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Academic Dissertation
for the Degree of
Doctor of Philosophy

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List of Original Publications

Häkli, H., Mannschreck, A.: Column Chromatography on Triacetylcellulose. Preparative Separation of Enantiomeric Diaziridines. Angew. Chem. Int. Ed. Engl. 16 (1977) N:o 6, 405-406 https://doi.org/10.1002/anie.197704051

Häkli, H., Mintas, M., Mannschreck, A.: Proton Magnetic Resonance Investigation of Inversion at Tervalent Nitrogen, 6. Preparative Separations of Enantiomeric Diaziridines by Liquid Chromatography on Triacetylcellulose. Racemizations Monitored by Polarimetry and by 1H NMR. Chem. Ber. 112, (1979), 2028-2038
https://doi.org/10.1002/cber.19791120613

Korvola, J., Häkli, H. and Paasivirta, J.: The Stereochemistry of the Catalytic Deuterization of Norbonene Compounds. III. Reaction of Dehydronorcamphor. Finn. Chem. Lett. (1974), 16-18

Paasivirta, J., Häkli, H.: Chemical Shift Reagents in the Study of Polycyclic Alcohols.X.* Structure Proof of 5,5-Dimethyl-6-Methylenenorbornan-2-exo-ol. Finn. Chem. Lett. 1974, 165-167

Paasivirta, J., Häkli, H., Widen, K.-G.: Chemical Shift Reagents in the Study of Polycyclic Alcohols IX*—1H NMR Spectraof Myrtenol and Some Other Primary Alcohols. Organic Magnetic Resonance Volume 6, Issue 7 (1974), 380-383
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CONTENTS

I INTRODUCTION

Nuclear magnetic resonance spectroscopy has undergone many improvements in the past thirty years since the first detection of NMR-signals. The literature in the field contains thousands of publications, which handle theoretical, instrumental and experimental aspects. Up to the present time it has been possible to improve the instruments from many points of view, such as high resolution magnets, field-to-frequency lock systems and signal averaging computers. Superconducting magnets, various double resonance techniques and pulsed Fourier transform NMR have been developed.

An important parameter in NMR-spectroscopy is the chemical shift, which depends on the frequency of the magnet. The proton chemical shifts are relatively unsensitive to changes in the environment. As a result many resonances in the ^{1}H NMR spectra of complex molecules overlap extensively rendering the evaluation of chemical shifts and coupling constants difficult. Possible means to achieve a spectral simplification are solvent-induced shifts, spin decoupling, isotopic substitution and higher frequency. One alternative to the above is to run the spectrum of the sample in the presence of a

paramagnetic shift reagent.[1] The use of paramagnetic species as a shift reagent depends on its ability to associate with the molecule under study and thereby bring the molecule under the influence of a strong local magnetic field. Thus, the role of an efficient shift reagent is to increase the chemical shifts between different nuclei without remarkably affecting coupling constants and broadening the lines. In favourable cases a complicated spectrum can be turned into a simple one which can be solved with first-order analysis. A good example of the action of the shift reagent is an application to the ^{1}H NMR-spectrum of cis-4-tert-butyl-cyclohexanol.[2] Without shift reagent one can identify only two proton signals. By addition consecutively $Eu(DPM)_3$-reagent (tris(2,2,6,6-tetramethyl-3,5-heptadione)europium(III)) up to the molar ratio 0.8 (shift reagent to substrate) one gets a first order spectrum and can analyze all eight signals from the spin-spin splittings.[2] Shift reagent techniques have been applied to the spectroscopy of other nuclei, such as ^{14}N, ^{13}C, ^{19}F and ^{31}P.[3-6] However, these nuclei resonate in a considerably wider chemical shift area than the protons. The main attention is thus directed to the use of chemical shift reagent in the ^{1}H NMR spectroscopy.

The effects of paramagnetism on NMR-spectra have been studied from the beginning of NMR spectroscopy, but the first detailed reports are from the year 1960.

