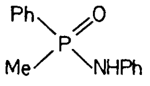
# Nuclear Magnetic Resonance Non-equivalence of the Enantiomers in Optically Active Samples of Phosphinic Amides

By Martin J. P. Harger
(*Department of Chemistry, The University, Leicester* LE1 7RH)

*Summary* The $^1$H n.m.r. spectra of optically active (but optically impure) samples of methylphenylphosphinic amide (**3**) and its *N*-phenyl (**1**) and *N*-*p*-nitrophenyl (**2**) analogues exhibit distinct signals for the *P*-methyl groups in the (*R*) and (*S*) enantiomers.

The ratio of the enantiomers in a sample of a chiral compound can be determined by n.m.r. spectroscopy if chemical modification with an optically active reagent gives diastereoisomers having appreciably different spectroscopic properties.[1] Alternatively, the enantiomers may exhibit useful spectroscopic differences when examined in an optically active solvent,[2] or in the presence of an optically active substance[3] such as a lanthanide shift reagent.[4] We now report that the enantiomeric composition of samples of



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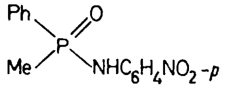

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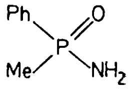

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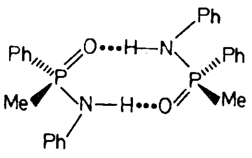

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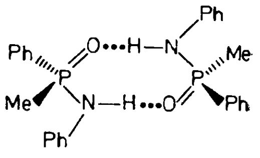

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some chiral phosphinic amides can be investigated directly by n.m.r. spectroscopy without the aid of any foreign optically active substance.

In the $^1$H n.m.r. spectrum[†] of pure (*S*)-(*N*-phenyl)methylphenylphosphinic amide (**1**),[5] $[\alpha]_D$ $-28·5°$ (MeOH), in $CDCl_3$ (0·23 M solution) the *P*-methyl group appears as a doublet, $J_{PH}$ 13·6 Hz, at $\delta$ 1·74. Addition of sufficient racemic (**1**) (0·23 M solution in $CDCl_3$) to give a solution in which the enantiomer ratio (*S*) : (*R*) is 95 : 5, results in the appearance of an additional small high field doublet, $J_{PH}$ 13·5—14 Hz, at $\delta$ 1·54. Continued addition of racemic (**1**) causes the small high field doublet progressively to increase in intensity and move to lower field, while the original low field doublet shifts less dramatically upfield. The separation between the two signals decreases linearly by *ca.* 0·023 p.p.m. for each 5% increase in the proportion of the (*R*) enantiomer in the mixture. Representative spectra are shown in the Figure, together with the spectrum of racemic (**1**) which gives a single *P*-methyl doublet, $J_{PH}$ 13·6 Hz, at somewhat higher field ($\delta$ 1·68) than is the corresponding signal for pure (*S*)-(**1**). Integration of the spectra shows that in each case the ratio of the intensities of the two *P*-methyl resonances is the same as the ratio of the two enantiomers in the mixture. It is therefore possible to measure the enantiomer ratio in an optically active sample of (**1**) without recourse to optically active reagents, solvents, or shift reagents.

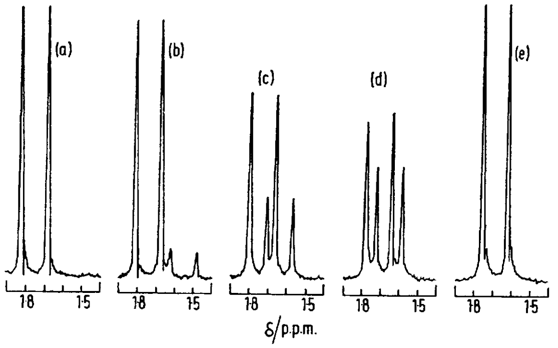

FIGURE. $^1$H N.m.r. spectra (100 MHz) of (**1**) in $CDCl_3$ showing the *P*-methyl resonance(s) for samples of various enantiomeric composition: (a) 100%(*S*); (b) 90%(*S*), 10%(*R*); (c) 70%(*S*), 30%(*R*); (d) 60%(*S*), 40%(*R*); (e) 50%(*S*), 50%(*R*).

In attempting to explain the remarkable behaviour of phosphinic amide (**1**), we recall evidence that this type of compound tends to form hydrogen-bonded dimers in non-polar solvents.[6] That being so, a chiral phosphinic amide such as (**1**) may exist in solution as diastereoisomeric dimers such as (**4**) and (**5**) depending on whether the associated amide molecules have the same or opposite configurations at phosphorus. Assuming that there is no marked preference for association of molecules of like or opposite configuration,[‡] rapid exchange of partners will mean that the major enantiomer in an unequal mixture is on average paired mostly with a molecule of like configuration, whereas the minor enantiomer will usually be paired with a molecule of opposite configuration. Thus the two enantiomers will be related differently to their time-averaged local environments and will in principle give rise to distinct n.m.r. spectra. As the ratio of the enantiomers in the mixture tends to unity, so the difference will decrease until in a solution of the racemate each enantiomer is associated equally with molecules of like and opposite configuration. In such a mixture the two enantiomers will have a common n.m.r. spectrum, which will not be the same as the spectrum of a pure single enantiomer.

Behaviour analogous to that of (**1**) is displayed by (*N*-*p*-nitrophenyl)methylphenylphosphinic amide (**2**) [$\Delta\delta_{P-Me}$ 0·26 p.p.m. for 96% (*S*), 4% (*R*)] and, significantly in as much as it shows that a substituent on nitrogen is not essential, by the primary phosphinic amide (**3**). However, in the latter case the difference in chemical shift of the *P*-methyl groups of the enantiomers is relatively small [$\Delta\delta_{P-Me}$ 0·046 p.p.m. for 95% (*S*), 5% (*R*)], suggesting that for (**1**) and (**2**) the aromatic substituents on nitrogen do make important contributions to the observed non-equivalence of the methyl groups in their enantiomers.

For all three amides (**1**)—(**3**) the less intense *P*-methyl n.m.r. signal, originating from the minor enantiomer, is the one at higher field. A molecule of the minor component in an enantiomer mixture will, on average, be associated mainly with a molecule of opposite configuration, as in the dimer (**5**). It may be that in this situation its *P*-methyl group experiences shielding by the $\pi$ electrons of the *P*-phenyl group of its partner. Such shielding would be less important for the major component because its molecules will usually be paired as in (**4**).

The non-racemic mixtures investigated so far have all contained an excess of the (*S*) enantiomer. If our interpretation of the observed spectra is correct, identical spectra will be obtained using mixtures with the same enantiomer ratios but with the (*R*) form in excess. We hope to test this prediction, and also to establish the ability of an optically active phosphinic amide such as (**1**) to induce spectroscopic differences in the enantiomers of a structurally distinct racemate.

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[†] N. m. r. spectra were recorded at 100 MHz and 15 °C with $Me_4Si$ ($\delta$ 0·00) as internal standard.

[‡] This assumption is made only to simplify the discussion; it is unnecessary and may not be strictly correct.

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