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Optical purity determination and ^{1}H-NMR spectral simplification with lanthanide shift reagents — VIII. An indacrinone precursor, 6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone

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Abstract: The 60 MHz ^{1}H NMR spectra of racemic 6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1 indanone (**1**) have been studied with the achiral shift reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium (III) (**2**) and the chiral reagents, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato] europium (III) (**3**) and tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium (III) (**4**). While some enantiomeric shift differences, $\Delta\Delta\delta$, were seen for some protons of **1** with **3**, dramatically larger values were obtained with **4**. The latter would be the reagent of choice for direct optical purity determinations of **1** using the 2-methyl resonance. Optimum conditions would use a **4**:**1** molar ratio of 0.1–0.25, providing near-baseline resolution for the peaks and freedom from overlap with interfering peaks. Less than 3% of the minor enantiomer should be detectable. The results are consistent with lanthanide complexation at the carbonyl. The value of $\Delta\Delta\delta$ for the C_2 methyl of 1.1 ppm with a **4**:**1** molar ratio of 1.50 appears to be among the highest reported values for simple ketones with **3** or **4**.

Keywords: *Optical purity determination; chiral lanthanide shift reagents; indacrinone precursor; 6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone; europium shift reagents; NMR.*

Introduction

The drug indacrinone, (6,7-dichloro-2-methyl-1-oxo-2-phenyl-5-indanyloxy)acetic acid, has recently received considerable study as a novel uricosuric diuretic [1–4]. The discovery of different potency and pharmacological properties, i.e. stereoselectivity in disposition and metabolism, of the two enantiomers has been notable [5–9]. ^{14}C-labelled enantiomers of indacrinone and analogues have been synthesized [10]. An elegant and efficient catalytic asymmetric alkylation using phase-transfer catalysis has been applied

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to the synthesis of an indacrinone precursor, 6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone (**1**) [11] in up to 92% enantiomeric excess and 95% yield. (*S*)-(+)-**1** was then converted to (*S*)-(+)-indacrinone. The latter mainly stimulates uric acid excretion whereas the (*R*)-(−) isomer mainly acts as a diuretic and natriuretic; a non-racemic mixture of the isomers could have particular applications [6, 9]. Because of these profound stereochemical implications, techniques for direct optical purity determination in this system are of importance.

The application of chiral lanthanide shift reagents has been mentioned in a footnote in one paper [11] for use with **1** and in another [10], presumably with indacrinone and its 2-(4-hydroxyphenyl) metabolite. However, there have been no full reports on the use of chiral shift reagents within this series and no work has been reported on achiral shift reagents. Therefore a full examination was undertaken of racemic **1** with the achiral reagent, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium(III) (**2**), known as $Eu(FOD)_3$, and with the chiral reagents, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) (**3**), known as $Eu(TFC)_3$ or $Eu(FACAM)_3$, and tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium(III) (**4**), known as $Eu(HFBC)_3$ or $Eu(HFC)_3$. The results confirm the utility of **4** for optical purity determinations of **1** and indicate the superiority of this reagent to **3**.

Experimental

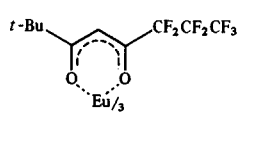
Racemic **1** (lot No. L-632,760-00Z05) was provided by Merck Sharp & Dohme Research Lab, Division of Merck & Co., Inc. (Rahway, NJ). Chloroform-*d* (99.8 atom % D) from Aldrich Chemical Corporation (Milwaukee, WI) or Norell, Inc. (Landisville, NJ) was dried and stored over 3A molecular sieves. Shift reagents were from Aldrich and were stored in a desiccator over P_2O_5. Materials were used as supplied except as noted.

In general, an accurately weighed portion of substrate (about 45–55 mg) was added to 400–1000 mg of $CDCl_3$ (containing about 0.4% tetramethylsilane (TMS) as internal standard) in an NMR sample tube and dissolved by shaking; increments of shift reagent were added, dissolved by shaking, and the spectra immediately recorded.

All spectra were recorded on a Varian EM-360A 60 MHz ^1H NMR spectrometer at a probe temperature of 28°C. Chemical shifts (first order strictly) are reported in parts per million (ppm) (δ) relative to TMS and are believed to be accurate to ±0.05 ppm. In spectra where TMS was obscured by shift reagent peaks, $CHCl_3$ (present as an impurity in the solvent) was used as the internal standard.

