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SCOPE AND LIMITATIONS OF ORGANOMETALLIC CHIRAL DERIVATISING AGENTS FOR THE ^{31}P NMR DETERMINATION OF THE ENANTIOMERIC PURITY OF CHIRAL η^2 DONORS

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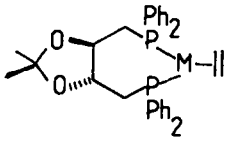
Abstract: The zerovalent platinum and palladium ethene complexes of 2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolan have been used as chiral derivatising agents for the ^{31}P NMR assay of the enantiomeric purity of certain alkenes and allenes.

The continued interest in asymmetric synthesis that is apparent in organic chemistry and pharmacology has stimulated the development of new, accurate methods for the determination of the enantiomeric purity of chiral compounds. While there are many non-chiroptical methods for the assay of chiral amines, alcohols and acids (usually involving NMR or chromatographic methods), there are very few reliable techniques for measuring the enantiomeric purity of chiral alkenes, alkynes and allenes, Some progress has been made in NMR analysis with the introduction of chiral silver shift reagents,[1] although the reported applications have been rather limited.[1,2] Progress in chiral gas chromatographic or hplc techniques has also been very slow[3] and there is considerable scope for development.

In organometallic chemistry, olefin, alkyne and allene complexes are abundant, and in particular there are many stable metal complexes of these η^2-donors with tertiary phosphine ligands. It was appropriate therefore to consider the use of ^{31}P NMR spectroscopy in a suitable low-valent metal phosphine complex which possessed an easily displaced ligand. The inherent advantage of a ^{31}P NMR method is that chemical shift dispersion is large, so that isomeric spheres are sufficiently chemical shift non-equivalent to permit integration of anisochronous resonances. In order to simplify the spectral analysis a chiral C_2-symmetric chelating biphosphine was chosen, and complexes with an easily displaced η^2-donor were sought. Following the characterisation of the platinum(0)[4] and palladium(0)-DIOP[5] ethene complexes, **1** and **2**, these complexes were investigated as potential chiral derivatising agents in which the ethene ligand may be displaced by the chiral η^2-donor under analysis. The resultant diastereoisomeric species may then be analysed by ^{31}P NMR spectroscopy and separate resonances integrated to give a direct measure of enantiomeric purity. This method is valid only if the enantiomeric η^2-donor is bound non-selectively (i.e. in the absence of kinetic resolution), and the spectral analysis may be complicated (but not impaired) when a non-C_2 symmetric alkene is

examined so that binding of the si or re face may occur giving constitutionally



1 M = Pt

2 M = Pd

isomeric species. The utility and limitations of this approach have been examined in this preliminary work using 1 and 2 as simple organometallic chiral agents.[6]

Derivatisation with Achiral Substrates

In order to define the ease of displacement of the ethene ligand in 1, a series of derivatisation reactions with achiral substrates was undertaken. Equimolar quantities of the complex 1 and the η^2-donor were allowed to react in tetrahydofuran solution at room temperature. Ethene displacement was often instantaneous, and the derivatised complex was obtained by removal of solvent and examined directly in d^6-benzene solution. Alternatively, the derivatisation reaction may be effected in situ in the NMR solvent, and similar results were obtained using either procedure. Phosphorus and platinum NMR data for these complexes are collected in Table 1. With non- C_2-symmetric η^2-donors, the phosphorus atoms in the resultant complex were anisochronous and anisogamous, coupling to each other and coupling differently to the less abundant ^{195}Pt nucleus. With 3,3-dimethylallene, the more substituted double-bond appeared to be bound as distinct ^1H-^{195}Pt coupling was observed for the methyl groups in the ^1H NMR spectrum of the complex.[4] Displacement of ethene by 1,1-diphenylethene did not proceed to completion, and even in the presence of $\geq$ 20 M excess of the alkene only 70% reaction had occurred. Simple cycloalkenes such as cyclopentene and cyclohexene, even in 100 M excess. did not displace the bound ethene, although the more strained norbornene reacted quantitatively. It is evident that only those η^2-donors with a low-lying LUMO appear to displace the ethene in 1 (and 2)[5] quantitatively i.e. sterically strained or electron-deficient η^2-donors. The mechanism of ethene displacement presumably occurs via an associative exchange process. In the ^1H NMR spectrum of 1 (0.02 M in CD_2Cl_2 or C_6D_6), no sign of signals due to free ethene may be discerned and the trans-related diastereotopic protons of the bound ethene remained sharp even in the presence of a 100 M excess of ethene. Given that some ethene at a concentration of $2x10^{-4}$ M was detectable, the former information implies that the dissociation constant for ethene loss is less than K_d = $2x10^{-6}$ M^{-1}. Taken together with the sluggishness (on the NMR time-scale) with which free and bound ethene exchanges in 1, this information suggests that exchange occurs by an associative mechanism with a very low association constant. Although associative ethene exchange occurs much more rapidly with 2,[5] the palladium complex was almost as equally unreactive as 1 towards unstrained alkenes such as cyclopentene or cyclohexene , and gave (at 298 K) exchange broadened ^{31}P NMR spectra with limonene (with which 1 did not react). This reactivity pattern obviously limits the application of this method.

