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Facile and performant enantiomeric excess analysis of diene iron tricarbonyl complexes through deuterium NMR

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Abstract: Complete and accurate stereoisomeric analysis of chiral [(η^4-dienal)$Fe(CO)_3$] complexes can be performed by deuterium NMR in a chiral (polypeptide–dichloromethane) solvent, through reduction of aldehydes to the corresponding deuteriated alcohols. This new application of Courtieu's method opens an efficient entry to stereoisomeric analysis of chiral organometallics. © 1997 Elsevier Science Ltd

Introduction

The use of planar chiral tricarbonyl (η^4-1,3-diene)iron complexes has been developed intensively since they could be used as synthons for enantioselective synthesis. This is mostly due to the protecting and stereodirecting effects of the $Fe(CO)_3$ moiety.[1] Part of our research program is focused on the stereoselective synthesis of nitrogen containing heterocycles using chiral [(η^4-dienal)$Fe(CO)_3$] complexes **1** as precursors.[2,3]

One emerging problem is the evaluation of the enantiomeric purity of these chirons. The enantiomeric excess of chiral iron complexes is usually assessed through determination of the specific rotation value, analysis by high performance liquid chromatography (HPLC)[4] or nuclear magnetic resonance (NMR), using chiral shift reagents (commonly $Eu(tfc)_3$ and $Eu(hfc)_3$) or various chiral derivatizing agents.[5] Meanwhile, this last method gives often poor results with iron complexes, owing to a loss of resolution and/or a weak chemical shift non equivalence ($\Delta\delta$).

On the other hand, a new and convenient method for enantiomeric analysis, using deuterium NMR in a chiral liquid crystal solvent, has been previously reported by Courtieu *et al.*[6] The solvent consists of a chiral nematic liquid crystal, obtained by dissolution of poly(γ-benzyl-L-glutamate), PBLG, in dichloromethane. In such an anisotropic medium, the discrimination originates from the fact that enantiomers interact differently with the asymmetric PBLG helix and, consequently, orient differently in the solvent. In a deuterium NMR spectrum, this Differential Ordering Effect (DOE) is expressed in different values of the quadrupolar splittings ($\Delta\nu_Q$) for each enantiomer. Thus, study of a monodeuteriated molecule containing one asymmetric centre leads to a proton-decoupled deuterium NMR spectrum consisting of only two doublets, one per enantiomer, centred on the same frequency and of respective quadrupolar splittings $\Delta\nu_Q{}^R$ and $\Delta\nu_Q{}^S$.[6]

Results and discussion

Deuterium was incorporated to complexes **1** by simple reduction using sodium borodeuteride,[7] leading quantitatively to diastereoisomeric mixtures of Ψ-endo and Ψ-exo alcohols **2**,[8] bearing two asymmetric centers: one of planar chirality, the other of isotopic chirality (Scheme 1).

Therefore, deuterium NMR spectra of racemic solutes **2** should be composed, if enantiomers are distinguished, of four doublets, two sets of two corresponding to the visualization of enantiomers for

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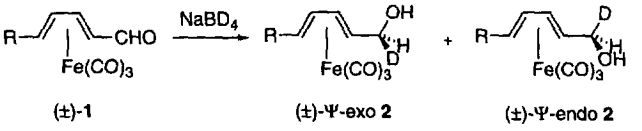
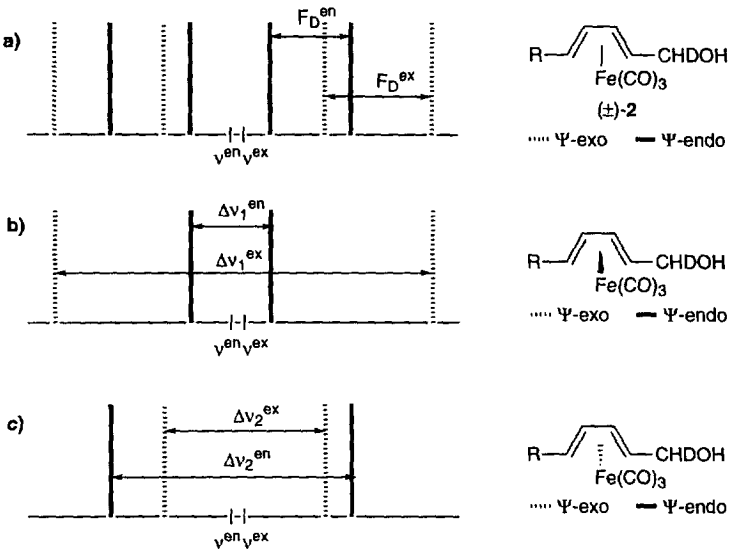


