Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(3a*S*,7a*S*)-1-{2-Oxo-1,3-bis[(*S*)-1-phenylethyl]perhydro-1,3,2λ^5-benzodiazaphosphol-2-yl}-1-phenylmethanol: a mixture of diastereoisomers in a disordered crystal

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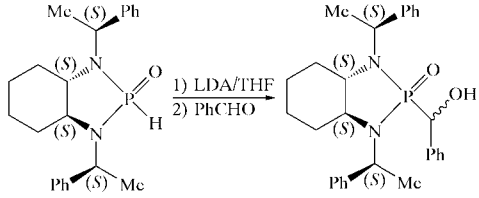
Received 23 March 2004
Accepted 8 April 2004
Online 11 May 2004

In the title compound, $C_{29}H_{35}N_2O_2P$, the stereogenic C center α to the P atom, formed during the Pudovik condensation reaction between a deprotonated chiral diazaphosphole and benzaldehyde, has disordered substituents, giving a mixture of Cα-*R* and Cα-*S* diastereoisomers. Moreover, this compound crystallizes with two independent molecules in the asymmetric unit. The observed configuration at the Cα atom is 0.741 (6)-*S* mixed with 0.259 (6)-*R*, indicating diastereoisomeric enrichment during crystallization. Data from solution and solid-state studies consistently point to an epimerization process at the Cα atom.

Comment

There are many examples in the literature of biologically active α-hydroxyphosphonates and α-phosphonic acids (*e.g.* Engel, 1977; Hilderbrand, 1983; De Clercq *et al.*, 1986; Kitamura *et al.*, 1995). Interest in this class of compounds has been motivated by the need to access a variety of phosphorous derivatives, particularly with substitutions at the Cα position, since such derivatives display required physiological properties (Yokomatsu & Shibuya, 1992; Öhler & Kotzinger, 1993; Berkowitz & Smith, 1995; Bennani & Hanessian, 1997).

In this area, the Pudovik reaction is a well known phosphonylation process that involves the addition of organophosphorous compounds containing a labile P—H bond to unsaturated systems (Pudovik & Konovalova, 1979). During the past decade, enantioselective syntheses of α-hydroxyphosphonates through the asymmetric Pudovik reaction of aldehydes have been reported. These reactions take place in the presence of chiral diols, amino alcohols and diamines as catalysts or using chiral auxiliaries (Davies *et al.*, 1998; Groaning *et al.*, 1998; Duxbury *et al.*, 1999; Yamagishi *et al.*, 1999; Rowe & Spilling, 2001). In this context, we recently obtained moderate diastereoselectivities for the carbonyl phosphonylation of aldehydes using *N*,*N*′-bis-[(*S*)-α-phenylethyl]bicyclic phosphorous acid diamides (Moreno *et al.*, 2004). When attempting to crystallize the adduct between a deprotonated chiral diazaphosphole and benzaldehyde (see scheme below), we observed an unexpected diastereoisomeric enrichment in the solid state. We now report the crystal structure of this compound, (I).



(I)

The asymmetric unit of (I) contains two independent molecules (Z' = 2), with all atoms in general positions. The stereogenic Cα atoms C23 and C73, incorporated during the condensation reaction, have disordered OH and H substituents, while the phenyl (C24 and C74) and P-containing moieties (P1 and P51) do not exhibit disorder (Figs. 1 and 2). Positions and site-occupancy factors for the disordered groups were refined (see *Experimental*), converging to similar models for both independent molecules. Merging of site-occupancy factors results in a stereochemistry for the Cα atom corresponding to a mixture of 0.741 (6)-*S* and 0.259 (6)-*R* molecules, randomly distributed in the crystal, with the remaining chiral C centers as follows: 1*S*, 2*S*, 7*S*, 15*S*, and 51*S*, 52*S*, 57*S*, 65*S*.

