Use of chiral lanthanide shift reagents in the elucidation of NMR signals from enantiomeric mixtures of polycyclic compounds†

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^{1}H and ^{13}C NMR is used to study the effects on a set of racemic polycyclic compounds of the application of the chiral shift reagents europium(III) tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] and europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. The study compares the chiral shift reagents to find the conditions resulting in optimum enantiomeric ($\Delta\Delta\delta$) and spectral resolution ($\Delta\delta$). Of the two reagents Eu(hfc)$_3$ proved to be the more efficient. In addition, the effect of the achiral lanthanide shift reagent Eu(fod)$_3$, used in combination with the chiral lanthanide shift reagents, was investigated.

Introduction

Polycyclic compounds are a key research topic with numerous investigations in the literature into their theoretical[1] and experimental properties (carbocations,[2] mechanism and reaction features[3]). Our contribution has been to seek new synthetic methodologies for the preparation of polycyclic compounds[4] and to investigate effects related to their geometry and steric parameters by NMR.[5] More recently we have turned our attention to the preparation of enantiomerically pure structures,[4c] so needing a good analytical method for the determination of enantiomeric excess. Some techniques described in the literature are: (a) gas chromatography (GC) on chiral columns with cyclodextrins; (b) high performance liquid chromatography (HPLC) on chiral columns with cyclodextrins; (c) chiral solvating agents for NMR (CSAs); (d) NMR spectroscopy using chiral derivatizing agents; and (e) NMR spectroscopy using chiral shift reagents (CSRs).[6]

GC was not suitable for our study due to the high boiling points of hexachlorinated polycyclic compounds. HPLC did not give satisfactory separations, chiral solvating agents in general give only small $\Delta\Delta\delta$ values and derivatizing agents, such as Mosher's Reagent, are not applicable to all the studied compounds. So, we started to explore further the application of chiral shift reagents.[7] In the literature several studies describe the behavior of chiral chemical shift reagents.[6a,8]

Although a variety of CSRs have been investigated, only a few are commercially available, like the tris[3-(trifluoromethylhydroxymethylene)camphorate] and tris[3-(heptafluoropropylhydroxymethylene)camphorate] lanthanides(III), La(tfc)$_3$ and La(hfc)$_3$. Of these reagents, Sanders *et al.*[9] reported that the application of Eu(hfc)$_3$ is practically analogous to the application of Eu(tfc)$_3$. Other authors[10] point out that Pr(hfc)$_3$ is more efficient than Eu(hfc)$_3$ in ^{1}H NMR, offering larger values of $\Delta\Delta\delta$ with smaller amounts of added reagent. Goering *et al.*[11] found no particular advantage in the use of Eu(hfc)$_3$ and Pr(hfc)$_3$ rather than Eu(tfc)$_3$. Although many lanthanide ions have been used for different specific purposes,[8a–c,12] Eu(III) has been by far the most commonly used for enantiomeric separations,[13] since it causes the least line broadening.[14]

In a previous paper[7a] we asserted that the combination of chiral Eu(tfc)$_3$ and achiral Eu(fod)$_3$ efficiently increased enantiomeric shift difference magnitudes and enhanced spectral resolution in ^{1}H NMR. In some cases addition of Eu(fod)$_3$ allows the separation of otherwise inseparable enantiotopic protons.

In the present paper we describe a systematic and qualitative investigation on several polycyclic compounds, evaluating the influence of (+)-Eu(tfc)$_3$, (+)-Eu(hfc)$_3$ or a specific mixture of chiral and achiral [Eu(fod)$_3$] reagents on the $\Delta\Delta\delta$ values in their ^{1}H and ^{13}C NMR. The object of the study was to find a simple theoretical model to adequately describe the various shift phenomena encountered during the routine use of chiral and achiral shift reagents with polycyclic substrates.

Results and discussion

A system containing a monodentate donor D (substrate) forms a multisite exchange system on the addition of a CSR (L) [equilibrium (1)]:

$$D \underset{K_2}{\overset{K_1}{\rightleftharpoons}} DL \underset{K_4}{\overset{K_3}{\rightleftharpoons}} D_2L \qquad (1)$$

This system may be extended to higher D_nL_m, resulting in a mixture of different adducts in solution, each one with its own rate constant. If all these constants had the same order of magnitude, a very complex exchange system would result if the lifetimes of the different entities were within the NMR timescale. In this case the initial set of resonances for D would be seen to undergo chemical exchange broadening.[15]