Scheme 1.



Ψ-endo and Ψ-exo diastereoisomers are attributed arbitrarly;[9] ν^{en} and ν^{ex} are the resonance frequencies of diastereoisomers; $\Delta\nu_1$ and $\Delta\nu_2$ are the quadrupolar splittings of enantiomers for diastereoisomers Ψ-endo and Ψ-exo; F_D, discrimination factor ($F_D = |\Delta\nu_1 - \Delta\nu_2|/2$), indicates the quality of the differenciation between enantiomers (as $\Delta\delta$ for CDA) (see Table 1).

Figure 1. Theoretical proton decoupled deuterium NMR spectra of alcohols **2** (1:1 diastereoisomeric mixtures): a) racemic iron complex, b) optically pure planar chiral complex moiety, c) antipode of b).

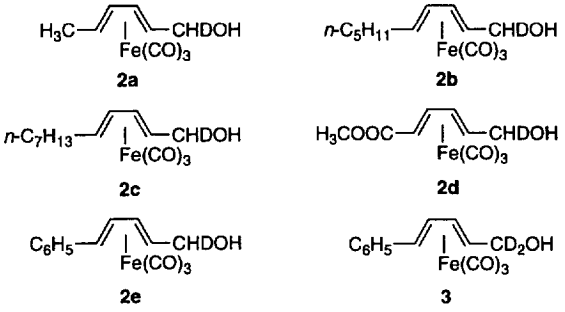
each diastereoisomer. By the way, only two doublets (one per diastereoisomer) will be observed if the planar chiral moiety is enantiopure (Figure 1).

Complexes (±)-**1a–c** were synthetized from the corresponding commercially available dienals by complexation using ironpentacarbonyl.[1b] Racemic and enantiopure (+)-**1d** complexes were prepared according to reference 1a, while racemic and enantiomerically pure ((+) and (−)) compounds **1e** were obtained by in situ reduction of (5-phenylpentadienoylchloride)irontricarbonyl complex[10] using bis(triphenylphosphine)copper borohydride.[11]

Monodeuteriated alcohols **2a–e** (Scheme 2) were synthesized as indicated above. As expected,[9] no notable diastereoselectivity was observed, except for **2d** (de=33%). Dideuteriated alcohol **3** has been obtained from lithium and aluminium deuteride reduction of the corresponding methyl ester, readily available from [(5-phenylpentadienoic acid)$Fe(CO)_3$] complex.[10]

We have recorded proton-decoupled deuterium NMR spectra of alcohols **2a–e**, dissolved in PBLG–dichloromethane solvent (see experimental section). Spectra are presented in Figure 2, results are listed in Table 1.

For all the racemic [(η^4-dienol)$Fe(CO)_3$] complexes **2**, it was possible to distinguish unambiguously the four stereoisomers from their deuterium NMR spectra. In all cases, quadrupolar splittings for each of enantiomers or diastereoisomers were different enough to allow a facile and complete stereoisomeric analysis of the corresponding optically active alcohols, as illustrated on Figure 2 for enantiomerically pure (complex moiety) **2d** and **2e**.[13] Moreover, it has to be noted that the discrimination factors F_D



Scheme 2.