With methyl propenoate as substrate, reaction occurs quantitatively to give constitutionally isomeric species related by binding of the si or re face. Evidently complexation was not face-selective and the constitutional isomers were observed in 50:50 ratio (Figure 1a).

Table 1 ^{31}P NMR Data for DIOP-Platinum Complexes of Achiral π^2-Donors

Compound	δ_P(ppm)	δ_{Pt}(ppm)	J_{PtP}	J_{PaPb}
DIOP-Pt-C_2H_4	13.7	-566	3585	-
DIOP-Pt- 	5.92	-227	3567	-
DIOP-Pt- 	14.0	-	3447	-
DIOP-Pt- 	a)11.2 b)7.69	-	a)3704 b)3360	71
DIOP-Pt- 	a)19.0 b)6.65	-	a)3463 b)2857	54
DIOP-Pt- 	a)13.8 b)8.95	-	a)3475 b)3862	57
	a')12.4 b')10.8	-	a')3434 b')3871	61

a) ^{31}P NMR spectra (101 MHz, 298K) in d^6-benzene, with shifts relative to 85% H_3PO_4; ^{195}Pt NMR spectra (19 MHz, 298K) in d^6-benzene, with shifts (absolute scale) relative to TMS. b)The two sets of resonances observed are due to the constitutionally isomeric si and re-bound alkene complexes(50:50; unassigned)

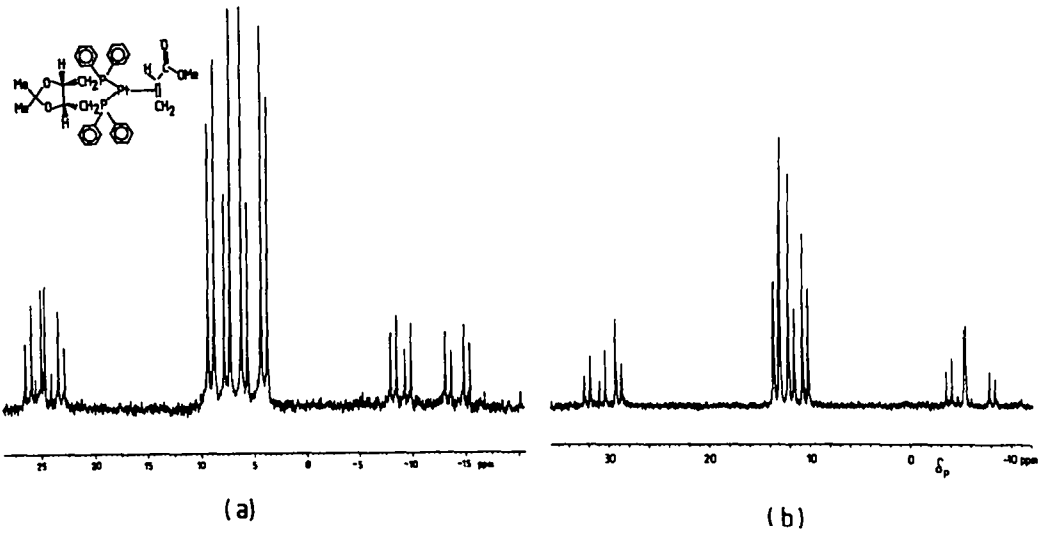
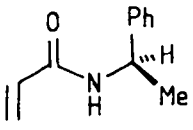


Figure 1 (a) ^{31}P n.m.r. spectrum of methyl propenoate complex of Pt(DIOP) [298 K, 101 MHz].
(b) ^{31}P n.m.r. spectrum of Pt DIOP complex of (R)-N-(1-phenylethyl)-propenamide

