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MANGANESE(II)–BIS(3-HEPTAFLUOROBUTYRYL-1*R*-CAMPHORATE): A VERSATILE AGENT FOR THE RESOLUTION OF RACEMIC CYCLIC ETHERS BY COMPLEXATION GAS CHROMATOGRAPHY

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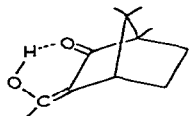
SUMMARY

Manganese(II)–bis(3-heptafluorobutyryl-1*R*-camphorate has been used to resolve fourteen racemic alkyl-substituted cyclic ethers (up to five-membered rings) by complexation gas chromatography with short analysis times. The resolving agent discriminates between enantiomeric oxiranes where chirality is due to monosubstitution, *gem*-, *cis*- or *trans*-disubstitution, or trisubstitution. Packed columns have also been used for the resolution of chiral oxiranes. Retention data and thermodynamic parameters were correlated for the 1:1 molecular association of 24 cyclic ethers with manganese(II)–bis(3-heptafluorobutyryl-1*R*-camphorate. For sixteen chiral solutes the difference of the free enthalpy change in the enantiomer discrimination has been calculated and is discussed.

INTRODUCTION

More than a decade ago the great potential of the enantiospecific coordination between racemic mixtures and optically active metal chelates as a means to discriminate between enantiomers was recognized both in nuclear magnetic resonance (NMR) spectroscopy[1,2] and in gas–liquid chromatography[3,4]. In both approaches to quantitative resolution, metal ions bonded to the same type of auxiliary chiral probe, *i.e.*, 3-acylated (+)-1*R*-camphor (1)[5], were used[1–4].



1

Thus, when paramagnetic and optically active tris-3-acyl-1*R*-camphorates of europium(III) (2) were added to solutions of a racemic donor substrate, externally enantiotopic nuclei were rendered diastereotopic, and the ratio of the enantiomers could be measured by the chemical shift non-equivalence in the NMR spectrum[1,2]. When optically active dicarbonyl-rhodium(I)–3-trifluoroacetyl-1*R*-camphorate (3)[4–6] was

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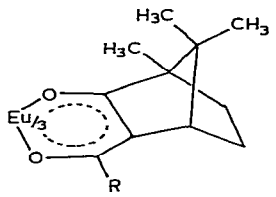
employed as chiral additive to a stationary phase, *e.g.*, the non-polar solvent, squalane, gas chromatography of a racemic olefin led to baseline resolved, separate peaks for the optical isomers of racemic 3-methylcyclopentene[7,8]. This result demonstrated for the first time that "complexation gas chromatography" does indeed exhibit the necessary kinetic (*i.e.*, a fast and reversible coordination of solute and metal chelate) and thermodynamic (*i.e.*, the free enthalpy difference of enantiomer discrimination, $\Delta_{S,R}(\Delta G) \neq 0$) parameters for "chiral recognition".



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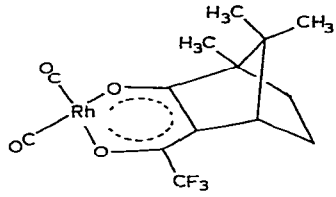
a: R = $-C(CH_3)_3$
b: R = $-CF_3$
c: R = $-CF_2CF_2CF_3$



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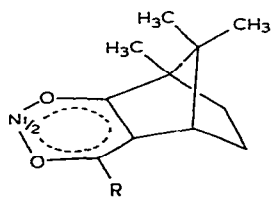
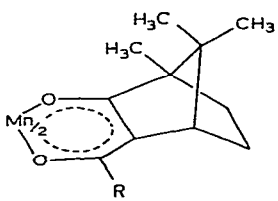
Two subsequent reports on the successful resolution of the cyclic ether, methyloxirane (propylene oxide) (7) on compound 2b (semi-quantitatively on a packed column)[9] and on nickel(II)–bis(3-trifluoroacetyl-1*R*-camphorate) (4a) (quantitatively on an open-tubular column)[10], have prompted further investigations on the resolution of a variety of racemic solutes such as alkyl-substituted oxiranes, oxetanes, thiiranes and N-chloroaziridines (nitrogen invertomers) as well as a cyclic ketone and an acyclic secondary alcohol on nickel(II)–bis(3-heptafluorobutyryl-1*R*-camphorate) (4b)[11,12]. Various applications of this technique for the determination of enantiomeric compositions and absolute configurations have been reported[13,14]. The method has great practical importance because no isolation, purification or derivatization of the solute prior to chromatographic injection is required for analysis[15]. Finally, a number of naturally occurring insect attractants (pheromones) with spiroketal structures have been analytically resolved for the first time[16,17].

The present investigation is part of a systematic study devised to probe structural features of the resolving metal chelate toward enantiomer discrimination. This research was stimulated by preliminary observations that the nature of the central metal ion has a profound effect on coordination strength, and that small variations in the 3-acyl residue of 1*R*-camphor (1) produce remarkable changes in the enantiospecificity of resolution.

The present paper reports on the resolving properties of four bis-3-perfluoroacyl-1*R*-camphorates of manganese(II) (5a–d) with racemic alkyl-substituted cyclic



4 a: R = CF_3 (TFA)
b: R = C_3F_7 (HFB)



5 a: R = C_6F_5 (PFB)
b: R = CF_3 (TFA)
c: R = C_3F_7 (HFB)
d: R = C_7F_{15} (PFO)

ethers by comparing the practical resolution factor, α, and by measuring the thermodynamic quantity, $\Delta_{S,R}(\Delta G)$ for chiral recognition. Manganese(II)–bis(3-heptafluorobutyryl-1*R*-camphorate (5c) has been found to be a versatile agent for the resolution of racemic cyclic ethers containing up to five-membered rings whereas manganese-(II)–bis(3-pentafluorobenzoyl-1*R*-camphorate) (5a) is useful for the resolution of racemic 2-alkyl-substituted tetrahydropyrans.

EXPERIMENTAL

Organic solutes

The oxiranes 6, 7, 15 and 16 were obtained from Merck-Schuchardt (Darmstadt, G.F.R.); 8 was obtained from EGA (Stamheim am Albuch, G.F.R.). All other oxiranes were prepared from the corresponding olefins (Fluka, Buchs, Switzerland; Riedel de Haen, Hannover, G.F.R.; K & K Chemicals, Plainview, NY, U.S.A.) by epoxidation with *m*-chloroperbenzoic acid (Fluka). In a typical experiment *ca.* 100 mg of *m*-chloroperbenzoic acid were dissolved in 2 ml of diethyl ether, 150 μl of olefin were added, and the reaction mixture was stored in a refrigerator for 24 h. The vapour of the reaction mixture containing the formed oxirane was injected into the chromatograph without isolation ("headspace technique"). The oxiranes were handled with appropriate care in closed systems.

Tetrahydrofurans were obtained from commercial sources (Fluka; EGA; Merck, Darmstadt, G.F.R.), and 2-alkyltetrahydropyrans were prepared from 2-bromotetrahydropyran according to ref. 18.

Reference solutes

Methane was used to measure the gas hold-up ("dead-volume"); the finite retention time of methane[19] did not obscure the thermodynamic parameters calculated from adjusted retention times.

Commercial *n*-octane was used throughout as the non-coordinating reference standard. All retention times of the solutes were related to that of *n*-octane (relative retention, *r*).

