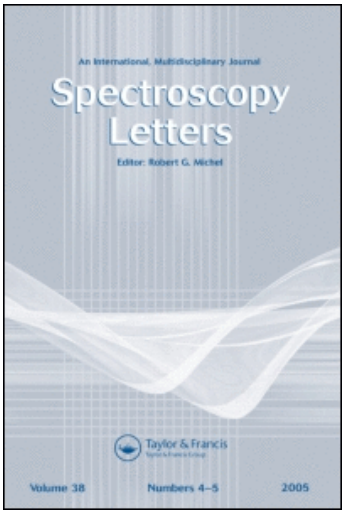

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DETERMINATION OF THE ENANTIOMERIC COMPOSITION OF CHIRAL Δ-2-OXAZOLINES-1,3 BY ^{1}H AND ^{19}F NMR SPECTROSCOPY USING CHIRAL LANTHANIDE-SHIFT REAGENTS

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DETERMINATION OF THE ENANTIOMERIC COMPOSITION OF CHIRAL Δ-2-OXAZOLINES-1,3 BY ^{1}H AND ^{19}F NMR SPECTROSCOPY USING CHIRAL LANTHANIDE-SHIFT REAGENTS

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ABSTRACT

The 300 MHz ^{1}H NMR spectra of 2-ethyl Δ^{2}-oxazoline **1m** have been studied in CCl_4, CD_3CN and C_6D_6 solutions, in the presence of the achiral lanthanide shift reagent (LSR), tris (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium III, **4** known as $Eu(fod)_3$, (see Sch. 1).

All the protons of **1m** were deshielded at various extent, and the sequence observed for their Δδ suggested a major complexation at the basic N(3) center of the heterocycle. Then the chiral monosubstituted oxazoline **1e** and the disubstituted oxazolines **1Aa−d** and **1Ba**, were studied in the presence of chiral

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**Part of thesis.

LSR, tris-[D, D dicampholylmethanato] europium III $Eu(dcm)_3$ **5** and tris-[3-(heptafluoropropylhydroxy-methylene)-d-camphorato] praseodym III $Pr(hfc)_3$ **6**. ^1H NMR, and eventually $^{19}F[^1H]$ NMR spectra were mostly recorded in C_6D_6 solution. Substantial to very important enantiomeric shift difference $\Delta\Delta\delta$ values were observed i/ for proton signals concerning the diastereomeric methyl group with all the oxazolines, for the ortho aryl protons of **1Aa** and **1Ac**, and i/ for the $^{19}F[^1H]$ signals of the fluorinated oxazolines **1Aa–b** and **1Ba**.

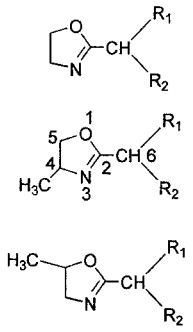
NMR results are discussed from substrate and CLSR structure standpoints.

For all tested chiral oxazolines there is at least one possibility to proceed to their enantiomeric discrimination either by ^1H or ^{19}F NMR using $Eu(dcm)_3$ or $Pr(hfc)_3$ as CLSR.

Key Words: Δ^2-oxazolines-1,3; Stereoisomer; Enantiomer; LSR; $Eu(fod)_3$; CLSR; $Eu(dcm)_3$ $Pr(hfc)_3$; Optical purity analysis

INTRODUCTION

The cyclic imino-ether or Δ^2-oxazoline-1,3 **1** is an interesting heterocyclic structure allowing the reversible masking of both entities: β-ethanolamine **2** and carboxylic acid **3**, (cf Sch. 2). This property has been widely exploited by Meyers et al.[1–6] for the enantioselective modification of masked carboxylic acid by α-ramification of the C_2-substituent. Other groups have also been interested in the elaboration and the exploitation of



1m $R_1 = H$, $R_2 = CH_3$

1e $R_1 = CH_3$, $R_2 = C_6H_5$

1A a $R_1 = H$, $R_2 = pFC_6H_4$

b $R_1 = H$, $R_2 = pCF_3C_6H_4$

c $R_1 = H$, $R_2 = pCH_3C_6H_4$

d $R_1 = H$, $R_2 =$ 1-naphtyl

1B a $R_1 = H$, $R_2 = pFC_6H_4$

4 $Eu(fod)_3$

tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium III

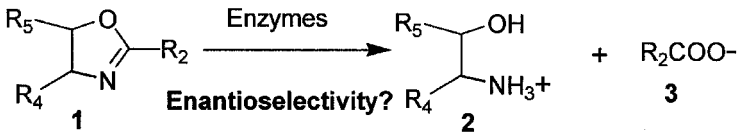
5 $Eu(dcm)_3$

tris-[D, D dicampholylmethanato] europium III

6 $Pr(hfc)_3$

tris-[3-(heptafluoropropylhydroxy-methylene)-d-camphorato] praseodym III

Scheme 1. Oxazolines and lanthanides reagents used in this paper.



Scheme 2. Enzymatic hydrolysis of oxazolines.

chiral oxazolines.[7–9] Recently, in the prodrugs field, Vorbrüggen et al.[10,11] have retained this structure for elaborating NSAID drugs (Non Steroidal Anti Inflammatory Drugs) based upon carboxylic acids as the active principles. In the "proinsecticide perspective", we have developed since several years, series of non-fluorinated[12–14] or fluorinated oxazolines.[14–17] A special attention was paid to study their metabolism in the biological tissues of insect.[12–17] So the enzymatic unmasking of carboxylates **3** and β-ethanolamines **2** from oxazolines **1** is now well-documented. Nevertheless the stereochemical course of chiral oxazolines metabolism in insect remains under interrogation: is it enantioselective, as evidenced for instance with chiral esters[18], or not? (cf Sch. 2). To be in a position to resolve this point, we are presently developing chromatographic, and particularly NMR methods allowing the determination of enantiomeric composition for chiral oxazolines.

Oxazolines **1** are of special interest for NMR studies with Lanthanide Shift Reagents (LSR), as presenting two potential binding sites: the nitrogen N(3) of the heterocyclic ring with a sp^2 unshared electron pair and the enol ether oxygen O(1). Each of these sites might permit potential binding of LSR in a monodentate fashion. As a matter of fact ethers[19] are known for their complexation with LSR by their basic oxygen center as well as oximes.[20] These latter compounds are also capable to complex by their basic nitrogen center [21] as imines,[22] and oxazoles.[23] More particularly the complexation of 2-amino-oxazoline, known as Aminorex, with LSR and CLSR has already been studied by Rothchild et al.[24]

Moreover, the relatively rigid five-membered ring and the closeness of the chiral center [C(4) or C(5) for **1Aa–d** or **1Ba**, and C(6) for **1e**] from the binding sites are molecular characteristics known to enhance the likelihood that chiral LSRs will elicite enantiomeric discrimination.[25]

The basic principles and techniques for use of achiral and chiral LSRs have been intensively previously discussed.[26–30]

This work deals with NMR chiral analysis of series of oxazolines presenting a chiral center in the masked β-ethanolamine moiety as **1Aa–d** and **1Ba**, or in the masked acid moiety as **1e**, using the Europium dicampholyl CLSR $Eu(dcm)_3$ **5** and the Praseodymium CLSR $Pr(hfc)_3$ **6**.

