

On the high efficiency of
cis-dichloro[(*S*)- α -methylbenzylamine](ethylene)platinum(II) as
chiral derivatizing agent for the determination of the enantiomeric
composition of chiral unsaturated ethers by ^{195}Pt -NMR
spectroscopy: a spectroscopic conformational and configurational
characterization in solution of diastereoisomeric complexes
cis-dichloro[(*S*)- α -methylbenzylamine][(*S*)- and
(*R*)-3-phenyl-3-methoxybut-1-ene]platinum(II)

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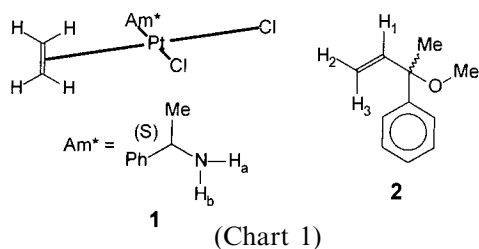
Abstract

The stereochemistry in solution of the diastereoisomeric complexes *cis*-dichloro[(*S*)- α -methylbenzylamine][(*S*)- and (*R*)-3-phenyl-3-methoxybut-1-ene]platinum(II) has been determined by ^1H -NMR spectroscopy: in the two species the ethereal ligand is involved by its oxygen atom in the formation of an interligand $\text{O}\cdots\text{H}-\text{N}$ hydrogen bond with the amine. The remarkable differentiation of the ^{195}Pt resonances is due to the different positions of amine substituents with respect to the metal. © 2000 Published by Elsevier Science S.A. All rights reserved.

Keywords: Chiral derivatizing agent; NMR; Enantiomeric purity; Unsaturated ethers; Stereochemistry

1. Introduction

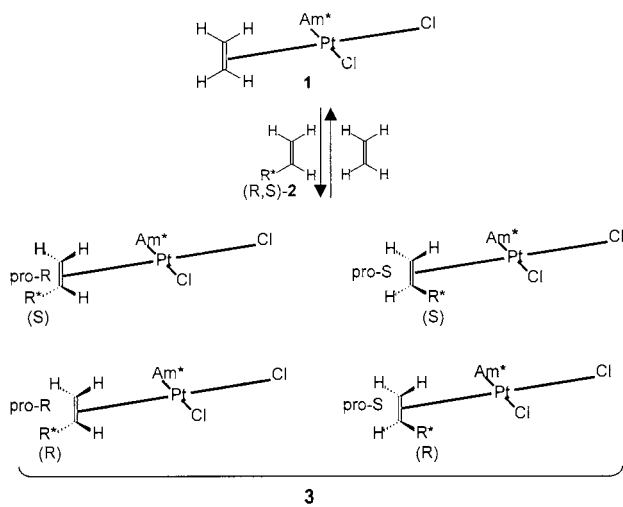
The usefulness of *cis*-dichloro[(*S*)- α -methylbenzylamine](ethylene)platinum(II) (**1**) (Chart 1) as chiral derivatizing agent (CDA) [1] for the determination of the enantiomeric composition of chiral unsaturated ethers and alcohols [2] by NMR spectroscopy has been widely demonstrated: its use is especially practical as the derivatization process only involves the exchange of the coordinated ethylene by the enantiomeric mixture to be analyzed (Scheme 1).



This reaction, which simply proceeds by mixing **1** and the unsaturated analyte in a chlorinated solvent, can be also performed directly in the NMR tube (CDCl_3). The coordination of the two prochiral faces of the double bond of each enantiomer of the unsaturated analyte produces two diastereoisomers whose ratio depends on its structure (Scheme 1). Therefore, a maximum number of four diastereoisomers is formed in

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Scheme 1.

solution. As, in principle, each of them can originate a single ^{195}Pt resonance, the determination of the enantiomeric composition can be simply performed by comparing the areas of the signals originated by each enantiomer.

In order to get more insight on the origin of the high efficiency of **1** as CDA towards unsaturated oxygenated chiral substrates, we have investigated, by NMR spectroscopy, the stereochemistry in solution of the diastereoisomeric complexes *cis*-dichloro[(*S*)- α -methylbenzylamine][(*S*)- and (*R*)-3-phenyl-3-methoxybut-1-ene]platinum(II) (**3**) containing the two enantiomers of 3-phenyl-3-methoxybut-1-ene (**2**): among the previously reported [2] applications of **1** as CDA, that one regarding **2** [2b] seemed quite interesting to investigate, in fact the complexation of the double bond of each enantiomer of **2** is completely diastereoselective and only two diastereoisomers originate, producing two well separated ^{195}Pt -NMR resonances.