Metal chelates

Preparation of bis-3-perfluoroacyl-1R-camphorates of manganese(II) (5a–d)

3-Acyl-1R-camphor ligands. The optically active 3-acyl-1*R*-camphor ligands were prepared by the acylation of (+)-1*R*-camphor according to the procedure described by McCreary *et al.*[2]. *General procedure:* The reaction was carried out under an atmosphere of high-purity grade nitrogen in a 250-ml flask equipped with nitrogen inlet, mercury valve, dropping funnel, mechanical stirrer and low-temperature thermometer. The solvent diethyl ether was dried with sodium–benzophenone under nitrogen. The flask was charged with a 5% solution of methyl lithium in ether (Merck) and cooled to −20°C. Diisopropylamine (Fluka) was carefully added (gas evolution!), and the mixture was stirred for 30 min at −20°C. A solution of (+)-1*R*-camphor (Merck) in ether, cooled to −20°C under nitrogen, was then added via a dropping funnel to the reaction flask. The mixture was stirred for 30 min at −20°C and then cooled to −60°C. The acid chloride (Riedel de Haen) was dissolved in ether and added via a dropping funnel at such a rate that the temperature was maintained at

−60°C. After 60 min at −60°C the reaction mixture was warmed to +20°C and hydrolyzed by pouring into ice–water and adding hydrochloric acid until pH 4 was reached. The organic phase was separated, and the aqueous phase was extracted four times with ether. The combined ether phases were washed twice with sodium chloride solution, dried over sodium sulphate and then chromatographed on silica with toluene as the eluent. The red-coloured β-diketone (reaction with traces of iron!) was distilled at 1 mmHg to yield a colourless liquid. *3-Heptafluorobutyryl-1R-camphor:* 10.2 g (67 mmol) 1*R*-camphor, 9.5 ml diisopropylamine, 42 ml methyl lithium (5% in ether), 15.5 g (66 mmol) heptafluorobutyryl chloride; yield: 8.1 g (35%) 3-heptafluorobutyryl-1*R*-camphor; b.p.: 70–80°C/1 mmHg; $[\alpha]_D^{20} = +124°$ (*c*, 2.6, CCl_4); mass spectrum (70 eV); *m/e* 348 (100%), 333 (29%), 320 (42%), 305 (31%), 179 (15%), 109 (5%), 151 (61%), 123 (31%). *3-Perfluorooctanoyl-1R-camphor:* 10.2 g (67 mmol) 1*R*-camphor, 9.5 ml diisopropylamine, 42 ml methyl lithium (5% in ether), 18.1 ml (67 mmol) perfluorooctanoyl chloride; yield: 9 g (23%) 3-perfluorooctanoyl-1*R*-camphor; b.p.: 81–85°C/0.05 mm Hg; $[\alpha]_D^{20} = +12.8°$ (neat); mass spectrum (70 eV): *m/e* 548 (17%), 533 (5%), 520 (7%), 481 (18%), 459 (16%), 439 (100%). *3-Pentafluorobenzoyl-1R-camphor:* 6.6 g (43 mmol) 1*R*-camphor, 6.2 ml diisopropylamine, 28 ml methyl lithium (5% in ether), 10 g (43 mmol) pentafluorobenzoyl chloride; yield: 4.1 g (28%) 3-pentafluorobenzoyl-1*R*-camphor; b.p.: 110°C/0.09 mmHg; m.p.. 53°C; mass spectrum (70 eV): *m/e* 346 (100%), 331 (24%), 318 (28%), 304 (22%), 283 (25%), 196 (97%).

Sodium-3-acyl-1R-camphorates. Conversion of the 3-acyl-1*R*-camphorate ligand to the sodium salt was carried out in a Schlenk tube under nitrogen. Benzene was dried with sodium–benzophenone under nitrogen. A 80% sodium hydride suspension in paraffin (Fluka) was washed with benzene until the paraffin was completely removed. Sodium hydride was suspended in benzene, and the β-diketone, dissolved in benzene, was slowly added. The mixture was stirred for 60 min at 22°C. Then the excess of sodium hydride was removed by filtration. Benzene was evaporated *in vacuo* and the residue was repeatedly reprecipitated from benzene–diethyl ether. Yield: 80%.

Manganese(II)–bis(3-acyl-1R-camphorates) (5a–d). 5 mmol of sodium (3-acyl-1*R*-camphorate) were dissolved in 50 ml of dry ethanol. 2.5 mmol of anhydrous manganese(II) chloride, dissolved in ethanol, were added and the mixture was refluxed for 1 h. The white precipitate of sodium chloride was removed by filtration and the solvent of the filtrate was evaporated *in vacuo*. The residue was extracted with *n*-hexane and the solution transferred into the tube of a sublimation apparatus. After evaporation of the solvent, the residue was sublimed at 140–160°C/0.02 mmHg. Yield: 30–40%. Higher yields of crude product were obtained when the purification by sublimation was omitted. *Manganese(II)–bis(3-heptafluorobutyryl-1R-camphorate) (5c):* m.p. 93°C (closed tube); mass spectrum (70 eV): *m/e* 749 (79%), 721 (21%), 348 (100%), 333 (40%), 320 (53%), 305 (40%). *Manganese(II)–bis(3-perfluorooctanoyl-1R-camphorate) (5d):* mass spectrum (70 eV): *m/e* 1149 (M^+) in electron impact (EI) and field desorption (FD) modes. *Manganese(II)–bis(3-pentafluorobenzoyl-1R-camphor) (5a):* mass spectrum: *m/e* 745 (M^+) in EI, *m/e* 745 (M^+) and 1491 ($2M^+$) in FD mode. All compounds described gave satisfactory elemental analyses. *Manganese(II)–bis(3-trifluoroacetyl-1R-camphorate) (5b):* this compound was prepared as described previously[20].

Instrumentation

A Carlo Erba Fractovap 2101 instrument equipped with a flame ionization detector and suitable for open-tubular column operation was used. High-purity grade nitrogen, free of water, was used as carrier gas. The splitting ratio was set at 1:50. The injector temperature was 120°C. The solutes were injected together with methane and the reference standard *n*-octane as air-diluted vapors drawn from "head-space" vials (Perkin-Elmer). The sensitivity of the instrument was set as high as possible and gave a signal-to-noise ratio of *ca.* 1:50.

Columns

The following five stainless-steel open-tubular columns, obtained from Schoeller Werke KG (Hellenthal, G.F.R.) were used: column A: 160 m × 0.4 mm (Sinox SH 2); column B: 160 m × 0.4 mm (Sinox SH 2); column C: 105 m × 0.4 mm (Sinox SH 2); column D: 100 m × 0.4 mm (Sinox SH 1); and column E: 26.6 m × 0.25 mm (Sinox SH 2).

The columns were checked and treated as described previously[15,21]. Exchange of manganese in 5 by iron from the column wall was observed on only one occasion, with column D and 5b.

Reference column

Coating of the open-tubular column was performed by the dynamic plug method[15]. The capillary was flushed with the coating liquid by nitrogen over-pressure using a home-made coating device made entirely from PTFE. Thus, column E was coated with 150 mg of squalane dissolved in 2 ml of methylene chloride (high-purity grade) at 0.4 atm (over-pressure) nitrogen. After the coating liquid emerged from the column the nitrogen pressure was maintained for 6 h. The column was connected to the injector and conditioned for 12 h at 60°C, and then 3 cm of the column end were flame heated to remove volatiles. The column was then connected to the detector in such a way that dead volumes in the flow system were minimized.