A preliminary study was performed with achiral LSR $Eu(fod)_3$ and achiral oxazoline **1m** chosen as a model, to confirm the complexation of such heterocycles and to optimize the solvent.

EXPERIMENTAL

Material

Commercial achiral oxazoline **1m** was purchased from Sigma Aldrich (L′Isle d′Abeau Chesne, Saint-Quentin Fallavier 38297, France).

Chiral oxazolines: monosubstitued **1e** and disubstituted **1Aa–d** and **1Ba** were prepared according to the Vorbrügen protocol.[10,11] Structural characterization of racemates and enantiomers that agree well with the proposed structures will be published elsewhere,[31] except for **1Aa** and **1Ba** that have previously been described.[14,16,17]

Achiral LSR: tris (6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium III, known as $Eu(fod)_3$, **4** and CLSR tris-[3-(heptafluoropropylhydroxy-methylene)-d-camphorato] praseodym III $Pr(hfc)_3$ **6** were obtained fromSigma Aldrich and CLSR tris-[D, D dicampholylmethanate] europium III $Eu(dcm)_3$ **5** from Acros Organics France (Noisy-Le-Grand, cedex, 93166, France). Deuterated solvents C_6D_6 and $CDCl_3$ were obtained from Euriso-Top (Gif-Sur-Yvette, 91191, France). The solvents were stored on 3 Å molecular sieves. Oxazolines and LSRs were stored in a dessicator over P_2O_5.

Measurement

Spectra were recorded on a 300 MHz (^1H) or 282 MHz (^{19}F) AC 300 Bruker equipped with a 5 mm probe and a Bruker Aspect 3000 computer.

The following abbreviations were used for the spectra description: s = singlet; bs = broad singlet; d = doublet; dd = doublet of doublet, t = triplet; q = quadruplet; m = multiplet, and p for pseudo i.e., pt = pseudo triplet.

Typical conditions for recording one-dimensional spectra were as follows: spectral width 5376 Hz (^1H) or 5617 Hz (^{19}F), data points 32 K (^1H) or 65 K (^{19}F), flip angle 30° (^1H) or 60° (^{19}F), pulse repetition 1 s (^1H) and (^{19}F), acquisition time 3.047 (^1H) or 5.832 s (^{19}F). Resolution enhancement was performed by using a gaussian window. The Fourier transform was carried out with 65 K (^1H) or 130 K (^{19}F), after zero filling so that the digital resolution was 0.17 Hz per point (^1H) or 0.08 Hz per point (^{19}F).

The different oxazolines were dissolved either in a mixture of deuterated chloroform / carbon tetrachloride (18/82, v:v), in deuterated benzene or in acetonitrile to give concentrations ranging from 1.4 to 9.4×10^{-2} mole·l^{-1} except for **1Ba** which concentration was 0.452 mole·l^{-1}. Measurements were mostly carried out at a probe temperature of $23 \pm 1°C$ and the proton chemical shifts were initially referenced to the solvent values of 7.16 and 7.27 ppm (RMN ^{1}H in C_6D_6 and $CDCl_3$, respectively). For $^{19}F[^1H]$ spectra the fluorine chemical shifts are reported in ppm relative to external reference CCl_3F (5% in C_6D_6,v/v).

In runs with LSRs, increments of solid reagent was accurately weighed and rapidly introduced into a vial containing an aliquot of standard solution of oxazoline. The LSR was dissolved by shaking and the resulting mixture was filtered through a micropipet equipped with a cotton plug then transferred into a 5 mm diameter NMR tube and the spectra immediately recorded.

In runs with CLSR, when enantiomeric shift differences were observed for selected resonances, reported chemical shifts are the average values for the two enantiomers.

RESULTS AND DISCUSSION

The 300 MHz ^{1}H NMR spectrum for **1m** as 1.4 to 9.4×10^{-2} mole·l^{-1} solution in $CDCl_3$ showed signals as follows (δ in ppm relative to TMS at 0.00 ppm): 1.18 (3H, t, $^3J = 7.53$ Hz **CH$_3$**), 2.28 (2H, qt, $^3J = 7.53$ Hz and $^5J = 1.47$ Hz, (**CH$_2$**)-CH$_3$), 3.81 (2H, tt, $^3J = 9.57$ Hz and $^5J = 1.47$ Hz (**CH$_2$**(4)-N), 4.22 (2H, t, $^3J = 9.57$ Hz, (**CH$_2$**(5)-O). To notice is the ^{5}J coupling of the homoallylic type between (**CH$_2$**)-N and (**CH$_2$**)-C=N,[14,15,32] that entails complication of the H(4)H(4′) part of the AA′XX′ system (O-**CH$_2$**-**CH$_2$**-N=C). Solution of **1m** in CD_3CN afforded a nearly similar spectrum (see Table 1) while for C_6D_6 solutions all the signals were significantly high-field shifted, reflecting appreciable aromatic solvent induced shifts, ASIS.[33] The same observations hold for all the studied oxazolines. It is also to notice that C_6D_6 entailed the complication of several spins systems comparatively to CD_3CN. For instance with **1m** and **1e**, second order AA′BB′ systems were observed for H(4)H(4′)H(5)H(5′) protons in place of AA′XX′ systems, and with **1Aa** and **1Ab** second order ABX systems were observed for H(4)H(5)H(5′) protons in place of AMX systems. Nevertheless this drawback is not critic as, in the perspective of enantiomeric discrimination, the best expected reporter nucleus are rather the CH_2(6), CH(6) and CH_3-C(4), CH_3-C(5) or CH_3-C(6)protons than the AA′BB′ or ABX ones. A remarkable difference in the geminal coupling can be seen between **1Ba** ($J = -14.1$ Hz) and **1Aa** ($J = -7.9$ Hz) corresponding to

Table 1. Solvent Effects on the ^{1}H NMR Spectra of Δ^2-Oxazolines-1,3 **1** (300 MHz)