The analysis of the effect of the addition of chiral lanthanide shift reagents into a solution containing a substrate can be accomplished in two ways: (a) by using a graph plotting the chemical shift *versus* the ratio between the number of moles of chemical shift reagent and the number of moles of substrate (n_{CSR}/n_S), the so called LIS (lanthanide induced shift) curves, and (b) by making an analysis of a sequence of spectra and choosing the best spectrum. The graphical representation of the data allows both visualization of the increment of induced chemical shifts and study of the stoichiometry of the adduct at the inflection point. At this point, the spectrum is essentially that of a coordinated ligand rather than that of the average of the free and complexed ligands, since further addition of metal complex causes no further increase in spectral shifts. We can therefore deduce that the n_{CSR}/n_S ratio at the inflection point indicates the stoichiometry of the adduct (D_nL_m).[8c,16]

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† Additional ^{1}H NMR spectra of alcohol **3** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/1999/2783, otherwise available from BLDSC (SUPPL. NO. 57665, pp. 4) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

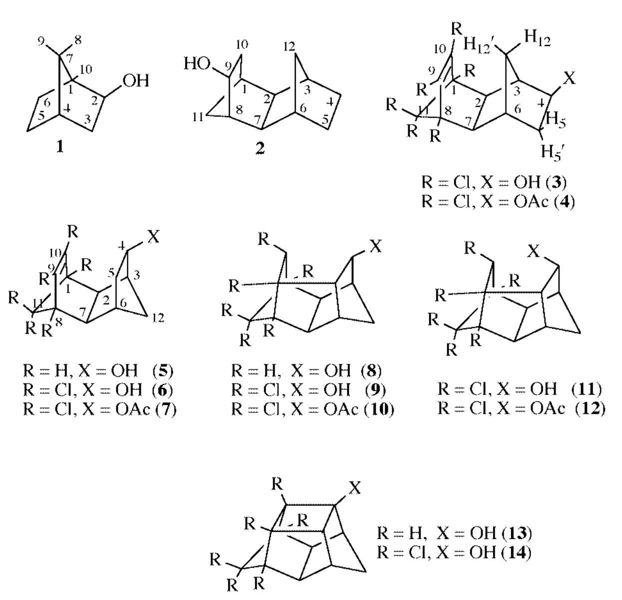

Fig. 1 Polycyclic compounds studied by LIS methodology.

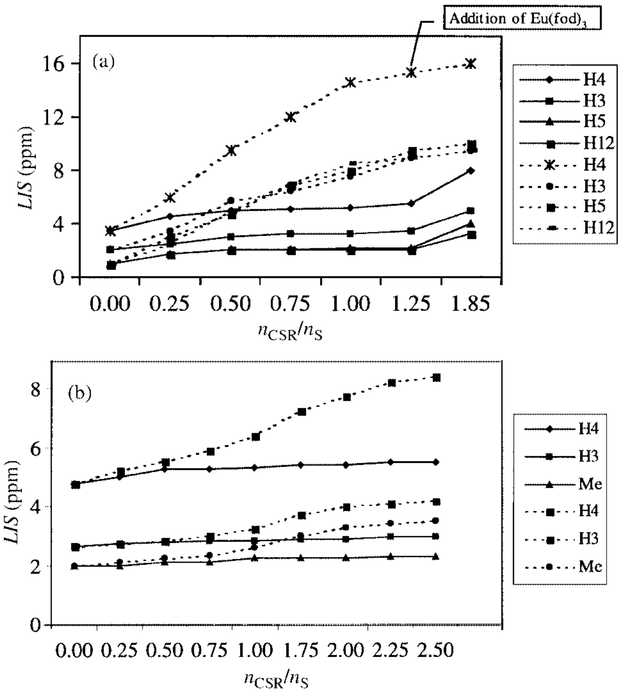

Fig. 2 Chemical shifts *versus* n_{CSR}/n_S ratios for substrates (a) **3** and (b) **7**. The full and broken lines illustrate, respectively, the solutions containing Eu(tfc)$_3$ and Eu(hfc)$_3$.

The fourteen compounds analyzed in this study are listed in Fig. 1. The efficiency of their enantiomeric resolution ($\Delta\Delta\delta$) by chiral shift reagents is examined in the following sections.

Effect of chiral lanthanide shift reagents (+)-Eu(tfc)$_3$ and (+)-Eu(hfc)$_3$ on spectral resolution and linewidth

The LIS curves (Fig. 2) show significant differences in the behaviour of the trifluoride [Eu(tfc)$_3$] and heptafluoride [Eu(hfc)$_3$] chiral chemical shift reagents (C-CSR).