Results and Discussion

Much successful work with shift reagents on drugs and related compounds has taken advantage of systems with appreciable Lewis basicity and minimal steric hindrance. Some useful review articles have been published [12–15]. Some drugs and analogues with which shift reagents, especially **2** and **3**, have been used incorporated such functional groups as imide (glutethimide [16]), amides and ureas of barbiturates (mephobarbital [17]), hydantoins (ethotoin [18]), amines (cocaine [19], amphetamine [20]) and thiobarbiturates (thiohexital [21], thiamylal [22]). In contrast to these substances, **1** is expected to provide less Lewis basicity for complexation with the lanthanide since it is an aryl ketone. Although a methoxy group is conjugated with the carbonyl across the aryl ring (an 'arylogous ester'), the mesomeric release of oxygen is substantially less than that



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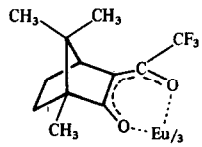

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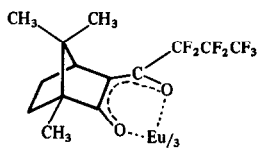

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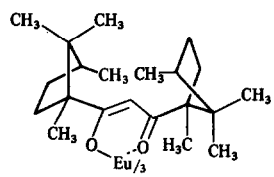

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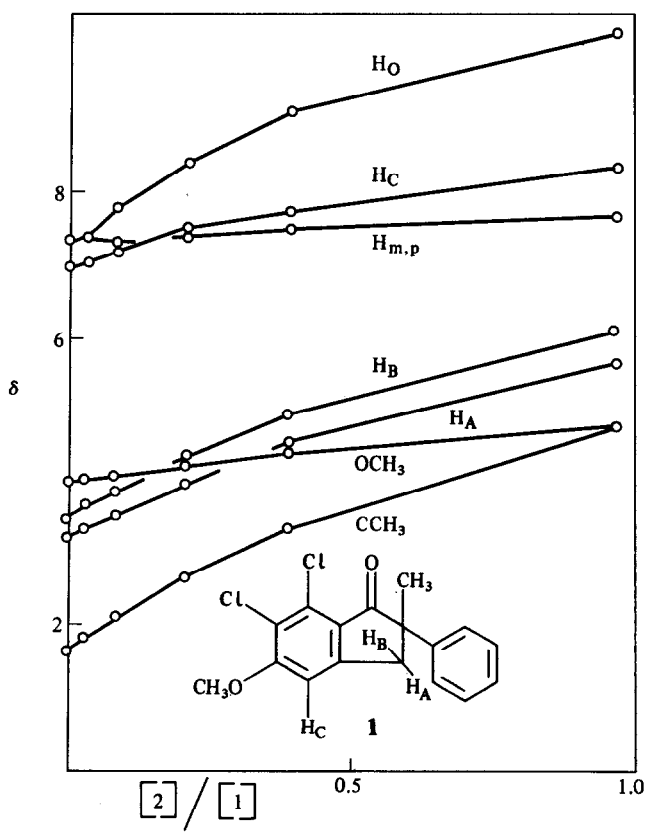

Figure 1
Variation of chemical shift, δ, with molar ratio of $Eu(FOD)_3$: **1**.

of nitrogen, as in amides or ureas. In addition, the two aryl chlorines will be inductively electron withdrawing in **1**. The 7-chlorine and the disubstitution by methyl and phenyl at the 2-position of the indanone ring should cause steric hindrance that could lead to some distortions and loss of conjugation between the carbonyl and the aryl ring, which would reduce potential electron release from the ring. The 2-phenyl is expected to be inductively electron withdrawing in any case. Nonetheless, **1** proved to be a very suitable substrate, consistent with europium complexation at the carbonyl, and revealed strikingly high values of the enantiomeric shift difference $\Delta\Delta\delta$ for the 2-CH_3 when treated with **4**. The enantiomeric shift difference $\Delta\Delta\delta$ is defined as the magnitude of $\delta_R - \delta_S$ for the resonance of a particular proton.

The lanthanide-induced shift $\Delta\delta$ is the chemical shift for a particular proton in the presence of shift reagent minus the corresponding chemical shift when no shift reagent was added; if a resonance is split by a chiral shift reagent into two signals, the mean value of the chemical shifts for the two enantiomers is used in the discussion and figures.

In $CDCl_3$, as a 0.308 molal solution, the spectrum of **1** showed peaks at 7.35 ppm (approx. singlet (s), 5H, C_6H_5), 7.0 ppm (s, 1H, at C_4), 4.0 ppm (s, 3H, OCH_3), 1.68 ppm (s, 3H, 2-CH_3), and an AB quartet centred at 3.4 ppm (2H, CH_2, J = 18 Hz). The

