Determination of Enantiomeric Purity by An Optically Active Nuclear Magnetic Resonance Shift Reagent of Wide Applicability

By ROBERT R. FRASER,* MICHEL A. PETIT, and JOHN K. SAUNDERS

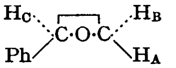
(*Department of Chemistry, University of Ottawa, Ottawa, Canada* K1N 6N5)

Summary Addition of the europium complex of 3-heptafluorobutanoyl-(+)-camphor to racemates of alcohols, sulphoxides, an epoxide, and an aldehyde causes separation of n.m.r. signals of the enantioners.

THE recent discovery of the shift reagent, Eu(dpm)$_3$[1], and examination of its influence on the n.m.r. spectra of various Lewis bases[2] have established its importance in structural organic chemistry. Changes in the lanthanide element[3] and in the diketone portion of the complex[4,5] have both improved the properties. Whitesides and Lewis[5] showed that addition of tris-(3-t-butylhydroxymethylene-(+)-camphorato)europium (**1**) to a solution of a primary amine and a secondary alcohol effected a separation of the n.m.r. signals arising from the (*R*) and (*S*) enantiomers. This finding is of importance in providing a simpler method of determining optical purity than others currently in use.[6] Unfortunately (**1**) had limitations, being unable to resolve the signals of 1-phenylethanol, benzyl methyl sulphoxide, octan-2-ol and cyclohexylmethylmethanol. We report the preparation of an optically active europium complex† which can differentiate signals for a much wider variety of enantiomeric mixtures.

TABLE 1

Effect of added (**1**) *and* (**2**) *on the n.m.r. spectra of racemates*

		Effect of (**1**)		Effect of (**2**)	
Compound	Proton	PS[a]	Δν[b]	PS[a]	Δν[b]
PhCH(Me)NH$_2$	Me	6·37	0·19	5·09	0·08
	CH	9·48	0·41	7·57	0·00
	H$_{ortho}$	4·01	0·12	3·25	0·06
PhCH(Me)OH	Me	2·14	0·00	2·65	0·05
	CH	3·55	0·01	4·64	0·07
	H$_{ortho}$	1·69	0·00	2·27	0·02
MeCH$_2$CH(Me)CH$_A$H$_B$OH	CH$_A$	4·24	0·00	5·55	0·05
	CH$_B$	4·24	0·00	5·54	0·11
	H$_A$	1·13	0·03	4·22	0·15
	H$_B$	1·32	0·03	4·27	0·75
	H$_C$	1·31	0·01	4·69	0·31
PhSOMe	Me	1·74	0·09	2·79	0·11
	H$_{ortho}$	1·82	0·02	2·78	0·12
PhCH$_A$H$_B$SOMe ..	H$_A$	2·16	0·00	2·22	0·06
	H$_B$	2·16	0·00	2·26	0·03
	Me	2·08	0·00	1·92	0·06
PhCH(Me)CHO	CH(O)	0·44	0·00	2·02	0·03
	CHMe	0·25	0·00	1·32	0·01

[a] The average downfield shift, in p.p.m. of the protons in the two enantiomers in the presence of 0·4 equiv. of (**1**) or (**2**). All spectra were measured at 31° on 0·2—0·3 M-solutions in CCl$_4$ using a Varian HA-100 spectrometer. Proton–proton spin decoupling was used to simply multiplet absorptions. [b] The difference in PS for structurally identical protons in the two enantiomers.

The increase in acidity of the complex Eu(fod)$_3$[4] over Eu(dpm)$_3$ suggested that a similar change in (**1**) would be of interest. Accordingly, we prepared 3-heptafluorobutanoyl-(+)-camphor and converted it into tris-(3-heptafluoropropylhydroxymethylene-(+)-camphorato)europium (**2**).‡ The effect of adding (**1**) and (**2**) to solutions of a various racemic mixtures is reported in Table 1. While (**1**) can differentiate between enantiomers in only two instances, (**2**) causes differential downfield shifts to protons in all seven pairs of enantiomers.§ Only for 1-phenylethylamine did (**1**) produce the larger nonequivalence. The data for the downfield shifts in general indicate (**2**) to be a stronger Lewis acid, which may be responsible for the generally greater resolving power of (**2**). As suggested previously,[5] differentiation of enantiomers may result from different equilibrium constants for formation of the two diastereomeric complexes of (*R*) and (*S*) enantiomers with (**1**) or (**2**). Our results indicate that other factors are also of influence. For example, even though (**1**) causes an equally large downfield shift in the signals of benzyl methyl sulphoxide, only (**2**) is able to resolve the enantiomeric signals. Another indication is the unusual concentration dependence of the downfield shifts resulting from the addition of (**2**) to styrene oxide in carbon tetrachloride. The nonequivalence of the H$_C$ and H$_{ortho}$ signals for the two enantiomers reaches a maximum when 0·32 equiv. of complex have been added and decreases as further complex is added In contrast the two H$_A$ protons and the H$_B$ protons show a nonequivalence which increases continuously up to 0·44 equiv. of added complex, the maximum investigated (data for 0·32 and 0·44 equiv. in Table 2). This behaviour may result from a concentration dependence of the equilibrium involving diastereoisomers¶ of (**2**). The temperature effects in Table 2 are also consistent with this interpretation. Both the downfield shifts and the nonequivalence of signals for the two enantiomers of styrene oxide in the presence of (**2**) are strikingly increased, but by varying amounts, as the temperature is lowered.[7] It is obvious that lowering of the temperature will augment the capability of (**2**) to differentiate the signals of a racemate.

