

Chiral Ligands: Unambiguous Assignment of Absolute Configuration by NMR Spectroscopy

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Two-dimensional rotating-frame nuclear Overhauser enhancement (ROESY) spectra are used to determine the relative configurations at the chiral carbon atoms in the two diastereoisomers of $[\sigma\text{-C}_6\text{H}_4\text{CHMeNMe}_2\text{Pd}(\text{Ph}_2\text{PCHMeCHMePPh}_2)]^+\text{PF}_6^-$ derived from (+) $\text{Ph}_2\text{PCHMeCHMePPh}_2$ **1** and $[\sigma\text{-C}_6\text{H}_4\text{CHMeNMe}_2\text{PdCl}]_2$ of known configurations, and hence to show that the (+) form of **1** has the *R,R* configuration.

The determination of the absolute configuration of molecules has assumed increasing importance in recent years in view of current interest in metal complexes containing chiral ligands which are valuable as catalysts for asymmetric synthesis.^{1,2} More generally, this information is of great significance in biological chemistry. In addition to physical methods such as X-ray diffraction and chiral exciton spectroscopy³ for such determinations, there have been proposed a number of essentially chemical methods, which may be convenient to use, but the reliability of which is not always beyond question. These include consideration of the supposed number of inversions or retentions of configuration at centres of chirality in the synthetic pathway from a substrate of known absolute configuration, and NMR methods that depend upon the validity of assumptions about changes in response to conformational variation. These latter methods are well suited to the determination of enantiomeric purity,⁴ but in special circumstances they can lead to erroneous conclusions about absolute configuration. Thus, it has recently been shown that several assignments of the absolute configurations of marine terpenoids using Mosher's 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid [MTPA] derivatisation method⁵ are incorrect,⁶ and that even in an improved form this may occasionally give dubious results. It is, therefore, important to have a convenient method that is not subject to such uncertainties.

It is well known that nuclear Overhauser effect (NOE) measurements can be used to determine the pattern of relative

inter-atomic distances in molecules of fixed geometry, and that some degree of internal molecular motion can be tolerated without recourse to molecular dynamical calculations.⁷ In this communication, we show how such measurements (*via* two-dimensional NOESY⁸ or ROESY⁹ experiments) can provide the basis of an unambiguous method for the determination of absolute configuration in diastereoisomeric metal complexes. We illustrate the technique by applying it to the important ligand (+) 2,3-bis(diphenylphosphino)butane [(+)-chiraphos]. This chelating ligand is extensively used in the form of its rhodium(I) complexes for the stereospecific hydrogenation of olefins and other substrates.² It forms the complex ions **1** and **2** by reaction with the dimers $[\sigma\text{-C}_6\text{H}_4\text{CHMeNMe}_2\text{PdCl}]_2$ derived from (*S*)- $\text{C}_6\text{H}_5\text{CHMeNMe}_2$ and (*R*)- $\text{C}_6\text{H}_5\text{CHMeNMe}_2$, respectively. In this work these were isolated as their PF_6^- salts by treatment with NH_4PF_6 .¹⁰ These chiral amines are readily obtained in optically pure forms by methylation of the commercially available precursors (*S*)- and (*R*)- $\text{C}_6\text{H}_5\text{CHMeNH}_2$.

In order to determine the configuration of the phosphorus ligand in the complexes, it is necessary to relate the configuration at C-2 or C-3 to the known configuration at C-6. These centres are some 5 Å apart, and, therefore, protons directly associated with them cannot be expected to show any significant NOE interactions as these depend on the inverse sixth power of the internuclear distance. However, it was possible to establish the required relationship using two-