Metal-containing columns

In a typical coating procedure the required amount of metal chelate and 150 mg of squalane were dissolved in 2 ml of methylene chloride (high-purity grade) and the solution was transferred into the coating device and purged through the column. The column was then installed in the chromatograph as described above. The columns were prepared as follows: column A: coated with 0.05 *m* manganese(II)–bis(3-heptafluorobutyryl-1*R*-camphorate) (5c) in squalane; column B: coated with 0.057 *m* manganese(II)–bis(3-pentafluorobenzoyl-1*R*-camphorate) (5a) in squalane; column C: coated with 0.097 *m* manganese(II)–bis(perfluorooctanoyl-1*R*-camphorate) (5d) in squalane; column D: coated with 0.096 *m* (dimer) (manganese(II)–bis(3-trifluoroacetyl-1*R*-camphorate))$_2$ (5b) in squalane; and columns E: coated with manganese (II)–bis(3-heptafluorobutyryl-1*R*-camphorate) (5c) in squalane in the concentrations: 0.051 *m* (E1), 0.069 *m* (E2), 0.096 *m* (E3), 0.107 *m* (E4), and 0.147 *m* (E5).

The efficiencies of the columns are shown in Table I.

N_{eff} was invariably higher for the non-interacting reference standard, *n*-octane, than for solutes coordinating with the metal chelate. As commonly observed in complexation chromatography[15], N_{eff} decreases as the retention increase R' increases. It

TABLE I

NUMBER OF EFFECTIVE PLATES (N_{eff}) FOR SOME OF THE COLUMNS USED

Temperature, 60°C

Column	N_{eff} *(n-octane)*	N_{eff} *(S-tert.-butyloxirane)*
A	207,000	133,000
B	210,000	175,000
E4	43,000	26,000

TABLE II

REPRODUCIBILITY OF THE RETENTION INCREASE R' AT 60°C (COLUMN A)

Solute		R'	R' *(after 21 days)*
Methyloxirane (7)	*R*	0.95	0.94
	S	1.13	1.14
Ethyloxirane (8)	*R*	0.89	0.90
	S	1.17	1.20
Isopropyloxirane (9)	*R*	0.83	0.83
	S	1.13	1.13
tert.-Butyloxirane (12)	*R*	0.58	0.58
	S	0.82	0.82

was shown that column A did not change its performance within two years of frequent use. In addition, the R' value for four solutes measured during three weeks of constant operation revealed constancy with the experimental error (Table II).

Calculation of the retention increase, R', and of the free enthalpy difference of enantiomer discrimination, $\Delta_{S,R}(\Delta G)$

Adjusted retention times, t'_{sol}, were measured as the distance between the maximum peak heights of the solute and the methane peak. t'_{sol} was then related to t'_{ref} of the non-coordinating inert reference standard, *n*-octane, which was coinjected, *i.e.*, $t'_{sol}/t'_{ref} = r$ (r = relative retention of a solute with respect to *n*-octane). The relative retention of a solute obtained from a column containing the metal chelate dissolved in squalane, r, and that of the same solute obtained from a column containing pure squalane, r_0, were then used to calculate R' according to the equation $(r - r_0)/r_0 = R'$.

For a typical set of measurements (column E5, see Table V) the chromatographic conditions were: nitrogen, 0.4 atm (over-pressure); chart speed, 4 cm/min; methane, 2 min; *n*-octane minus methane, 6.5 min. Graphical acquisition of retention parameters proved to be more reliable (*i.e.*, $r = \pm 0.001$) than data processing with a conventional computer (time interval: 1 sec). Because of the small R' value generally observed with manganese(II) ($R' = 0.5$–1.5) the error in R' introduced by the uncertainty in r and r_0 is higher ($R' = \pm 0.02$) compared to that measured for nickel(II) ($R' = 20$–60)[11].

Packed columns

Packed columns were prepared as described previously[22].

RESULTS AND DISCUSSION

Resolution factor α for enantiomer separation of racemic cyclic ethers on optically active manganese(II) chelates

In a previous investigation of the fast and reversible interaction of (achiral) Group V and VI σ-donor solutes with bis-3-trifluoroacetylcamphorates of manganese(II), cobalt(II) and nickel(II), a pronounced influence of the central metal ion on coordination strength and selectivity has been noted[22]. Thus, as exemplified for selected solutes in Table III, the extent of coordination between oxygen- and sulphur-containing donor molecules with the transition metal ion increases markedly in the order Mn < Co ≪ Ni.

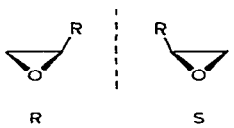
TABLE III

STABILITY CONSTANT K OF THE 1:1 MOLECULAR ASSOCIATION OF σ-DONOR SOLUTES WITH BIS-3-TRIFLUOROACETYLCAMPHORATES OF Mn(II), Co(II) AND Ni(II) ($5 \cdot 10^{-2}$ *m* (DIMER) IN SQUALANE) AT 75°C[22]

Solute	K		
	Mn(II)	*Co(II)*	*Ni(III)*
Tetrahydrofuran	34	132	594
p-Dioxane	19	93	783
Methyloxirane	7.4	16.1	53.2
Methylthiirane	1.0	6.7	51.1
Diethyl ether	2.9	6.4	21.0
Diethyl sulphide	1.5	16.7	126

Guided by the information revealed from Table III we originally selected bis-3-perfluoroacyl-1*R*-camphorates of the strongly coordinating nickel(II) ion (4a–b) as optically active stationary phases (in squalane) for the quantitative enantiomer resolution of alkyl-substituted oxiranes, thiiranes and *N*-chloroaziridines[10–15]. Although excellent separations of optical isomers were obtained with 4b, the high R' values for the strongly interacting solutes precluded short analysis times. The question therefore arose, whether chelates of the weakly coordinating manganese(II) would nevertheless permit efficient enantiomer discrimination at short retention times. Four manganese(II) –bis(3-perfluoroacyl-1*R*-camphorates), *i.e.*, 5a–d, were therefore prepared, dissolved in squalane, and coated onto stainless-steel open-tubular columns of varying length.

As can be seen from Fig. 1, the racemic monoalkyl-substituted oxiranes, 7–9 and 12, are efficiently resolved on 5c (0.05 *m* in squalane, column A) at 60°C with short retention times.



7 R = CH_3
8 R = C_2H_5
9 R = iso-C_3H_7
12 R = *tert.*-C_4H_9

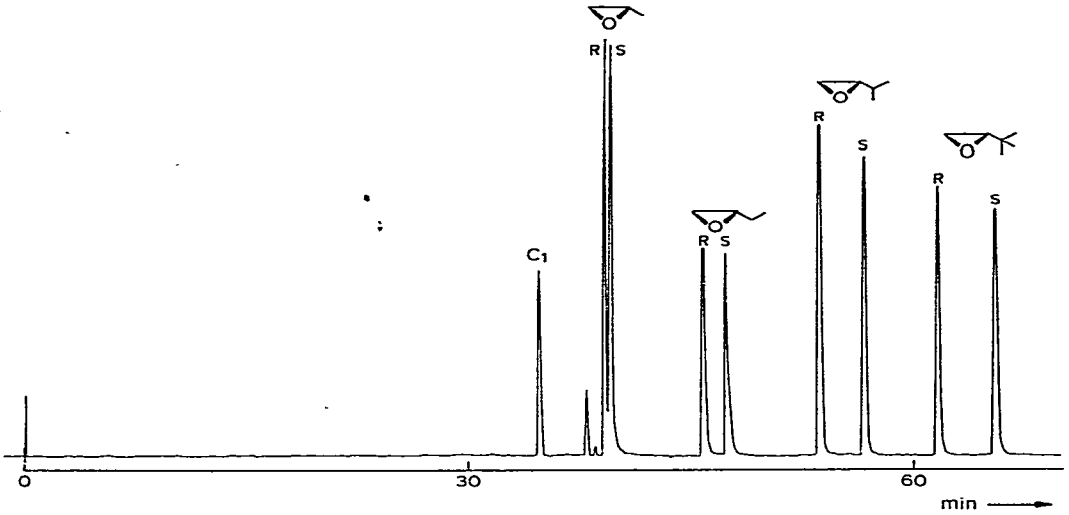
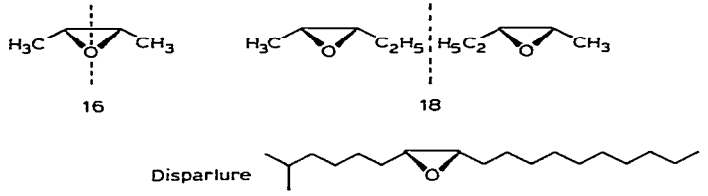


Fig. 1. Resolution of racemic monoalkyl-substituted oxiranes, 7, 8, 9 and 12, on 5c (0.05 *m* in squalane) at 60°C (column A).