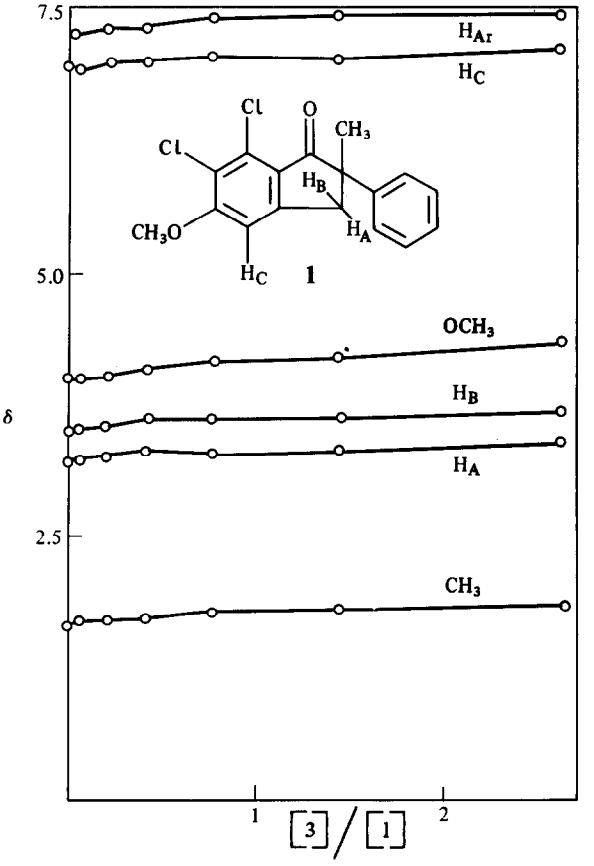

Figure 2
Variation of chemical shift, δ, with molar ratio of Eu(FACAM)$_3$: **1**. The mean value of δ has been used where a resonance is split into two signals.

main effects of additions of **2** are to separate the C_6H_5 peaks into a downfield 2H absorption typical of the *ortho* protons and a 3H absorption (*meta*, *para*). The substantially greater slope of the plots of chemical shift against **2**:**1** molar ratio for the *ortho* protons relative to the C_4 proton is consistent with europium binding at the carbonyl rather than the methoxy. Similarly, the slope for the 2-CH_3 is much greater than for the methoxy. These results are summarized in Fig. 1.

With the chiral reagent **3**, a small $\Delta\Delta\delta$ for the 2-CH_3 of 2.0 Hz is first seen in a 0.34 molal solution of **1** with a **3**:**1** molar ratio of 0.41. Although this $\Delta\Delta\delta$ can be increased to 4.0 Hz at higher **3**:**1** molar ratios, analytic utility is limited by an interfering peak from **3** near 1.6 ppm. Separation of the phenyl protons with **3** was much less apparent than with **2**, and lanthanide-induced shifts $\Delta\delta$ were generally lower. It is interesting that with **2** there are obvious effects but with **3** very little or no effect (based on $\Delta\delta$ values). However, these results are unusual but are not unique; similar observations have been made in the authors' laboratories for ethchlorvynol with **2** and **3** (S. Eberhart and R. Rothchild, unpublished results). Results with **3** are summarized in Figs 2 and 3.

In contrast, results with **4** were extremely favourable. For a 0.327 molal solution of **1**, a **4**:**1** molar ratio of only 0.023 gave a $\Delta\Delta\delta$ of 2.3 Hz for the 2-CH_3 with about 40%

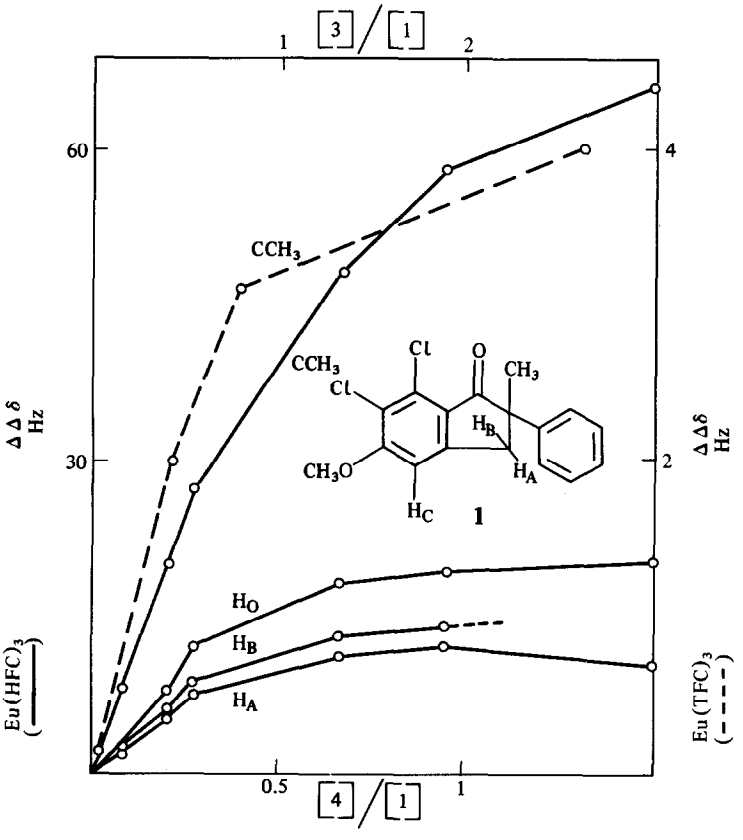

Figure 3
Variation of enantiomeric shift difference $\Delta\Delta\delta$ (in Hz) with molar ratio of Eu(FACAM)$_3$: **1** (broken line), and of Eu(HFBC)$_3$: **1** (solid lines).