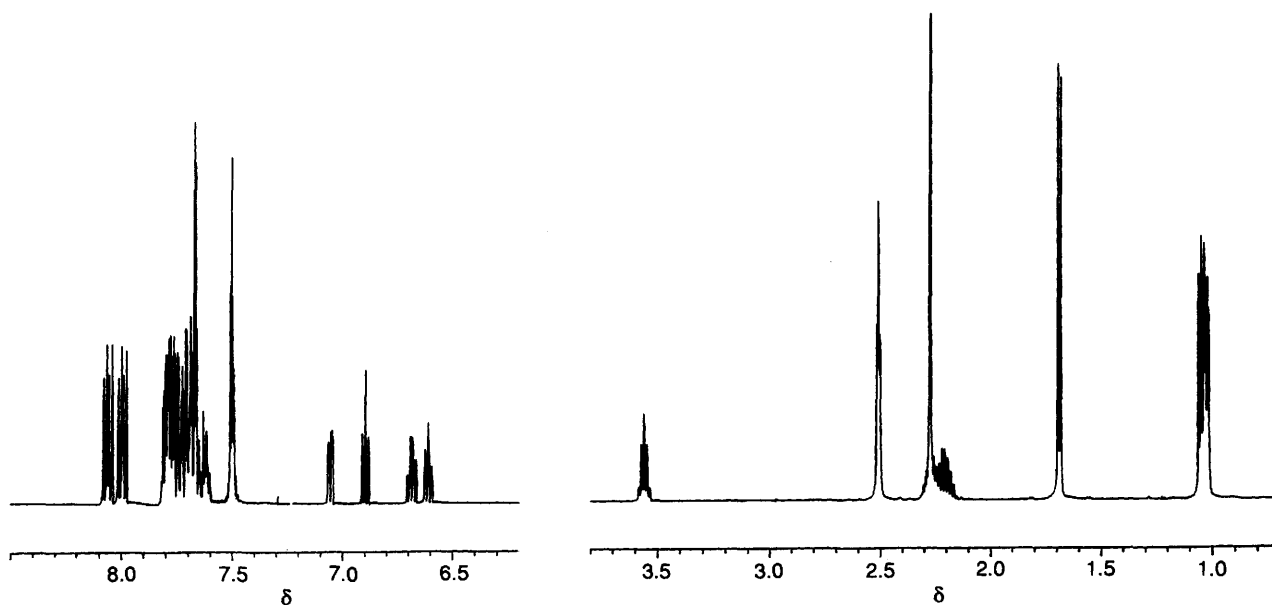


Fig. 1 One-dimensional ^1H NMR spectrum of the PF_6^- salt of **1** in CDCl_3 measured at 500.14 MHz on a Bruker AMX spectrometer

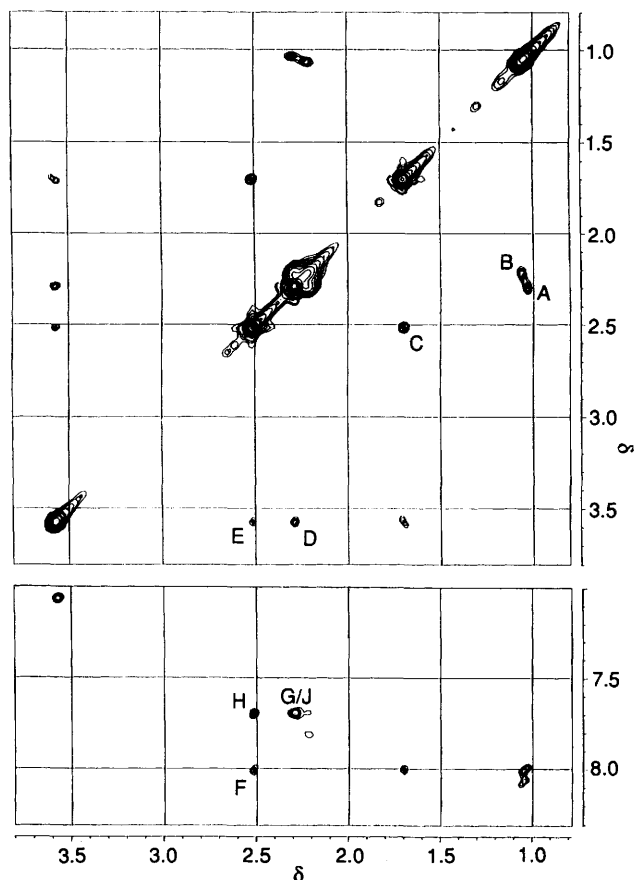


Fig. 2 Part of the two-dimensional phase-sensitive ROESY experiment performed on the PF_6^- salt of **1** at a measuring frequency of 500.14 MHz. The spin-locking time was 75 ms and the data were acquired into a 512×1024 matrix and then transformed into 512×512 points using a sine-bell window in each dimension. Peaks on the main diagonal are positive, and all off-diagonal peaks have negative intensity. NOE correlations referred to in the text are as follows: A-3-H-3-Me, B-2-H-2-Me, C-6-Me-5'-Me, D-6-H-5-Me, E-6-H-5'-Me, F-4'-Ph-5'-Me, G-4-Ph-5-Me, H-4-Ph-5'-Me, I-4'-Ph-3-Me, J-4-Ph-3-H.

dimensional NOE experiments *via* the intermediacy of the *N*-methyl and *ortho*-phenyl protons which displayed selective enhancements. It should be noted that although the experiments were actually performed using the complexes **1** and **2**, identical results would be obtained from the complexes of (-)-2,3-bis(diphenylphosphino)butane derived from (*R*)- $\text{C}_6\text{H}_5\text{CHMeNMe}_2$ and (*S*)- $\text{C}_6\text{H}_5\text{CHMeNMe}_2$, respectively.

Fig. 1 shows the 500 MHz ^1H NMR spectrum of **1**, and relevant chemical shifts in this and in **2** are given in Table 1, the assignments being aided by selective decoupling of the two types of ^{31}P nucleus, double-quantum filtered COSY spectra, and NOE data from 2D-ROESY spectra. Key features of the assignments are: (a) NOEs were observed between 11-H and the *ortho*-protons of the phenyl groups on P-1; allied to selective ^{31}P decoupling this identified P-1, and hence by elimination also P-4 and its associated *ortho*-phenyl protons. (b) Selective ^{31}P decouplings of P-1 and P-4 also identified the 3-Me and 2-Me protons. (c) 3-H and 2-H were identified from their COSY and ROESY interactions with 3-Me and 2-Me, respectively.