The results imply that a strong coordination interaction between solute and metal chelate, as observed for Ni(II)[10–13], is not a prerequisite for chiral recognition in complexation gas chromatography. The observation of sharp Gaussian chromatographic peaks together with the complete absence of peak-tailing, frequently encountered with strongly coordinating solutes[15], renders 5c a very promising resolving agent for weakly interacting racemic donor molecules. It is also important to note that the column efficiency and performance for enantiomer resolution remained constant over a 24-month period of frequent use (column A) and that repeated coatings were highly reproducible (column E).

Encouraged by these results, it was tempting to further elucidate the resolving power of 5c toward racemic oxiranes which exhibit only subtle differences in the configurational relationship of their respective mirror images; one of the challenges to resolution science is to successfully discriminate between optical isomers differing only in the relative spatial position of a methyl *vs.* an ethyl group. Thus, when one of the two methyl groups in the optically inactive (*meso*) *cis*-2,3-dimethyloxirane (16) is replaced by an ethyl group, the enantiomers of *cis*-2-ethyl-3-methyloxirane (18) result.



As shown in Fig. 2, the enantiomers of *trans*-2-ethyl-3-methyloxirane (17) as well as the enantiomers of *cis*-2-ethyl-3-methyloxirane (18) are clearly separated on 5c at 60°C (α = 1.04). The successful resolution of a chiral *cis* configurated oxirane is especially noteworthy as this structural element is found in the insect attractant

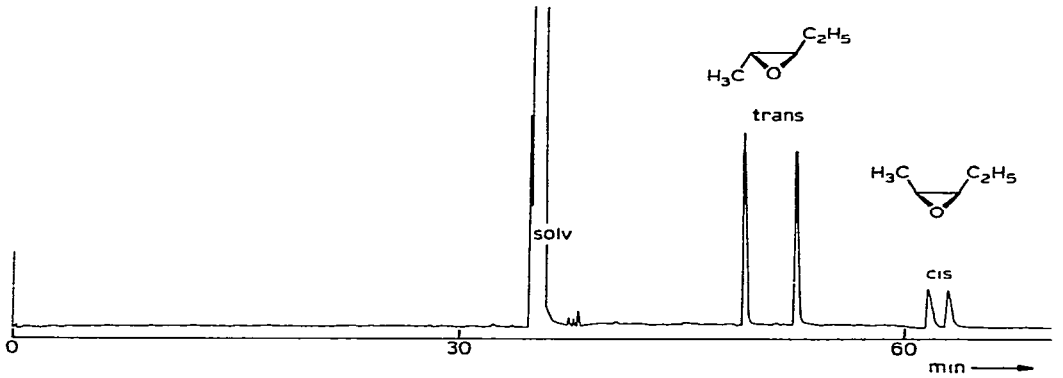
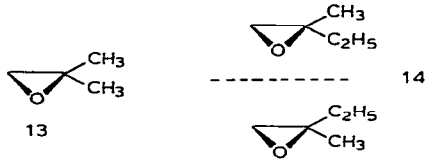


Fig. 2. Resolution of racemic *trans*-2-ethyl-3-methyloxirane (17) and *cis*-2-ethyl-3-methyloxirane (18) on 5c (0.05 *m* in squalane) at 60°C (column A).

disparlure (*cis*-7,8-epoxy-2-methyl-octadecane) isolated from *Lymantria dispar*, the enantiomers of which can be discriminated by the gypsy moth[23].

In another remarkable example, the enantiomers of 2-ethyl-2-methyloxirane (14), formally derived by replacing each of the methyl groups in achiral 2,2-dimethyloxirane (13) by an ethyl group, are nearly baseline separated on 5c in 50 min at 60°C (α = 1.02) (Fig. 3).



Finally, when one methyl group is formally substituted for an ethyl group in isopropyloxirane (9) additional chirality is introduced in the side-chain and, consequently, four configurational isomers of *sec.*-butyloxirane, namely two enantiomeric

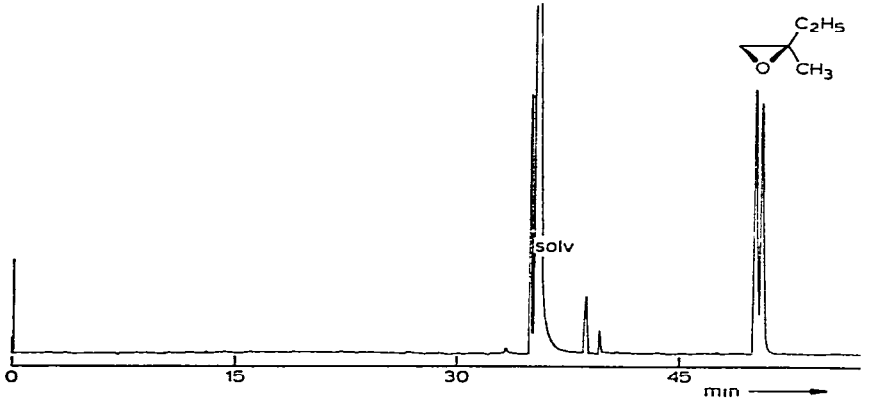
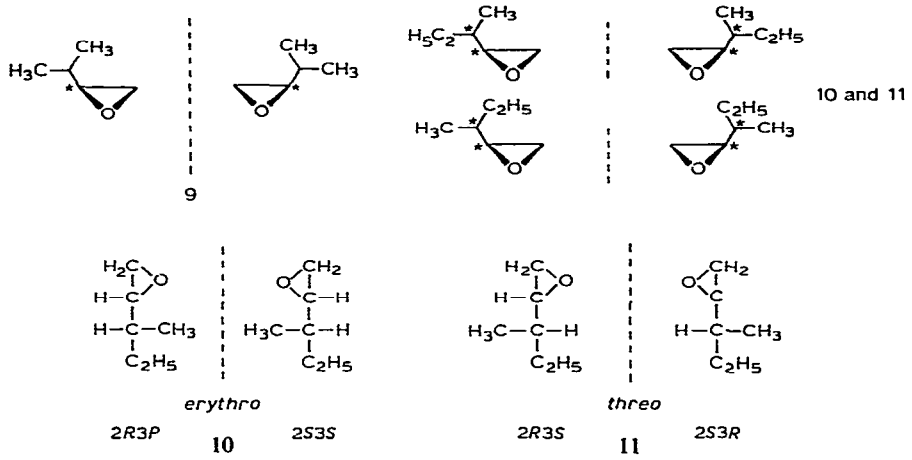


Fig. 3. Resolution of racemic 2-ethyl-2-methyloxirane (14) on 5c (0.05 *m* in squalane) at 60°C (column A).

pairs of *erythro* (10) and *threo* (11) diastereomers, are obtained. Both 10 (α = 1.07) and 11 (α = 1.19) are quantitatively resolved on 5c.