With Eu(tfc)$_3$ the inflections in the LIS curves appear at n_{CSR}/n_S ratios ranging from 0.2 to 0.5, denoting the formation, in this interval, of a combination of D$_n$L adducts, as exemplified by substrate **3** in Fig. 2. The n_{CSR}/n_S ratios are greater than 0.5 for only some of the protons. In general the corresponding spectra have poor resolution with broad lines and small $\Delta\delta$, (see supplementary data). Some studies[8c,17] have already reported complexes containing more than one substrate coordinated to europium, including one with Eu(tfc)$_3$ itself.[11]

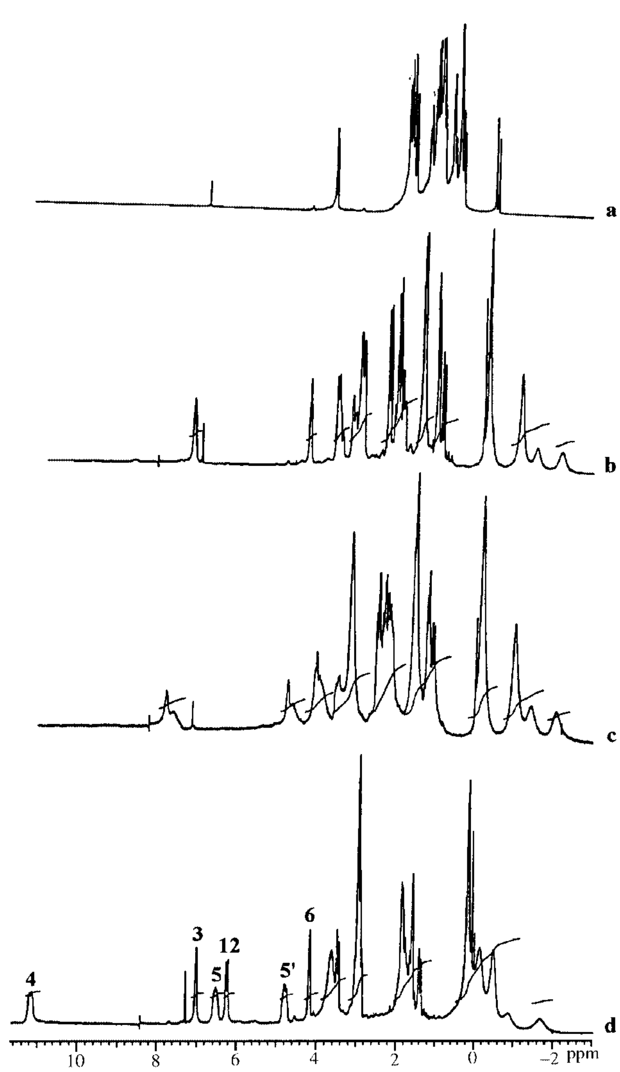

Fig. 3 ^{1}H (200 MHz) spectra of alcohol **2** in presence of a combination of Eu(tfc)$_3$ and Eu(fod)$_3$. The amounts (in mg) of C-CSR and A-CSR (added to solutions containing 20 mg substrate) are *ca.* (a) 0:0; (b) 35:0; (c) 40:0 and (d) 45:20 mg.

An increase of $\Delta\delta$ and an improvement in spectral resolution was observed on addition of achiral Eu(fod)$_3$ [Fig. 2(a), Fig. 3]. In a previous paper,[7a] we proposed some possible explanations for this effect.

Users of shift reagents for spectral resolution enhancement, are interested in the relative degrees of signal broadening produced by the shift reagents (CSR). We therefore carried out an experiment to assess broadening due to the chiral and achiral chelates. Assuming that the line broadening associated with the shift reagents is proportional to the square of the magnetic field intensity,[15a] we carried out a series of experiments on the same shift reagent at two magnetic field intensities (4.7 and 7.0 T); no significant lineshape differences were observed.† Consequently, we acquired all the spectra for the line-broadening study at the same magnetic field intensity (4.7 T).