Some comments in relation to the unusual disorder observed in (I) are worthwhile. (i) Chiral centers C1, C2, C7 and C15 (and the corresponding chiral C atoms of the second

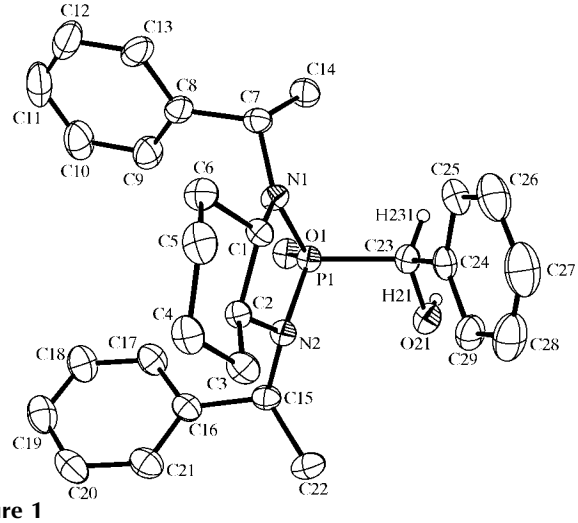


Figure 1
The structure of one of the two independent molecules in (I), with displacement ellipsoids at the 20% probability level. The minor component of the disorder for the substituents at C23 has been omitted (*i.e.* O22, H22 and H232), so that the Cα-*S* major isomer in the solid state is shown. For clarity, H atoms, except H21 and H231, have been omitted.

 DOI: 10.1107/S0108270104008492

molecule) exhibit the same absolute configuration as they do in the starting material, as expected from the synthetic route. This fact confirms the assignment of the configurations at atoms C23 and C73. (ii) Although of limited reliability in the present case, because of the relatively low anomalous dispersion of the P atoms and the polar character of the space group, the refinement of the Flack (1983) parameter is in agreement with the assigned absolute configuration. An attempt to refine the inverted structure leads to a Flack parameter close to 1. Finally, no symptoms of twinning appeared during data collection and structure refinement. (iii) In order to check the reproducibility of the observed absolute configuration, a single crystal obtained from another batch was studied; on the basis of 6129 collected reflections ($2\theta_{max} = 50°$, and $R_1 = 0.04$ for 634 refined parameters and 4493 independent data), the absolute configuration for the Cα atom converged to 0.746 (6)-*S* mixed with 0.254 (6)-*R*, with a Flack parameter of 0.01 (10), a result very close to that obtained for the refinement reported here.

The three above-mentioned points provide strong evidence that the absolute configuration of (I) has been assigned correctly. However, the diastereoisomeric enhancement of ~50% observed in the solid state does not agree with that found in solution. Diastereoisomers were easily distinguishable by ^{31}P NMR spectroscopy; for the crude of the reaction, an isomeric *R*/*S* ratio of 1.8:1.0 was estimated, in contrast with the 1.0:1.9 ratio observed in the solid state. Hence, we assume that this enrichment in the minor diastereoisomer probably occurs *via* a thermodynamically controlled epimerization at the Cα atom during the crystallization process, while the major isomer in solution corresponds to the kinetic product of the condensation reaction. In order to check this hypothesis, a chemical correlation was carried out. Compound (I) was hydrolyzed to give the corresponding phosphonic acid, which was purified by ion exchange chromatography and then converted to the monocyclohexylammonium salt using a classical procedure (see *Experimental*). A comparison with the reported $[\alpha]_D$ values for the enantiomerically pure salts (Smaardijk *et al.*, 1985) indicated that the major isomer for (I) in solution is Cα-*R*.

The two independent molecules of (I) have similar geometries (Table 1). A fit between the two molecules, carried out for non-H atoms, gives an r.m.s deviation of 0.23 Å, mainly because of a degree of free rotation for the phenyl groups. The bicyclic ring system consists of a six-membered cycle in a chair configuration fused with a five-membered ring in an envelope configuration, a conformation observed in numerous perhydrobenzodiazophosphole-based molecules (*e.g.* Koeller *et al.*, 1993; Blazis, Koeller, Rath & Spilling, 1995; Wyatt *et al.*, 1999). The crystal packing of (I) is dominated by hydrogen bonds within the asymmetric unit, which are favored by the $Z' > 1$ value and disorder at the Cα atoms (Table 2 and Fig. 3). Each oxide group forms a bifurcated hydrogen bond with the H atoms belonging to the disordered hydroxy groups of the other independent molecule. This symmetric arrangement generates a non-crystallographic inversion center, positioned close to the centroid of the O1···O51 line. However, there is no doubt that the space group of (I) is actually non-centrosymmetric, in agreement with the chiral character of the molecules. The emulated space group, $P2_1/c$, does not fit the diffraction pattern, for which 255 intensities are above a 3σ threshold in the set of 432 reflections, corresponding to the extinction expected for a *c*-glide plane.