In Fig. 4 the resolving power of 5c for racemic alkyl-substituted cyclic ethers of varying ring size is compared. Methyloxirane (7) is almost quantitatively resolved while 2-methyloxetane (21) and 2-methyltetrahydrofuran (23) are fully separated; 2-methyltetrahydropyran (28), however, shows no separation. The extraordinarily strong retention of the four-membered ring with manganese(II) is noteworthy because this metal ion has been considered as a rather weak acceptor when compared with nickel(II) (*cf.* Table III). It is clear that with the nickel chelate 4b, monoalkyl-substituted oxetanes cannot easily be analysed at reasonable retention times. This

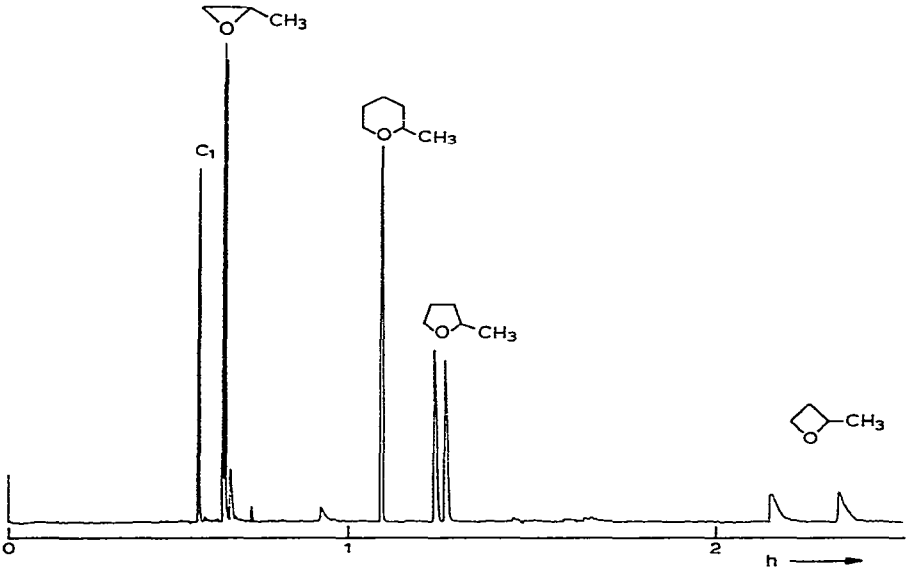


Fig. 4. Influence of ring-size on resolution of racemic 2-methyl-substituted cyclic ethers 7, 21, 23 and 28 on 5c (0.05 *m* in squalane) (column A).

consideration again points to the need, in some cases, to exploit metal chelates which are able to discriminate between optical isomers at a low overall coordination interaction.

As for racemic alkyl-substituted tetrahydrofurans, which are resolvable on 5c, (see Fig. 5) the increasing retention times observed when going from 2,5-dimethyl- to 2-methyl- and 3-methyltetrahydrofuran can be accounted for by the decrease of steric hindrance in the order 25 > 23 > 24. It is interesting to note that the order of peak emergence for the *cis*- and *trans*-diastereomers of 2,5-dimethyltetrahydrofuran (26 and 25) is opposite to that generally observed for oxiranes[10,11] (*cf.* Fig. 2).

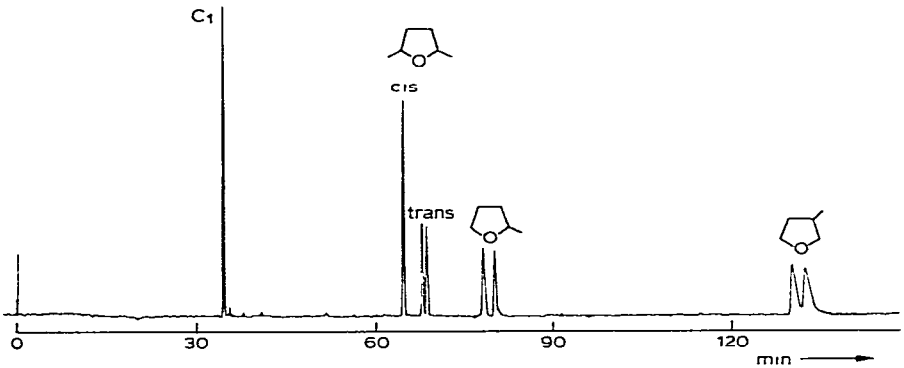


Fig. 5. Separation of diastereomeric and enantiomeric alkyl-substituted tetrahydrofurans 23–26 on 5c (0.05 *m* in squalane) at 60°C (column A).

The introduction of a bulky acyl residue into the optically active metal chelate as in the case of manganese(II)–bis(3-pentafluorobenzoyl-1*R*-camphorate) (5a) considerably improves resolution for solutes with conformationally flexible rings such as tetrahydrofurans and especially tetrahydropyrans. A representative example is presented in Fig. 6. The decreasing resolvability of the 2-alkyl-substituted tetrahydropyrans 28–30 on 5a in the order methyl > ethyl > isopropyl is surprising, but it has precedence in the behaviour of alkyl-substituted oxiranes on 4b[11] (*cf.* Table VII).

In Table IV the resolution factor α for enantiomer separations of 17 racemic alkyl-substituted cyclic ethers of varying ring size on four bis-3-perfluoroacyl-1*R*-camphorates of manganese(II) (5a–d) differing in size and length of the perfluoroacyl residue are grouped together for comparison. The results are self-explanatory, but some comments are nevertheless appropriate. Thus, 5a (PFB) does not perform very well for the resolution of chiral oxiranes, but, as already mentioned, it is recommended for the separation of chiral four- to six-membered ring cyclic ethers. In comparison to 5c (HFB) the dimer 5b (TFA)[22] shows only small α values. This observation is compatible with results obtained on the comparison of 2b and 2c as paramagnetic chiral shift reagents to induce magnetic non-equivalence in racemic substrates by NMR spectroscopy[24]. Further lengthening of the side chain is counterproductive as shown for 5d (PFO). Thus, 5c, dissolved in squalane, is the optically active stationary phase of choice for the resolution of racemic alkyl-substituted cyclic ethers containing up to five-membered rings. As established for racemic oxiranes, 5c resolves all types of chiral species caused by different alkyl-substitution patterns, *i.e.*, mono-substitution, *gem*-, *cis*- and *trans*-disubstitution, and trisubstitution.

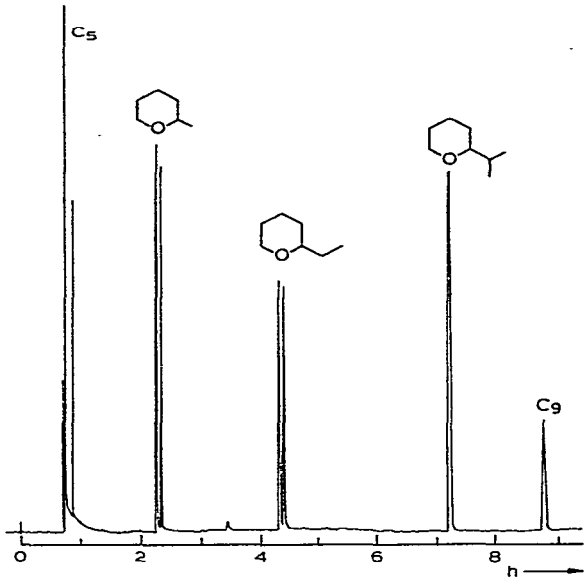


Fig. 6. Separation of racemic 2-alkyl-substituted tetrahydropyrans 28–30 on 5a (0.057 *m* in squalane) at 50°C (column B). Reference standards: *n*-pentane and *n*-nonane.

