# Stereochemistry of Diphenylphosphide Displacement at Saturated Carbon. Conformation and Relative Reactivity of Menthyl- and Neomenthyldiphenylphosphine Homogeneous Hydrogenation Complexes

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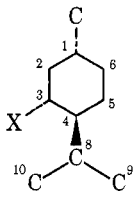
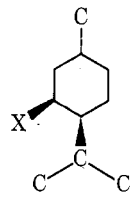
Menthyl and neomenthyl chloride react with alkali metal diphenylphosphides to produce epimeric, tertiary phosphines with inversion of configuration. The stereochemistry and conformation of the products neomenthyldiphenylphosphine (NMDPP) and menthyldiphenylphosphine (MDPP) were determined by $^1H$ NMR and $^{13}C$ NMR spectroscopy. Conformational and configurational differences between NMDPP and MDPP are also reflected in their behavior as chiral ligands in asymmetric homogeneous hydrogenation systems. Rh(I) complexes prepared from these epimers showed differences in both activity and the direction and degree of asymmetric induction when used as catalysts for the homogeneous hydrogenation of α-methylcinnamic acid.

In previously reported studies on the chemistry of lithium diphenylphosphide[2] it has been established that vinyl halides undergo stereospecific displacement with retention of configuration to give vinyldiphenylphosphines. Thus, reaction of lithium diphenylphosphide with *cis*- and *trans*-1,2-dichloroethanes leads to *cis*- and *trans*-1,2-vinylenebisdiphenylphosphines, respectively,[3] while *cis*- and *trans*-β-bromostyrenes provide *cis*- and *trans*-β-styryldiphenylphosphines, respectively.[4] Both of these results were established through characterization of the corresponding phosphine oxides. The latter work showed that the displacement occurred with retention of configuration rather than by two successive inversions as would be possible in the former case.

We now wish to report that nucleophilic replacement of halide ion from a saturated carbon by the diphenylphosphide moiety occurs with inversion of configuration at carbon as is found in normal SN2 displacements. Reaction of menthyl chloride (**1**) or menthyl bromide (**2**) with lithium, sodium, or potassium diphenylphosphide provided a compound that has been shown by 220-MHz proton NMR and by $^{13}C$ NMR to have the neomenthyldiphenylphosphine (NMDPP) structure (**3**). Conversely, treatment of neomenthyl chloride (**4**) with an alkali metal diphenylphosphide gives the epimeric menthyldiphenylphosphine (MDPP, **5**). Oxidation of **3** and **5** with 3% hydrogen peroxide produces the corresponding phosphine oxides **6** and **7**, respectively, and NMR spectra of the oxides confirm the above stereochemical conclusions.





**1**, X = Cl **7**, X = $Ph_2P{=}O$ **3**, X = $Ph_2P$
**2**, X = Br **8**, X = OH **4**, X = Cl
**5**, X = $Ph_2P$ **9**, X = H **6**, X = $Ph_2P{=}O$

Reaction of the menthyl and neomenthyl halides with lithium diphenylphosphide in refluxing THF solution was found to be quite sluggish when compared with the reaction of an unhindered secondary alkyl halide such as cyclohexyl chloride. Refluxing a mixture of **1** with lithium diphenylphosphide in a 1:1 molar ratio required at least 24 h to completely dissipate the characteristic red phosphide anion color while the reaction of cyclohexyl chloride with lithium diphenylphosphide is complete within 3 h. The reaction time can be reduced to about 12 h if a large excess of the menthyl halide is used.

It is not yet clear if the replacement of a halide bonded to a tetrahedral carbon with inversion of configuration is a general phenomenon. The fact that lithium, sodium, and potassium diphenylphosphide give the same result indicates that the mechanism of replacement is different for vinyl halides than for alkyl halides. This is true because a mixture of products is obtained with sodium diphenylphosphide in the reaction of the vinylenebis dichlorides and β-bromostyrenes. It cannot be definitively concluded that there is a displacement of the alkyl halide by a "diphenylphosphide ion" because potassium diphenylphosphide, with its more ionic metal to phosphorus bond, is not as effective as the sodio compound.