δ ppm (Multiplicity)		CH_3-C_4	CH_3-C_5	H_4	$H_{4'}$	H_5	$H_{5'}$	H_6	$H_{2'}$[f]	$H_{3'}$[f]	Other CH_3
1m	$CDCl_3$[a]	–	–	~3.81 (m)		~4.22 (m, ~9.6)		2.28 (qt, 7.5, 1.5)	–	–	1.18 (t, 7.5)
	C_6D_6[b]	–	–	~3.45 (m)		~3.60 (m)		2.13 (qt, 7.5, 1.4)	–	–	1.10 (t; 7.5)
	CD_3CN[a]	–	–	~3.71 (m)		~4.17 (m, ~9.4)		2.22 (qt, 7.6, 1.5)	–	–	1.12 (t, 7.6)
1Aa	$CDCl_3$[c]	1.23 (d, 6.6)	–	4.13 (m, $J_{AB}=9.4$, $J_{BX}=7.4$)	–	3.70 (dd, $J_{AX}=-7.9$, $J_{BX}=7.4$)	4.27 (dd, $J_{AX}=-7.9$, $J_{AB}=9.4$)	3.50 (bs)	~7.24 (m)	~6.96 (pt, ~8.6)	–
	C_6D_6[d]	0.97 (d, 6.4)	–	~3.80 (m)	–	~3.26 (pt, ~7.4)	~3.74 (m)	3.32 (bs)	~7.03 (pdd, ~5.5, ~8.7)	~6.76 (pt, ~8.7)	–
	CD_3CN[e]	1.15 (d, 6.6)	–	4.10 (m)	–	3.72 (dd, 7.6, −8.1)	4.29 (dd, 9.4, −8.1)	3.54 (bs)	~7.29 (m,)	~7.06 (m, ~8.9)	–
1Ba	$CDCl_3$[c]	–	1.30 (d, 6.2)	3.40 (dd, $J_{AX}=7.2$, $J_{AM}=-14.1$)	3.93 (dd, $J_{MX}=9.5$, $J_{AM}=-14.1$)	4.65 (m, $J_{AX}=7.2$, $J_{MX}=9.5$)	–	3.56 (bs)	~7.27 (m)	~7.01 (pt, ~8.7)	–
	C_6D_6[e]	–	0.83 (d, 6.1)	3.11 (dd, 7.1, −14.1)	3.59 (dd, 9.4, −14.0)	~4.07 (m)	–	3.34 (bs)	~7.03 (m)	~6.75 (pt, ~8.8)	–
	CD_3CN[e]	–	1.23 (d, 6.2)	3.30 (dd, 7.1, −14.1)	3.84 (dd, 9.4, −14.2)	~4.63 (m)	–	3.53 (bs)	~7.30 (m)	~7.06 (pt, ~8.9)	–
1Ab	$CDCl_3$[e]	1.26 (d, 6.6)	–	~4.18 (m)	–	3.78 (pt, ~7.7)	~4.34 (dd, −8.1, 9.6)	3.66 (bs)	~7.42 (pd, ~8.1)	~7.58 (pd, ~8.1)	–
	C_6D_6[d]	0.97 (d, 6.6)	–	~3.80 (m)	–	3.24 (pt, ~7.6)	~3.71 (dd, −7.9, 9.4)	3.29 (bs)	~7.05 (pd, ~8.1)	~7.28 (pd, ~7.9)	–
	CD_3CN[e]	1.16 (d, 6.4)	–	~4.11 (m)	–	3.74 (dd, ~7.5, −8.1)	~4.31 (dd, −8.1, 9.4)	3.65 (bs)	~7.24 (pd, ~7.9)	~7.65 (pd, ~8.1)	–

1Ac	$CDCl_3$[d]	1.26 (d, 6.6)	–	~4.18 (m)	–	3.76 (pt, ~7.7)	~4.32 (dd, −7.9, 9.4)	3.58 (bs)	~7.17 (pd, ~8.1)	~7.12 (pd, ~8.1)	2.34 (s)
	C_6D_6[d]	0.99 (d, 6.4)	–	~3.83 (m)	–	3.27 (pt, ~7.6)	~3.73 (dd, −7.9, 9.4)	3.49 (bs)	~7.24 (pd, ~7.9)	~6.96 (pd, ~7.7)	2.06 (s)
	CD_3CN[d]	1.15 (d, 6.5)	–	~4.09 (m)	–	3.70 (dd, ~7.6, −8.0)	~4.27 (dd, −8.1, 9.2)	3.50 (bs)	~7.14 (m)	~7.14 (m)	2.31 (s)
1Ad	$CDCl_3$[d]	1.24 (d, 6.6)	–	~4.17 (m)	–	3.75 (pt, ~7.5)	~4.28 (dd, −7.6, 9.4)	4.07 (bs)	~7.4–8.0 (7H, m)		–
	C_6D_6[d]	0.94 (d, 6.5)	–	~3.81 (m)	–	3.18 (dd, ~7.5, −7.9)	~3.64 (dd, −8.0, 9.3)	3.92 (bs)	~7.18–7.7 (7H, m)		–
	CD_3CN_d	1.12 (d, 6.4)	–	~4.09 (m)	–	3.71 (pt, ~7.7)	~4.27 (dd, −8.3, 9.2)	4.02 (bs)	~7.4–8.0 (7H, m)		–
1e	$CDCl_3$[a]	–	–	3.80 (pt, 9.6)		4.17 (m)		3.69 (q, 7.2)	~7.1–7.3 (5H, m)		1.50 (d, 7.1)
	C_6D_6[b]	–	–	3.4–3.6 (m)		3.4–3.6 (m)		3.68 (q, 7.2)	~7.0–7.4 (5H, m)		1.56 (d, 7.2)
	CD_3CN[a]	–	–	3.65–3.8 (m)		4.16 (m)		3.65–3.8 (m)	~7.2–7.4 (5H, m)		1.46 (d, 7.2)

[a] H_4 and H_5 protons constitute an AA′XX′ system.
[b] H_4 and H_5 protons constitute an AA′BB′ system.
[c] H_4 and H_5 protons constitute an ABX system for **1Aa** which data δ and J were determined from the spectrum obtained under decoupling of CH_3-C_4 and using the sub-spectra method, and constitute an AMX system for **1Ba**.
[d] H_4 and H_5 protons constitute an ABX system that was not studied by the sub-spectra method, and their chemical shift δ were approximated as the multiplet center. This approximation was evidenced in the case of **1Aa** as entailing only ~0.1 Hz error. In these cases the couplings were assigned by reference to the calculated spectra concerning **1Aa** and **1Ba**.
[e] H_4 and H_5 protons constitute an AMX system. The couplings were assigned by reference to the calculated spectra concerning **1Aa** and **1Ba**.
[f] H_2' and H_3' constitute an AA′XX′ system which is complicated by couplings with the ^{19}F nucleus. However, as the patterns are simple, the spectra are schematically described as first order systems with approximated chemical shifts and couplings.

the known increase in J_{gem} resulting from the substitution of the methylene group by electronegative groups.[34]

For the fluorinated oxazolines **1Aa**, **1Ba** and **1Ab**, ^{19}F resonances will be presented below.

