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EVALUATION OF NICKEL(II) BIS[α-(HEPTAFLUOROBUTANOYL)-TERPENEKETONATES] AS CHIRAL STATIONARY PHASES FOR THE ENANTIOMER SEPARATION OF ALKYL-SUBSTITUTED CYCLIC ETHERS BY COMPLEXATION GAS CHROMATOGRAPHY

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SUMMARY

A method is described which permits the determination of thermodynamic data for molecular association, as well as the enantioselectivity $-\Delta_{R,S}(\Delta G^\circ)$, from relative retention data by complexation gas chromatography. Thus, the solute–solvent association equilibria between two achiral, and fifteen chiral alkyl-substituted cyclic ethers and twelve non-racemic nickel(II) bis[α-(heptafluorobutanoyl)terpeneketonates] in squalane have been measured at 60°C. The selectivity of the solute–solvent association between alkyl-substituted oxiranes and the twelve nickel terpeneketonates follows a common trend which is rationalized in terms of opposing electronic and steric effects of the Lewis bases. The origin of the striking influence of ring size of cyclic ethers on the association strength with the twelve nickel terpeneketonates, which varies by two orders of magnitude, is unknown. Improved chiral stationary phases for the enantiomer separation of alkyl-substituted cyclic ethers have been found. The highest enantiomeric bias on racemic oxiranes is induced by nickel(II) bis[3-(heptafluorobutanoyl)-(1*R*,2*S*)-pinan-4-onate], containing a bicyclic terpene structure, and by nickel(II) bis[5-(heptafluorobutanoyl)-(*S*)-carvonate], containing a monocyclic terpene structure, respectively. The enantioselectivity, $-\Delta_{R,S}(\Delta G^\circ)$, is generally high when the solute–solvent interaction is intermediate. For chiral alkyl-substituted oxiranes a consistent relationship between molecular configuration and the order of elution is observed for almost all of the twelve nickel terpeneketonates used as solvent. The synthesis of these solvents is described in detail.

INTRODUCTION

Chiral bis[3-(heptafluorobutanoyl)-(1*R*)-camphorates] of manganese(II), cobalt(II) and nickel(II)[1,2] have been successfully employed as enantioselective stationary phases for the gas chromatographic (GC) separation of underivatized racemic

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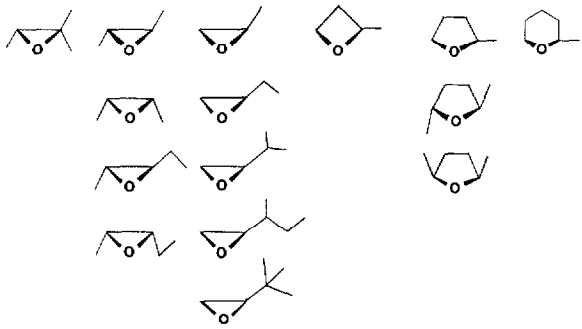
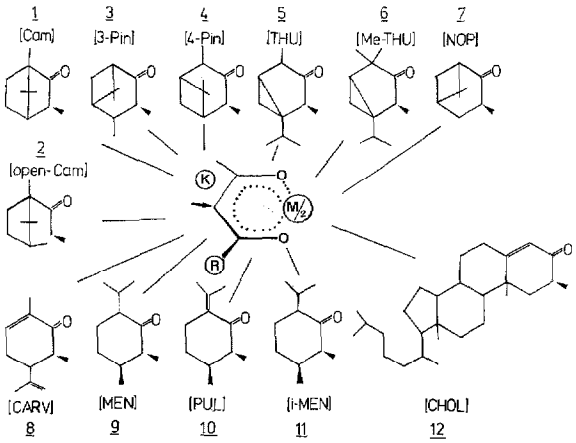


Scheme 1. Alkyl-substituted cyclic ethers as solutes for complexation GC.

Lewis bases, such as cyclic ethers and thio ethers, N-chloroaziridines, acetals, esters, lactones, ketones and alcohols[3–7]. Various applications associated with the precise determination of enantiomeric ratios (enantiomeric excess, ee) and absolute configurations have been reported by our own laboratory and by other groups[8,9].

In extension of these studies, a number of non-racemic nickel(II) bis[α-(heptafluorobutanoyl)terpeneketonates] have now been synthesized, and the influence of constitutional and configurational modifications on the enantiomer discrimination of fifteen racemic cyclic ethers (*cf.*, Scheme 1) has been scrutinized. Only mono- and bicyclic terpeneketones, which were readily available from natural sources in essentially enantiomerically pure form and which lent themselves to a regioselective α-acylation followed by bis chelation with the nickel(II) ion, were selected in the present investigation (*cf.*, Scheme 2).

The unique molecular architectures displayed by terpeneketoenolates have previously been utilized by Mc Creary *et al.*[10] in an effort to optimize chiral lanthanide "shift reagents", *e.g.*, paramagnetic europium(III) tris[α-(heptafluorobutanoyl)ter-



Scheme 2. A selection of mono- and bicyclic terpeneketones as chiral constituents of nickel(II) β-ketoenolates. R = $-C_3F_7$; M = Ni.

pene ketonates], for the discrimination of enantiomers by NMR spectroscopy. The chemical shift anisochrony of enantiotopic nuclei, rendered diastereotopic in the presence of a non-racemic chiral shift reagent, arises from at least two, mutually dependent, contributions which are related to the stability and geometry of the resulting diastereomeric association complexes in solution[11]. Because the individual contributions to chemical shift non-equivalence are indistinguishable, meaningful thermodynamic data, describing chiral recognition as well as simple correlations of absolute configuration with the sense of induced shifts, are not readily available from NMR studies using lanthanide "shift reagents"[11], despite the general utility of chiral solvating agents for the elucidation of donor–acceptor interactions[12].

The separation of enantiomers by complexation GC entirely depends on the difference in the stabilities of the diastereomeric 1:1 association complexes between the racemic substrate (hereafter called "solute") and the non-racemic metal bis chelate (hereafter called "solvent", the complexing agent), allowing a somewhat more straightforward interpretation of the thermodynamic data for chiral recognition. Furthermore, thermodynamic parameters of molecular association can readily be obtained from GC retention data[13,14] and, when applied to enantiomer separation[15], the difference in the free enthalpy change for molecular association between the solute and the solvent, *i.e.*, $-\Delta_{R,S}(\Delta G^\circ)$ (*vide infra*), provides valuable information on the enantioselectivity of the donor–acceptor interaction between the racemic solute and the non-racemic metal bis chelate. The determination of the elution order of the solute on a GC column containing a solvent of predefined chirality in the stationary phase must necessarily complement the assessment of chiral recognition, $-\Delta_{R,S}(\Delta G^\circ)$. It is important to establish the true sign of $-\Delta_{R,S}(\Delta G^\circ)$ and to detect peak inversions, which may arise from reversal of enantioselectivities caused by the inherent thermodynamics of chiral recognition[16] for solutes that are members of homologous series of compounds. In the present study, therefore, both the magnitude and the sign of enantiomer discrimination is determined between alkyl-substituted cyclic ethers and various chiral metal bis chelates. Structural elements of the solvent necessary for efficient chiral recognition are systematically investigated.

The procedures described were designed for the purpose of obtaining correct thermodynamic data for enantioselectivity. For practical enantiomer analysis, the use of vitreous open-tubular columns in connection with polysiloxane solvents was found to be more advantageous in complexation GC[6,7].

EXPERIMENTAL

Instrumentation

A Carlo Erba (Hofheim/Taunus, F.R.G.) Fractovap 2101 gas chromatograph, equipped with a flame ionization detector and suitable for operation with metal open-tubular columns, was used. High-purity-grade nitrogen was used as the carrier gas. The injector temperature was 120°C. The splitting device was set to 1:100. The solutes were injected together with methane, and the reference standard, *n*-octane, as air-diluted vapours. In order to avoid overloading, which results in peak tailing and broadening, the instrument was set to its highest sensitivity at a tolerable signal-to-noise ratio ($>1:10$). The split line and detector exhaust gases should be ventinaled into a hood.

Open-tubular columns

Nickel open-tubular columns (100 m × 0.5 mm I.D. and 75 m × 0.5 mm I.D., 200 seamless tubing, 99.53% Ni, 0.24% Mn), obtained from Handy and Harman Tube Co. (Norristown, PA, U.S.A.), were used. Prior to use, the columns were washed with *n*-hexane, chloroform, acetone and water. The rinsing was then repeated in the reverse order.