Derivatisation with Chiral η^2-Donors

A similar spectrum to that shown in Figure 1a was obtained with enantiomerically pure (R)-(+)-N-(1-phenylethyl)-propenamide, 2, as substrate, (Figure 1b). Four sets of doublets together with their ^{195}Pt satellites are observed, and the anisogamy of the two phosphorus atoms in each constitutionally isomeric species is evident from the very different appearance of the high and low frequency satellites. With the racemic propenamide, each of the diastereoisomeric complexes gives rise to four sets of doublets (plus satellites). Although some of the multiplets were second order so that peak intensities were distorted, each spectrum of this type contains 24 pairs of diasteroisomeric resonances so that in this (and any subsequent) case, it was possible to identify at least one pair of resonances which could be integrated to give a reliable estimate of enantiomeric composition. In order to establish that derivatisation is non-stereoselective, a series of propenamides of known enantiomeric composition [derived from enantiomerically pure (R) or (S)-α-phenylethylamine] was derivatised. The integrated enantiomeric compositions were typically within (± 2%) of the known values: this error is very similar to that estimated in the preparation of the mixtures of predetermined composition [by weighing (± 2%)].



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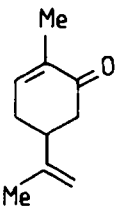

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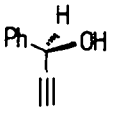

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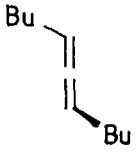

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A similar experiment was performed using 5-isopropenyl-2-methyl-2-cyclohexene(carvone,3) as substrate. In this case, it was possible to accurately measure

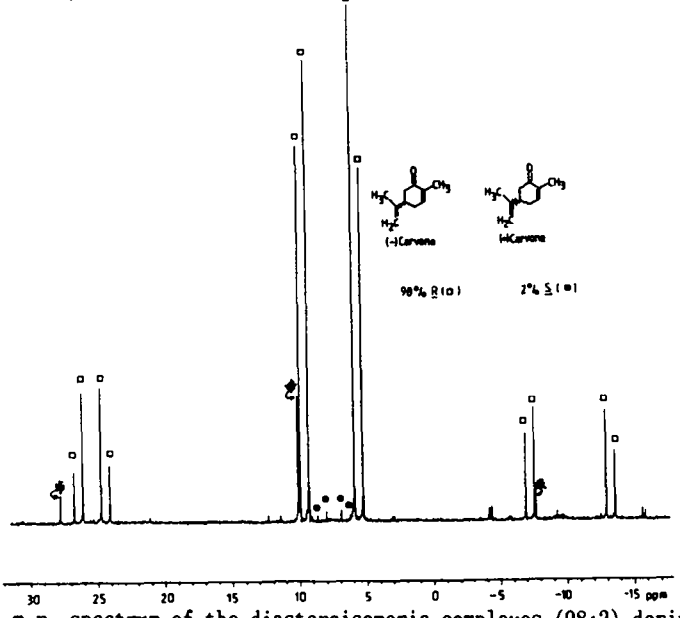
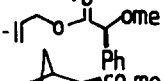
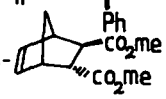
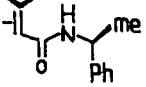


Figure 2 ^{31}P n.m.r. spectrum of the diasteroisomeric complexes (98:2) derived from a commercial sample of (R)-carvone [asterisk indicates residual DIOPPtethene]

the percentage of the residual (S)-enantiomer in a commercial sample of the (R)-enantiomer (Fluka 22060). In Figure 2 (5000 scans), the spectrum of the (R)-(+)carvone complex is shown and the enantiomeric purity of the sample is 96% [i.e. 98% (R), 2% (S)]. A stacked plot of the ^{31}P NMR spectra obtained from mixtures of (R) and (S)-carvone of pre-determined composition is shown (Figure 3) in which a good agreement between nmr-determined and known enantiomeric composition was obtained.

A feature of this system which is particularly notable is that the carvone must be regioselectively bound to platinum by the more electron-poor double bond and stereoselectively bound to the less-hindered si-si face of the endocyclic double bond.