Effects of Eu(fod)$_3$ on ^{1}H NMR Spectra of Oxazolines 1m and 1e

Despite the above-mentioned complications we selected C_6D_6 as the best solvent for assays with LSR and CLSR expecting spectra simplification, as generally observed with such chelating agents, and taking into account the stretcher spectral lines observed for substrates **1** in this solvent compared to $CDCl_3/CCl_4$(18:82, v/v).

Adding increments of the achiral LSR Eu(fod)$_3$ to C_6D_6 solutions of **1m** and **1e** corresponding to [L]/[S] = [**4**]/[**1**] ratio of 1/32, 1/16 and 1/8 produced for all protons of the heterocycle and of the side-chain, substantial lanthanide-induced shifts (LIS) summarized in Figs. 1 and 2. Good linear correlations were obtained ($r^2 > 0.99$) between the induced shifts $\Delta\delta$ for the different protons of **1m** and **1e** and the variable ratio [**4**]/[**1**],resulting in the following sequence for the induced shifts measured by the slopes:

$$\mathbf{H(4)\#H(6) > H(5) > CH_3(6)}$$

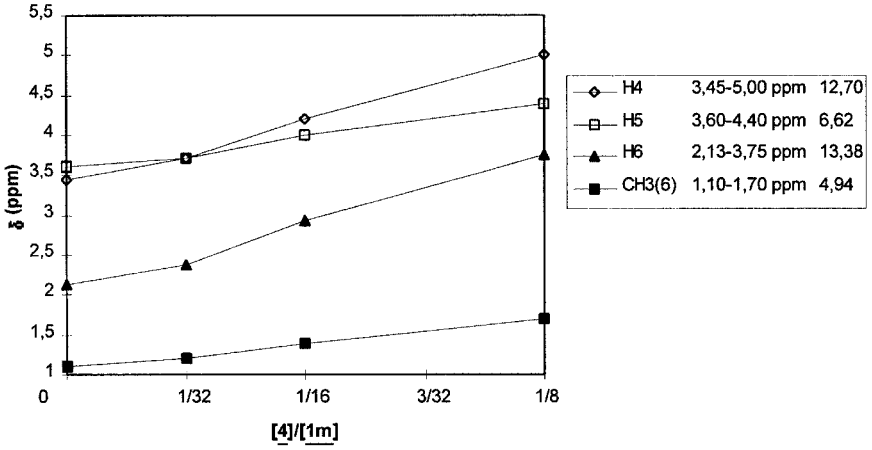


Figure 1. Lanthanide induced shifts $\Delta\delta$ elicited by Eu(fod)$_3$ **4** for the protons of oxazoline **1m**. Variation of the chemical shifts (C_6D_6 solution) with the molar ratio [**4**]/[**1m**] for the protons H(4), H(5), H(6), and CH_3(6). The corresponding limit values and the slope of the linear correlation are specified.

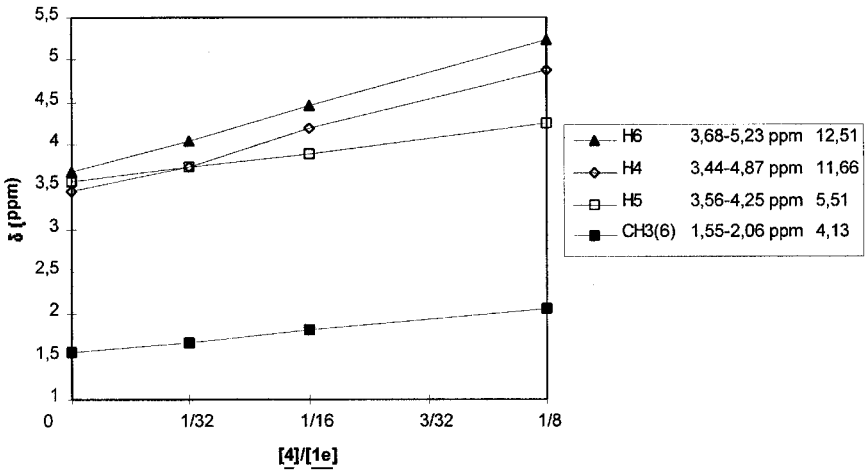


Figure 2. Lanthanide induced shifts Δδ elicited by Eu(fod)$_3$ **4** for the protons of oxazoline **1e**. Variation of the chemical shifts (C_6D_6 solution) with the molar ratio [**4**]/[**1e**] for the protons H(4), H(5), H(6), and CH_3(6). The corresponding limit values and the slope of the linear correlation are specified.

The larger Δδ magnitudes seen for H(4) vs. H(5) are consistent with the hypothesis of a pseudo contact mechanism described by the McConnell equation,[35] and predominant LSR binding to the N(3) site close to H(4). This conclusion agrees with that of Rothchild et al. concerning Aminorex, a particular oxazoline.[24] N(3) site is evidently favored vs. O(1) on electronic grounds. But, to explain the fact that H(4) and H(6) undergo similar Δδ despite H(6) is farthest from N(3) than H(4), we suppose that a smaller contribution of the O(1) site is also existing. However, the hypothesis of bidentate chelation is not plausible because it would entail important line broadenings which are not presently observed.[36,37]

Effects of Eu(fod)$_3$ on ^{1}H NMR Spectra of Oxazolines 1Aa and 1Ba

The likelihood that a methyl at position C(4) and C(5) will offer suitable analytical "marker" group in NMR chiral analysis for oxazolines α-N and α-O substituted by a methyl group was tested with achiral LSR Eu(fod)$_3$ **4** and oxazolines **1Aa** and **1Ba**. The results of incremental additions of **4** to C_6D_6 solutions of racemic **1Aa** and **1Ba** resulted in significant induced shifts Δδ (LIS) for all protons, cf Figs. 3 and 4. In these cases, attempts of correlations between the Δδ for the different protons of **1Aa** and **1Ba** and the