Coating of the columns[17]

The columns were coated dynamically. In a typical coating procedure, 15.1 mg of compound **1** and 200 mg of squalane [0.1 *m* (molality) of **1**] were dissolved in 3.5 ml of chloroform. [It is important for thermodynamic measurements to produce a film thickness of 1.0–1.5 μm. Therefore, concentrated coating solutions, *ca.* 10% (w/w), were used.] The solution was transferred to a laboratory-made coating device, fashioned entirely from PTFE. Approximately 0.6 bar of nitrogen overpressure were used to force the solution through the column. The nitrogen pressure was maintained for 5 h after the solution had passed the column. The column was connected to the gas chromatograph and conditioned at 0.3 bar nitrogen with a temperature programme of 30–80°C at 2°/min and 80°C (isothermal) for 24 h. After conditioning, the carrier gas pressure was raised to 1.5 bar and *ca.* 5 cm of the column end were heated with a flame in order to remove volatiles. Before starting the thermodynamic measurements the column was conditioned at 60°C for 24 h.

Calculation of the retention increase, R′, and of the free enthalpy difference for enantiomer discrimination, $\Delta_{R,S}(\Delta G^\circ)$[17]

Methane was used to measure the gas hold-up (dead-volume); its finite but negligible short retention time did not falsify the thermodynamic parameters calculated from adjusted retention times. Commercial *n*-octane was used as an inert reference standard to determine relative retentions, *r*. 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 reference standard, *n*-octane, which was simultaneously injected, *i.e.*, $t'_{sol}/t'_{ref} = r$ the relative retention of a solute with respect to *n*-octane. The relative retention of a solute, obtained from a column containing the solvent in squalane, *r*, and that of the same solute obtained from a column containing pure squalane, r_0, were used to calculate R' according to $R' = (r - r_0)/r_0$. The ratio of R' for the respective enantiomers was then used to calculate the enantioselectivity according to $-\Delta_{R,S}(\Delta G^\circ) = RT \cdot \ln(R'_R/R'_S)$ (for derivation, *vide supra*). Graphic acquisition of retention data proved to be as reliable, *i.e.*, $r = \pm 0.005$, as data processing with a conventional integrating system (time interval: 0.1 s).

Solutes

The solutes were commercially available or were prepared from the alkenes by epoxidation with *m*-chloroperbenzoic acid[17]. Optically active reference compounds

with established stereochemistries used for peak assignment were prepared as described[18,19]. Oxiranes were handled with the appropriate care in closed systems.

Solvents 1–12

Strict adherence to the mode of preparation of solvents is recommended. Solvents prepared and purified by alternative routes may exhibit different physical and chromatographic properties[7].

Nomenclature

For simplicity and clarity the configuration of the solvents is specified as follows. The symbols *R* or *S*, respectively, which precede the conventional name of the terpenone, specify the chirality of the starting material regardless of descriptor reversals that may arise in subsequent chemical modifications (an ambiguity in specifying enol or keto forms of certain β-diketones).

The numbering of the carbon atoms of terpenones is that adopted in ref. 20. The thermodynamic data were extrapolated to ee = 100% for solvents which were not enantiomerically pure.

(1*R*)-Camphor, (1*S*)-thujan-3-one (containing the epimer), (*S*)-carvone, (1*R*)-menthone and (*R*)-pulegone were obtained from Haarmann and Reimer (Holzminden, F.R.G.). (1*R*)-Campholylmethane was obtained from (1*R*)-campholic acid[10], (1*R*,2*R*)-pinan-3-one from (1*R*,2*R*,3*R*)-pinan-3-ol (isopinocampheol) and (1*R*,2*S*)-pinan-4-one from (1*R*)-pin-2-en-4-one[(−)-verbenone][19]. (1*S*)-4-Methylthujan-3-one was obtained from (1*S*,4*R*)-thujan-3-one[18,21] and (1*R*,5*S*)-nopinone from (1*S*)-β-pinene[10].

General procedure for (heptafluorobutanoyl)terpeneketones[10]

The reaction was carried out in a nitrogen atmosphere, using a dry, three-necked, round-bottom flask, equipped with a nitrogen inlet, dropping funnel, a low-temperature thermometer and an efficient mechanical stirrer. The calculated amount of methyl-lithium (170 ml of a 0.8 *M* solution, 136 mmol) was diluted in 100 ml of dry diethyl ether and cooled to −20°C. An equimolar quantity of N,N-diisopropylamine (19 ml, 136 mmol) was added dropwise (evolution of methane!). After stirring for 30 min at −20°C, an equimolar amount of ketone (136 mmol), dissolved in 20 ml of dry diethyl ether, was slowly added. The mixture was stirred for 20 min at −20°C and then cooled to −60°C. An equimolar amount of heptafluorobutanoyl chloride (20 ml, 136 mmol) (Fluka, Buchs, Switzerland), dissolved in 20 ml of dry diethyl ether, was added at such a rate as to keep the temperature below −50°C. The reaction mixture was stirred for 1 h at −50°C and was subsequently allowed to warm to room temperature within 2 h. For work-up, the mixture was poured into 100 g of ice-water and acidified with hydrochloric acid to pH≈2; the aqueous phase was repeatedly extracted with diethyl ether. The pooled organic layers were washed with aqueous sodium bicarbonate and brine, dried over sodium sulphate and then concentrated. The residue was purified by column chromatography on silica and fractional distillation. [Upon chromatography of the β-diketones on silica, the formation of a red product,

believed to be an iron(III) tris chelate, was generally observed. To increase the yield of the diketone, the concentrated eluates were diluted in ethanol, and a few ml of a 20% aqueous solution of sodium cyanide were added to remove iron ions. The mixture was diluted in water, acidified to pH 2–3 with cold 1 *M* sulphuric acid and the aqueous phase was extracted with ethyl acetate. The diketone was recovered in the usual manner.]

In the following, the polarimetric measurements refer to optical rotations, α, rather then to specific rotations, $[\alpha]$, of neat liquids (which require knowledge of the density) measured with a 1-dm cell. The elemental analysis and spectroscopic data corresponded to those expected for the β-diketones and the solutes derived therefrom.

3-Heptafluorobutanoyl-(1R)-camphor[15]

Prior to chromatography, unreacted camphor was removed by sublimation at 35°C (14 Torr). Chromatography on silica gel with benzene–light petroleum (b.p. 60–90°C) (2:3, v/v). Yield: 23%, b.p. 57°C (0.05 Torr), α_D^{20} + 170.8° (neat).

Heptafluorobutanoyl-(1R)-campholylmethane

Yield: 32%, b.p. 70°C (0.07 Torr), α_D^{20} + 50.5° (neat).

4-Heptafluorobutanoyl-(1R,2R)-pinan-3-one

Chromatography on silica gel with chloroform–light petroleum (b.p. 60–90°C) = (2:3, v/v). Yield: 8%, b.p. 65°C (0.4 Torr), α_D^{20} + 36.3° (neat).

3-Heptafluorobutanoyl-(1R,2S)-pinan-4-one

Chromatography on silica gel with chloroform–light petroleum (b.p. 60–90°C) (2:3, v/v). Yield: 15%, b.p. 59°C (0.15 Torr), α_D^{20} + 10.8° (neat).

2-Heptafluorobutanoyl-(1S,4R)-thujan-3-one

Chromatography on silica gel with chloroform–light petroleum (b.p. 60–90°C) (2:3, v/v). Yield: 22%, b.p. 70°C (0.7 Torr), α_D^{20} − 11.2° (neat).

2-Heptafluorobutanoyl-(1S)-4-methylthujan-3-one

Chromatography on silica gel with dichloromethane–light petroleum (b.p. 60–90°C) (2:3, v/v). Yield: 26%, b.p. 74°C (0.4 Torr), α_D^{20} − 145.2° (neat).

3-Heptafluorobutanoyl-(1R,5S)-nopinone

Chromatography on silica gel with chloroform–light petroleum (b.p. 60–90°C) (2:3, v/v). Yield: 38%, b.p. 70°C (0.5 Torr), α_D^{20} + 22.9° (neat).

5-Heptafluorobutanoyl-(R)-carvone

Chromatography on silica gel with dichloromethane–light petroleum (b.p. 60–90°C) (2:3, v/v). Yield: 27%, b.p. 80°C (0.2 Torr), α_D^{20} + 184.2° (neat).

2-Heptafluorobutanoyl-(1*R*)-menthone and 2-heptafluorobutanoyl-(1*R*)-isomenthone were prepared by acylation of an epimeric mixture and subsequent separation by column chromatography of the β-diketones.

Epimerization of (1R)-menthone

A mixture of concentrated sulphuric acid (150 ml) and water (15 ml) was cooled to −30°C. (1*R*)-Menthone (26 g) was added, and the reaction mixture was allowed to warm to 30°C with mechanical stirring. The yellow reaction mixture was transferred in ice–water and was extracted with diethyl ether. The organic phase were dried with sodium sulphate, concentrated and distilled to give 19 g of isomenthone–menthone (2:3), α_D^{20} + 29.7° (neat). After acylation, the residue was distilled to remove unreacted ketones. The fraction boiling at 60–75°C (0.02 Torr) was repeatedly chromatographed on silica [benzene–light petroleum (b.p. 60–90°C) (2:3)] to give the following compounds.