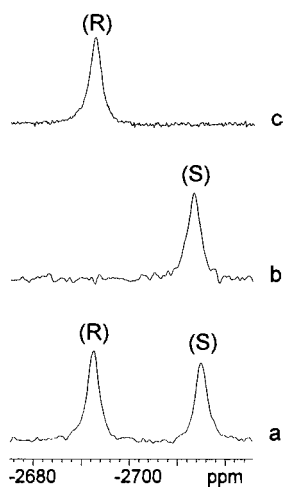


Fig. 1. ^{195}Pt -NMR (64.3 MHz, CDCl_3 , 25°C, ppm referred to Na_2PtCl_6 as external standard) spectra of: (a) **3**, (b) **3a**, (c) **3b**.

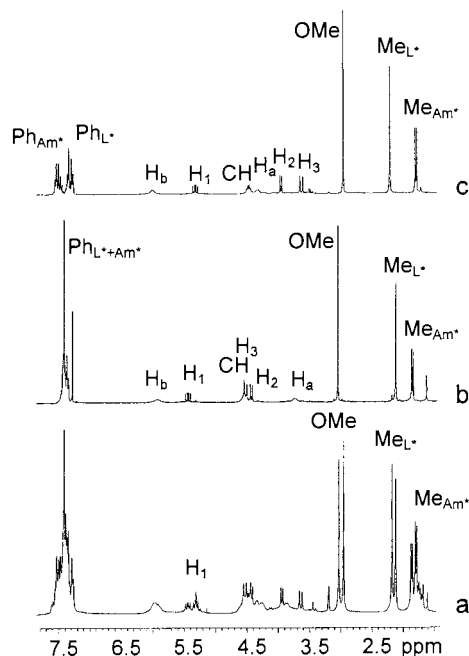


Fig. 2. ^1H -NMR (300 MHz, CDCl_3 , 25°C, ppm referred to TMS as external standard) spectra of: (a) **3**, (b) **3a**, (c) **3b**.

2. Results and discussion

The ^{195}Pt -NMR spectrum of the diastereoisomeric complexes **3**, obtained by mixing equimolar amounts of **1** and (*R,S*)-**2** in CDCl_3 (Fig. 1a), shows two well-separated absorptions centered at -2693 and -2715 ppm, having equal intensities, as well as two sets of ^1H -NMR absorptions are observed for protons or groups of equivalent protons of the complex (Fig. 2a), indicating that the complexation of the two enantiomers of **2** is completely diastereoselective. The two pure diastereoisomers have been obtained by fractional crystallization of **3** from dichloromethane/diethyl ether, 1:1 (fraction **3a**) and 1:2 (fraction **3b**), and each of them showed only one ^{195}Pt -NMR absorption (Fig. 1b, c) and one group of ^1H -NMR resonances (Fig. 2b, c).

The complete attribution of the ^1H -NMR resonances of **3a** and **3b** has been performed by DQF-COSY analysis and the corresponding characterization data are collected in Table 1. For both complexes the two amine protons, named as H_a and H_b , not only are remarkably differentiated in positions but also they have different multiplicities, the high frequency proton (H_b , 5.87 ppm in **3a** and 5.95 ppm in **3b**) being a broad triplet and the low frequency one (H_a , 3.68 ppm in **3a** and 4.28 ppm in **3b**) a broad doublet. In fact, the former shows geminal coupling with the other amine proton and also vicinal coupling with the methine proton on the chiral carbon atom, whereas the latter only shows the geminal coupling (the vicinal coupling is less than 2 Hz), thus reflecting the different relative positions of the two amine protons with respect to the

Table 1
¹H-NMR (300 MHz, CDCl₃, 25°C) chemical shifts (δ , ppm, TMS as external standard) and coupling constants (J , Hz) of the pure diastereoisomers **3a** and **3b**