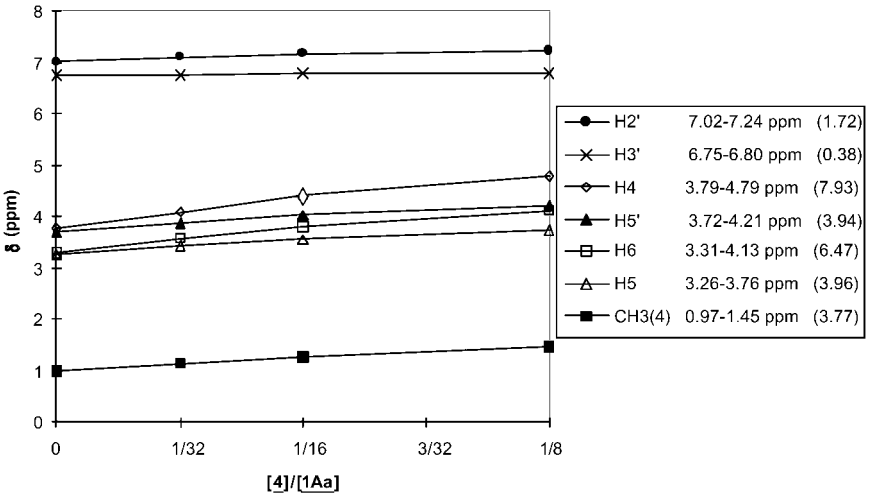


Figure 3. Lanthanide induced shifts Δδ elicited by Eu(fod)$_3$ **4** for the protons of oxazoline **1Aa**. Variation of the chemical shifts (C_6D_6 solution) with the molar ratio [**4**]/[**1Aa**] for the protons H(2′), H(3′), H(4), H(5), H(5′), H(6), and CH_3(4). The corresponding limit values and the slope (in parenthesis) of the linear correlation are specified.

variable ratio [**4**]/[**1**] resulted in poor correlation linear coefficients (r^2ranging from 0.95 to 0.98). Nevertheless qualitative sequences for Δδ have been drawn for the following protons:

for **1Aa** H(4)#H(6) > H(5)#H(5′)#CH_3(4) > H(2′) > H(3′)
for **1Ba** H(6)#H(4′)#H(4) > H(5) > CH_3(5)#H(2′) > H(3′).

Again, the larger Δδ magnitudes seen for H(4) and (4′) vs. H(5) and H(5′) are consistent with the hypothesis of a pseudo contact mechanism and predominant LSR binding to N(3) closer to H(4) than O(1). This site appears as favored vs. O(1) on electronic grounds for **1Aa** and also on steric standpoint in the case of **1Ba**. This hypothesis agrees with the observation of significantly more pronounced Δδ for all protons of **1Ba** vs. **1Aa** excepted CH_3(5) vs. CH_3(4), (cf Figs. 3 and 4). The smaller Δδ magnitude observed for CH_3(5) in **1Ba** can be explained by the greater distance from the binding site N(3).

A general comparison of the NMR LIS data obtained with LSR **4** and all the oxazolines **1** led to the following sequences for the given molar ratio [**4**]/[**1**] = 1/8:

Δδ in ppm for H(4): **1m** (1.55) > **1e** (1.43) > **1Ba** (1.11 and 1.15) > **1Aa** (1.00).

Δδ in ppm for H(6): **1m** (1.62) > **1e** (1.55) > **1Ba** (1.15) > **1Aa** (0.82).

These results agree nicely with our previous hypothesis and show that the LIS concerning H(4) and H(6) are diminished by the steric effects exerciced by C(6), C(5) and C(4) substituents.

It is to notice that $Eu(fod)_3$ incremental addition entailed ^1H NMR spectral simplification for **1Aa** as the second order system corresponding to H(4), H(5) and H(5′) was transformed into a first order system even with the moderate molar ratio [**L**]/[**S**] = [**4**]/[**1Aa**] = 1/8. By contrast the complexation of **1Ba**, resulted in ^1H NMR spectral complication with the transformation of a first order AMX system for H(4), H(4′) and H(5) into a second order ABX system.

Effects of CLSR $Eu(dcm)_3$ on ^1H NMR Spectra of Chiral Oxazolines 1

On the basis of LSR results, CLSR $Eu(dcm)_3$ **5** known to elicit the best differential shift dispersion ΔΔδ for enantiomers (28, 30) was first tested with racemic oxazolines **1Aa–d**, **1Ba** and **1e** expecting good potential for methyl groups: $CH_3(4)$, $CH_3(5)$ or $CH_3(6)$ and for the C_6 methylene group considered

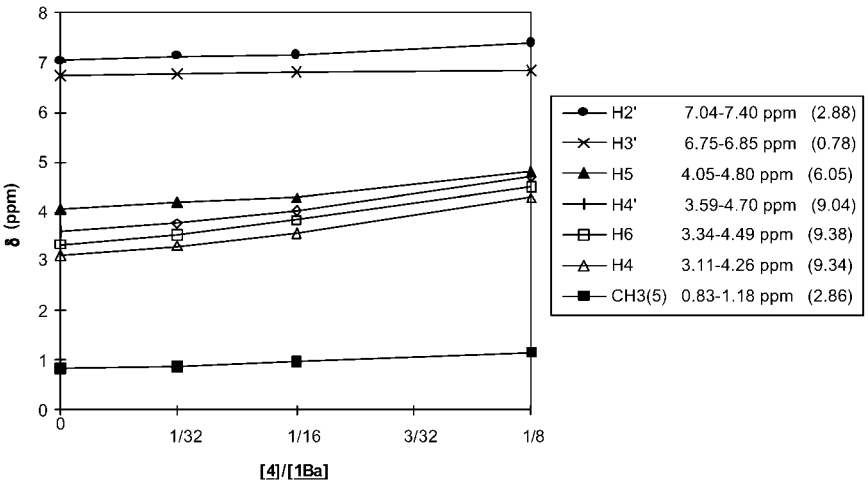


Figure 4. Lanthanide induced shifts Δδ elicited by $Eu(fod)_3$ **4** for the protons of oxazoline **1Ba**. Variation of the chemical shifts (C_6D_6 solution) with the molar ratio [**4**]/[**1Ba**] for the protons H(2′), H(3′), H(4), H(4′), H(5), H(6) and $CH_3(5)$. The corresponding limit values and the slope (in parenthesis) of the linear correlation are specified.