2-Heptafluorobutanoyl-(1R)-menthone. Yield: 4.7 g (20%), b.p. 69°C (0.02 Torr), m.p. 38°C, $[\alpha]_D^{20}$ + 80° (*c* 1,3, $CHCl_3$); $[\alpha]_D^{20}$ + 83.5° (*c* 1, $CHCl_3$) for the β-diketone prepared directly from menthone without prior epimerization.

2-Heptafluorobutanoyl-(1R)-isomenthone. Yield: 2.1 g (9%), b.p. 68°C (0.02 Torr), α_D^{20} + 148° (neat), $[\alpha]_D^{20}$ + 115.7° (*c* 3, $CHCl_3$). Chromatography on silica gel with chloroform–light petroleum (b.p. 60–90°C) (2:3, v/v). Yield 26%, b.p. 70°C (0.4 Torr), α_D^{20} + 12.4° (neat).

6-Heptafluorobutanoyl-(R)-pulegone. Yield: 26%, b.p. 87°C (0.5 Torr), α_D^{20} −62.1° (neat).

2-Heptafluorobutanoyl-(+)-cholest-4-en-2-one As the lithium salt of the ketone precipitated at −60°C, dry tetrahydrofuran was added to the reaction mixture[18]. The reaction mixture was extracted with ethyl acetate. Chromatography on silica gel with dichloromethane–light petroleum (b.p. 60–90°C) (2:3, v/v). Yield: 36%.

General procedure for nickel(II) bis[3-(heptafluorobutanoyl)terpeneketonates]1–12

The nickel bis chelates were prepared via the corresponding sodium salts of the β-diketonates[15]:

Sodium (heptafluorobutanoyl)terpeneketonates

In a nitrogen atmosphere, *ca.* 0.3 g of a sodium hydride suspension in paraffin (80%, w/w) were freed from paraffin by repeatedly washing with dry toluene. The sodium hydride (0.24 g, 10 mmol) was suspended in toluene and transferred to a Schlenk tube. The β-diketone (7 mmol) was dissolved in toluene and added dropwise to the suspension (evolution of hydrogen!). After stirring for 2 h, the excess of sodium hydride was removed by filtration or decanting and was repeatedly washed with solvent. The pooled filtrates were concentrated *in vacuo*. The resulting glassy products (yield: 80–95%) were dried in an high vacuum and were employed without further purification.

Nickel(II) bis[3-(heptafluorobutanoyl)terpeneketonates] 1–12

Stoichiometric amounts of the sodium β-diketonate and nickel(II) dichloride hexahydrate were dissolved in ethanol, and the mixture was refluxed for 1 h. The sodium chloride formed was filtered off and the green solution was concentrated *in vacuo*. Further purification was carried out with accompanying loss of product by sublimation at 150–200°C at high vacuum (0.01 Torr). Yield: 30–80% of a green solid, soluble in most organic solvents.

Nickel(II) bis[3-(heptafluorobutanoyl)-(1R)-camphorate] **1**. $[\alpha]_D^{20}$ + 129.3° (*c*

0.7, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 754(46), 753(35), 752(100), 724(79), 696(24).

Nickel(II) bis[(heptafluorobutanoyl)-(1R)-campholylmethanate] **2**. Mass spectrum [*m/e* (rel. int.)]: 784(42), 765(4), 701(12), 504(17), 420(100), 125(46).

Nickel(II) bis[4-(heptafluorobutanoyl)-(1R,2R)-pinan-3-onate] **3**. $[\alpha]_D^{20}$ +86.6° (*c* 0.2, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 752(46), 737(16), 709(62), 404(100), 333(55), 305(10).

Nickel(II) bis[3-(heptafluorobutanoyl)-(1R,2S)-pinan-4-onate] **4**. $[\alpha]_D^{20}$ +4.3° (*c* 0.23, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 752(2), 709(2), 404(2), 333(8), 305(100), 265(19), 177(21), 149(63), 83(81).

Nickel(II) bis[2-(heptafluorobutanoyl)-(1S,4R)-thujan-3-onate] **5**. Field desorption mass spectrum: base peak *m/e* = 753.

Nickel(II) bis([2-heptafluorobutanoyl)-(1S)-4-methylthujan-3-one] **6**. $[\alpha]_D^{20}$ −92.1° (*c* 0.37, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 781(18), 481(17), 346(42), 331(47), 69(100).

Nickel(II) bis[3-(heptafluorobutanoyl)-(R)-nopinonate] **7**. $[\alpha]_D^{20}$ −51° (*c* 0.47, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 724(100), 709(17), 682(55), 390(91), 362(42), 348(42).

Nickel(II) bis[5-(heptafluorobutanoyl)-(S)-carvonate] **8**. $[\alpha]_D^{20}$ +400° (*c* 0.6, $CHCl_3$). Mass spectrum [*m/e* (ref. int.)]: 748(85), 707(100), 665(18), 551(26), 403(23), 346(18).

Nickel(II) bis[2-(heptafluorobutanoyl)-(1R)-menthonate] **9**. $[\alpha]_D^{20}$ −28.0° (*c* 0.4, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 756(13), 741(40), 406(5), 350(20), 55(100).

Nickel(II) bis[6-(heptafluorobutanoyl)-(R)-pulegone] **10**. $[\alpha]_D^{20}$ −25.9° (*c* 0.15, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 752(23), 737(10), 404(30), 348(16), 149(100).

Nickel(II) bis[2-heptafluorobutanoyl)-(1R)-isomenthonate] **11**. $[\alpha]_D^{20}$ −110.2° (*c* 0.4, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 756(44), 406(4), 350(28), 55(100).

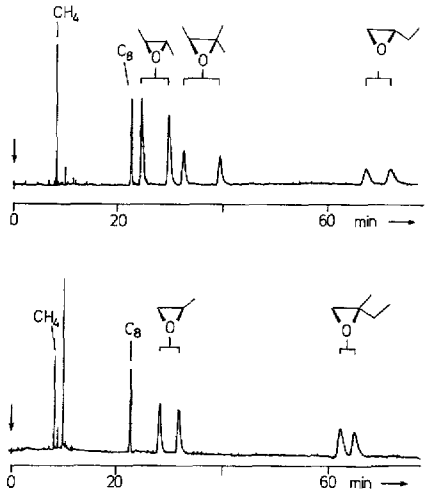


Fig. 1. Enantiomer separation of racemic oxiranes on nickel(II) bis[3-(heptafluorobutanoyl)-(1*R*)-camphorate] (0.1 *m* in squalane) at 60°C by complexation GC. Nickel open-tubular column, 100 m × 0.5 mm I.D.; 2.5 ml/min N_2 (0.55 bar). Reference standard: *n*-octane. Lower chromatogram: methyloxirane; 2,2-ethylmethyloxirane. Upper chromatogram: *trans*-2,3-dimethyloxirane; trimethyloxirane; ethyloxirane.

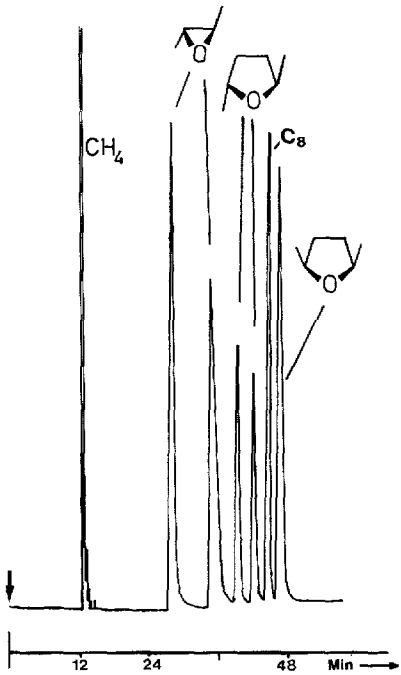


Fig. 2. Enantiomer separation of α,α'-dimethyl-substituted cyclic ethers on nickel(II) bis[3-(heptafluorobutanoyl)-(1*R*)-camphorate] (0.1 *m* in squalane) at 60°C by complexation GC. Nickel open-tubular column, 75 m × 0.5 mm I.D.; 0.8 bar N_2. Elution order: methane; enantiomers of *trans*-2,3-dimethyloxirane; enantiomers of *trans*-2,5-dimethyltetrahydrofuran; *n*-octane (reference standard) and *cis*-2,5-dimethyltetrahydrofuran (achiral).