In conclusion, we have established, using both chemical and crystallographic evidence, that the title compound can undergo epimerization at the Cα atom, which has been shown previously to be an important chiral center for biological activity for these P-containing molecules. To our knowledge, epimerization processes involved in the Pudovik condensation reaction have not been well documented until now. This

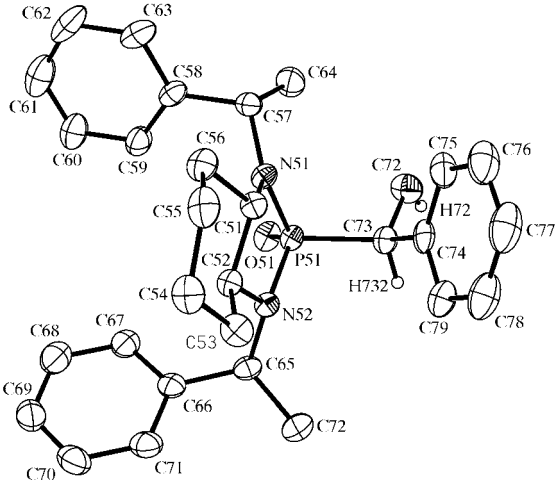


Figure 2
The structure of the other independent molecule in (I), with displacement ellipsoids at the 20% probability level. The major component of the disorder for the substituents at C73 has been omitted (*i.e.* O71, H71 and H731), so that the Cα-*R* minor isomer in the solid state is shown. For clarity, H atoms, except H72 and H732, have been omitted.

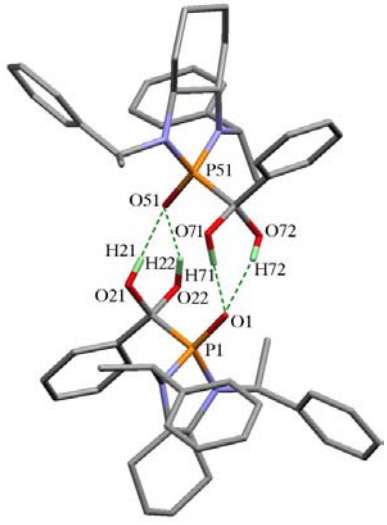


Figure 3
View of the hydrogen bonds (dashed lines) in the asymmetric unit of the title compound. H atoms other than the disordered hydroxy H atoms have been omitted. The major disorder component is represented by atoms O21 and O71.

potential complication probably deserves more attention when using this valuable synthetic tool.

Experimental

For the synthesis of (I), a solution of diisopropylamine (0.182 ml, 1.29 mmol) in tetrahydrofuran (THF, 6 ml) was cooled to 213 K, and *n*-butyllithium (0.471 ml, 1.18 mmol) was added. To this solution was added the diazaphosphole oxide (1.18 mmol) dissolved in THF (3 ml), previously prepared as reported elsewhere (Moreno *et al.*, 2004). The resulting solution was maintained at 213 K for 1 h, and benzaldehyde (1.29 mmol) was added. After an additional reaction time of 4.5 h at 213 K, the reaction mixture was quenched with aqueous ammonium chloride (0.5 ml) and diluted with $CHCl_3$ (60 ml). The solution was washed with water (2 × 25 ml), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product (yield 65%). Single crystals of (I) were obtained by repeated slow evaporation of an AcOEt solution (m.p. 467 K); $[\alpha]_D$ = 13.10 (*c* 1, $CHCl_3$); ^{31}P NMR (in $CHCl_3$, referenced to external 85% H_3PO_4): δ 36.3 (Cα-*R* isomer) and 34.7 p.p.m. (Cα-*S* isomer). To a crop of crystals of (I) (0.38 g, 0.93 mmol) dissolved in dioxane (2 ml) was added aqueous 4 *N* HCl (1 ml). After 2 h, the suspension had dissolved completely. The solution was stirred at room temperature and the progress of the reaction was monitored by ^{31}P NMR spectroscopy until completion (~12 h). The solution was then concentrated *in vacuo* and the residue was passed through an ion exchange column (Amberite IR-120+), eluting with water. The first 50 ml fraction was evaporated to yield the diastereoisomeric mixture of α-hydroxyphosphonic acid resulting from the hydrolysis of (I). The phosphonic acid was dissolved in ethanol and cyclohexylamine was added. The solution was cooled to 263 K for 12 h and the precipitated cyclohexylammonium salt was collected by filtration [50% yield; m.p. 483 K (decomposition); $[\alpha]_D$ = −4.42 (*c* 0.77, MeOH–H_2O 50% *v*/*v*); e.e. = 31% (Blazis, Koeller & Spilling, 1995)].