Fig. 4 illustrates graphically the half-height width *versus* n_{CSR}/n_S for substrate **8**. The half-height width of signals of Eu(fod)$_3$-containing solution stabilized at a certain proportion of n_{CSR}/n_S while, under the same conditions, that for Eu(tfc)$_3$-containing solutions increased. Fig. 5 illustrates that the half-height width of signals of substrate **8** in presence of only Eu(tfc)$_3$ is greater than that with only Eu(fod)$_3$. Taking into account that the major contribution to line broadening is due to chemical exchange line broadening,[15] there can be two possible explan-

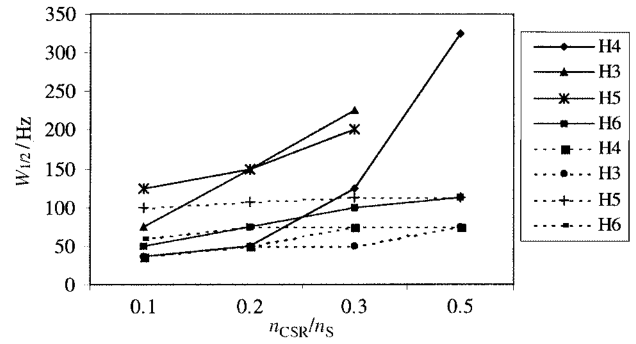

Fig. 4 Half-height width *versus* n_{CSR}/n_S ratios for substrate **8**. The full and broken lines illustrate, respectively, the solutions containing $Eu(tfc)_3$ and $Eu(fod)_3$.

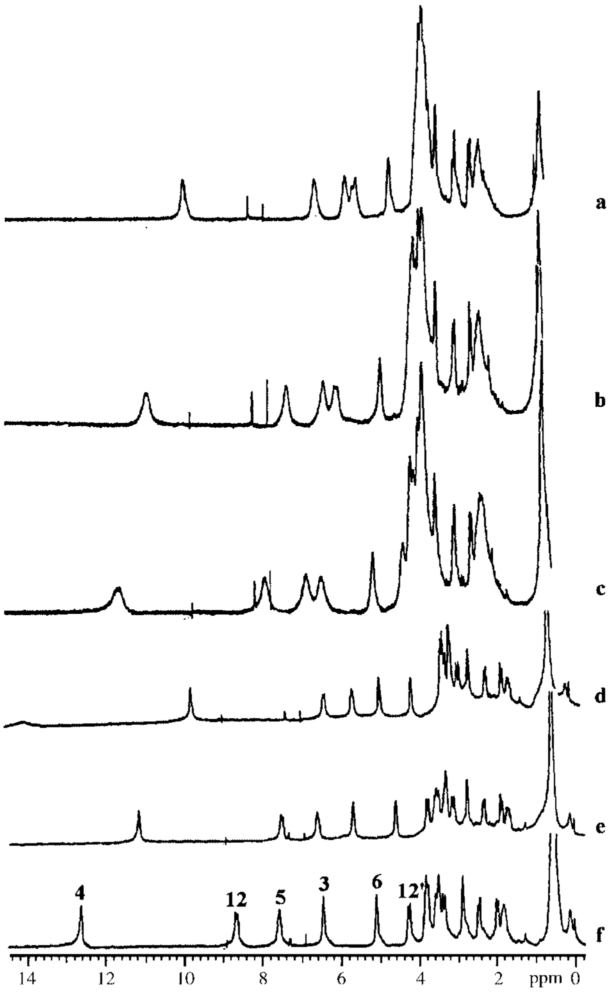

Fig. 5 ^1H (200 MHz) spectra of alcohol **8** in presence of $Eu(tfc)_3$ and $Eu(fod)_3$. The amounts (in mg) of C-CSR are *ca.* (a) 30; (b) 40; (c) 50 and A-CSR are *ca.* (d) 30; (e) 40; (f) 50 (added to solutions containing 20 mg of substrate).

ations for this: first, more species (D, DL, D_2L, *etc.*)[15] could coexist at equilibrium in a $Eu(tfc)_3$-only solution than a $Eu(fod)_3$-only one; and, second, the reagents could have different rate constants, with, in the case of $Eu(fod)_3$, signals narrowing by fast equilibration, as was already observed in a mixture of $Eu(fod)_3$ and $Eu(tfc)_3$.[7a] Lindoy[13b] observed that when $Eu(fod)_3$ is added to substrate solutions the linewidths at first broaden and later narrow. This he attributed to multi-site fast-exchange line broadening. In his experiments the maximum and minimum linewidths were observed when the CSR–substrate ratios were *ca.* 0.33 and 1, respectively. Hofer and Wurtz[18] point out that the appearance of very broad lines, even at low reagent concentrations, usually indicates an uncontrolled poly-coordination with a variety of important complexes in solution.