Nickel(II) bis[2-heptafluorobutanoyl)-(+)-cholest-4-en-2-onate] **12**. $[\alpha]_D^{20}$ −108.7° (*c* 0.46, $CHCl_3$). Mass spectrum [*m/e* (rel. int.)]: 1216(5), 580(12), 281(35), 207(22), 57(100).

RESULTS AND DISCUSSION

Enantiomer separation of racemic alkyl-substituted cyclic ethers on metal(II) bis[3-(perfluoroacyl)-(1*R*)-camphorates] **1** (*cf.*, representative chromatograms in Figs. 1 and 2) has previously been examined by variation (i) of the central metal ion, *i.e.*, manganese(II), cobalt(II) and nickel(II)[15], and (ii) of the 3-perfluoroacyl residue, *i.e.*, –C(O)R, with R = CF_3, *n*-C_3F_7, *n*-C_7F_{15} and C_6F_5[19]. These studies revealed that the solute–solvent interaction, $-\Delta G°$, and the observed enantioselectivity, $-\Delta_{R,S}(\Delta G°)$, are greatly dependent on the composition of compound **1**. Thus, while the acceptor properties of the metal ion in **1** toward cyclic ethers increases markedly in the order manganese(II) < cobalt(II) ≪ nickel(II) spanning a factor up to 50, no such dramatic effect was noted in the observed enantioselectivity. Strong donor–acceptor interactions, as found for nickel(II), are not a prerequisite for efficient enantiomer discrimination. This is confirmed by the observation that, *e.g.*, isopropyloxirane is not separated by nickel(II) bis[3-(heptafluorobutanoyl)-(1*R*)-camphorate] but is quantitatively resolved by the weakly coordinating manganese(II) bis[3-(heptafluorobuta-

noyl)-(1*R*)-camphorate[6,15]. Lengthening the perfluoroalkyl side chain in **1** [M = manganese(II)] leads to a pronounced increase in enantiomer discrimination when going from R = CF_3 to *n*-C_3F_7 without further improvement when going to *n*-C_7F_{15}.

Preliminary screenings showed that the composition of the metal bis chelates markedly determined the strength of the donor–acceptor interaction as well as the observed enantioselectivity. Since the extent of coordination may sometimes be quite low, we used the strong acceptor, nickel(II), as the central metal ion. Furthermore, in the present study, all terpeneketones were converted into β-diketones via heptafluorobutanoyl acylation (R = C_3F_7).

In Scheme 2, *constitutional formulae* of the nickel(II) bis[α-(heptafluorobutanoyl)terpene ketonates] **1–12**, which have been prepared and investigated as chiral stationary phases for enantiomer separation of alkyl-substituted cyclic ethers, are depicted. The structural elements selected in the present study involve: (i) bicyclic terpene moieties, rigidly fused with the metal chelate ring, *i.e.*, [CAM], [NOP], [3-PIN], [4-PIN], [THU] and [Me-THU]; (ii) monocyclic terpene moieties, rigidly fused with the metal chelate ring, *i.e.*, [MEN], [i-MEN], [PUL], [CARV], [CHOL] and (iii) a monocyclic terpene moiety, non-rigidly attached to the metal chelate ring, *i.e.*, [open-CAM].

In Scheme 3 *configurational formulae* of the nickel(II) bis[α-(heptafluorobutanoyl)terpeneketonates] **1–12**, prepared from terpeneketones of specified configuration and high enantiomeric purity, are shown for comparison.

Enantiomer separation by complexation GC can be used as a versatile tool for the determination of thermodynamic parameters for chiral recognition. The GC enantiomer separation of racemic Lewis base solutes on chiral non-racemic Lewis acid metal coordination compounds requires (i) that the stabilities of the diastereomeric donor–acceptor association complexes are different, (ii) that complex formation is reversible and (iii) that the equilibrium is established rapidly, with respect to the GC time-scale.

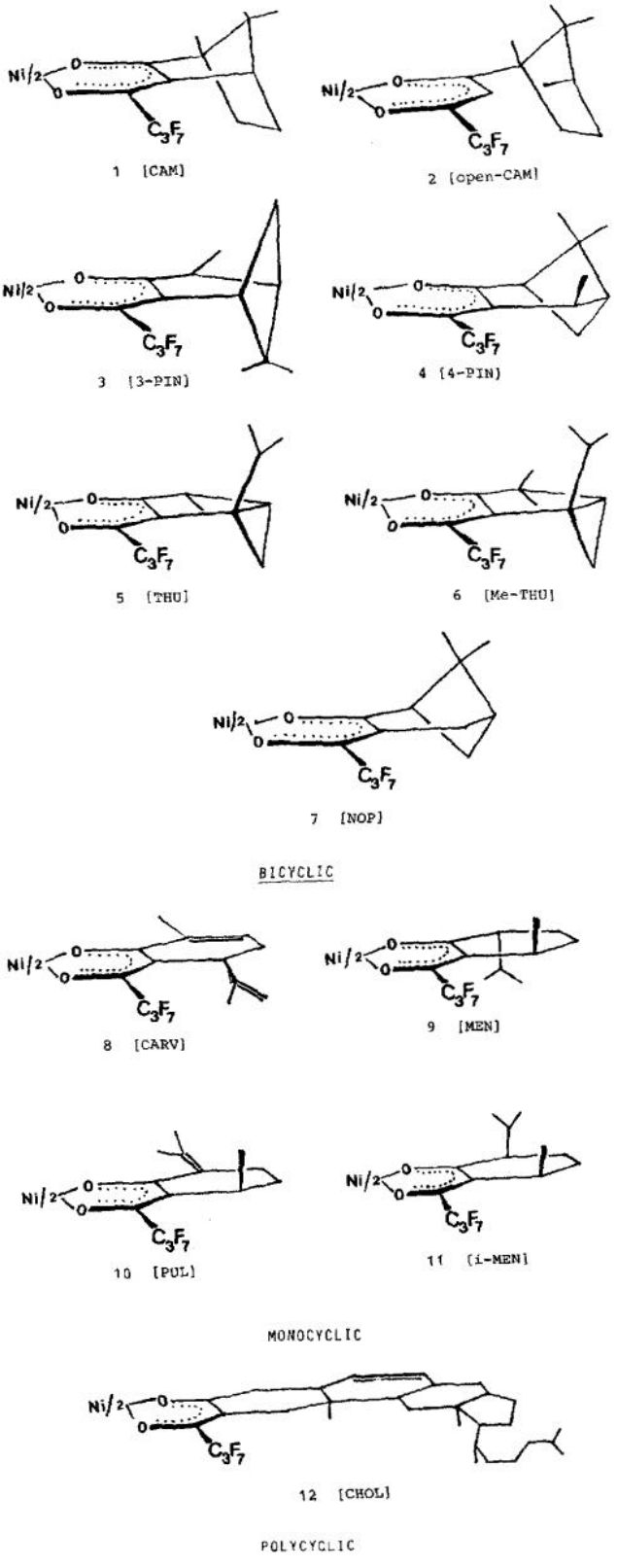
While the chemical interaction between the solute and the solvent is expressed by the association constant, K, or the free enthalpy of association, $-\Delta G^\circ$, the difference in $-\Delta G^\circ$ for a pair of enantiomers, $-\Delta_{R,S}(\Delta G^\circ)$ (*R* and *S* denote oppositely configurated enantiomers), represents a thermodynamic quantity for enantiomer discrimination.

It has previously been shown that thermodynamic data describing chiral recognition may readily be obtained from relative retention data by complexation GC[15]. Thus, when a Lewis base B is chromatographed on a stationary phase containing the solution of a Lewis acid A, *e.g.*, a metal coordination compound in an inert solvent, *e.g.*, squalane, the retention of B is not only dependent on the physical partition equilibrium between the gaseous and liquid phases but is also determined by the reversible and rapid chemical association equilibrium in the liquid phase

$$A + B \rightleftharpoons AB$$

leading to a retention increase, R'. The latter is related to the association constant, K, and to the activity of A in S, a_A, by the linear relationship[13,14]

$$K \cdot a_A = \frac{r - r_0}{r_0} = R' \qquad (1)$$



Scheme 3. Configurational formulae of nickel(II) bis[α-(heptafluorobutanoyl)terpeneketonates] **1–12**

R' can be calculated from the readily accessible relative retention data, r_0 and r, where r = relative adjusted (= corrected for the dead-volume of the column) retention of B with respect to an inert reference standard, not interacting with A, on a column containing the activity a_A in S, and r_0 = relative adjusted retention of B with respect to the inert reference standard on a reference column containing the pure solvent, S.

