First Resolution of a Free Secondary Phosphine Chiral at Phosphorus

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A single diastereoisomer of (−)-menthylmesitylphosphine has been isolated in 94% purity, thereby effecting the first resolution of a free secondary phosphine chiral at phosphorus.

Although the first resolution of a simple acyclic tertiary phosphine chiral at phosphorus was reported in 1961,[1] the resolution of a similar secondary phosphine does not appear to have been investigated hitherto, despite the observation by NMR spectroscopy of diastereoisomers of compounds due to slow inversion at a pyramidal secondary phosphine-*P* stereocentre.[2,3] The amphoteric nature of a secondary phosphine, in particular its basicity (protonation of a chiral secondary phosphine produces an achiral phosphonium ion),[4] is the chief reason for sensitivity to racemisation of such compounds. Thus, when protected from protons by coordination to metal ions [$M^+ \leftarrow PHR^1R^2$],[5] borane [$H_3B \leftarrow PHR^1R^2$],[6] or chalcogens [$X \leftarrow PHR^1R^2$, where X = O, S, or Se],[7] secondary phosphines have been resolved, but recovery of the optically active secondary phosphines from the adducts has not been accomplished. Here we report that the diastereoisomers of (−)-menthylmesitylphosphine (Fig. 1) can be separated by fractional crystallisation of the mixture from acetonitrile containing sodium acetylacetonate (Na[acac]) as proton scavenger, thereby effecting the first resolution of a free secondary phosphine chiral at phosphorus. In 1979 the synthesis of (−)-menthylphenylphosphine was reported but no attempts were made to separate the pair of diastereoisomers observed.[3]

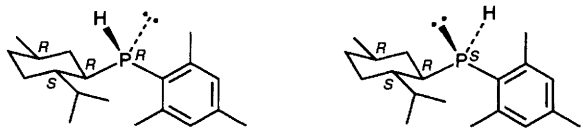

Fig. 1 Diastereoisomers of (−)-menthylmesitylphosphine

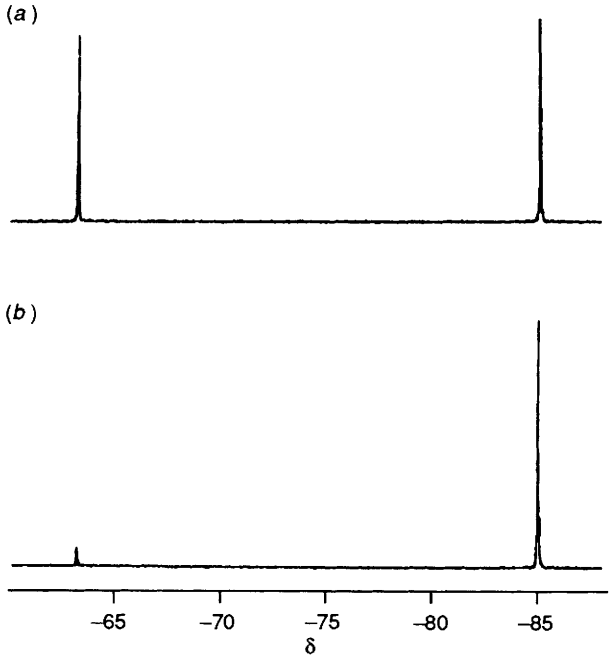

Fig. 2 $^{31}P\{^1H\}$ NMR spectrum of (−)-menthylmesitylphosphine in CD_3CN (equilibrium mixture) (*a*); similar spectrum of secondary phosphine in CD_3CN–Na[acac] showing enrichment of one diastereoisomer (*b*)