	Complex 3a		Complex 3b	
	δ ^a	J	δ ^a	J
H ₁	5.38 (dd)	1–3, 13.8; 1–2, 8.5	5.27 (dd)	1–3, 13.8; 1–2, 8.5
H ₂	4.38 (d)	2–1, 8.5	3.90 (d)	2–1, 8.5
H ₃	4.47 (d)	3–1, 13.8	3.58 (d)	3–1, 13.8
Me _L	2.07 (s)		2.16 (s)	
OMe	2.99 (s)		2.91 (s)	
Ph _L	7.46–7.26 (m)		7.30–7.20 (m)	
Me _{Am}	1.80 (d)	6.9	1.74 (d)	6.9
Ph _{Am}	7.46–7.26 (m)		7.45–7.40 (m)	
CH _{Am}	4.49 (m)		4.42 (m)	
NH _b	5.87 (bt)	b-a, 8.0; b-CH _{Am} , 8.0	5.95 (bt)	b-a, 8.0; b-CH _{Am} , 7.5
NH _a	3.68 (bd)	a-b, 8.0; a-CH _{Am} , <2.0	4.28 (bd)	a-b, 7.5; a-CH _{Am} , <2.0

^a Multiplicity in parentheses: bt, broad triplet; bd, broad doublet; d, doublet; dd, double doublet; m, multiplet; s, singlet.

methine one determined by the values of the dihedral angle H–N–C–H [3]. The comparison of the chemical shifts of corresponding protons of the two diastereoisomers also reveals that the greatest nonequivalences (differences of the chemical shifts of the two complexed enantiomers) are measured for the protons H₂ and H₃ of the methylene vinyl group, which must lie in very different stereochemical environments in **3a** relative to **3b**. Besides these preliminary indications, the stereochemistry of the ligands in the two complexes has been fully defined by detecting the n.O.e. effects in the 2D NOESY maps, due to the intra- and interligand dipole–dipole interactions between protons in spatial proximity each other. The Figs. 3 and 4 collect the most significant 2D NOESY traces for **3a** and **3b**, respectively. As far as the pure diastereoisomer **3a** is concerned, very different n.O.e. patterns of the two amine protons H_b and H_a are found (Fig. 3a, b): the former originates n.O.e. on the methyl protons of the amine and on the vinyl proton H₃, the latter only produces n.O.e. on the methine proton of the amine. The methyl protons of the amine also produce a relevant n.O.e. on the same vinyl proton H₃ (Fig. 3c). Therefore, the amine ligand must have the N–C bond perpendicular to the coordination plane with the amine proton H_b directed towards the unsaturated ligand and *trans* to the methine proton of the amine and its methyl group pointing at the methylene vinyl group. The analysis of the traces d and e of Fig. 3 allows us to define the arrangement of the ethereal ligand: its methyl protons originate dipolar interactions with both amine protons H_a and H_b in addition to a very intense n.O.e. on the methine vinyl proton H₁; the methoxy protons produce n.O.e.s only at the amine proton H_b and at the vinyl proton H₃. Therefore, its methyl group lies on the opposite side of the coordination plane relatively to the N–C bond of the amine ligand, bent at the two amine

protons and hence pointing at the metal center, whereas the methoxy group is directed towards the amine proton H_b and faced to the double bond, as depicted in Fig. 5. The proximity between the methoxy group and the amine proton H_b is according to the formation of an interligand O···H–N hydrogen bond, as already evidenced for other platinum(II) complexes containing an oxygenated unsaturated ligand *cis* to a primary amine [4]. Therefore, being prefixed and *S* the absolute configuration of the amine ligand, the unsaturated ligand must have the *S* absolute configuration with the pro-*S* face coordinated.

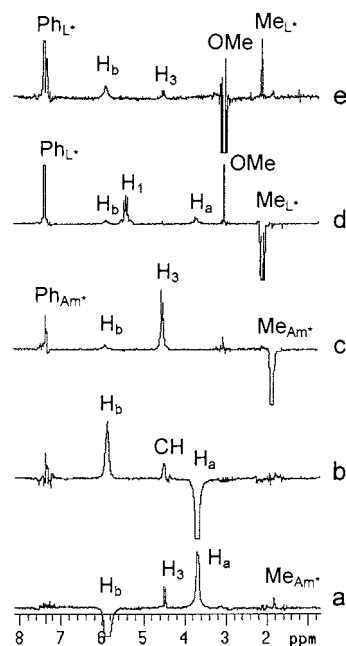


Fig. 3. 2D NOESY analysis (300 MHz, CDCl₃, 25°C, mix 0.6 s, ppm referred to TMS as external standard) of **3a**. Traces corresponding to the following protons: (a) H_b, (b) H_a, (c) methyl of amine, (d) methyl of **2**, (e) OMe.