With

$$K = a_{AB}/a_A a_B \tag{2}$$

it follows from eqn. 1 that the retention increase, R', defines the activity fraction of the complexed *vs.* uncomplexed solute B in the liquid phase (A in S), *i.e.*:

$$R' = a_{AB}/a_B \tag{3}$$

Because only a trace of solute B (approximately 10^{-8} g) as well as dilute solutions of A in S (0.05–0.1 *m*; note that the molality concentration scale is chosen because *m* is temperature independent and the weight rather than the volume of S is determined for practical purposes) are used in complexation GC, eqns. 1 and 3 can be simplified to:

$$K_{(m)} m_A = \frac{r - r_0}{r_0} = \frac{m_{AB}}{m_B} = R' \tag{4}$$

K and $-\Delta G^\circ$, and, by measurements at different temperatures, the corresponding Gibbs–Helmholtz parameters $-\Delta H^\circ$ and ΔS°, can be obtained from eqn. 4. When R' is distinct for a pair of enantiomers on a chiral metal chelate A, peak separation will occur according to eqns. 5 and 6:

$$\frac{R'_R}{R'_S} = \frac{K_R}{K_S} = \frac{r_R - r_0}{r_S - r_0} \tag{5}$$

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

Thus, the thermodynamic quantities for enantiomer discrimination, $-\Delta_{R,S}(\Delta G^\circ)$, and, by measurements at different temperatures, the corresponding Gibbs–Helmholtz parameters, $\Delta_{R,S}(\Delta H^\circ)$ and $\Delta_{R,S}(\Delta S^\circ)$, are accessible from the differences in the retention increases, R', of the enantiomers. Note that r_0 is alike for enantiomers and that the concentration of the metal bis chelate, m_A, does not need to be known, eliminating possible errors in $-\Delta_{R,S}(\Delta G^\circ)$.

In the present investigations, as well as in previous studies, the retention increase, R', rather than K or $-\Delta G^\circ$, is consulted as criterion for the solute–solvent association, because this quantity is not biased by errors in m_A. It should be noted that the validity of eqn. 4 as well as the high precision of $-\Delta_{R,S}(\Delta G^\circ)$ have previously been verified in an investigation of four racemic alkyl-substituted oxiranes at five concentrations of manganese(II) bis[3-(heptafluorobutanoyl)-(1*R*)-camphorate] in squalane (m = 0.05–0.15)[6].

The ratio R'_R/R'_S of a solute depends on the enantiomeric composition (enantiomeric excess, ee) of the solvent. In the present study, $-\Delta_{R,S}(\Delta G^\circ)$ always refers to enantiomer discrimination caused by an enantiomerically pure (ee = >99%) nickel(II) bis chelate. When the metal bis chelate was not obtained in an enantiomerically pure form, *e.g.*, [3-PIN] and [4-PIN], the relative retention, r_{ee} (measured with the metal bis chelate of given ee), was extrapolated to r_{100} (corresponding to ee = 100%) via eqns. 7 and 8[22]:

$$r_{R100} = \frac{1}{2}(r_{Ree} + r_{See}) + \frac{50}{ee}(r_{Ree} - r_{See}) \tag{7}$$

$$r_{S100} = \frac{1}{2}(r_{Ree} + t_{See}) - \frac{50}{ee}(r_{Ree} - r_{See}) \tag{8}$$

with

$$ee(\%) = \frac{R - S}{R + S} \cdot 100 \tag{9}$$

Note that in eqns. 7 and 8, for ee $\rightarrow$ 0, $r_R - r_S \rightarrow 0$.

The solute–solvent association equilibria between two achiral and fifteen chiral alkyl-substituted cyclic ethers and twelve non-racemic nickel(II) bis[α-(heptafluorobutanoyl)terpeneketonates] **1–12** in squalane have been measured at 60°C. The results are shown in the table. Listed therein are the retention increases, R', for the respective enantiomers and the measure of enantioselectivity, $-\Delta_{R,S}(\Delta G^\circ)$, derived therefrom. The elution order of the individual enantiomers is also reported.

According to eqn. 1, both K and $-\Delta G^\circ$ can be calculated from R' from a knowledge of the concentration of the solvent in squalane at the very moment of the measurement. Due to uncertainties, such as partial insolubility and decomposition of the metal bis chelate as well as losses of stationary phase during the GC experiment, absolute values of R', K and $-\Delta G^\circ$ may involve an unacceptable systematic error. However, the relative comparison of the quantities $RT \cdot \ln(R_R/R'_S) = RT \cdot \ln(K_R/K_S) = -\Delta_{R,S}(\Delta G^\circ)$ becomes independent of the concentration of the solvent when the screening of the solutes is performed at the same time or in very close succession. It is important to note that $-\Delta_{R,S}(\Delta G^\circ)$ for each individual solute is not affected by errors in m, since enantiomer separation is the result of a single chromatographic experiment. Nevertheless, the magnitude of the absolute retention increase, R', will also be considered in order to allow the distinction between (i) the ability of the solutes to undergo association with the solvent, as expressed by R', K and $-\Delta G^\circ$, on the one hand, and (ii) the extent to which the association equilibria differ for a pair of enantiomers, as expressed by $-\Delta_{R,S}(\Delta G^\circ)$, on the other hand. It has already been demonstrated[6,15,19] that the intuitive assumption that a strong donor–acceptor interaction is a necessary requirement for efficient enantiomer discrimination is incorrect and that small interactions may cause high "chiral recognition factors", $\chi = -\Delta_{R,S}(\Delta G^\circ)/-\Delta G^\circ$.

TABLE I

RETENTION INCREASE, R', AND $\Delta_{R,S}(\Delta G°)$ FOR CYCLIC ETHERS AND **1–12** AT 60°C

First row: R'[a] and elution order of enantiomers *R,S*. Second row: $\Delta_{R,S}(\Delta G°)$.

Solute	*[CAM]* **1**		*[open-CAM]* **2**		*[3-PIN]* **3**		*[4-PIN]* **4**		*[THU]* **5**	
Methyloxirane	53.40 (*R*) 63.88 (*S*)	0.12	20.46 (*R*) 25.22 (*S*)	0.14	9.24 [b]		10.46 (*R*) 13.51 (*S*)	0.16	49.24 (*S*) 63.39 (*R*)	0.17
Ethyloxirane	54.46 (*R*) 59.00 (*S*)	0.05	16.03 (*R*) 19.46 (*S*)	0.13	9.09 (*R*) 11.04 (*S*)	0.13	12.06 (*R*) 20.76 (*S*)	0.36	37.06 (*S*) 40.85 (*R*)	0.07
Isopropyloxirane	56.74 [b]	[c]	15.35 [b]	[c]	10.29 (*R*) 11.92 (*S*)	0.10	11.98 (*R*) 24.45 (*S*)	0.48	47.76 (*S*) 56.64 (*R*)	0.08
erythro-sec.-Butyloxirane	[b]		[b]		[b]		[b]		[b]	
threo-sec.-Butyloxirane	[b]		[b]		[b]		[b]		[b]	
tert.-Butyloxirane	38.70 (*R*) 43.43 (*S*)	0.08	14.81 (*R*) 17.48 (*S*)	0.11	7.21 [b]	[c]	13.41 (*R*) 24.61 (*S*)	0.40	26.80 (*S*) 29.87 (*R*)	0.07
2,2-Ethylmethyloxirane	35.01 (*S*) 36.56 (*R*)	0.03	13.64 [b]	[c]	4.30 [b]	[c]	6.92 [b] 10.07 [b]	0.25	29.65 [b] 33.76 [b]	0.09
trans-2,3,Dimethyloxirane	22.47 (2*R*) 30.25 (2*S*)	0.20	16.22 (2*R*) 24.14 (2*S*)	0.26	5.18 (2*R*) 6.64 (2*S*)	0.16	6.22 (2*R*) 11.36 (2*S*)	0.40	33.03 (2*S*) 55.25 (2*R*)	0.35
cis-2,3-Dimethyloxirane	112.6		22.33		23.79		29.00		20.88	
trans-2-Ethyl-3-methyloxirane	7.79 (2*R*) 9.32 (2*S*)	0.12	8.49 [b] 12.69 [b]	0.26	3.90 [b] 5.43 [b]	0.22	5.94 [b] 12.50 [b]	0.49	26.13 [b] 39.89 [b]	0.28
cis-2-Ethyl-3-methyloxirane	42.54 (2*R*) 45.46 (2*S*)	0.05	39.87 [b] 40.74 [b]	0.01	22.01 [b]	[c]	28.03 [b] 32.54 [b]	0.10	11.77 [b]	[c]
2,2,3-Trimethyloxirane	19.00 (3*R*) 24.89 (3*S*)	0.18	15.85 (3*R*) 26.42 (3*S*)	0.34	4.28 (3*R*) 5.05 (3*S*)	0.11	4.97 (3*R*) 6.42 (3*S*)	0.17	25.77 (3*S*) 42.31 (3*R*)	0.33
2-Methyloxetane	[d]		[d]		34.44 [b] 67.60 [b]	0.45	42.53 [b] 87.82 [b]	0.48	[d]	
2-Methyltetrahydrofuran	56.63 (*S*) 60.33 (*R*)	0.04	8.16 [b] 8.57 [b]	0.03	8.44 [b] 13.14 [b]	0.30	20.89 [b] 29.60 [b]	0.23	60.4 [b] 101.4 [b]	0.35
trans-2,5-Dimethyltetrahydrofuran	2.25 [b] 2.64 [b]	0.10	1.28 [b] 1.50 [b]	0.11	0.22 [b] 0.64 [b]	0.70	0.69 [b] 2.42 [b]	0.83	1.78 [b] 2.39 [b]	0.20
cis-2,5-Dimethyltetrahydrofuran	6.21		2.29		2.35		9.50		11.54	
2-Methyltetrahydropyran	13.84 (*S*) 14.47 (*R*)	0.03	0.45	[c]	0.22 [b] 0.31 [b]	0.22	0.47 [b] 0.77 [b]	0.32	2.54 [b] 3.21 [b]	0.15