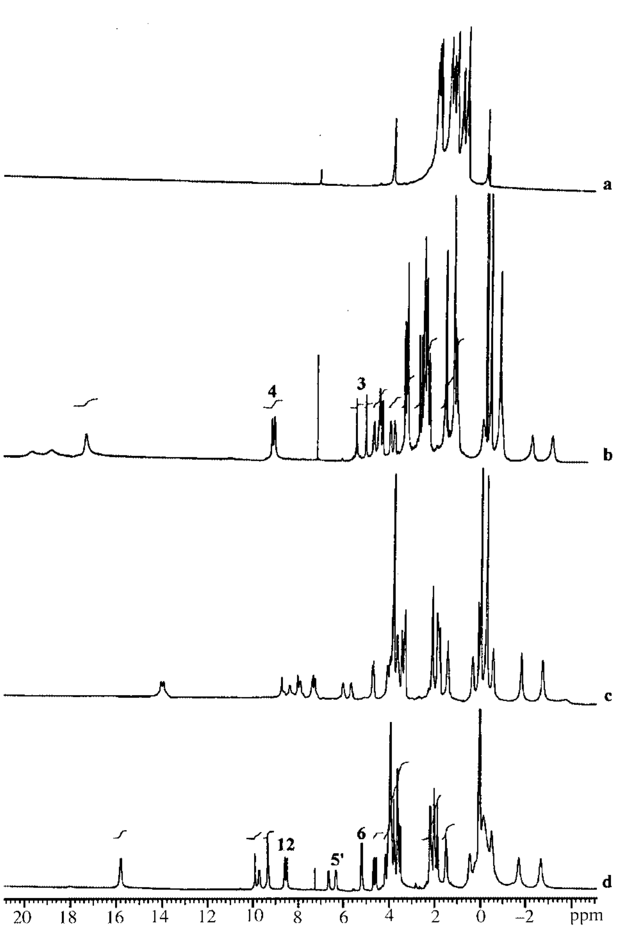

Fig. 6 ^1H (300 MHz) spectra of **2** in presence of $Eu(hfc)_3$. The amounts (in mg) of C-CSR and A-CSR (added to solutions containing 10 mg substrate) are *ca.* (a) 0 : 0; (b) 20 : 0; (c) 40 : 0 and (d) 40:10.

When $Eu(hfc)_3$ is used as the CSR, the LIS curves are linear and ascendant until higher n_{CSR}/n_S ratios (around 1.0), as shown in Fig. 2. In some cases, this linearity persists even further [Fig. 2(b)]. This suggests the formation of DL or DL_2 adducts at the inflection points. Self-association (L_2) and adduct formation (hepta- and octacoordinate complexes) are well known in the literature.[8b,c,19]

For instance, Sievers[8b] reports that $Eu(fod)_3$ forms a dimer in the solid state and could aggregate as an oligomer in deuteriochloroform solution. Evans and Wyatt[20] offer another example: tris(dipivalomethanato)europium, $Eu(dpm)_3$, gives a 1 : 1 adduct with hexamethylphosphoramide. Hofer and Wurtz[18] observed the formation of a 1 : 2 (DL_2) adduct between $Eu(dpm)_3$ and 1,4-diaryltetrahydro-1*H*,3*H*-furo[3,4-*c*]furan. Goering *et al.*[16] proposed on the basis of the LIS curve shapes that $Eu(hfc)_3$ forms 1 : 1 complexes with some alcohols, amines and sulfoxides.

For $Eu(hfc)_3$, values of n_{CSR}/n_S between 0.5–1.0 are enough to give good spectral resolution for all substrates (Fig. 6). The addition of $Eu(fod)_3$ to a solution containing $Eu(hfc)_3$, did not appreciably change $\Delta\delta$ values or spectral resolution. The unique effect of the $Eu(fod)_3$ addition was to sharpen the signals when they were broadened. These facts suggest that it is plausible to suppose that these reagents have similar behaviour and rate constants (K_1, K_2, *etc.*).[15]

Use of chiral lanthanide shift reagents (+)-$Eu(tfc)_3$ and (+)-$Eu(hfc)_3$ in the elucidation of signals from enantiomeric mixtures

In general, the application of chiral lanthanide shift reagents

Table 1 ^{1}H (200 MHz[a]) $\Delta\Delta\delta$ values in ppm of the polycyclic compounds in the presence of Eu(tfc)$_3$[b]