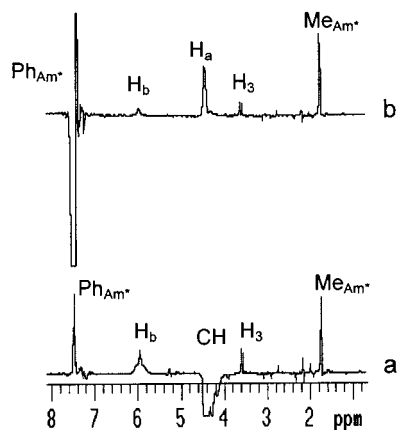


Fig. 4. 2D NOESY analysis (300 MHz, CDCl_3 , 25°C, mix 0.6 s, ppm referred to TMS as external standard) of **3b**. Traces corresponding to the following protons: (a) methine of amine, (b) phenyl of amine.

The most relevant inter-n.O.e.s detected for the other pure diastereoisomer, crystallized from dichloromethane/diethyl ether, 1:2, are the following (Fig. 4): the methine proton of the amine produces n.O.e.s at the frequency of the amine proton H_b and at the vinyl proton H_3 (Fig. 4a), whereas no dipole–dipole interaction between the methyl group and any vinyl proton is detected. In addition, the phenyl protons (Fig. 4b), that in this case produce absorptions well separated from the phenyl resonances of the ethereal ligand (Table 1), originate n.O.e.s on both amine protons H_a and H_b . Therefore, as in **3a**, the N–C bond of the amine is perpendicular to the coordination plane, with one amine proton, H_b , bent at H_3 and hence at the ethereal ligand, but, in this case, the methine proton at the chiral carbon atom of the amine does point at H_3 and hence at the metal (instead of the methyl group as in **3a**). The methyl and methoxy groups of the ether give similar n.O.e.s as in **3a**, therefore, the first lies on the opposite side of the coordination plane with respect to the amine, pointing at the metal and the latter is close to the amine proton H_b , being once again involved in the interligand $\text{O}\cdots\text{H}-\text{N}$ interaction (see Fig. 5). Therefore, the unsaturated ligand, coordinated by its pro-R

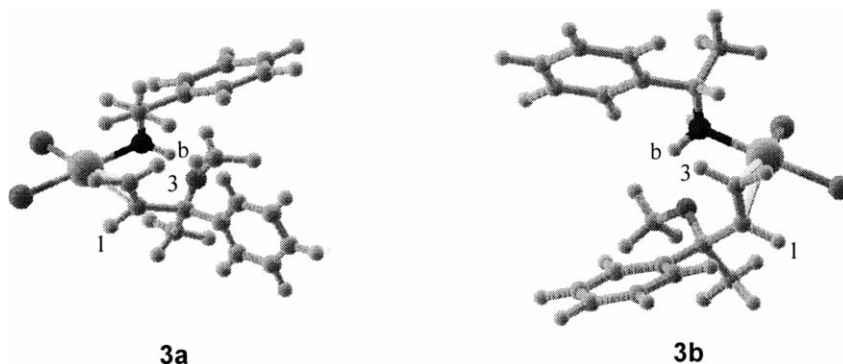


Fig. 5. Representation of **3a** and **3b**.

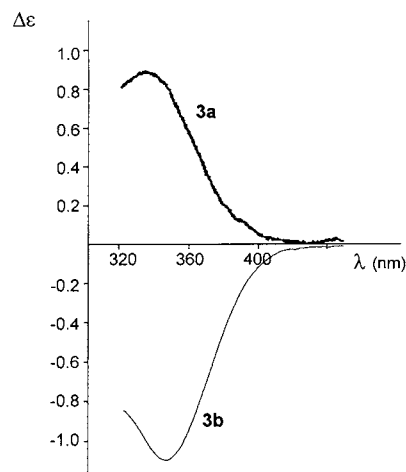


Fig. 6. Circular dichroism spectra of **3a** and **3b** in CHCl_3 .

face, has R absolute configuration at the chiral carbon atom.

The previously reported configurational assignments for the vinyl carbon atom made chiral on complexation to the metal are confirmed by circular dichroism (CD) analysis: in fact earlier investigations on platinum(II)-olefin complexes [5] demonstrated that the positive sign of the lowest energy band of the CD spectrum is correlated to its S absolute configuration, the reverse correlation holds in the case of the CD band having a negative sign. In our case (Fig. 6), the lowest energy CD band at 334 nm has a positive sign for **3a** and a negative for **3b** confirming the S and R absolute configuration, respectively, of complexed vinyl carbon atom.