We have also examined the use of (**2**) for the quantitative determination of the optical purity of a partially resolved sample of benzyl methyl sulphoxide [α_D 86° (*c* 0·8 EtOH), 90% optical purity[8]]. A 0·13M-solution of this compound in CCl$_4$ containing 0·45 equiv. of (**2**) showed two singlet methyl peaks separated by 6·1 Hz which were slightly broadened ($W_{\frac{1}{2}}$ 2·0 Hz). In this case better resolution was observed at 66° at which temperature $W_{\frac{1}{2}}$ was 1·7 Hz and the nonequivalence 5·2 Hz. Integration showed that the major enantiomer comprises 94·5 ± 0·5% of the mixture. The

---

† Other modifications of (**1**), in which the t-butyl group was replaced by a Me, CF$_3$ or Ph possessed inferior properties.

‡ Acylation[5] of optically pure +-camphor gave 3-heptafluorobutanoylcamphor (45%). This diketone was converted into (**2**) (35%) by the procedure of Eisentraut and Sievers (*J. Amer. Chem. Soc.*, 1965, **87**, 5254). Satisfactory analytical data were obtained for (**2**) and its diketone precursor.

§ Both (**1**) and (**2**) were unsuccessful in 'resolving' signals of racemic 2-methylcyclohexanone and 3-methylpiperidine.

¶ Compounds (**1**) and (**2**) can exist in four diastereomeric forms. We have observed separation and sharpening of the absorptions for at least two t-butyl groups of (**1**) at lower temperatures, an observation compatible with a freezing out of individual diastereomers.

TABLE 2

Effect of temperature on downfield shifts and nonequivalence of shifts for (R,S) *styrene oxide and* (**2**).

		PS[a] (Δν)[a]			
Amount of (**2**)	Temp. (°C)	H_A	H_B	H_C	H_{ortho}
0·32 equiv.	41	3·00(0·10)	3·08(0·45)	3·31(0·23)	1·70(0·05)
	20	3·65(0·14)	3·58(0·76)	3·82(0·46)	1·74(0·06)
	−20	4·63[b]	4·80(1·35)	5·17(0·90)	2·56(0·16)
0·44 equiv.	41	4·22(0·17)	4·33(0·64)	4·75(0·09)	2·30(0·02)
	26·5	4·79(0·22)	4·90(0·88)	5·36(0·22)	2·67(0·00)
	−6	6·21(0·39)	6·29(1·65)	6·79(0·50)	3·59(0·00)

[a] As in Table 1. [b] Not determinable owing to signal overlap.

optical purity of the sulphoxide is therefore 89%, in good agreement with the value derived from its optical rotation.

The authors thank the National Research Council of Canada for financial support.

(*Received, September* 16*th*, 1971; *Com.* 1622.)

[1] C. C. Hinckley, *J. Amer. Chem. Soc.*, 1969, **91**, 5160; J. K. M. Sanders and D. H. Williams, *Chem. Comm.*, 1970, 422.

[2] A complete list of earlier works is given by J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641.

[3] J. Briggs, G. H. Front, F. A. Hart, G. P. Moss, and M. L. Staniforth, *Chem. Comm.*, 1970, 749.

[4] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.

[5] G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, 1970, **92**, 6979.

[6] K. Mislow and M. Raban, *Topics Stereochem.*, 1967, **2**, 199; for recent examples see also D. Dugas, M. Verny, and R. Vessiere, *Tetrahedron*, 1971, **27**, 1715; W. H. Pirkle, R. L. Muntz, and I. C. Paul, *J. Amer. Chem. Soc.*, 1971, **93**, 2817; L. Mamlok, A. Marquet, and L. Lacombe, *Tetrahedron Letters*, 1971, 1039.

[7] Similar temperature effects have been described by N. Ahmad, N. S. Bhacca, J. Selbin, and J. D. Wander, *J. Amer. Chem. Soc.*, 1971, **93**, 2564.

[8] K. Mislow, M. M. Green, and M. Raban, *J. Amer. Chem. Soc.*, 1965, **87**, 2761.