Product	n_{CSR}/n_S	H3	H4	H5	H10	Me	Me8	Me10
1	0.61[c]	—	—	—	—	—	0.033*	0.080*
	0.56[d]	—	—	—	—	—	0.036	0.043
2[m]	0.62[d]							
3[m]	1.29[c]							
	1.84[e]							
4	0.64[c]	—	—	—	—	0.023*	—	—
5	0.54[c]	—	—	—	0.86	—	—	—
	0.93[c]	—	—	0.120	0.120*	—	—	—
	0.72[f]	—	—	0.100	0.090	—	—	—
6[m]	0.75[c]							
	1.12[g]							
7[m]	0.73[c]							
	1.67[h]							
8	0.46[i]	0.120	0.060	—	—	—	—	—
9	1.14[c]	—	0.100	—	0.040	—	—	—
10[m]	0.97[c]							
	1.51[d]							
11	1.98[j]	—	—	—	0.022	—	—	—
12	1.11[c]	—	—	—	0.007	0.022	—	—
13	0.45[c]							
	0.70[k]							
14[m]	0.96[c]							
	1.63[l]							

[a] Product **3** was recorded at 300 MHz. [b] Superimposed signals indicated by *. [c] n_{CSR} refers only to chiral reagent; in those cases with no enantiomeric separation, some tested concentrations are mentioned. The amounts (in mg) of Eu(tfc)$_3$ and Eu(fod)$_3$ added to solutions containing 20 mg of substrate were: [d] 45:20; [e] 30:15; [f] 60:15; [g] 35:20; [h] 60:10; [i] 30:20; [j] 70:20; [k] 50:30; [l] 40:20. [m] Values of $\Delta\Delta\delta$ were not observed.

Table 2 ^{1}H (300 MHz) $\Delta\Delta\delta$ values in ppm of the polycyclic compounds in the presence of Eu(hfc)$_3$[a]

Product	n_{CSR}/n_S	H2	H3	H4	H5	H5′	H7	H9	H10	H12	H12′	Me
2	0.30[b]		0.406	0.104	0.220*	0.179				0.102*		
	0.44[b]	—	0.572*	0.119	0.348*	0.275	—	—	—	0.120		—
	1.28[c]		0.310*		0.293*	0.219					0.100	
3	0.48[b]	—	0.125	—	—		—	—	—	—	—	—
	0.79[b]	0.047	0.121*	—	0.088*		—	—	—	—	—	—
	1.67[d]	0.052	0.181		0.110							
4	1.25[b]	—	0.298	0.083	0.165		0.044	—	—	—	—	—
7	1.91[e]	—	—	0.092	—		—	—	—	—	—	0.034
9	0.64[b]	—	0.136	0.051	0.077		—	—	0.011	—	0.064	—
13	0.55[b]	—	0.093*	—	0.141*		—	0.094	—	0.067	—	—
14	0.96[b]	—	0.342*	—	0.053*		—	—	—	0.098	—	—

[a] Superimposed signals indicated by *. [b] n_{CSR} refers only to chiral shift reagent. The amounts (in mg) of Eu(hfc)$_3$ and Eu(fod)$_3$ added to solutions containing 10 mg of substrate were: [c] 40:40; [d] 30:20; [e] 40:10.

has been limited by the broadening of lines that hinders the observation of $\Delta\Delta\delta$ for specific protons. The generation of a shifted spectrum containing well-resolved isolated resonances that are suitable for integration is primarily a matter of trial and error. Sometimes, the largest values of $\Delta\Delta\delta$ are accompanied by broadened and/or superimposed signals. Moreover, the maximum $\Delta\Delta\delta$ value for a specific proton might not happen at the same n_{CSR}/n_S ratio as that for another proton.

The resulting effects of (+)-Eu(tfc)$_3$ and (+)-Eu(hfc)$_3$ on polycyclic compounds are summarized in Tables 1 and 2 (only the optimal[21] $\Delta\Delta\delta$ values).

Table 1 confirms that, Eu(tfc)$_3$ gives poor $\Delta\Delta\delta$ values. Only in a tight range of Eu(tfc)$_3$ concentration were $\Delta\Delta\delta$ values detected. Table 1 also shows that half of the compounds were not resolved with trifluoride reagent, even with variation of the concentration of chiral reagent and with addition of Eu(fod)$_3$.