Table 2. Diastereoisomer Discrimination of ^{1}H NMR and ^{19}F NMR Signals of Δ^{2}-Oxazolines-1,3 by Complexation with $Eu(dcm)_3$ **5**[a]

	^{1}H NMR						^{19}F NMR					
	Solvent	[L]/[S]	Proton	$\Delta\delta$ (ppm)	$\Delta\nu$ (Hz)	h%[d]	Solvent	[L]/[S]	$\Delta\delta$ (ppm)	$\Delta\nu$ (Hz)	$\delta_{1/2}$ (Hz)	h%
	$CCl_4/CDCl_3$[b]	1/8	$CH_3(4)$	0.71	28.4	77**	$CCl_4/CDCl_3$[b]	1/8	0.05	9.5	1.8	3***
			$H_{2'}$	0.26	45.0	3***						
1Aa[e]	**C_6D_6**	1/8	$CH_3(4)$	0.38	0.0	100*	C_6D_6	1/8	0.14	7.3	1.1	3***
			$H_{3'}$	0.03	8.7	6***						
	C_6D_6	1/4	$CH_3(4)$	0.88	0.0	100*	C_6D_6	1/4	0.18	13.8	—	0***
												Fig. 6a
			$H_{2'}$	0.32	53.0	4***						
						Fig. 5a						
1Ba[e]	**C_6D_6**	1/8	$CH_3(5)$	0.42	15.0	60**	C_6D_6	5/4	0.40	5.1	2.1	8***
			$H_{2'}$	0.07	2.3	38**						
1Ab[e]	**$CCl_4/CDCl_3$**[b]	1/6	$CH_3(4)$	0.68	26.6	62**	$CCl_4/CDCl_3$[b]	1/4	0.02	3.0	1.1	6***
												Fig. 6b
	C_6D_6	1/8	$CH_3(4)$[c]	0.70	—	—*	C_6D_6	1/4	0.09	3.5	0.7	0***
												Fig. 6c

IAc	C_6D_6	1/8	$CH_3(4)$	0.46	0.0	100*
			pCH_3-C_6H_4	0.03	4.6	9***
						Fig. 5c
			$H_{3'}$	0.05	8.0	9***
						Fig. 5b
			$H_{2'}$	0.19	30.0	0***
						Fig. 5b
1Ad	C_6D_6	1/8	$(CH_3)_4$[c]	0.19	—	—*
Ie	C_6D_6	1/8	CH_3	0.36	0.0	100*

[a]All experiments were performed at 23°C.
[b]$CCl_4/CDCl_3$ (82,18, v/v).
[c]The signal of one of the diastereoisomers is overlapped by a CLSR signal.
[d]h% = (valley height/average peak height) × 100.
A simplified description (qualitative) is also presented,
***very good discrimination with baseline resolution (or almost), $0 \leq h \leq 10$.
**good discrimination, but without baseline resolution, $10 \leq h \leq 90$.
*no discrimination (or very bad), $90 \leq h \leq 100$.
[e]Assignements of the signals were achieved by overloading with one enantiomer. S enantiomers present the most deshielded signals in both ^1H and ^{19}F NMR spectra, see Figs. 5 and 6.

as interesting reporter nucleus in view of their simple multiplicity, their proximity to the chiral center and of the significant $\Delta\delta$ observed for the methyls of **1Aa** and **1Ba**. In most experiments temperature was fixed at $23 \pm 1°C$, the molar ratio [**5**]/[**1**] was 1/8, the solvent was C_6D_6. The enantiomeric separation of the signals was appreciated by three criterions: differential shift dispersion $\Delta\Delta\delta$, which was rather expressed in Hz by $\Delta\nu = |\nu_R - \nu_S|$, the half height width $\delta_{1/2}$ and by the relative valley height h% (see Table 2).

In ^{1}H NMR spectra moderate $\Delta\nu$ were only observed for the CH_3 signals of oxazolines **1Aa** and **1Ab** (in $CCl_4/CDCl_3$ solution) **1Ba** (in C_6D_6 solution), with important relative valley heights **h**% of 77, 62 and 60%, and molar ratio [**5**]/[**1**] = 1/8, 1/6 and 1/8, respectively. More important [**L**]/[**S**] ratio are not usefull due to noticeable peak broadening resulting also in the occultation of the ^{3}**J** coupling for $\underline{CH_3}CH$ even with low molar ratio [**5**]/[**1**], (1/6 and 1/8). No discrimination has been obtained for $CH_3(4)$ and $CH_3(6)$ for oxazolines **1Ac** and **1e** respectively. The methylene $CH_2(6)$ and the methine CH(6) are not good reporter signals for resolving the enantiomers of the oxazolines **1Aa–d** and **1Ba**, and **1e**, respectively. For oxazolines **1Aa** and **1Ac** H(2′) and H(3′) protons constitute attractive analytical "marker signal" eliciting nearly the complete resolution of enantiomers, see Figs. 5a (h% = 4), and 5b (h% = 9 and 0). The downfield $H_{2'}$ signal was consistently broader and lower in height for racemic **1Aa** and **1Ac** than the upfield signal (see Figs. 5a and 5b) presumably the result of differential lanthanide-induced broadening for the short-lived diastereomeric complexes.[24] Quantitative studies of enantiomeric excess should therefore be based on peak areas rather than on peak heights. For **1Ac** the $\underline{CH_3}$-(C_6H_4) protons give also good results, see Fig. 5c, (h% = 9). The convenience of these marker signals is remarkable taking into account their distance from the chiral center.

Effects of CLSR Eu(dcm)$_3$ on ^{19}F NMR Spectra of Chiral Oxazolines 1

For fluorinated oxazolines CLSR **5** appeared as eliciting nearly a total resolution between the ^{19}F[^{1}H] NMR signals of enantiomers in spite of the distance of the ^{19}F nucleus from the chiral center and from the complexation site, and of the very low $\Delta\delta$ generally observed (see Table 2). Thus, even when using moderate [**5**]/[**1**] ratio, with **1Aa**, **1Ba** and **1Ab** the following results {h%, ([**5**]/[**1**])} were respectively observed: {3%, (1/8)} in $CCl_4/CDCl_3$ and C_6D_6 and {0%, (1/4)} in C_6D_6; {8%, (5/4)} in C_6D_6; {0%, (1/4)} in C_6D_6. In all cases overloading indicated that S enantiomer presents the most deshieded signal (see Fig. 6a–c). A noticeable and favorable solvent effect is observed when changing $CCl_4/CDCl_3$ for C_6D_6 with