In another report, synthetic procedures for NMDPP and MDPP are detailed for the reaction of sodium diphenylphosphide with the appropriate chloride.[5] The choice of sodium diphenylphosphide was dictated by the results of comparative yield experiments with lithium, sodium, and potassium diphenylphosphide and menthyl chloride. The NMDPP yield ratios were 1:1.55:1.16, respectively, when the reactions were carried out according to a standard procedure.[5]

The orientations of substituents occurring on the cyclohexane rings in **3**, **5**, **6**, and **7** were deduced by $^1H$ NMR and $^{13}C$ NMR spectroscopy. The line widths of the $^1H$ NMR resonances representing H-3 in **5** and **7** are much greater than those of H-3 in **3** and **6** because the multiplicity occurring in the former absorptions is caused by the spin–spin interactions of axial–axial as well as axial–equatorial protons, whereas in the latter case the fine structure was due to equatorial–axial and equatorial–equatorial couplings. The $^1H$ NMR data therefore indicate that the diphenyl phosphine and the diphenyl phosphine oxide groups occupy equatorial positions in **5** and **7** but axial orientations in **3** and **6**.

Table I. 25.2-MHz $^{13}C$ NMR Spectral Data for Menthyl and Neomenthyl Compounds

| Carbon atoms | 5 Menthyl phosphine[a] | 3 Neomenthyl phosphine | 7 Menthyl phosphine oxide | 6 Neomenthyl phosphine oxide | 9 Menthane[b] | 8 Menthol[b] |
|---|---|---|---|---|---|---|
| 1 | 34.0 (2.5)[c] | 27.7 (5.8) | 33.6 (13.3) | 28.5 (2.5) | 36.0 | 32.2 |
| 2 | 37.9 (1.3) | 39.5 (2.5) | 36.6 (1.9) | 38.6 (0.5) | 33.4 | 45.9 |
| 3 | 38.2 (21.8) | 35.8 (19.9) | 39.6 (70.5) | 37.0 (68.1) | 30.2 | 71.2 |
| 4 | 45.7 (13.1) | 50.3 (15.8) | 43.8 (3.1) | 50.5 (2.4) | 44.4 | 50.7 |
| 5 | 25.9 (8.8) | 26.4 (9.8) | 25.2 (12.0) | 26.0 (1.7) | 30.2 | 23.8 |
| 6 | 35.3 | 36.3 | 34.7 (1.3) | 36.2 | 33.2 | 35.3 |
| 7 | 22.6 | 22.7 | 22.6 | 22.8 | 22.8 | 22.6 |
| 8 | 28.5 (20.5) | 30.1 (9.6) | 28.5 (3.2) | 29.9 (2.5) | 36.0 | 26.1 |
| 9 | 15.5 (1.2) | 22.4 (1.2) | 16.0 | 22.7 | 19.3 | 16.3 |
| 10 | 21.7 | 21.2 (0.9) | 21.8 | 21.4 | 19.3 | 21.3 |

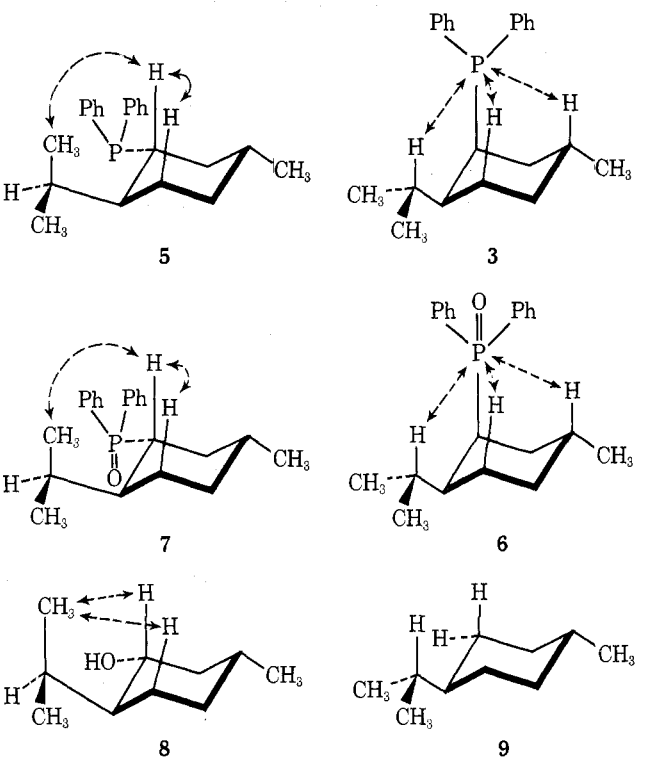
[a] Expressed in parts per million relative to internal $Me_4Si$. [b] Obtained from J. Jautelat, J. B. Grutzner, and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, **65**, 288 (1970), by converting the chemical shift data from (relative to $CS_2$) to $Me_4Si$ by subtracting their value from 192.8 ppm. [c] The $^{13}C$–$^{31}P$ coupling constants are recorded in parentheses. $J$ and $\delta$ are estimated to be accurate to ±1 Hz or ±0.04 ppm.