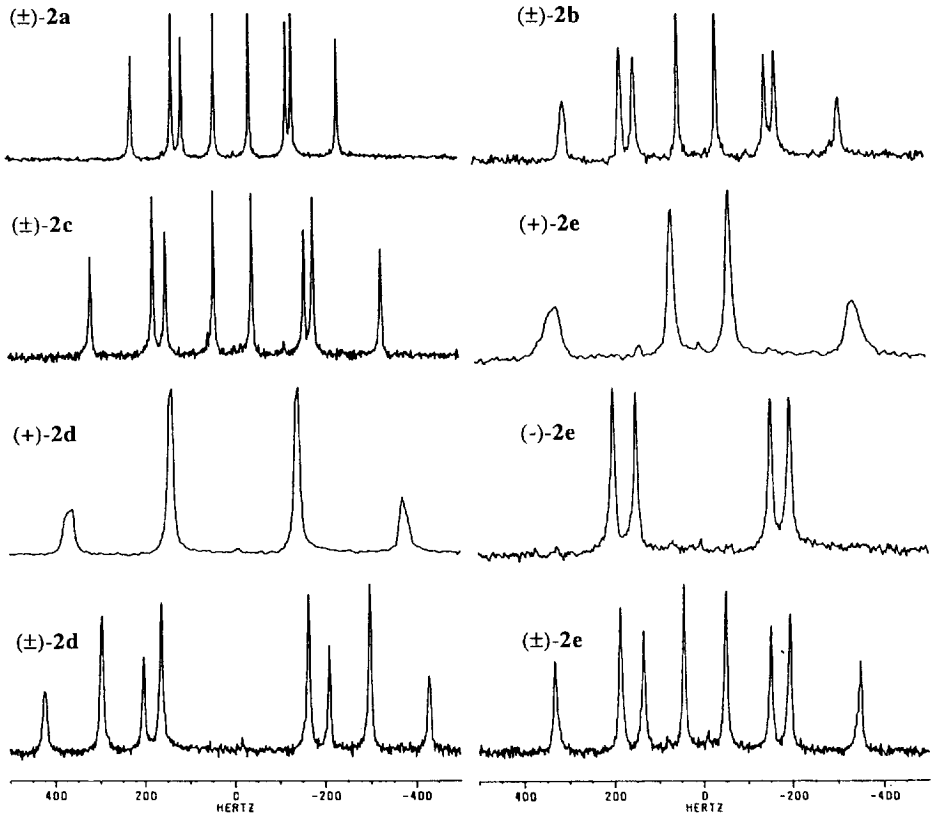


Figure 2. Proton decoupled deuterium NMR spectra (46.01 MHz) of alcohols **2a–e** in the PBLG/CH_2Cl_2 liquid crystalline solvent.[12]

obtained with these organometallic materials (94 to 221 Hz) are larger than those usually obtained with organic series (commonly less than 50 Hz).[6c,d] In comparison to chemical shift non-equivalences obtained by classical NMR methods (chiral derivatizing or solvating agents, chiral lanthanide shift reagents), the splittings non-equivalences obtained herein make this method an excellent candidate for enantiomeric analysis of iron organometallics.

Furthermore, due to its large application field,[6] this method should be suitable with iron complexes bearing any organic function allowing the incorporation of at least one deuterium. For instance, it has been previously reported that spectra from compounds containing prochiral center (from a -CD_2-

Table 1. Values of quadrupolar splittings $\Delta\nu$ and discrimination factors F_D for enantiomers of diastereoisomers Ψ-endo and Ψ-exo of alcohols (±)-**2a–e**

Alcohol	Temperature (K)	$\Delta\nu_1^{en}$ (Hz)[a]	$\Delta\nu_2^{en}$ (Hz)[a]	F_D^{en} (Hz)	$\Delta\nu_1^{ex}$ (Hz)[a]	$\Delta\nu_2^{ex}$ (Hz)[a]	F_D^{ex} (Hz)
2a	302	79	267	94	232	455	112
2b	301	85	346	131	293	613	160
2c	300	85	354	135	306	643	169
2d	300	327	595	134	410	852	221
2e	301	94	381	144	287	682	198

[a] Precision: ± 1 Hz

moiety) are identical with spectra from compounds containing isotopic chiral center (from a -CHD-moiety).[6b] As we studied monodeuteriated alcohols obtained from aldehydes, we can then assume that enantiomeric analysis can be made with iron complexes containing acid or derivated functions, as reduction will lead to dideuteriated alcohols. This fact has been verified by study of the dideuteriated alcohol (±)-**3**, which spectrum was exactly superposable to those obtained from the corresponding monodeuteriated alcohol (±)-**2e**.