TABLE IV

RESOLUTION FACTOR α OF ENANTIOMER SEPARATION FOR RACEMIC CYCLIC ETHERS ON FOUR 3-PERFLUOROACYL-1*R*-CAMPHORATE-BIS-CHELATES OF MANGANESE(II) (5a–d) IN SQUALANE AT 60°C

Perfluoroacyl: PFB = pentafluorobenzoyl (0.057 *m*, column B); TFA = trifluoroacetyl (0.096 *m* [dimer], column D); HFB = heptafluorobutyryl (0.05 *m*, column A); PFO = perfluorooctanoyl (0.097 *m*, column C). NM = Not measured; NR = not resolved.

Solute	*No.*	*Metal chelate*			
		5a (PFB)	*5b (TFA)*	*5c (HFB)*	*5d (PFO)*
Methyloxirane	7	NR	1.02	1.08	1.06
Ethyloxirane	8	1.03	1.04	1.15	1.11
Isopropyloxirane	9	1.03	1.04	1.17	1.17
sec.-Butyloxirane (*erythro*)	10	1.02	NM	1.07	NM
sec.-Butyloxirane (*threo*)	11	1.02	NM	1.19	NM
tert.-Butyloxirane	12	1.05	1.04	1.15	1.16
2-Ethyl-2-methyloxirane	14	NR	NR	1.02	1.01
trans-2,3-Dimethyloxirane	15	1.05	1.06	1.30	1.25
cis-2-Ethyl-3-methyloxirane	18	1.02	1.03	1.04	1.02
Trimethyloxirane	19	1.02	1.03	1.20	1.17
2-Methyloxetane	21	1.13	1.02	1.11	1.11
2-Methyltetrahydrofuran	23	1.09	1.01	1.04	1.03
3-Methyltetrahydrofuran	24	1.06	1.01	1.02	NR
trans-2,5-Dimethyltetrahydrofuran	25	1.01	NR	1.02	NR
2-Methyltetrahydropyran	28	1.02	NR	NR	NR
2-Ethyltetrahydropyran	29	1.01	NR	NR	NR
2-Isopropyltetrahydropyran	30	NR	NR	NR	NR

The previous investigation on the 1:1 molecular association of (achiral) σ-donor solutes with bis-3-trifluoroacetylcamphorates of Mn(II), Co(II) and Ni(II) in squalane[22] was performed on Chromosorb P AW DMCS (80–100 mesh) on packed columns. Preliminary experiments[22] on enantiomer resolution of chiral solutes with this packing were unsuccessful. It has now been found, however, that 5c, when dissolved in OV-101 (0.1 *m*) and coated on Chromosorb W AW DMCS (80–100 mesh) can resolve racemic oxiranes, *e.g.*, 7–9, in less than 15 min with a 2.2-m packed column as shown in Fig. 7. This result may be the first step toward preparative enantiomer resolution by complexation gas chromatography.

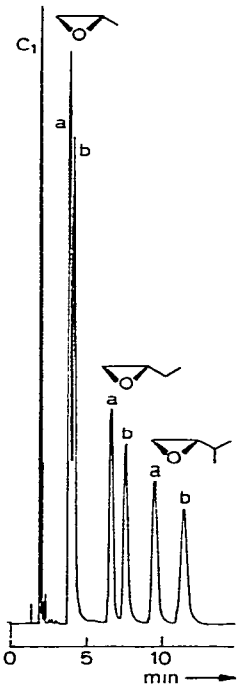


Fig. 7. Resolution of racemic monoalkyl-substituted oxiranes 7–9 on 5c (0.1 *m* in OV-101, 10% on Chromosorb W AW DMCS, 80–100 mesh) at 50°C (2 m × 2.2 mm glass column; nitrogen 0.5 atm (overpressure)). a = *R*; b = *S*.

Thermodynamic parameters of chiral recognition

The resolution factor α for enantiomer separation defines the ratio of the corrected retention time of the *S*-enantiomer, t'_S, over that of the *R*-enantiomer, t'_R (or *vice versa*, $\alpha > 1$). α is therefore merely a useful practical expression for chromatographic separation. Although sometimes used as a measure for "chiral recognition", eqn. 1[25–27]

$$-\Delta_{S,R}(\Delta G) = RT \ln \alpha \quad (1)$$

does not appear to have a chemical meaning in the present case, since t' is the sum of *two* contributions to retention, *i.e.*, firstly, the (identical) physical partition of the two enantiomers between the gaseous and liquid phases and, secondly, the (different)

chemical diastereomeric equilibration between the enantiomers and the optically active metal chelate in the liquid phase. When, for practical purposes, the retention times are related to that of an inert reference standard (a saturated hydrocarbon, for instance), and when two columns, *i.e.*, a column containing the metal chelate dissolved in the solvent (squalane), and a reference column containing the pure solvent (squalane), are employed, then the following simplified equation relates the stability constant, $K_{(m)}$, the molality m_A of the metal chelate A in the solvent and R' of the coordinating solute B[22]:

$$K_{(m)} \cdot m_A = \frac{r - r_0}{r_0} = R' \qquad (2)$$

where

r = relative corrected retention of B with respect to an inert reference standard (not interacting with the metal chelate A) on a column containing the molal concentration m_A

r_0 = relative corrected retention of B with respect to the inert reference standard on a reference column containing the pure solvent

For very dilute concentrations of A and B in the solvent (activity coefficient[22], $\gamma_i \rightarrow 1$; activity[22], $a_i \rightarrow m_i$), $K_{(m)}$ of the fast and reversible association equilibrium A + B $\rightleftharpoons$ AB in the liquid phase may be expressed by:

$$K_{(m)} = m_{AB}/m_A \cdot m_B \qquad (3)$$

TABLE V

RETENTION DATA AND THERMODYNAMIC PARAMETERS FOR THE 1:1 ASSOCIATION OF THE RACEMIC ALKYLOXIRANES 7, 8, 9 AND 12 ON MANGANESE (II)–BIS(3-HEPTAFLUOROBUTYRYL-1*R*-CAMPHORATE) (5c) OF DIFFERENT CONCENTRATIONS IN SQUALANE AT 60°C

All measurements were performed with the same column (column E, 26.6 m × 0.25 mm), retention data are related to the inert reference standard *n*-octane.

*Chiral oxirane**	*Concentration of 5c in squalane (m)***									
	0	*0.051*					*0.069*			
	r_0***		r§	R'§§	K_{rel}	$-\Delta_{S,R}(\Delta G)$§§§	r§	R'§§	K_{rel}	$-\Delta_{S,R}(\Delta G)$§§§
Methyloxirane (7)	0.038	*R*	0.078	1.05	0.80	0.12	0.087	1.29	0.76	0.12
		S	0.086	1.26	0.95		0.097	1.55	0.92	
Ethyloxirane (8)	0.100	*R*	0.201	1.01	0.76	0.18	0.226	1.26	0.75	0.19
		S	0.232	1.32	*1.00*		0.269	1.69	*1.00*	
Isopropyloxirane (9)	0.177	*R*	0.336	0.90	0.68	0.21	0.383	1.16	0.69	0.22
		S	0.397	1.24	0.94		0.465	1.63	0.96	
tert.-Butyloxirane (12)	0.294	*R*	0.471	0.60	0.46	0.24	0.527	0.79	0.47	0.25
		S	0.549	0.87	0.66		0.634	1.16	0.69	

* Arguments on the assignment of absolute configuration to the chromatographic peaks will be presented elsewhere.

** Weighing error: ±0.004.

*** Mean of four measurements, ±0.001.

§ Mean of seven measurements, ±0.001.

§§ Accuracy ±0.02.