Table 2 ^{31}P NMR Data for DIOP-Platinum Complexes of Chiral η^2-Donors

Entry[a]	Compound		δ_{P_a}	δ_{P_b} (ppm)	J_{PtP_a}	J_{PtP_b}	$J_{Pt_aP_b}$ (Hz)
1	DIOP-Pt- 		13.8	9.88	3409	3881	65
			12.5	10.8	3537	3938	65
2	DIOP-Pt- 		14.7	12.2	3887	3796	66
			13.8	12.4	3774	3760	66
3	DIOP-Pt- 		14.8	12.7	3456	3376	67
			14.5	12.0	3439	3367	68
4	DIOP-Pt 		17.6	10.3	3246	3246	72
			17.3	11.0	3060	3060	71
5	DIOP-Pt- 	*	12.8	9.9	3801	3759	57
		•	13.6	9.6	3838	3752	57
		*	13.3	10.8	3470	3500	64
		•	13.3	10.8	3470	3500	61
6	DIOP-Pt- 	*	17.1	9.61	3235	3026	65
		•	17.6	6.01	3252	2942	57
		*	16.2	9.83	3238	3026	65
		•	(-)	7.21	(c)	2947	59

(a) * or • related species are si and re-bound constitutional isomers; other pairs are diastereoisomeric species derived form the (+) or (-) chiral η^2-donor (b) Spectra recorded (101 MHz, d^6-benzene, 298 K) with shifts in ppm (rel. 85% H_3PO_4) (c) not resolved.

The selective complexation of one face of the double bond was also observed with racemic cyclonona-1,2-diene and trans- dimethylnorbornene-2,3-dicarboxylate, but no evidence for the selective complexation of one enantiomer was found (i.e. a 50:50 ratio of diastereoisomers was measured). In the former case, approach of the metal to the other face is hindered by the ring, while in the latter selective complexation of the more open exo-face occurs, as expected.[5] The NMR data for these systems are collated in Table 2.

In comparison to the ^{31}P NMR spectra for these platinum complexes, it was reasoned that the corresponding ^{195}Pt spectra would be much simpler and perhaps more readily interpreted. ^{195}Pt Spectra were obtained (19 MHz, C_6D_6, 298 K) for the platinum DIOP complexes of enantiomerically pure and racemic N-(1-phenylethyl)-propenamide. In each of the four isomeric complexes obtained with racemic propenamide, the Pt($I=\frac{1}{2}$) nucleus is coupled to the two non-equivalent phosphorus atoms so that four doublets may be expected

for each diastereomeric complex. Although the spectra were recorded with long acquisition times (60,000 scans, 0.05 M solutions), a poor signal to noise was obtained, so that

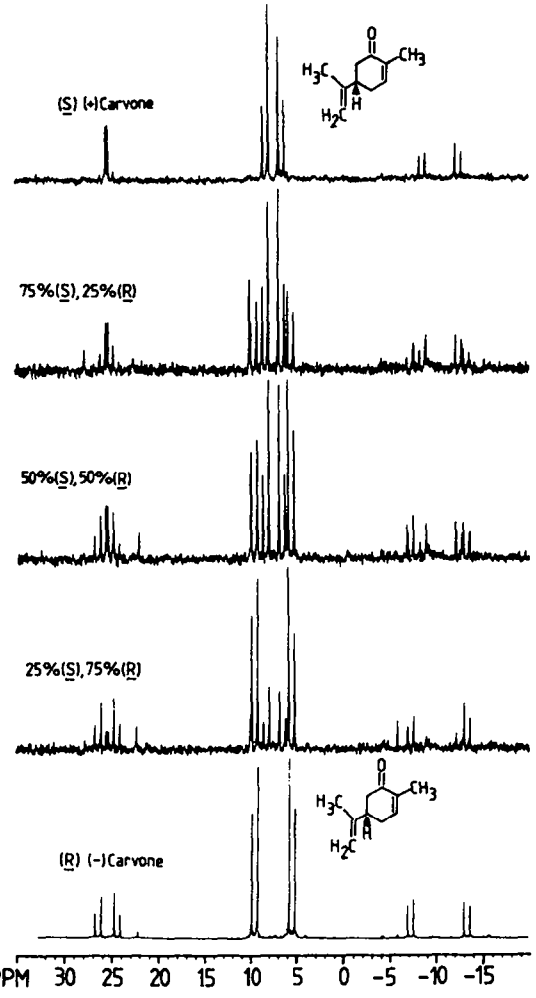


Figure 3 ^{31}P n.m.r. of the diastereomeric complexes of (R) and (S) carvone of varying composition with (R)PtDIOP

without employing polarisation transfer methods, the direct use of ^{195}Pt is limited.

