$ e Å^{-3}
$wR(F^2) = 0.089$	$\Delta\rho_{min} = -0.24$ e Å^{-3}
$S = 1.02$	Absolute structure: Flack (1983),
3372 reflections	1397 Friedel pairs
174 parameters	Flack parameter: 0.05 (10)
H-atoms treated by a mixture of constrained and independent refinement	

Table 1
Selected bond lengths (Å) and torsion angles (°).

	(I)	(II)
O1—P1	1.4911 (12)	1.4858 (17)
P1—N8	1.6239 (14)	1.641 (2)
P1—C6	1.8037 (16)	1.798 (3)
P1—S1	2.0838 (6)	2.0898 (9)
N8—C9	1.4691 (19)	1.484 (3)
C9—C10	1.529 (2)	1.517 (4)
C9—C11	1.520 (2)	1.523 (3)
O1—P1—N8—C9	−49.64 (15)	52.4 (2)
C6—P1—N8—C9	−174.94 (13)	175.19 (19)
S1—P1—N8—C9	69.34 (13)	−70.80 (19)
P1—N8—C9—C11	100.38 (14)	73.5 (2)
P1—N8—C9—C10	−135.65 (12)	−162.08 (17)

Table 2
Hydrogen-bond geometry (Å, °).

	D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
(I)	N8—H8$\cdots$O1^i	0.81 (2)	2.06 (2)	2.8609 (18)	171.6 (18)
(II)	N8—H8$\cdots$O1^i	0.87	2.11	2.966 (3)	169

Symmetry code: (i) $x - 1, y, z$.

Atom H8 was located *via* difference electron-density maps in both (I) and (II), and the positional and displacement parameters were refined freely in (I), while the displacement parameter was initially refined and finally fixed in (II). All other H atoms were placed in idealized positions and refined using a riding model, with U_{iso}(H) values constrained to be $1.2U_{eq}$ (for CH and CH$_2$ H atoms; C—H = 0.95–1.00 Å) and $1.5U_{eq}$ (for CH$_3$; C—H = 0.98 Å) of the carrier atom.

For both compounds, data collection: *SMART* (Bruker, 2006); cell refinement: *SAINT-Plus* (Bruker, 2006); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *XP* in *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2009).

organic compounds

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