$^{13}C$ NMR spectral data not only confirm the above conclusions but also help resolve the location of the isopropyl group at C-4 and the secondary methyl group at C-1 in the four compounds. These latter determinations were achieved by comparing the $^{13}C$ chemical shifts of carbon atoms occurring in the four compounds with those of menthol (**8**) and methane (**9**) and then correlating the $^{13}C$ NMR spectral data with the well-known fact that the 1,3-diaxial type steric interaction causes upfield shifts in the resonances of the interacting $^{13}C$ nuclei. Comparison of the $^{13}C$ chemical shift of the methyl carbons C-7, -9, and -10 (see Table I) indicates that they are very similar in **5**, **7**, and **8** and, since the orientation of the isopropyl and methyl groups in **8** is known to be equatorial, it is reasonable to assume that these groups in **5** and **2** must also occupy the same positions, namely equatorial. The upfield shifts observed in the resonance positions of C-9, C-5, and C-8 in **5**, **7**, and **8** (see Table I) in relation to the $^{13}C$ signals of respective carbon atoms in **9** are attributed to the steric interactions as depicted in the structures of **5** and **7** (see Chart I). In **3** and **6** where diphenylphosphine and diphenylphosphine oxide groups at C-3 have axial orientations, steric interactions between C-9 methyl and C-5 axial protons (present in **5**, **7**, and **8**) do not occur and as a result C-9 resonances experience downfield shifts in **3** and **6**. These observations, coupled with the fact that the chemical shifts of C-7 and C-10 in **3** and **6** are very similar (see Table I) to those of the respective carbon atoms in **5**, **7**, and **8**, clearly suggest that the substituents at C-1 and C-4 in **3** and **6** have the same stereochemistry as in **5**, **3**, **7**, and **8**. The variance of the resonance positions of C-1, C-5, and C-8 in **3** and **6** as compared to **5** and **7** (see Table I) is largely due to the various steric interactions represented in the conformational drawings of the respective compounds (see Chart I). The dissimilarity in the chemical shifts of C-3, C-2, and C-4 signals in **3**, **5**, **6**, **7**, and **8** (see Table I) is due to the $\alpha$ and $\beta$, effects caused by differences in the electronegativities of the substituents at C-3 as well as the steric interactions shown in Chart I.

The configurational and conformational differences between NMDPP (**3**) and MDPP (**5**) are reflected in their behavior as ligands in homogeneous hydrogenation systems. Previously we reported that NMDPP was effective as a chiral ligand in soluble Rh(I) hydrogenating complexes.[6] Both NMDPP and MDPP have been utilized as ligands in asymmetric hydrosilylations catalyzed by metal complexes.[7] In the latter reaction they induce opposite chiralities.

The reduction of $\alpha$-methylcinnamic acid was studied in order to evaluate possible differences between these epimeric ligands both with respect to the activity of Wilkinson-type hydrogenation catalysts derived from them and the chiral sense of their asymmetric influence.

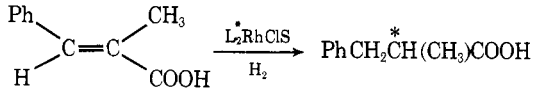
**Chart I. Conformational Drawings of Compounds Used in NMR Studies Showing 1,3-Diaxial Type Interactions**




In order to promote appreciable reduction in a reasonable period of time extended conditions (higher temperature and pressure) compared to the typical Wilkinson catalyst conditions were used. Extended conditions are necessary to ensure the reduction of more hindered olefinic substrates. To further promote reduction, triethylamine was added to the reaction to convert the substrate to a carboxylate anion which is reduced more rapidly than the free acid.[8] The precise reaction conditions are summarized in Chart II and in the Experimental Section.