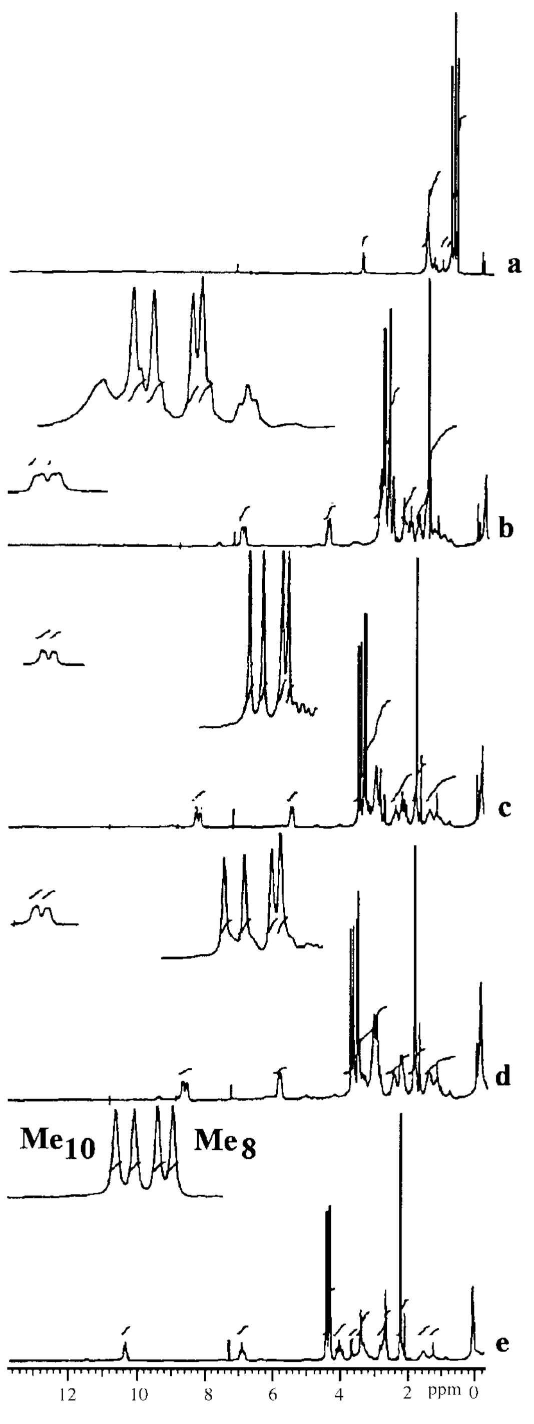

Fig. 7 ^{1}H (200 MHz) spectra of alcohol **1** in presence of a combination of Eu(tfc)$_3$ and Eu(fod)$_3$. The amounts (in mg) of C-CSR and A-CSR (added to solutions containing 20 mg of substrate) are *ca.* (a) 0:0; (b) 35:0; (c) 55:0; (d) 65:0 and (e) 45:20.

Fig. 7 illustrates clearly for substrate **1** the improvement in the enantiomeric separation of the signals and of peak sharpness on addition of achiral reagent Eu(fod)$_3$, to a solution containing the chiral reagent (more details may be found in ref. 7(*a*).

For the compounds listed in Table 2, with the exception of substrate **9**, Eu(tfc)$_3$ had no effect, but with Eu(hfc)$_3$ all of these substrates show enantiomeric separation. The combination of chiral and achiral shift reagents was necessary only for substrate **7**. Moreover, for the heptafluoride reagent, enantiomeric resolution was observed over a large concentration range.

The data for substrate **9** show that only half of the concentration of Eu(hfc)$_3$ relative to Eu(tfc)$_3$ is necessary to obtain enantiomeric separations. Although higher magnetic field was used to acquire the ^{1}H NMR spectra of solutions with Eu(hfc)$_3$, less-broadened signals were obtained. Also, a better spectral resolution followed by a higher number of separated protons was achieved.

Use of chiral lanthanide shift reagents (+)-Eu(tfc)$_3$ and (+)-Eu(hfc)$_3$ in the elucidation of ^{13}C signals from enantiomeric mixtures

As has been reported,[22] ^{13}C resonances are more sensitive to contact contributions than proton resonances involving the same number of intervening bonds at the site of metal-atom coordination, so the induced and enantiomeric chemical shifts, especially for the nuclei distant from the complexation center, should be less for ^{13}C than for ^{1}H. Although its effects were not always large, Eu(hfc)$_3$ caused ^{13}C enantiomeric shift differences for all substrates, with the exception of substrate **7** (which also did not show good separations[21] in ^{1}H), as summarized in Table 3. The optimal[21] ^{13}C $\Delta\Delta\delta$ values for substrates **4**, **9**, **13** and **14** were obtained at the same n_{CSR}/n_S ratios as the best ^{1}H $\Delta\Delta\delta$. For compounds **2** and **3** these values remained in the same range of n_{CSR}/n_S ratios for which ^{1}H $\Delta\Delta\delta$ were observed. The reagent Eu(tfc)$_3$ failed to present enantiomeric shift differences on ^{13}C NMR.