ROESY spectra were obtained for spin-locking (mixing) times ranging from 50–200 ms and that of **1** with a spin-locking time of 75 ms is shown in Fig. 2. Its use to relate the configuration at C-3 to the known configuration at C-6 involves three stages. (a) There is a strong NOE interaction

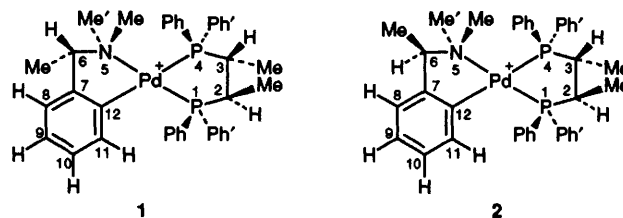


Table 1 Proton chemical shifts^a (δ) in **1** and **2** in CDCl_3 solution

| Proton | Compound 1 ^b | Compound 2 ^c |
|---------------------|-------------------------|-------------------------|
| <i>ortho</i> -1-Ph | 8.07 | 8.01 |
| <i>ortho</i> -1'-Ph | 7.80 | 7.85 |
| <i>ortho</i> -4-Ph | 7.70 | 7.73 |
| <i>ortho</i> -4'-Ph | 8.00 | 7.98 |
| 8-H | 7.06 | 6.92 |
| 9-H | 6.90 | 6.92 |
| 10-H | 6.62 | 6.59 |
| 11-H | 6.69 | 6.64 |
| 6-H | 3.56 | 4.24 |
| 5-Me | 2.28 | 2.07 |
| 5'-Me | 2.51 | 2.76 |
| 6-Me | 1.70 | 1.39 |
| 2-H | 2.22 | 2.15 |
| 3-H | 2.28 | 2.29 |
| 2-Me | 1.05 | 1.05 |
| 3-Me | 1.03 | 1.02 |

^a Relative to $\text{Si}(\text{CH}_3)_4$. ^b $\delta(^{31}\text{P}-1) = +62.7$; $\delta(^{31}\text{P}-4) = +44.4$; $J_{\text{P}-1\text{P}-4} = 39.9$ Hz. ^c $\delta(^{31}\text{P}-1) = +63.4$; $\delta(^{31}\text{P}-4) = +43.9$; $J_{\text{P}-1\text{P}-4} = 39.3$ Hz. ³¹P Chemical shifts to high frequency relative to external 85% H_3PO_4 .

from 6-Me to the *N*-methyl resonance at δ 2.51 and a very weak one visible at longer spin-locking times to that at δ 2.28 showing that these resonances arise from 5'-Me and 5-Me, respectively. This is confirmed by a strong NOE from 6-H to the resonance at δ 2.28 and a weaker one to that at δ 2.51. (b) The P-4 *ortho*-phenyl proton resonances at δ 8.00 show a strong NOE to 5'-Me and these, therefore, arise from 4'-Ph. The P-4 *ortho*-phenyl proton resonances at δ 7.70 show approximately equal NOEs to 5'-Me and 5-Me and are, therefore, assigned to 4-Ph. In more detail these features can be attributed to puckering of one or both of the chelate rings as is common in many complexes. Even if the palladium and its ligating atoms are coplanar such puckering can lead to a staggered conformation of the NMe_2 and PPh_2 groups about the N-P vector. However, its occurrence does not frustrate the stereochemical assignments. (c) 3-Me shows a strong NOE to the 4'-Ph and none to 4-Ph, while 3-H shows a strong NOE to 4-Ph and none to 4'-Ph.

Thus, a set of strong NOE interactions along the sequence 6-Me-5'-Me-4'-Ph-3-Me shows that the configuration in **1** at C-3 is as drawn and hence that (+) 2,3-bis(diphenylphosphino)butane is in the *R,R* form. In the case of **2** the ROESY spectrum shows a different pattern of NOE interactions from which the clear sequence 6-H-5'-Me-4'-Ph-3-Me was identified, again confirming the configuration to be as drawn.

This result provides confirmation of the now generally accepted absolute configuration of (+) 2,3-bis(diphenylphosphino)butane, which is based on the assumption of inversions at adjacent carbon atoms¹¹ in a low-yielding synthesis although the opposite view has been expressed.¹² In addition, an X-ray structure of the complex cycloocta-1,5-diene-(2*S*,3*S*)-2,3-bis(diphenylphosphino)butanerhodium(I) perchlorate¹³ supports this configuration.

It is important to note that this method is a rigorous one since it depends on the determinations of relative interatomic distances, and not upon assumptions about chemical shifts or other NMR parameters.

We wish to thank the Royal Society and the Leverhulme Trust for financial support and Johnson Matthey for gifts of PdCl₂.

Received, 19th May 1993; Com. 3/02871B

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