§§§ kcal/mol, error: ±0.005.

and from eqns. 2 and 3 one obtains

$$R' = m_{AB}/m_B \tag{4}$$

i.e., R' defines the ratio of complexed (m_{AB}) and uncomplexed (m_B) solute B in the liquid phase (A in the solvent).

For a pair of enantiomeric solutes, *S* and *R*, we obtain from eqn. 2

$$\frac{K_{(m)S}}{K_{(m)R}} = \frac{r_S - r_0}{r_R - r_0} = \frac{R'_S}{R'_R} \tag{5}$$

or:

$$-\Delta_{S,R}(\Delta G) = RT \ln R'_S/R'_R \tag{6}$$

Thus, the free enthalpy difference of enantiomer discrimination can be calculated directly from the ratio of R' of one enantiomer over that of the other. This value should be of high accuracy since r_0 is identical for both enantiomers and since m_A need not to be known. (Note that only if $r \gg r_0$, which is probably seldom the case, does eqn. 6 approach eqn. 1.) In principle, when measurements are performed at different temperatures, the Gibbs–Helmholtz parameters $\Delta_{S,R}(\Delta H)$ and $\Delta_{S,R}(\Delta S)$ are also accessible.

Eqn. 2, which has previously been derived and verified in an investigation on the 1:1 molecular association of (achiral) σ-donor solutes with bis-3-trifluoroacetyl-

0.096				*0.107*				*0.147*			
r [§]	R' [§§]	K_{rel}	$-\Delta_{S,R}(\Delta G)$ [§§§]	r [§]	R' [§§]	K_{rel}	$-\Delta_{S,R}(\Delta G)$ [§§§]	r [§]	R' [§§]	K_{rel}	$-\Delta_{S,R}(\Delta G)$ [§§§]
0.110	1.89	0.80	0.12	0.114	2.00	0.81	0.12	0.131	2.45	0.82	0.11
0.124	2.26	0.95		0.129	2.39	0.97		0.148	2.89	0.97	
0.282	1.82	0.77	0.17	0.287	1.87	0.76	0.18	0.329	2.29	0.77	0.17
0.337	2.37	*1.00*		0.346	2.46	*1.00*		0.398	2.98	*1.00*	
0.457	1.58	0.67	0.21	0.476	1.69	0.69	0.21	0.539	2.05	0.68	0.21
0.562	2.18	0.92		0.588	2.32	0.94		0.672	2.80	0.94	
0.610	1.07	0.45	0.24	0.631	1.15	0.47	0.24	0.699	1.38	0.46	0.23
0.745	1.53	0.64		0.776	1.64	0.67		0.871	1.96	0.66	

camphorates of manganese(II), cobalt(II) and nickel(II) in squalane[22], has now been used to determine thermodynamic parameters of enantiomer discrimination for racemic alkyl-substituted cyclic ethers resolved on bis-3-perfluoroacyl-1*R*-camphorates of manganese(II) (5).

Initially, the validity of the linear relationship between R' and m_A was studied for four enantiomeric pairs of the alkyl-substituted oxiranes 7–9 and 12, at five concentrations of 5c in squalane with the short column E. The data (Table V) show good linearity of R' and m_A at low metal chelate concentrations (0.051–0.107 *m*) within the boundaries of the error in concentration ($\pm$ 0.004 *m*) and in R' ($\pm$ 0.02). However, the values for R' measured at the high concentration 0.147 *m* are too low by a factor of 0.84 $\pm$ 0.02 for all solutes when related to the average of $K_{(m)}$ obtained at all other concentrations. The origin of this discrepancy is unknown: not only a "salting out" effect, but also the beginning self-association of the metal chelate or partial insolubility at the high concentration in squalane may contribute to this observation. It is important to note, however, that the *relative* stability constants, K_{rel}, which were arbitrarily related to the solute with the strongest interaction with 5c (*i.e.*, to *S*-ethyloxirane (8)), show a very good agreement at all five concentrations (Table V, third row). Relative stability constants are important, in our opinion, when relationships between structure and selectivity in homologous series are studied, and a relative comparison is involved *per se* when pairs of enantiomers are investigated. The thermodynamic quantity for enantiomer discrimination, $\Delta_{S,R}(\Delta G)$, calculated from eqn. 6, also shows an excellent agreement for all sets of measurements (Table V, fourth row). The consistency of the relative thermodynamic data observed for solutes of different volatility (and hence, of different r_0 values) at different metal chelate concentrations reinforces the validity of the simplified eqn. 2[22] and justifies its application for practical purposes.

The thermodynamic data compiled in Table V merit the following comment. The coordination strength, as expressed by K_{rel}, for the *S* enantiomers of methyl-, ethyl- and isopropyloxirane (7–9) with Mn(II) is nearly the same despite an increasing steric hindrance of the substitutent (in that order). A decrease of coordination ability with Mn(II) is noted only for the bulky *S*-*tert*.-butyloxirane (12). However, a steady decrease of interaction with Mn(II) is observed for the *R* antipodes, which in general show a higher constraint to interaction. This leads, *in toto*, to an increase in $\Delta_{S,R}(\Delta G)$, in the order: methyl < ethyl < isopropyl < *tert*.-butyl. Hence, the data in Table V provide a deeper insight into mechanisms of chiral recognition than the mere consideration of the practical resolution factor α (Table III). We have therefore measured R', which is proportional to $K_{(m)}$, for 24 cyclic ethers on the manganese chelates 5a and 5c (Table VI). Achiral solutes were also included in order to obtain a more comprehensive insight into the relationship between structure and reactivity for members of homologous series. For chiral solutes $\Delta_{S,R}(\Delta G)$ is also reported in Table VI.

The influence of an alkyl-substituent toward the coordination strength of the oxygen lone-pair is certainly governed by steric and electronic effects which tend to oppose each other and which are not readily separated from each other. For oxiranes, an increase in methyl-substitution of the ring leads first to an increase in interaction with Mn(II) (6 < 7 < 13 < 15 < 16), but then causes a decrease in coordination (20 < 19 < 16), whereby 5a appears to be more sensitive to steric hindrance than 5c. The

TABLE VI

RETENTION DATA AND THERMODYNAMIC PARAMETERS FOR THE 1:1 ASSOCIATION OF CYCLIC ETHERS ON MANGANESE(II)-BIS(3-PERFLUOROACYL-1*R*-CAMPHORATE) CHELATES IN SQUALANE AT 60°C

Perfluoroacyl : PFB = pentafluorobenzoyl (0.057 *m*, column B); HFB = heptafluorobutyryl (0.05 *m*, column A). AS = Achiral solute.