In a 24-h period a Rh(I) catalyst (presumably $RhL_2{}^*ClS$ in solution, where L* is the chiral tertiary phosphine ligand and S is a solvent molecule[9]) prepared from NMDPP produced about 1.5 times the amount of reduction of $\alpha$-methylcinnamic acid as did a similar catalyst system from MDPP (Chart II). The epimeric catalysts produced enantiomeric products and the percent enantiomeric excess (%

**Chart II. Comparative Yields and Stereochemistries for Hydrogenations with NMDPP and MDPP Catalysts**




| L* | 24-h yield, % | % ee |
|---|---|---|
| NMDPP | 100 | 60 (*R*) |
| MDPP | 67 | 17 (*S*) |

ee = % *R* − % *S* or vice versa) was more than three times greater for the NMDPP catalyst.

The lower activity of the MDPP catalyst may reflect a stronger binding of the ligand to the rhodium in this case as compared to NMDPP. Models suggest that the phosphorus in MDPP is less hindered than that in NMDPP and therefore NMDPP may dissociate more readily to give the coordinately unsaturated intermediate required for catalytic activity.[10] This effect may be accentuated under the relatively high ligand loadings (L*:Rh = 15:1) used in these extended condition experiments.

## Experimental Section

**Lithium diphenylphosphide** was prepared from diphenylphosphinous chloride and lithium metal in dry tetrahydrofuran (THF) solution under a nitrogen atmosphere following the method of Aguiar and Archibald.[2b]

**Neomenthyldiphenylphosphine (3).**[11] To a nitrogen-filled flask containing a solution of 6.01 g (0.035 mol) of (−)-menthyl chloride in 25 ml of THF was added 17 ml of a solution of lithium diphenylphosphide in THF prepared from 0.030 mol of diphenylphosphinous chloride and 0.12 mol of lithium. The mixture was refluxed for 26 h after which a yellow solution and a white precipitate had replaced the characteristic red color of the lithium diphenylphosphide. The mixture was poured into 50 ml of water and the phosphine was extracted into ether. The ether solution was dried ($Na_2SO_4$) and evaporated, and the residual oil was kept under nitrogen in a refrigerator for 60 h during which time crystals had separated. These were filtered and washed with methanol, yield 1.16 g (10%). In other preparations the phosphine was vacuum distilled, bp 165–170 °C (0.2 mm), then recrystallized repeatedly from petroleum ether (bp 30–60 °C), ir $\nu_{max}$ ($CHCl_3$) 1432 $cm^{-1}$ (no absorptions near 1180 or 1120 $cm^{-1}$). The phosphine was further characterized as the benzylneomenthyldiphenylphosphonium bromide prepared by reaction of 1.2 g of the phosphine with 6.0 g of benzyl bromide for 14 h at ambient temperature followed by 3 h at reflux. The excess benzyl bromide was removed in vacuo and ether was added to the residue. A white solid formed which was recrystallized from benzene–acetonitrile, mp 220–223 °C, ir $\nu_{max}$ ($CHCl_3$) 1437, 1106 $cm^{-1}$.

**Neomenthyldiphenylphosphine Oxide (6).** To a nitrogen-filled flask containing 0.016 mol of lithium diphenylphosphide prepared from 0.35 g of lithium and 2.3 ml of diphenylphosphinous chloride in 30 ml of THF was added 2.0 g (0.012 mol) of (−)-menthyl chloride in 15 ml of THF. The solution was refluxed for 24 h until the characteristic red color of the phosphide had dissipated and a yellow solution containing a white precipitate remained. The mixture was poured into 50 ml of 3% hydrogen peroxide and the organic solvent phase was allowed to evaporate. Crystals formed at the phase interface which were filtered off and recrystallized from ethanol. The yield was 1.2 g, 31%. Further recrystallization from hexane–benzene provided the oxide having mp 217–221 °C, ir $\nu_{max}$ ($CHCl_3$) 1433, 1175, 117 $cm^{-1}$.