Treatment of dichloromesitylphosphine with (−)-menthylmagnesium chloride (1.14 equiv.) in THF at −78 °C affords chloromenthylmesitylphosphine in high yield as an equimolar mixture of the two diastereoisomers epimeric at phosphorus according to the $^{31}P\{^1H\}$ NMR spectrum. Upon reduction with LAH in diethyl ether, the secondary chlorophosphine yields (−)-menthylmesitylphosphine in 48% yield after seven recrystallisations from highly purified acetonitrile.[8] The almost air-stable product crystallizes from hot acetonitrile as long needles having mp 79–88 °C, and is readily soluble in benzene, dichloromethane, diethyl ether and *n*-hexane.† In [$^2H_6$]benzene, the $^{31}P\{^1H\}$ NMR spectrum of the phosphine consists of two singlets for the pair of diastereoisomers at δ −62.62 (55%) and δ −84.24 (45%). In [$^2H_3$]acetonitrile, the signals for the diastereoisomers appear at δ −63.47 (43%) and δ −85.16 (57%) [Fig. 2(*a*)]. Attempted fractional crystallisation of the equilibrium mixture from neat acetonitrile met with no success. When repeated in acetonitrile containing sodium acetylacetonate (0.04% m/v) over the temperature range of 60 −35 °C however, the fractional crystallisation of the mixture (20 g l^{-1}) afforded *ca.* 50% of the material enriched in the diastereoisomer having δ − 85.16, while the mother liquor was correspondingly enriched in the diastereoisomer having δ −63.47.‡ The progress of the separation was monitored by recording the $^{31}P\{^1H\}$ NMR spectra of the various fractions in acetonitrile containing 0.04% sodium acetylacetonate. Six consecutive recrystallisations of the less soluble component of the mixture from the solvent containing base gave the diastereoisomer having δ −85.16 in 94% purity, as indicated in Fig. 2(*b*). Dissolution of the enriched diastereoisomer in highly purified acetonitrile in the absence of the base led to immediate epimerization at phosphorus and the establishment of the equilibrium 43:57 mixture of the diastereoisomers within the time of recording the NMR spectrum (*ca.* 5 min).

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Footnotes

† Satisfactory elemental analyses were obtained.

‡ *Selected spectroscopic data* for less soluble diastereoisomer: ^1H NMR (299.95 MHz, CD_3CN containing 0.04% Na[acac]) δ 0.714 (d, $^3J_{HH}$ 6.60 Hz, 3 H, CH*Me*), 0.84 (d, $^3J_{HH}$ 6.00 Hz, 3 H, CH*Me*$_2$), 0.95 (d, $^3J_{HH}$ 6.90 Hz, 3 H, CH*Me*$_2$), 0.70–1.36 (m, 6 H, unresolved), 1.62–1.76 (m, 2 H, unresolved), 1.96–2.08 (m, 1 H, C*H*Me$_2$), 2.13–2.23 (m, 1 H, PCH), 2.23 (s, 3 H, *p*-Me), 2.47 (s, 6 H, *o*-Me), 4.37 (d of d, $^1J_{HP}$ 215.36 Hz, $^3J_{HH}$ 5.85 Hz, 1 H, PH), 6.90–6.93 (m, 2 H, aromatics); $^{31}P\{^1H\}$ (80.98 MHz, C_6D_6, ref. H_3PO_4) δ −84.24; IR (KBr) ν_{PH}/cm^{-1} 2318 cm^{-1}; MS *m/z* 290 ($C_{19}H_{31}P$, $M^{\cdot+}$); $[\alpha]_D$ −186 (*c* 0.273, MeCN containing 0.04% Na[acac]) (purity 94%).

For more soluble diastereoisomer: ^1H NMR (299.95 MHz, CD_3CN containing 0.04% Na(acac]) δ 0.708 (d, $^3J_{HH}$ 6.60 Hz, 3 H, CH*Me*), 0.77 (d, $^3J_{HH}$ 6.90 Hz, 3 H, CH*Me*$_2$), 0.94 (d, $^3J_{HH}$ 6.90 Hz, 3 H, CH*Me*$_2$), 0.68–1.35 (m, 5 H, unresolved), 1.48–1.58 (m, 1 H, unresolved), 1.63–1.73 (m, 2 H, unresolved), 1.75–1.89 (m, 1 H, PCH), 2.22 (s, 3 H, *p*-Me), 2.37 (s, 6 H, *o*-Me), 2.38–2.48 (m, 1 H, C*H*Me$_2$), 3.90 (d of d, $^1J_{HP}$ 216.56 Hz, $^3J_{HH}$ 9.45 Hz, 1 H, PH), 6.86–6.90 (m, 2 H, aromatics); $^{31}P\{^1H\}$ (80.98 MHz, C_6D_6, ref. H_3PO_4) δ −62.62; IR (KBr) ν_{PH}/cm^{-1} 2338.

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