Solute	*No.*	r_0*	*5a (PFB)*		*5c (HFB)*	
			*R'***	$-\Delta(\Delta G)$***	*R'***	$-\Delta(\Delta G)$***
Oxirane	6	0.019	0.37	AS	0.53	AS
Methyloxirane	7	0.038	0.37 0.37	0	0.97 1.18	0.13
Ethyloxirane	8	0.100	0.41 0.45	0.06	0.89 1.16	0.18
Isopropyloxirane	9	0.177	0.46 0.50	0.05	0.84 1.14	0.20
sec.-Butyloxirane (*erythro*)	10	0.475	0.47 0.51	0.05	0.70 0.83	0.11
sec.-Butyloxirane (*threo*)	11	0.484	0.51 0.55	0.05	0.85 1.21	0.23
tert.-Butyloxirane	12	0.294	0.31 0.38	0.13	0.58 0.82	0.23
2,2-Dimethyloxirane	13	0.058	0.38	AS	1.21	AS
2-Ethyl-2-methyloxirane	14	0.165	0.35 0.36	0.02	1.01 1.06	0.03
trans-2,3-Dimethyloxirane	15	0.067	0.54 0.64	0.11	1.19 1.85	0.29
cis-2,3-Dimethyloxirane	16	0.091	0.87	AS	1.96	AS
cis-2-Ethyl-3-methyloxirane	18	0.206	0.94 0.97	0.02	1.65 1.77	0.05
Trimethyloxirane	19	0.122	0.47 0.49	0.03	1.46 1.93	0.18
Tetramethyloxirane	20	0.238	0.24	AS	1.07	AS
2-Methyloxetane	21	0.144	9.20 10.5	0.09	12.5 14.2	0.08
Tetrahydrofuran	22	0.158	4.24	AS	4.52	AS
2-Methyltetrahydrofuran	23	0.225	1.58 1.83	0.10	2.40 2.54	0.04
3-Methyltetrahydrofuran	24	0.305	4.00 4.29	0.05	4.54 4.67	0.02
trans-2,5-Dimethyltetrahydrofuran	25	0.330	0.35 0.37	0.04	0.76 0.80	0.03
cis-2,5-Dimethyltetrahydrofuran	26	0.300	0.35	AS	0.75	AS
Tetrahydropyran	27	0.318	1.84	AS	2.17	AS
2-Methyltetrahydropyran	28	0.447	0.17 0.20	0.11	0.20 0.20	0
2-Ethyltetrahydropyran	29	1.128	0.07 0.08	0.09	0	0
2-Isopropyltetrahydropyran	30	2.089	0	0	0	0

* r_0 is related to the inert reference standard *n*-octane.

** *R'* is proportional to the stability constant $K_{(m)}$. The relative retention *r* observed can be recalculated from eqn. 2.

*** kcal/mol.

TABLE VII

COMPARISON OF THERMODYNAMIC PARAMETERS OF ENANTIOMER DISCRIMINATION FOR RACEMIC ALKYL-SUBSTITUTED CYCLIC ETHERS ON OPTICALLY ACTIVE METAL(II)–BIS(3-PERFLUOROACYL-1*R*-CAMPHORATE) CHELATES IN SQUALANE AT 60°C

Perfluoracyl; PFB = pentafluorobenzoyl (0.057 *m*, column B); TFA = trifluoroacetyl (0.096 *m* (dimer), column D); HFB = heptafluorobutyryl (0.05 *m*, column A); PFO = perfluorooctanoyl (0.097 *m*, column C). NR = Not resolved.

Chiral solute	*No.*	*Mn (II)*								*Ni (II)*	
		5a (PFB)		*5b (TFA)*		*5c (HFB)*		*5d (PFO)*		*4b (HFB)**	
		R'	$-\Delta_{S,R}(\Delta G)$ **	*R'*	$-\Delta_{S,R}(\Delta G)$ **	*R'*	$-\Delta_{S,R}(\Delta G)$ **	*R'*	$-\Delta_{S,R}(\Delta G)$ **	*R'*	$-\Delta_{S,R}(\Delta G)$ **
Methyloxirane	7	NR		NR		0.97 1.18	0.13	1.53 1.66	0.05	58.5 69.3	0.11
Ethyloxirane	8	0.41 0.45	0.06	0.31 0.36	0.10	0.89 1.16	0.18	1.02 1.25	0.13	58.9 63.3	0.05
Isopropyloxirane	9	0.46 0.50	0.05	0.33 0.38	0.09	0.84 1.14	0.20	0.81 1.12	0.21	NR	
tert.-Butyloxirane	12	0.31 0.38	0.13	0.29 0.34	0.11	0.58 0.82	0.23	0.49 0.73	0.26	39.0 43.5	0.07
2-Ethyl-2-methyloxirane	14	0.35 0.36	0.02	NR		1.01 1.06	0.03	NR		35.5 37.3	0.03
trans-2,3-Dimethyloxirane	15	0.54 0.64	0.11	0.46 0.55	0.12	1.19 1.85	0.29	1.31 1.90	0.25	24.4 32.4	0.19
Trimethyloxirane	19	0.47 0.49	0.03	0.77 0.84	0.06	1.46 1.93	0.18	1.39 1.80	0.17	24.6 33.1	0.20
2-Methyltetrahydrofuran	23	1.58 1.83	0.10	1.60 1.64	0.02	2.40 2.54	0.04	1.96 2.03	0.02	58.4 62.2	0.04
trans-2,5-Dimethyltetrahydrofuran	25	0.35 0.37	0.04	NR		0.76 0.80	0.03	NR		2.33 2.91	0.15

* Nickel(II)–bis(3-heptafluorobutyryl-1*R*-camphorate) (0.1 *m* in squalane)[28].

** kcal/mol.

remarkable complexation ability of the four-membered ring with Mn(II), which accounts for the long retention of 2-methyloxetane (21) on 5c (Fig. 4), is not well understood. In the tetrahydrofuran series, methyl-substitution at the carbon atom proximal to the oxygen causes a strong destabilization of adduct formation whereby the geometric relationship of two methyl substituents, *i.e.*, in 25 and 26, is not important. This is in contrast to oxiranes, where *cis* isomers show a stronger interaction with Mn(II) than the *trans* isomers. The conformationally flexible tetrahydropyrans 28–30 show only a negligible coordination ability with Mn(II). The failure of 5a to resolve 2-isopropyltetrahydropyran (30) (Fig. 6) is simply explained by the absence of any interaction with the metal ion, *i.e.*, $R' = K_{(m)} = 0$. For chiral oxiranes, the chelate 5c induces much higher enantiomeric bias than does 5a. For chiral tetrahydrofurans and tetrahydropyrans this situation is reversed.

In Table VII thermodynamic parameters of selected racemic cyclic ethers with four bis-3-perfluoroacyl-1*R*-camphorates of manganese(II) (5) are compared with those of nickel(II)-bis(3-heptafluorobutyryl-1*R*-camphorate) (4b)[28]. Inspection of the data shows the remarkable difference in the acceptor properties of Mn(II) and Ni(II) in regard to cyclic ethers. In agreement with results reported in Table III, the nickel may show a fifty-fold stronger coordination with oxygen donor molecules in some cases. However, at the same time the difference of interaction for pairs of enantiomers is not pronounced enough to give $\Delta_{S,R}(\Delta G)$ values which would strikingly exceed those observed for the manganese chelate 5c. Thus, the latter resolving agent is to be preferred for practical reasons since it separates enantiomers with shorter retention times. Some differences in the enantiospecificity of Mn(II) and Ni(II) are present nevertheless. Thus, the enantiomers of isopropyloxirane (8) are not discriminated by 4b, whereas *trans*-2,5-dimethyltetrahydrofuran (25) is much better resolved on Ni(II) than on Mn(II). Hence, the results in Tables V–VII vividly demonstrate that small changes in the perfluoroacyl residue of camphor, as well as variations in the choice of the metal ion, may cause profound differences in coordination selectivity and enantiospecificity. Before the wealth of the data can be fully rationalized, the spatial relationship and the coordination geometry of the solute–metal chelate adduct must be elucidated. The exact configurational structure of, and the extent of self-association for, the metal chelates must also be determined. In the future, the construction of molecular models might elucidate some of the observed results.

CONCLUSION

Racemic alkyl-substituted cyclic ethers which do not possess suitable functions for diastereomeric derivatization or for conventional chromatographic enantiomer separation have now been resolved with short analysis times by "complexation gas chromatography" on optically active bis-3-perfluoroacyl-1*R*-camphorates of manganese(II) in squalane. The compounds can be resolved *in situ*, *i.e.*, without isolation, purification or derivatization. Thermodynamic parameters of enantiomer discrimination, readily obtained from relative retention data, permit an insight into the mechanism of "chiral recognition" via coordination.

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