Crystal data

$C_{29}H_{35}N_2O_2P$
M_r = 474.56
Monoclinic, $P2_1$
a = 9.6413 (11) Å
b = 17.3888 (11) Å
c = 15.8778 (11) Å
β = 95.373 (8)°
V = 2650.2 (4) Å^3
Z = 4
D_x = 1.189 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 85 reflections
θ = 4.7–13.0°
μ = 0.13 mm^{-1}
T = 300 (1) K
Irregular, colorless
0.60 × 0.55 × 0.45 mm

Data collection

Bruker *P*4 diffractometer
2θ/ω scans
Absorption correction: ψ scan (*XSCANS*; Siemens, 1996)
T_{min} = 0.926, T_{max} = 0.942
15 139 measured reflections
7715 independent reflections
5554 reflections with $I > 2\sigma(I)$
R_{int} = 0.028
θ_{max} = 29.0°
h = −13 → 11
k = −1 → 23
l = −21 → 21
3 standard reflections
every 97 reflections
intensity decay: 1.5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.129
S = 1.03
7715 reflections
633 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0681P)^2 + 0.0908P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}
Absolute structure: Flack (1983), 446 Friedel pairs
Flack parameter = −0.02 (8)

Table 1
Selected geometric parameters (Å, °).

P1—O1	1.4823 (18)	P51—O51	1.4833 (19)
P1—N1	1.644 (2)	P51—N51	1.648 (2)
P1—N2	1.663 (2)	P51—N52	1.658 (2)
P1—C23	1.844 (3)	P51—C73	1.847 (4)
O21—C23	1.443 (4)	O71—C73	1.426 (4)
O22—C23	1.444 (7)	O72—C73	1.412 (12)
C23—C24	1.494 (4)	C73—C74	1.511 (4)
O1—P1—N1	116.53 (12)	O51—P51—N51	117.07 (13)
O1—P1—N2	117.52 (12)	O51—P51—N52	116.53 (13)
N1—P1—N2	96.51 (12)	N51—P51—N52	96.44 (12)
O1—P1—C23	108.18 (14)	O51—P51—C73	108.41 (15)
N1—P1—C23	111.47 (14)	N51—P51—C73	110.89 (14)
N2—P1—C23	105.89 (13)	N52—P51—C73	106.73 (14)
O21—C23—O22	107.6 (4)	O72—C73—O71	106.2 (6)
O21—C23—C24	110.2 (3)	O72—C73—C74	109.9 (6)
O22—C23—C24	111.6 (4)	O71—C73—C74	111.0 (3)
O21—C23—P1	106.5 (2)	O72—C73—P51	110.0 (6)
O22—C23—P1	106.8 (4)	O71—C73—P51	105.6 (2)
C24—C23—P1	113.9 (2)	C74—C73—P51	113.8 (2)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O21—H21···O51	0.85	1.89	2.718 (4)	165
O22—H22···O51	0.93	1.71	2.587 (7)	156
O71—H71···O1	0.97	1.72	2.688 (4)	176
O72—H72···O1	0.72	1.90	2.608 (12)	167

Atoms O21 and O71 belonging to the hydroxy groups bonded to atoms C23 and C73 were found to be disordered with, respectively, atoms O22 and O72. The coordination of atoms C23 and C73 is completed by disordered H atoms, placed at idealized positions. Site-occupancy factors (SOFs) were refined in two parts, independently for each molecule, with the sum of the SOFs for the two disordered components in each molecule constrained to 1. H atoms of the hydroxy groups were found in difference maps and were included in the disorder model with SOFs corresponding to those of the parent O atoms. Finally, all other H atoms were placed at idealized positions. All H atoms were treated using a riding model, with constrained distances and U_{iso}(H) values fixed at xU_{eq}(parent atom) (C—H = 0.98 Å and *x* = 1.2 for methine H atoms, C—H = 0.97 Å and *x* = 1.2 for methylene H atoms, C—H = 0.96 Å and *x* = 1.5 for methyl H atoms, and C—H = 0.93 Å and *x* = 1.2 for aromatic H atoms). O—H distances were fixed at the values found from difference maps (*x* = 1.5).

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *SHELXTL-Plus* (Sheldrick, 1998); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL-Plus*; software used to prepare material for publication: *SHELXTL-Plus*.

We thank CONACYT for financial support (project No. 39500-Q and grant No. 91275).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1717). Services for accessing these data are described at the back of the journal.

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