valley. A molar ratio of 0.076 increased this $\Delta\Delta\delta$ to 8.0 Hz with less than 6% valley; clear $\Delta\Delta\delta$ was also seen for each proton of the CH_2 (about 2.4 and 2.0 Hz). Separation of the *ortho* and *para* C_6H_5 protons was apparent with some $\Delta\Delta\delta$ suggested in the former. With a **4**:**1** molar ratio at 0.267, $\Delta\Delta\delta$ for the 2-CH_3 of 27.2 Hz (2% valley) provides outstanding ease of optical purity assay. The near-baseline resolution of the methyl peaks and the sharpness of the peaks (FWHM 2.5 Hz) provides excellent analysis conditions. A lower limit of detection of 3% of the minor enantiomer is assured; no peaks of **4** interfere. With a **4**:**1** molar ratio of 1.50, $\Delta\Delta\delta$ for the 2-CH_3 has increased to 66 Hz (1.1 ppm) although interfering peaks make this a poor analytical choice. However, $\Delta\Delta\delta$ for the *ortho* protons is about 20 Hz (0.33 ppm) providing the possibility of analyses using these resonances. Results with **4** are presented in Figs 3 and 4.

The results using **4** with **1** are dramatically better than with **3**, suggesting that enhanced Lewis acidity resulting from the heptafluoropropyl side-chain relative to the trifluoromethyl may be extremely important in this case [23, 24]. The magnitude of $\Delta\Delta\delta$ for the 2-CH_3 of **1** with **4** appears to be among the highest reported values (obtained at near ambient temperatures) for any ketones; comparable values are rarely reported except with the very costly reagent, tris[*d*,*d*-dicampholylmethanato] europium(III) (**5**) [25]. Part

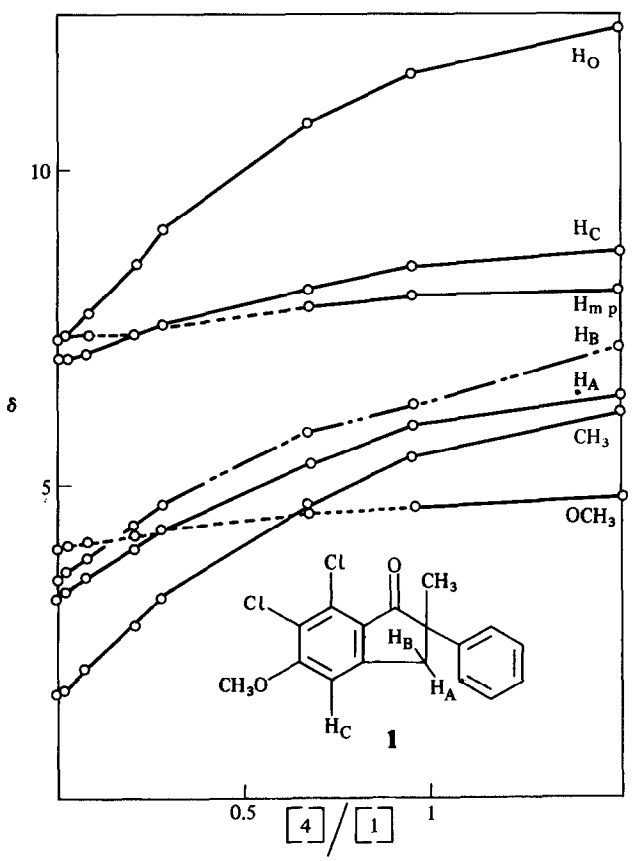

Figure 4
Variation of chemical shift, δ, with molar ratio of Eu(HFBC)$_3$: **1**. The mean value of δ has been used where a resonance is split into two signals.

of this may reflect a special high sense of 'magnetic nonequivalence' between the enantiomers of **1** but a specific advantage of the shift reagent is also evident. The drastically greater slopes observed in the δ plots of the 2-methyl against the methoxy, which are particularly striking with **2** (Fig. 1) or **4** (Fig. 4), are completely consistent with lanthanide complexation near or at the carbonyl. Clearly, the location of the chiral centre at C-2, close to the bound europium on (or near) the carbonyl, must be important as well as the orientation of the C-2 methyl towards the lanthanide atom.

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