3. Conclusions

The exchange in solution of the ethylene of **1** by the two enantiomers of **2** leads to two diastereoisomers only. As already remarked for other complexes containing an unsaturated ethereal compound *cis* to a primary amine [4], the high diastereoselectivity in their coordi-

nation is determined by the interligand N–H···O hydrogen bond, which reduces the conformational freedom of the two ligands and restrains their relative positions, thus enhancing the relevance of steric factors in determining the preference for the complexation of one prochiral face of the double bond with respect to the other. This interaction is also responsible for the rigid constraints imposed to the positions of the substituents at the two ligands relative to the metal: the two complexed enantiomers of the quaternary unsaturated ether **2** have the same conformation with respect to the metal and the two diastereoisomers differ for the positions of the amine substituents with respect to it. These differences are, in turn, the factor primarily affecting the differentiation of their platinum-195 chemical shifts, which is the basis of the use of **1** as CDA for the analyses of unsaturated ethers by ^{195}Pt -NMR spectroscopy [2]. As a matter of fact, the same complex **1** is not effective as CDA for nonoxygenated chiral compounds, where no such interligand hydrogen bond can be formed, thus resulting in conformational homogeneity to a low extent.

4. Experimental

4.1. General comments

^{195}Pt -NMR spectra were recorded in CDCl_3 at 64.3 MHz. All ^{195}Pt -NMR chemical shifts are referred to Na_2PtCl_6 as external standard and the ^{195}Pt resonance of *cis*-dichloro[(*S*)- α -methylbenzylamine](ethylene)platinum(II) (**1**) is at low frequency (-2780 ppm) with respect to the absorptions due to complexes containing the substrate **2**. Standard pulse sequences have been employed for ^{195}Pt -NMR measurements. The 2D NMR spectra were obtained by using standard sequences. The DQF-COSY (Double-Quantum Filtered COrelated Spectroscopy) experiments were recorded with a spectral width of 2000 Hz; 512 increments of eight scans and 2K data points were acquired. The relaxation delay was 5 s. The data were zero-filled to $2\text{K} \times 1\text{K}$ and a Gaussian function was applied for processing in both dimensions. The NOESY (Nuclear Overhauser and Exchange Spectroscopy) spectra were recorded in the phase-sensitive mode, by employing a mixing time of 0.6 s. A spectral width of 2000 Hz was used in both ω_1 and ω_2 dimensions. The pulse delay was maintained at 5 s; 512 hypercomplex increments of eight scans and 2K data points each were collected. The data matrix was zero-filled at $2\text{K} \times 1\text{K}$ and a Gaussian function was applied for processing in both dimensions.

Circular dichroism spectra of **3a** and **3b** were recorded in the 280–450 nm region on a Jasco J-600 dichrograph at 25°C (CHCl_3 solution; ca. 3.6–4.0 mM; 1-mm cell). The CD analysis of complexes **3a** and **3b**

was performed both immediately after dissolution of the samples.

Melting points were determined using a Koffler hot-stage apparatus.

4.2. Materials

Racemic 3-phenyl-3-methoxybut-1-ene (**2**) was prepared according to a literature procedure [6] from the corresponding alcohol [7]. Characterization data are reported in Ref. [2b].

cis-Dichloro[(*S*)- α -methylbenzylamine](ethylene)platinum(II) (**1**) has been prepared according to a literature procedure [8].

4.3. General procedure: preparation and crystallization of *cis*-dichloro[(*S*)- α -methylbenzylamine](3-phenyl-3-methoxybut-1-ene)platinum(II) [**3**, **3a**, **3b**]

On reaction of **1** (0.80 g, 1.93 mmol) in CH_2Cl_2 (10 ml) with racemic **2** (0.31 g, 1.93 mmol) and removal of the solvent, **3** (1.05 g, 1.92 mmol) has been obtained as a pale yellow microcrystalline solid (m.p. 145–147°C). Crystallization of crude product **3** at -20°C from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (1:1) afforded **3a** as pale yellow crystals (0.39 g, 37% yield), having m.p. 149°C. Anal. Calc. for $\text{C}_{19}\text{H}_{25}\text{Cl}_2\text{NOPt}$: C, 41.54; H, 4.59; N, 2.55. Found: C, 41.35; H, 4.46; N, 2.76%. By adding diethyl ether ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O} = 1:2$) to the mother-liquors, a second fraction of a microcrystalline solid **3b** was obtained (0.40 g, 38% yield), having m.p. 151°C. Anal. Calc. for $\text{C}_{19}\text{H}_{25}\text{Cl}_2\text{NOPt}$: C, 41.54; H, 4.59; N, 2.55. Found: C, 41.43; H, 4.38; N, 2.61%. Characterization data of **3a** and **3b** are reported in Table 1.

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