Experimental

Materials

Europium(III) tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] [(+)-Eu(tfc)$_3$], europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [(+)-(98%)-Eu(hfc)$_3$], europium(III) tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionate] [(99%)-Eu(fod)$_3$] and chloroform-d_l (99.8% atom D) were purchased from Aldrich Chemical Co. and used as supplied. The studied compounds were synthesized following procedures described in the literature.[4,23]

Method

NMR spectra were obtained with Varian VXR-200 and Varian YH-300 spectrometers, respectively with magnetic fields of 4.7 and 7.0 T at 22 °C. Standard Varian software was used to acquire and process the NMR spectra. Typically, 7.2 μs pulse width (flip angle = 45.0°) and 6.2 μs pulse width (flip angle = 45.0°) were used, respectively, for the ^{1}H and ^{13}C NMR sequences recorded on magnetic field of 4.7 T. The pulse widths for ^{1}H and ^{13}C NMR sequences recorded on magnetic field of 7.0 T were, respectively, 10.5 μs (flip angle = 45.0°) and 7.0 μs (flip angle = 45.0°). The ^{1}H NMR spectra were obtained with 32 transients and processed with 16 K addresses. The ^{13}C NMR spectra were obtained with 1024 transients and processed with 64 K addresses and 1.0 Hz line broadening. A 5 mm standard Varian probe was used. Chemical shift values are expressed as δ (parts per million) relative to TMS as an internal standard. The solutions containing Eu(hfc)$_3$ were recorded at 300 MHz, Eu(tfc)$_3$ at 200 MHz, with the exception of substrate **3**.

The $\Delta\Delta\delta$ values were collected by the following procedure: 10, 15 or 20 mg of samples were weighed and dissolved into 5 mm tubes with 0.5 ml of CDCl$_3$. The first spectrum was obtained without chemical shift reagent, then sequential portions[24] (5 mg) of solid chiral reagent (C-CSR) were added at, on average 2 hour intervals until no further increase of chemical shift was observed. When the resolution of the spectrum was lost and signal broadening interfered with the enantiomeric resolution, successive portions (5 mg) of solid achiral reagent (A-CSR) were added until the signals sharpened again and the relative chemical shift of signals of the enantiomer pairs was enhanced. The alternate addition of chiral and achiral reagents

Table 3 ^{13}C (75 MHz) $\Delta\Delta\delta$ values in ppm of the polycyclic compounds in the presence of Eu(hfc)$_3$

Product	n_{CSR}/n_S	C1	C2	C3	C4	C5	C6	C7	C8	C10	C11	C12
2	1.11[a]	0.080				0.046		0.047	0.140	0.154	0.067	0.027
3	0.95[b]			0.87		1.00						
4	1.25[b]			0.160	0.167	0.120						
7[c]	—											
9	0.64[b]			0.387	0.450	0.320						0.214
13	0.55[b]		0.040	0.160		0.073	0.060	0.066				0.094
14	0.96[b]		0.087	0.167		0.327	0.147	0.094				0.140

[a] The amount (in mg) of Eu(hfc)$_3$ and Eu(fod)$_3$ added to solutions containing 10 mg of substrate was 40:30. [b] n_{CSR} refers only to chiral shift reagent. [c] Values of $\Delta\Delta\delta$ were not observed.

was repeated until the optimum enantiomeric separation was reached.[7a]

The assignments of ^{1}H and ^{13}C NMR of the structures studied are described in the literature.[5,23,25]

Conclusions

Although both chiral shift reagents give observable values of $\Delta\Delta\delta$ for certain of the studied polycyclic compounds, (+)-Eu(hfc)$_3$ gives better spectral resolution and ^{1}H and ^{13}C NMR enantiomeric separations than (+)-Eu(tfc)$_3$.

The magnitudes of both the chemical shifts and the line broadening depend on the adduct formed between the complex and the substrate. The examination of LIS graphics, spectra and the linewidth measurements, in presence of Eu(tfc)$_3$, suggests that a mixture of adducts (D, D$_2$L, DL$_2$, *etc.*)[15] could be present in solution. However, the data for Eu(hfc)$_3$ suggest the presence of few adducts in solution, with the possible formation of complexes like DL and/or DL$_2$, as has been reported elsewhere for Eu(fod)$_3$.[8b,18] A final remark must be made about acidity, which has an effect on the extent of self-association[8b,19] and could partly explain the higher propensity of Eu(hfc)$_3$ and Eu(fod)$_3$ to form self-associated species.

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