[a] Measured at, or extrapolated to, 0.1 *m* (molality) solvent in squalane. Extrapolated to ee = 100%, if necessary.

[b] Not measured.

[c] No separation detectable.

[d] Exceedingly high retention.

[Me-THU] **6**	*[NOP]* **7**	*[CARV]* **8**	*[MEN]* **9**	*[PUL]* **10**	*[i-MEN]* **11**	*[CHOL]* **12**
8.73 (*S*) 14.35 (*R*) 0.33	2.69 [c]	1.97 (*S*) 2.17 (*R*) 0.06	1.76 [c]	0.44 (*S*) 0.64 (*R*) 0.25	1.71 (*S*) 2.39 (*R*) 0.22	1.56 [c]
9.56 (*S*) 15.83 (*R*) 0.33	3.11 [c]	1.81 (*S*) 2.76 (*R*) 0.28	1.63 [c]	0.41 (*S*) 0.55 (*R*) 0.20	1.28 (*S*) 2.27 (*R*) 0.38	1.82 [c]
8.90 (*S*) 14.49 (*R*) 0.32	3.42 (*R*) 3.72 (*S*) 0.06	1.58 (*S*) 2.79 (*R*) 0.38	1.10 [c]	0.38 (*S*) 0.45 (*R*) 0.11	0.72 (*S*) 1.73 (*R*) 0.58	1.39 [c]
5.33 (2*R*) 7.45 (2*S*) 0.22	2.81 (2*R*) 3.48 (2*S*) 0.14	1.28 (2*S*) 2.10 (2*R*) 0.33	0.89 [c]	1.82 [b] 1.89 [b] 0.03	0.57 [b] 0.89 [b] 0.03	1.13 [c]
9.71 (2*R*) 16.44 (2*S*) 0.35	3.51 (2*R*) 4.07 (2*S*) 0.10	1.80 (2*S*) 3.54 (2*R*) 0.45	1.13 [c]	1.89 [b] 2.03 [b] 0.05	0.78 [b] 2.06 [b] 0.64	1.32 [c]
4.97 (*R*) 7.60 (*S*) 0.28	2.85 (*R*) 3.37 (*S*) 0.11	1.09 (*S*) 1.68 (*R*) 0.29	0.65 (*R*) 0.72 (*S*) 0.07	0.24 (*R*) 0.35 (*S*) 0.26	0.42 (*S*) 0.93 (*R*) 0.52	1.12 [c]
4.69 (*R*) 5.92 (*S*) 0.15	2.24 (2*S*) 2.72 (2*R*) 0.13	0.66 [b] 0.74 [b] 0.08	0.42 [b] 0.43 [b] 0.02	0.13 [c]	0.31 [c]	0.53 [c]
4.45 (2*S*) 6.78 (2*R*) 0.28	2.11 (2*R*) 2.41 (2*S*) 0.09	0.85 (2*S*) 1.04 (2*R*) 0.13	0.41 (2*S*) 0.60 (2*R*) 0.26	0.15 (2*S*) 0.33 (2*R*) 0.51	0.49 (2*S*) 1.23 (2*R*) 0.62	0.66 [c]
11.68	7.23	2.59	3.56	0.66	1.63	3.67
3.30 (2*S*) 4.32 (2*R*) 0.18	2.06 (2*R*) 2.18 (2*S*) 0.04	0.60 [b] 0.77 [b] 0.17	0.26 (2*S*) 0.34 (2*R*) 0.18	0.10 [b] 0.18 [b] 0.34	0.31 (2*S*) 0.80 (2*R*) 0.61	0.54 [c]
11.02 (2*R*) 11.28 (2*S*) 0.02	7.87 (2*R*) 8.25 (2*S*) 0.03	2.70 [b] 2.79 [b] 0.02	2.51 [b] 2.60 [b] 0.02	0.55 [c]	1.42 (2*S*) 1.61 (2*R*) 0.08	3.60 [c]
3.49 (3*S*) 3.72 (3*R*) 0.04	2.42 (3*S*) 2.59 (3*R*) 0.04	0.73 [c]	0.38 [b] 0.46 [b] 0.13	0.15 [c]	0.46 [c]	0.92 [c]
89.6 (*S*) 147.3 (*R*) 0.33	47.5 (*S*) 70.8 (*R*) 0.26	21.4 (*S*) 28.0 (*R*) 0.18	9.50 (*S*) 14.25 (*R*) 0.27	2.27 (*S*) 2.74 (*R*) 0.12	7.58 (*S*) 10.53 (*R*) 0.22	16.53 [c]
6.70 (*S*) 6.93 0.02	7.82 (*R*) 10.55 (*S*) 0.20	2.09 [b] 2.22 [b] 0.04	0.77 (*S*) 1.08 (*R*) 0.22	0.23 [c]	0.67 [c]	2.20 [c]
[b]	[b]	[b]	[b]	[b]	[b]	[b]
[b]	[b]	[b]	[b]	[b]	[b]	[b]
0.42 [c]	0.27 [c]	0.15 [c]	0.05 [c]	0.03 [c]	0.06 [c]	0.14 (*S*) 0.17 (*R*) 0.12

Selectivity of solute–solvent association (horizontal comparison)

The interaction between cyclic ethers and the nickel bis chelates **1–12** show remarkable differences. As shown for methyloxirane, the interaction with **1–12**, when normalized to $m = 0.1$ mol/kg, decreases in the order:

[CAM] > [THU] > [open-CAM] > [4-PIN] > [3-PIN] > [Me-THU] >

[NOP] > [CARV] > [CHOL] > [MEN] > [i-MEN] > [PUL]

Despite the dramatic differences in donor–acceptor association, whereby [CAM] shows the strongest and [PUL] the weakest coordination of methyloxirane, respectively, the measure for chiral recognition, $-\Delta_{R,S}(\Delta G^\circ)$, differs only by a factor of 2 from the weakly interacting [PUL], including an higher enantiomer discrimination than that of [CAM]. This result is also of practical interest, because efficient enantiomer separation already caused by a rather weak solute–solvent interaction permits rapid enantiomer analyses via short retention times. In general, the nickel bis chelates containing bicyclic terpene moieties exhibit much stronger acceptor properties than those containing monocyclic terpene structures. While the decrease in interaction by a factor of 10 upon going from [THU] to [Me-THU] may be rationalized by steric arguments, the reverse situation, *i.e.* , the increase of interaction when going from [NOP] to [Me-NOP = 4-PIN] is difficult to comprehend. It should be mentioned that any interpretation of the selectivity of association between a single solute with different solvents (horizontal comparison) can only be very tentative, because the nickel bis chelates may possess different molecular structures, such as coordination geometries and/or different states of self-association, etc. (*vide infra*).

Selectivity of solute–solvent association (vertical comparison)

The vertical comparison of the retention increase, R', between cyclic ethers, differing in alkyl substitution, E/Z geometry and ring size, with one particular nickel bis chelate **1–12** directly reveals steric, electronic and any strain effects of the solute–solvent association. For studying these effects [CHOL] is a useful test compound, because the retention increase, R', is identical for both enantiomers, $-\Delta_{R,S}(\Delta G^\circ) = 0$.