At last, spectra of racemic alcohols **2a–e** exhibit a noteworthy similitude in the relative positions of signals of diastereoisomers and enantiomers. As values of quadrupolar splittings represent the averaged molecular orientation in the liquid crystalline phase, we assume that this latest is mainly governed by the bulky $Fe(CO)_3$ moiety. Considering these observations, study of optically active complexes of known absolute and relative configurations, is underway in order to verify if, as for aminoacids,[6a] a simple analysis of the NMR spectrum can give a direct access to the absolute configurations of Ψ-endo and Ψ-exo iron complexes, for which determination remains a problem.[9]

In conclusion, we have reported herein a facile and performant NMR method for complete stereoisomeric analysis of diene irontricarbonyl complexes, bearing at least one deuterium. This method is actually extended to other organometallic series, asymmetric by virtue of planar chirality or by the presence of a stereogenic metallic center.

Experimental

Poly(γ-benzyl-L-glutamate), PBLG, was purchased from Sigma (M_W: 150000–350000). Deuterium NMR spectra have been recorded on a MSL 300 Bruker spectrometer equipped with a multinuclear 10mm probe[12] at 46.01 MHz; the temperature was controlled to ±1°C. Broad band decoupling was achieved using 1 W of rf power. Typically, 2 Kwords interferograms (for a 3000 Hz spectrum width) are acquired and only zero filling (up to 8 Kwords) was used to achieve good digital resolution.

Preparation of NMR samples: Samples were prepared in 5 mm o.d. NMR tubes. PBLG (72 mg, 12% w/w ratio in CH_2Cl_2) was introduced in the NMR tube. 10–15 mg (maximum) of iron complex dissolved in dichloromethane (400 mL) was added. The sample was mixed by centrifugation of the tube (1 min, 3000 rpm) alternatively in both directions (6–10 times), until a homogeneous and birefringent solution was obtained. NMR samples were prepared just before the NMR experiment, as introduction of iron complexes modifies structure of the liquid crystalline phase after a few hours, then leading to characteristic powder NMR spectra.

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9. Considering that nucleophile reacts exclusively on the opposite face to the bulky $Fe(CO)_3$ moiety, the diastereoselectivity of the reduction depends on the conformer population of the aldehyde group. As outlined in reference 1a, aldehydes give usually poor diastereoselectivities and the relative stereochemistry of the resulting products is difficult to establish unambiguously.
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12. It has to be noted that, in our experimental conditions (5 mm tubes in 10 mm probe, no lock during acquisition), external peaks are usually broader than internal ones. Anyway, we could verify that this phenomenon does not affect the integration ratios; in the case of (+)-**2d** and (+)-**2e**, longer acquisition times (5–6 times) have increased this broadening. Better resolution should be obtained using a selective 5 mm deuterium probe (see ref 6).
13. (+)-(2*S*,5*R*)-**2d**: $[\alpha]$=+200.9 (c 5.2, $CHCl_3$); (+)-(2*R*,5*S*)-**2e**: $[\alpha]$=+379.4 (c 4.2, $CHCl_3$); (−)-(2*S*,5*R*)-**2e**: $[\alpha]$=−375.0 (c 6.2, $CHCl_3$); for determination of absolute configurations, see Djedaini F.; Grée D.; Martelli J.; Grée R.; Leroy L.; Bolard J.; Toupet L. *Tetrahedron Lett.* **1989**, *30*, 3781–3784.

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