**(*E*)-α-Methylcinnamic Acid.**[13] Benzaldehyde (106 g, 1 mol), sodium acetate (82.0 g, 1 mol), and propionic anhydride (160 g, 1.23 mol) were heated at reflux for 35 h. The reaction mixture was then poured onto ice and acidified with hydrochloric acid. The acid solution was extracted with ether. The ether extract was extracted with 2 M sodium hydroxide solution and the basic extract was, in turn, washed with ether and then acidified. The crude product separated as an oil and was extracted into ether. The ether extract was washed with water, dried, and concentrated to give an oil which crystallized on standing. The crude acid was recrystallized from 60–80 °C petroleum ether in three crops, total yield 128.1 g (79%), mp 80–81 °C.

**Asymmetric Hydrogenations.** A homogeneous catalyst solution was prepared by stirring (30 min) a mixture of $[Rh(COD)Cl]_2$[12] (16.6 mg, 33.7 μmol) and either NMDPP or MDPP (171 mg, 95% phosphine, 5% phosphine oxide, 0.5 mmol phosphine) in 1:1 (v/v) benzene–ethanol (100 ml, freshly deoxygenated with nitrogen) under 3.5 atm of hydrogen. The prereduced catalyst solution was added to a solution of (*E*)-α-methylcinnamic acid (4.05 g, 25 mmol) and triethylamine (0.4 g, 4 mmol) in deoxygenated 1:1 benzene–ethanol (100 ml). The resulting reaction mixture was hydrogenated at 300 psi and 60 ± 5° for 24 h.

**Hydrogenation with NMDPP Catalyst.** After the reduction period the reaction mixture was evaporated under vacuum and the residue was partitioned between 10% sodium hydroxide (50 ml) and methylene chloride (50 ml). The aqueous layer was separated, washed with ether, and then acidified with hydrochloric acid. The acidified solution was extracted twice with 30-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to give a crude acid product (3.85 g, 94%). The NMR spectrum was that of 2-methyl-3-phenylpropanoic acid and there were no signals characteristic of unreduced substrate. The crude acid was distilled, bp 99–107 °C (0.4 mm), 3.7 g (90%), $[\alpha]^{19}D$ −16.2 °C (*c* 11.59, benzene), which corresponds to a 60% ee of the *R* isomer based on $[\alpha]^{20}D$ 27.02° for the pure enantiomer.[14]

**Hydrogenation with MDPP Catalyst.** This reduction was carried out in exactly the same manner as that with NMDPP. The crude acid product (3.9 g) was shown by NMR to contain about 67% 2-methyl-3-phenylpropanoic acid and 33% unreacted α-methylcinnanic acid. The crude acid mixture was distilled, bp 92–94 °C (0.02 nm), to give 1.8 g of a mixture containing 94.4% 2-methyl-3-phenylpropanoic acid and 5.6% starting material. This mixture had $[\alpha]^{21}D$ +4.3° (*c* 11.08, benzene) which corresponds to 15.9% ee, or 16.8% ee correcting for the amount of achiral starting material present on the assumption that it has only a dilution effect on the rotation.

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**Registry No.**—**1**, 16052-42-9; **3**, 43077-29-8; **4**, 13371-12-5; **5**, 43077-31-2; **6**, 43077-30-1; **7**, 43077-32-3; $L_2RhClOEt$, 58191-29-0; (*E*)-α-methylcinnamic acid, 1895-97-2; benzaldehyde, 100-52-7; propionic anhydride, 123-62-6; lithium diphenylphosphide, 58191-08-5; (*R*)-2-methyl-3-phenylpropanoic acid, 14367-67-0; (*S*)-2-methyl-3-phenylpropanoic acid, 14367-54-5.

**Supplementary Material Available.** $^{13}C$ NMR figures for compounds **3**, **5**, **6**, and **7** (2 pages). Ordering information is given on any current masthead page.

## References and Notes

(1) (a) Requests for additional information should be directed as follows: concerning phosphide displacements (A.M.A.); NMR data and analysis (N.S.B.); homogeneous hydrogenation experiments (J.D.M.). (b) Department of Chemistry, Rutgers University, Newark, N.J. 07102.
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(15) **Note Added in Proof.** Since completion of our study and its submitted for publication, an article by F. Bohlmann, R. Zeisberg, and E. Klein, *Org. Magn. Reson.*, **7**, 426 (1975), tends to confirm our $^{13}C$ spectral assignments of the four new compounds.