The effect of alkyl substitution at the α-carbon atom of cyclic ethers on the donor–acceptor association equilibrium is thought to arise mainly from electronic and steric factors. Unfortunately, these contributions to association selectivity cannot readily be separated from each other. Moreover, the electronic and steric effects of alkyl groups will oppose each other, because the +I-effect of the alkyl substituent tends to increase the donor properties of the lone pairs of oxygen and will be counterbalanced by steric hindrance, created by bulky alkyl groups. Thus, the donor–acceptor association of monoalkyl-substituted oxiranes with [CHOL] slightly increases upon going from methyl- to ethyloxirane and then steadily decreases with increasing steric hindrance, whereby interestingly the configuration of the *sec*-butyl group shows a remarkable steric effect. Introduction of a second alkyl group in a geminal- or *trans*-position leads to a strong steric destabilization of association, because one alkyl group is disposed in a position *syn* to the coordinating lone pair of oxygen. Contrarily, *cis*-dialkyl substitution entails an increase in interaction compared to monoalkyl substitution, and this is clearly due to an electronic effect, because the alkyl substituents may adopt a position *anti* to the lone pair of oxygen. As might have been expected, the trialkyl-substituted oxirane (trimethyloxirane) shows an association behaviour intermediate between those of *cis*- and *trans*-dialkyloxiranes. Allowing for some small individual changes owing to the compositional diversity of the solvents,

the general trend of association selectivity between oxiranes and [CHOL] is also observed for all other nickel bis chelates, regardless of the overall strength of the association equilibria. It follows then that the small degree to which this general trend fluctuates for the individual enantiomers of the solute determines the extent of chiral recognition caused by the solvent, as expressed by $-\Delta_{R,S}(\Delta G^{\circ})$ (*vide supra*).

An high selectivity of the association equilibria, differing by two orders of magnitude, is observed as the result of changing the ring size of α-methyl-substituted cyclic ethers. Thus, while methyloxirane and 2-methyltetrahydrofuran exhibit a comparable association strength with [CHOL], that of 2-methyloxetane is stronger by a factor of ten and that of 2-methyltetrahydropyran is weaker by approximately the same factor. This remarkable influence of ring size upon coordination with nickel bis chelates

$$\text{oxane} < \text{oxolane} \leqslant \text{oxirane} \ll \text{oxetane}$$

is evident for all solvents investigated and was previously discovered for [CAM][15]. The exceedingly strong interaction of oxetanes and nickel bis chelates may give rise to extreme retention times, preventing the acquisition of thermodynamic data for donor–acceptor association.

Enantioselectivity

While the donor–acceptor association selectivity between alkyl-substituted cyclic ethers and the nickel bis chelates **1–12** follows the same trend (vertical comparison), regardless of the strength of interaction (horizontal comparison), remarkable differences are observed for the individual enantiomers of the solute, as expressed by $-\Delta_{R,S}(\Delta G^{\circ})$. Thus, inspection of the table reveals that

$$[\text{CHOL}] \ll [\text{NOP}] < [\text{MEN}] < [\text{3-PIN}]$$

entail negligible chiral recognition, while

$$[\text{CARV}] < [\text{Me-THU}] < [\text{4-PIN}] < [\text{i-MEN}]$$

display the highest enantioselectivity for oxiranes. The largest figure for oxiranes, $-\Delta_{R,S}(\Delta G^{\circ}) = 0.60$–$0.65$ kcal/mol, has been observed with [i-MEN], while $-\Delta_{R,S}(\Delta G^{\circ}) = 0.83$ kcal/mol was found for *trans*-2,5-dimethyltetrahydrofuran and [4-PIN] at 60°C.

The unique molecular architectures displayed by the terpene backbones of the nickel bis chelates **1–12** offer interesting insights into trends of enantiomer discrimination.

Variation of conformational flexibility by formal opening of the chelate terpene fusion: [CAM] vs. [open-CAM]. This comparison shows that a rigid polycyclic structure is not a prerequisite for efficient chiral recognition. Quite unexpectedly, a slightly higher enantiomeric bias is observed for the conformationally flexible solvent [open-CAM]. A similar observation has been made by McCreary *et al.*[10] with europium(III) tris chelates containing ketoenolates related to [open-CAM] which

showed efficient chemical shift differences of enantiotopic protons by NMR spectroscopy.

Variation of ring size in the bicyclic terpene moiety: [CAM], [PIN] and [THU]. This comparison does not demonstrate any significant influence of strained rings in the terpene moiety on enantiomer discrimination.

Inversion of the bicyclic terpene moiety with respect to the metal chelate ring: [4-PIN] vs. [3-PIN]. This comparison reveals a remarkable difference of chiral recognition for bulky monoalkyl-substituted oxiranes, whereby [3-PIN] shows none or only negligible enantiodifferentiation, indicating that the position of the cyclobutane unit in pinanone, juxtaposed *syn* to the perfluoroalkyl residue, impairs enantiomer discrimination. No such effect is noted for cyclic ethers containing four-, five- and six-membered rings.

Increase in steric constraint by methyl substitution: [Me-THU] vs. [THU] and [4-PIN] vs. [NOP]. This comparison shows that methyl substitution of the terpene moiety significantly increases enantiomer discrimination for monoalkyl-substituted oxiranes. [NOP] exhibits consistently lower enantiodifferentiation as compared to [4-PIN]. However, the stronger enantioselectivity of [THU] as compared to [Me-THU] for trimethyloxirane and 2-methyltetrahydrofuran should be noted, stressing the complexity of chiral recognition phenomena in complexation GC.

Transformation of bicyclic to monocyclic terpene moieties by formal ring opening between C_1 and C_6: [3-PIN] vs. [CARV] and [4-PIN] vs. [i-MEN]. This comparison shows that solvents with monocyclic terpene moieties are as efficient as, and in some cases even superior to, their bicyclic counterparts with respect to enantiomer discrimination. This result implies again that steric rigidity is not a precondition for efficient chiral recognition.

Variation of the geometric relationship between the 1,4-dialkylcyclohexane substituents in monocyclic terpene moieties: [MEN] vs. [PUL] vs. [i-MEN]. This comparison should illuminate the effect of the position of the isoprop(en)yl group (*trans*, *cis*, planar) with respect to the methyl group at the carbon atom with fixed stereochemistry. For oxiranes, with the exception of trimethyloxirane, efficient enantiomer discrimination is found with [i-MEN] and to a lesser extent with [PUL] but not with [MEN], indicating a pronounced effect of the relative geometry of the 1,4-dialkylcyclohexane substituents on $-\Delta_{R,S}(\Delta G^\circ)$. With increasing bulk or ring size of the cyclic ethers, chiral recognition is induced also by [MEN]. As expected, [PUL], possessing a configuration between that of [MEN] and [i-MEN], exhibits also an enantiomer discrimination intermediate between those of these stereoisomers.

Inversion of the 1,4-dialkyl(idene)cyclohexane substituents in monocyclic terpene moieties: [PUL] vs. *[CARV].* This comparison should shed light on the rôle of an alkyl group juxtaposed *syn* to the perfluoroalkyl group. However, the results allow no clear-cut decision on the influence of steric bulk at the chiral centre of C_4, because either [CARV] or [PUL] shows a moderate chiral recognition effect for a particular solute. In keeping with the observations made with the series of solvents [i-MEN], [PUL] and [MEN], it can be predicted that [CARV] will entail an intermediate enantiomer discrimination as compared to either one of the nickel bis chelates obtained from α-heptafluorobutanoyl-carvomenthonate [CARVMEN] **13** and -iso-carvomenthonate [i-CARVMEN] **14**. Unfortunately, these terpene ketones are not readily accessible in epimerically and enantiomerically pure form.

Planarization through incorporation of unsaturation into the terpene moiety with concomitant π-orbital conjugation with the quasiaromatic metal chelate ring: [PUL] and [CARV]. The comparison of solvents containing an essentially planar conjugated π system, [CARV] and [PUL], with solvents containing bulky bicyclic terpene moieties, *e.g.*, [CAM] or [3-PIN], with regard to their ability to induce enantioselectivity towards alkyl-substituted cyclic ethers reiterates once again that chiral recognition may be brought about by rather simple molecular architectures.

Correlation between absolute configuration and order of elution

The correlation between the molecular configuration of the enantiomers of the solute and their relative order of elution from the solvent of defined chirality ought to give additional insight into the mechanisms of enantiomer discrimination by complexation GC. In this study, the absolute configuration of the enantiomeric fractions which are eluted as the first or second peak, respectively, for most cyclic ethers and the nickel(II) bis chelates **1–12** has been determined by simultaneous coinjection of enantiomers with known stereochemistry[18]. This study aimed at recognizing certain trends of chiral recognition between solutes belonging to a class of homologous compounds and solvents representing different constitutional (*cf.*, Scheme 1) and/or configurational (*cf.*, Scheme 2) compositions. It has previously been found that *S*-methyloxirane and (2*S*,3*S*)-2,3-dimethyloxirane exhibit a stronger interaction with nickel(II) bis[3-(heptafluorobutanoyl)-(1*R*)-camphorate] **1**, obtained from natural (+)-D-(1*R*)-camphor, and were therefore eluted as the second peak[23]. This observation led to the formulation of a quadrant rule, which empirically predicts the elution order of alkyl-substituted three-membered heterocycles from GC column, containing **1**, derived from (1*R*)-camphor.