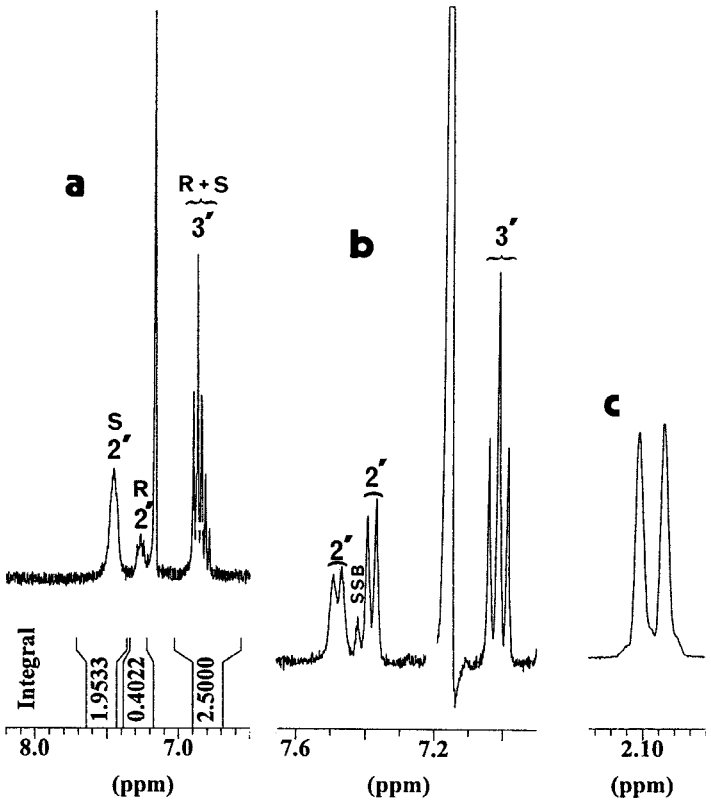


Figure 5. Effects of Eu(dcm)$_3$ **5** on ^{1}H NMR signals of oxazolines(C_6D_6 solution), **a** aromatic protons of **1Aa** (sample reinforced in S enantiomer), [**5**]/[**1**] = 1/4, **b** aromatic protons of **1Ac**, SSB = spinning side band, [**5**]/[**1**] = 1/8, **c** $\underline{CH_3}$-C_6H_5-protons of **1Ac**, [**5**]/[1] = 1/8.

simultaneously a reduction in $\delta_{1/2}$ and an increase in $\Delta\nu$ resulting in a lower h%, particularly for **1Ab** (see Fig. 6b,c).

Effects of CLSR Pr(hfc)$_3$ on ^{1}H NMR Spectra of Chiral Oxazolines 1

Owing to the absence of good proton reporter for the enantiomeric discrimination of the non-fluorinated oxazolines **1Ad** and **1e** using Eu(dcm)$_3$ **5**, experiments were also undertaken with Pr(hfc)$_3$ **6**. This praseodymium CLSR is often used for inducing high-field LIS with methyl

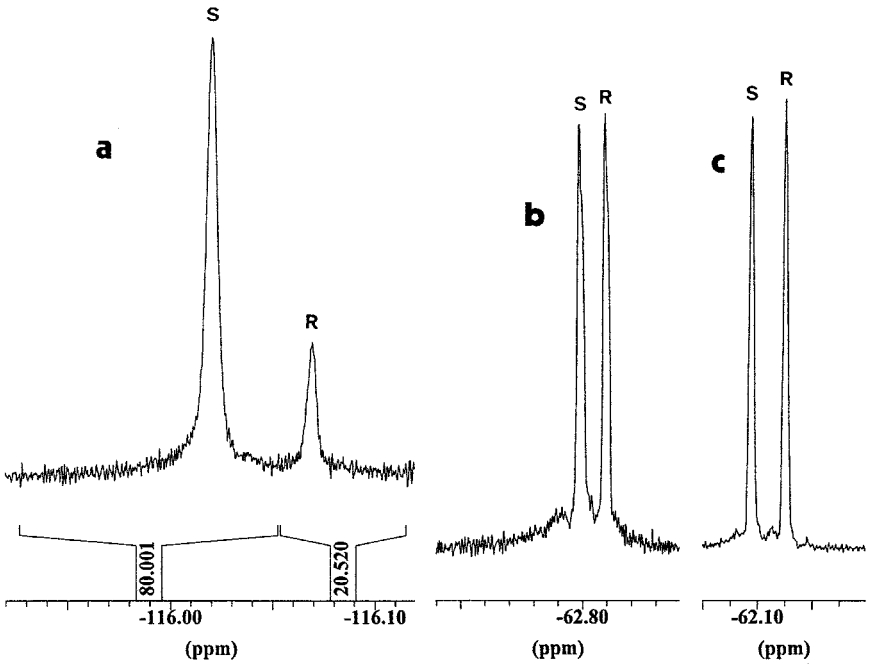


Figure 6. Effects of Eu(dcm)$_3$ **5** on ^{19}F NMR signals of oxazolines, **a** **1Aa** in a C_6D_6 solution with [**5**]/[**1Aa**] = 1/4 and [**1Aa**S]/[**1Aa**R] = 4/1, **b** **1Ab** in a $CDCl_3/CCl_4$ solution with [**5**]/[**1Ab**] = 1/4, **c** **1Ab** in a C_6D_6 solution with [**5**]/[**1Ab**] = 1/4.

reporter (27, 28), (38) and we expected a better enantiomeric resolution for the CH_3(4), (5) and (6) of our chiral oxazolines **1**, especially for the non-fluorinated ones.

The results presented in Table 3 revealed that the enantiomeric discrimination of the methyl groups is generally improved comparatively to those obtained with Eu(dcm)$_3$. Thus, for **1Aa**, **1Ab**, **1Ac** and **1e** there is a significant discrimination of the enantiomers but the relatively important h% (30, 34, 40, and 24, respectively) prevent a quantitative exploitation of the spectra, see Fig. 7a for **1e**. With **1Ac** we tried to optimize the parameters: temperature, solvent and [**L**]/[**S**] ratio. Improvement of the resolution by increasing $\Delta\nu$ via the increase of [**6**]/[**1**] ratio appeared as rapidly limited by severe line-broadening. Changing C_6D_6 by CD_3CN is favorable for the criterion $\delta_{1/2}$[30] and by contrast unfavorable for the $\Delta\nu$ criterion. Temperature testing indicated $\theta = 30°C$ as an optimal condition. In fact, an increase in θ entails a favorable decrease of $\delta_{1/2}$ which is counterbalanced by a concomitant decrease of $\Delta\nu$. This trend is relevant of a rather

Table 3. Diastereoisomer Discrimination of ^{1}H NMR and ^{19}F NMR Signals of Δ^2-Oxazolines-1,3 by Complexation with $Pr(hfc)_3$ **6**[a]

	^{1}H NMR[e]						^{19}F NMR					
	Solvent	[L]/[S]	Δδ (ppm)	Δν (Hz)	$\delta_{1/2}$[f] (Hz)	h%[g]	Solvent	[L]/[S]	Δδ (ppm)	Δν (Hz)	$\delta_{1/2}$ (Hz)	h%[g]
1Aa	C_6D_6	1/4	−2.58	58.5		30**	C_6D_6	1/4	−0.03	1.4	0.7	50**
1Ba	C_6D_6	1/4	−1.44	0.0		100*	C_6D_6	1/4	−0.18	3.0	1.8	32**
							C_6D_6	5/4	−0.23	7.5[h]	2.1	0***
1Ab	C_6D_6	1/4	−2.57	50.5		34**	C_6D_6	1/4	−0.15	0.8	—	93*
1Ac	C_6D_6	1/32	−0.26	4.6	3.2	61**						
	C_6D_6[b]	1/32	−0.17	2.8	1.9	40**						
	C_6D_6	1/4	−2.31	44.4	—	92*						
	CD_3CN[b]	1/32	−0.10	2.1	1.4	41**						
	CD_3CN	1/4	−0.55	12.5	6.7	54**						
	CD_3CN[b]	1/4	−0.48	9,8	4,7	36**						
	CD_3CN[c]	1/4	−0.38	6.6	—	65**						
	CD_3CN[d]	1/2	−0.55	11.5	6.9	40**						
1Ad	C_6D_6	1/24	−0.14	9	2	5***						
						Fig. 7bc						
1e	C_6D_6[b]	1/32	−0.18	2.2		24**						
						Fig. 7a						