Apart from the electronic requirement that the η^2-donor possesses a low-lying LUMO, there is a further structural limitation which must be considered before using this method. If the substrate possesses a polar group at the chiral centre which can bind to the metal centre, then enantio-selectivity in binding may be observed. This is the case for the α-hydroxy alkyne, 5, for which only one diastereoisomeric complex was observed following reaction of the racemic alkyne with 1. This sort of kinetic resolution is well established in metal- assisted asymmetric syntheses. More intriguingly the chiral allene 6 was also not amenable to NMR analysis by this method: binding of the racemic or enantiomericallly enriched allene occurred readily but gave identical spectra in which a 76:24 ratio of constitutionally isomeric species was observed and a marked enantioselectivity in binding was also apparent.

In summary, the applicability of these chiral derivatising agents is limited to substrates which are somewhat strained or electron-poor η^2-donors and in which the element

of chirality is remote from the metal . Such features contrast to the requirements for the silver lanthanide shift reagent method[1,2] and suggest that the method for analysis should be chosen with the substrate structure in mind.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WM 360 or a Bruker AC 250 spectrometer. ^{31}P NMR spectra were recorded on a Bruker AC 250 spectrometer (101 MHz) or on a Jeol FX 90 (36 MHz), while ^{195}Pt spectra were obtained on a Jeol FX 90 operating at 19.2 MHz. Data were recorded with 16K data points and integrals were measured for spectra without data manipulation, and compared to those with 1 Hz line-broadening introduced by exponential multiplication of the FID. Typically ^{31}P spectra were obtained with a pulse width of 5.0 corresponding to a flip angle of 45°, and a relaxation delay of 1.5 seconds. Mass spectra were recorded on a VG 7070 E spectrometer, and combustion analyses were determined using a Carlo-Erba 1106 analyser. Infra-red spectra were recorded on a Perkin-Elmer 577 spectrophotometer, and melting points were determined on a Reichert-Kofler block and are uncorrected. Solvents were purified according to standard procedures and all operations involving organometallic intermediates were conducted under a nitrogen atmosphere using Schlenck techniques.

2,2-Dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolaneplatinum(0)ethene

To a cooled solution (-78°C) of R-DIOPplatinum dichloride (191 mg, 0.25 mmol) in dry dichloromethane (4 cm^3) was bubbled a stream of ethene (2 min). A solution of sodium borohydride (21.9 mg, 0.58 mmol) in ethanol (4 cm^3) was added by syringe, under an ethene atmosphere, and the mixture stirred at -78°C (1 h) before slowly warming to room temperature. At the first sight of darkening, the solution was transferred into ethene-saturated ethanol (30 cm^3) and the precipitate which formed collected by filtration as an off-white microcrystalline solid (139 mg, 76%), mp>150°C (dec.). Found: C,54.9; H, 4.9; $C_{33}H_{36}P_2O_2Pt$ requires C,54.9; H,5.0. $\delta_H(CD_2Cl_2)$ 7.77-7.66(4H,m,ArH), 7.53-7.47(4H,mArH), 7.44-7.30(12H,m,ArH), 3.95-3.21(2H,m,CHO), 3.65-3.42(2H,dtd,J_{vic} 15.8 Hz,J_{PtH} 35Hz,J_{PH} 14.8 Hz,CH_2P), 2.45-2.35(2H, m,CH_2P), 2.06-2.01(2Hm,J_{PtH} 57 Hz,CH_2), 1.85-1.81(2H,m,J_{PtH}57 Hz,CH_2), 1.30(6H,s,CMe_2), $\delta_P(C_6D_6)$+13.7,(J_{PtP} 3585). $\delta_{Pt}(C_6D_6)$-566 ppm, m/e(FAB,thiodiethanol) 693(DIOPPt)$^+$, 565, 488, 380.

Derivatisation experiments with DIOP-platinum ethene were performed directly by shaking the substrate (typically 5M-excess) and the ethene complex together in d^6-benzene in an NMR tube (Fisons Whirlimixer) and the spectrum was recorded immediately. Alternatively to a solution of DIOP-Pt(C_2H_4)[15mg, 0.02 mmol] in dry tetrahydrofuran (1.5 cm^3) was added the substrate (0.02 mmol) injected directly or, if required, as a solution in tetrahydrofuran (1 cm^3). After stirring for ten minutes solvent was removed under reduced pressure and the residue redissolved in d^6-benzene and the spectrum recorded subsequently.

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