Thus, when the heterocycle is viewed from the heteroatom X in the direction of the horizontal C–C bond, the absolute configuration of the enantiomer eluted as the second peak from (1*R*)-**1** (M = Ni) is that in which the bulkier group(s) is (are) situated on the upper left at C_1 and/or the lower right at C_2. Although in most cases the validity of the quadrant rule was confirmed, a number of exceptions were found when it was extended to other solvents or solutes with larger ring sizes[7,15].

Inconsistency of the quadrant rule may have its origin not only in structural requirements but also in the temperature-dependent reversal of enantioselectivity due to the inherent thermodynamics of chiral recognition which leads to a change of the sign of $\Delta_{R,S}(\Delta G^\circ)$ at the isoenantioselective temperature[16]. With this in mind, it is surprising to find that the elution order of cyclic ethers on all nickel bis chelates **1–12** shows a rather consistent trend, save for some exceptional cases, lending further support to the justification of formulating rules which correlate absolute configurations of the solute with its retention behaviour on metal bis chelates of predefined chirality in complexation GC. Inspection of Tables I and II shows that a consistent elution order for members of homologous solutes is observed on solvents that induce a large enantiomer discrimination, $-\Delta_{R,S}(\Delta G^\circ)$. The following discussion will focus on solvents that entail a strong enantiomer discrimination. It will be seen that an high degree of consistency between the molecular configuration and the elution order for mono-, di- and trialkyl-substituted oxiranes is observed (*cf.*, the table). The following trends are noteworthy.

Variation of conformational flexibility by formal opening of the chelate terpene

fusion: [(1R)-CAM] vs. [(1R)-open-CAM]. This comparison shows that opening of the camphor skeleton between C_3 and C_4 slightly improves the degree of enantiomer discrimination, but does not change its sign for monoalkyl-substituted oxiranes.

Increase of steric constraint and introduction or removal, respectively, of a new chiral centre by methyl substitution: [Me-THU] vs. [THU] and [4-PIN] vs. [NOP]. This comparison shows that methyl substitution, which either destroys or creates a chiral centre, has no influence on the sign of $\Delta_{R,S}(\Delta G^\circ)$, which is obviously governed by the chirality of the equivalent bicycle terpene skeleton. It should be noted that [THU] used in this study actually represented a mixture of epimers with regard to C_4 with an unknown molar ratio, and [Me-THU] may be thought to produce the same overall effect as a mixture of the epimeric [THU]s. The inverse retention behaviour of *trans*-2,3-dimethyloxirane on [4-PIN] *vs.* [NOP] is noteworthy, but insignificant, in view of the poor enantiomer discrimination of the latter.

Inversion of the bicyclic terpene moiety of equivalent stereochemistry with respect to the metal chelate ring: [4-PIN] vs. [3-PIN]. This comparison does not reveal any change in the sign of $\Delta_{R,S}(\Delta G^\circ)$, suggesting that the equivalent chirality of the positional isomers (1*R*,2*S*)-pinan-4-one and (1*R*,2*R*)-pinan-3-one determines the elution order for alkyl-substituted oxiranes, irrespective of their inverted fusion with the β-diketonate ring.

Transformation of bicyclic to monocyclic terpene moieties of equivalent stereochemistry by formal ring opening between C_1 and C_8: [4-PIN] vs. [i-MEN]. This comparison shows that formal ring opening of the bicyclic terpene moiety to the monocyclic terpene structure with the same chirality on the carbon atoms does not lead to an identical elution order for any of the solutes investigated.

Transformation of bicyclic to monocyclic terpene moieties of equivalent stereochemistry at the carbon atom carrying the isoprop(en)yl substituent: [Me-THU] and [THU] vs. [CARV]. This comparison indicates that the consistency of the elution order for mono-, *trans*-di and trisubstituted oxiranes as well as 2-methyloxetane is governed by the (equivalent) chirality of the carbon atom carrying the bulky isoprop(en)yl group, juxtaposed *syn* to the perfluoroalkyl group.

Inversion of the p-menthane moiety with equivalent stereochemistry at the carbon atom carrying the isoprop(en)yl substituent: [CARV] vs. [i-MEN]. This comparison indicates that the consistency of the elution order for mono-, *trans*-di and trisubstituted oxiranes, as well as 2-methyloxetane is governed by the (equivalent) chirality of the carbon atom carrying the bulky isoprop(en)yl group residing in different positions with respect to the perfluoroacyl group.

Variation of the geometric relationship between the 1,4-dialkylcyclohexane substituents in monocyclic terpene moieties, [MEN] vs. [PUL] vs. [i-MEN], and their inverted order: [PUL] vs. [CARV]. This comparison shows that changing the chirality of the carbon atom carrying the isopropyl group in [MEN] *vs.* [i-MEN] changes the elution order for *tert.*-butyloxirane but not for *trans*-2,3-dimethyloxirane and 2-methyloxetane. Having the bulky isopropylidene group in a planar position [PUL] causes a reversed elution order for *tert.*-butyloxirane compared to [i-MEN]. The identical elution orders for *trans*-2,3-dimethyloxirane and 2-methyloxetane on [i-MEN], [PUL] and [MEN] can be explained only by assuming that for these solutes the chirality carrying the methyl group juxtaposed *syn* to the perfluoroalkyl group is important in determining the sign of $\Delta_{R,S}(\Delta G^\circ)$, irrespective of the relative geometry of the bulky isopropyl(idene) group.

CONCLUSIONS

The results of this investigation may be summarized as follows:

The selectivity of the solute–solvent association (vertical comparison) between alkyl-substituted oxiranes and compounds **1–12** follows a common trend, which is rationalized in terms of opposing electronic and steric effects of the Lewis bases.

The origin of the striking influence of the ring size of cyclic ethers on the association strength with **1–12** which varies by two orders of magnitude, *i.e.* oxane < oxolane ⩽ oxirane ⩽ oxetane remains elusive.

There is no clear-cut relationship between the strength of solute–solvent association and the magnitude of enantiomer discrimination, *i.e.*, the chiral recognition factor, $\chi = -\Delta_{R,S}(\Delta G^\circ)/-\Delta G^\circ$. varies at random, although, in general, enantioselectivity is high when the donor–acceptor interaction is impaired on steric grounds.

For chiral alkyl-substituted oxiranes, a consistent relationship between molecular configuration and the order of elution is observed for almost all solvents **1–12**. The reliability of empirical rules that correlate configuration and peak emergence improves as the propensity of the solvent to induce enantiomer discrimination increases.

The magnitude and the sign of enantioselectivity, $-\Delta_{R,S}(\Delta G^\circ)$, between alkyl-substituted cyclic ethers and **1–12** can neither be predicted nor rationalized by simple molecular models, owing to the complexity of the nature of the solvent under the conditions of the GC experiment.

The present study has revealed improved chiral stationary phases for the enantiomer separation of alkyl-substituted cyclic ethers. The highest enantiomeric bias of solvents with a bicyclic terpene structure is induced by [4-PIN] and of those with a monocyclic terpene structure by [CARV].

The preparation of the solvents **1–12** possessing interesting molecular architectures will stimulate further investigations of enantiomer separation of other classes of compounds by complexation GC and by substitution of nickel(II) by lanthanide(III) ions may complement[11] the arsenal of chiral lanthanide shift reagents for the NMR spectroscopic discrimination of enantiotopic nuclei.

While the conditions of the use of the solvents **1–12** were chosen to obtain reliable thermodynamic data for solute–solvent association, the employment for practical purposes of high-resolution glass and fused-silica columns as well as polysiloxanes as co-solvents for **1–12**[6,24] has greatly improved the state of the art of enantiomer separation by complexation GC and various applications have been reported[4,7,8]. Thus, [NOP] and [4-PIN] have been used as versatile solvents for the enantiomer separation of diols as their acetonides or *n*-butylboronates[25], and [PUL] has been employed, *inter alia*, for the enantiomer separation of the pheromone chalcogran (2-ethyl-1,6-dioxaspiro[4.4]nonane)[26] and [Me-THU] for that of the pheromone of the olive fly, 1,7-dioxaspiro[5.5]undecane[27]. Finally, [CARV] has recently been employed as a versatile stationary phase for the first semipreparative enantiomer separation of spiroketals by complexation GC[28].

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