[a] Most of the experiments were performed at $\theta = 23°C$, except other specifications, [b]$\theta = 30°C$, [c]$\theta = 40°C$ and [d] $\theta = 33°C$.
[e]Data concerning $CH_3(4)$ for **1Aa – d**, $CH_3(5)$ for **1Ba** and $CH_3(6)$ for **1e**.
[f]Under irradiation of H_4.
[g]Same conventions as in Table 2.
[h]Overloading indicated that S enantiomer presents the most deshielded signal.

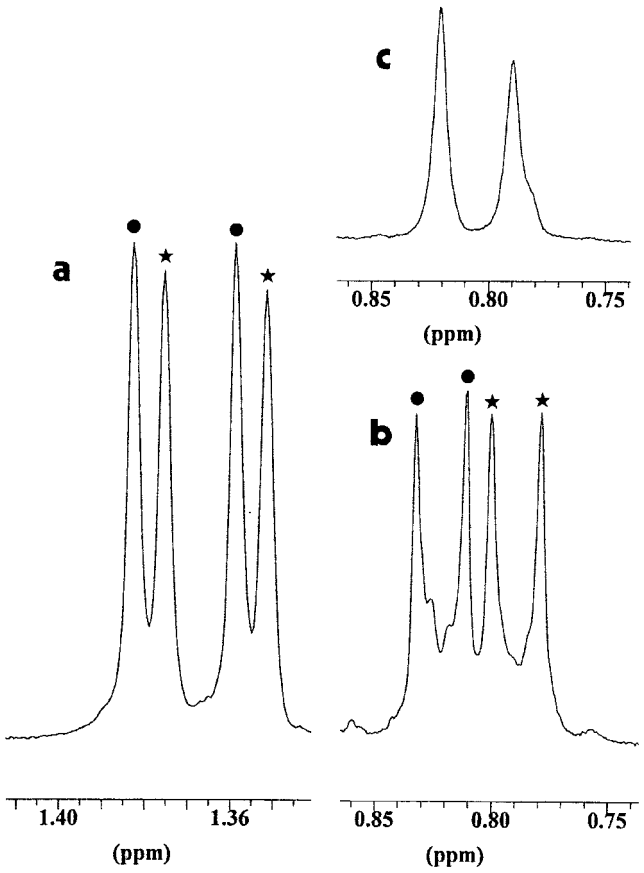


Figure 7. Effects of $Pr(hfc)_3$ **6** on ^1H NMR methyl signals of oxazolines. **a** racemic **1e** in a C_6D_6 solution with [**6**]/[**1e**] = 1/32, **b** racemic **1Ad** in a C_6D_6 solution with [**6**]/[**1Ad**] = 1/24, without H(4) decoupling, **c** see b, but with H(4) decoupling.

strong complexation behaviour of oxazoline **1Ac** according to Whitesides' observations concerning CLSRs and primary amines.[30] By contrast for oxazoline **1Ad** the methyl signal is almost baseline-resolved, see Fig. 7c. For oxazoline **1Ba** there is no resolution.

Table 4. Comparison of the LIS Δδ Induced by Eu(fod) **4**, $Eu(dcm)_3$ **5** and $Pr(hfc)_3$ **6** for the Protons of Oxazolines **1**

			Δδ (ppm)[a]				
		[L]/[S]	H_4	H_6	H_5	$H_{5'}$	$CH_3(4)$
$Eu(fod)_3$	**1Aa**	1/8	1.00	0.82	0.49	0.50	0.48
$Eu(dcm)_3$	**1Aa**[b]	1/16	0.6	0.5	0.10	0.29	0.30
	1Ad	1/8	0.3	0.23	0.17	0.14	0.19
		1/16	0.09	0.07	0.06	0.06	0.07
$Pr(hfc)_3$[c]	**1Ac**	1/32	−0.53	−0.47	−0.28	−0.25	−0.26
	1Ad	1/24	−0.30	−0.10	−0.08	−0.10	−0.14

[a]The solvent was C_6D_6 except for[b].
[b]The solvent was $CDCl_3/CCl_4$.
[c]The high-field shift Δδ is noted with a minus sign.

Effects of CLSR $Pr(hfc)_3$ on ^{19}F Spectra of Chiral Oxazolines 1

Comparatively to $Eu(dcm)_3$ as CLSR, $Pr(hfc)_3$ provides lesser resolution concerning the $^{19}F[^1H]$ signals of oxazolines **1Aa** and **1Ab**. By contrast enantiomers of oxazoline **1Ba** are baseline-resolved with this CLSR for a moderate **[L]/[S]** ratio of 5/4.

Comparison of the LIS Induced by LSR 4 and CLSR 5 and 6

The Δδ induced by CLSR **5** and **6** were obtained using the average between the values observed for the enantiomers ($|\Delta\delta_R - \Delta\delta_S|/2$) for the most representative protons of compounds **1Aa**, **1Ac** and **1Ad**, and compared to that elicited for achiral LSR **4**, see conclusion below and Table 4.

CONCLUSION

CLSR $Eu(dcm)_3$ **5** and $Pr(hfc)_3$ **6** elicit efficient complexation of oxazolines, mainly by their basic N(3) site, as observed with achiral LSR **4**.

Complexation with $Eu(dcm)_3$ allows the enantiomeric discrimination of oxazolines **1Aa** and **1Ac** by ^1H NMR analysis of aromatic protons or

arylmethyl groups, and of fluorinated oxazolines **1Aa**, **1Ba** and **1Ab** by $^{19}F[^{1}H]$ NMR analysis. From the same analytical standpoint, $Pr(hfc)_3$ is very convenient for the non-fluorinated oxazolines **1Ad** and **1e**, using ^{1}H NMR analyse of their methyl groups.

This work is on continuation by testing other CLSR and chiral solvating agents (CSA). These NMR methods will be applied to organic extracts of insect biological media incubated with racemic oxazolines in order to determine possible chiral recognition in their enzymatic hydrolysis.

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