In the first publication Jackson et al. showed, that the adding of paramagnetic cobalt(II)-ion to the known aqueous diamagnetic salts caused a clear division into two signals in the ^{17}O resonance NMR-spectra.[7] The other line comes from the water of hydration of the diamagnetic ion and the other from the solvent water. But the real step forward was achieved 1969, when Hinckley reported a study done with the dipyridine adduct of $Eu(DPM)_3$, the influence of which he studied on the ^1H NMR spectrum of cholesterol.[1] The proton signals shifted to lower field without noticeable broadening of signals. Early 1970 Sanders and Williams reported that unsolvated $Eu(DPM)_3$ was better as a shift reagent, while the absence of pyridine will eliminate the competition of the ligands.[8]

Lanthanide Shift Reagent (LSR), in which some of the ligand hydrogens are substituted with fluors, for instance $Eu(FOD)_3$ (FOD = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione), gives shift effects with very weakly binding substrate molecules like thiols.[9,10] The number of compounds that are suitable for LSR-studies is very high: alcohols, ketones, esters, ethers, amines, aldehydes, ketals, epoxides, nitriles, sulfoxides, thiocarbamates, phosphates etc.

The popularity of LS-reagent is based on four properties. Firstly, the extremely short electron spin relaxation time of the lanthanide-ion causes sharp resonance lines in the spectrum (except Gd^{3+}).[11] Secondly

tripositive Ln-ion β-diketonate complex (lanthanides = Ln) is coordinatively unsaturated and so readily forms labile adducts with Lewis base substrates.[1,12] Thirdly, with some exceptions, the exchange reaction of substrate molecules that are free in solution with those molecules that are bound with LSR is very fast in NMR-time scale at room temperature.[13] Thus the resultant shift of NMR-signal can be controlled by changing the concentrations of LSR and substrate. The signals can be shifted either to higher or lower field by choosing a suitable lanthanide-ion. Usually the signals of the protons and of the other nuclei too move to lower field with LSR that contains Eu, Er, Tm or Yb. On the other hand Pr, Nd, Tb, Dy and Ho move them to higher field.[14,15] The two last-named properties, fast exchange reaction and the direction of the shift effects give an opportunity to minimize the overlapping of the signals by choosing carefully the concentrations of LSR and the substrate.

Shift reagents have been used for many different purposes. In a study by Liu spin-spin coupling constants were resolved from samples with LSR whereas without LSR they were not observed.[16] The chemical shifts have also been estimated by exrapolating the observed shifts to zero concentration of LSR.[17] Dynamic processes like internal inversion of cyclohexane skeleton[18] and the internal rotation of dimethylamides have been examined in the presence of LSR.[21] Ho first applied LS-reagent

to measure the mean molecular weight of polymers in solution.[19] Whitesides and Lewis in 1970 applied optically active Ln^{3+}-camphor complexes to determine the enantiomeric purity of optically active substrates.[20] Finally, the most challenging LSR application is the determination of structures in solution. This method depends on the dipolar interaction between unpaired electrons and the nucleus which causes so-called dipolar or pseudocontact shift (PC). PC is directly proportional to the position of the nucleus in relation to the main axis of the paramagnetic susceptibility tensor.[22]

During the intervening nine years the stream of publications concerned with this area of NMR spectroscopy has grown from a trickle to a great river. During this time more than ten reviews have been appeared.[23]

The purpose of the present study is to elucidate the structures of some monoterpene alcohols isolated from nature, norbornane derivatives and one model compound through $Eu(DPM)_3$ complexes. In addition, the optical purity of enantiomeric mixtures and the thermodynamic properties of optically active diaziridines is studied with the aid of optically pure $Eu(HFBC)_3$. In connection with the structure investigations a computer program is constructed which determines the best solution for the structure of the LSR-substrate complex.

II THE CHEMICAL SHIFT

Generally, the chemical shift is obtained as the sum of many different factors.[24-26]

$$\sigma_N = \sigma_N^{dia} + \sigma_N^{para} + \Sigma\sigma_N^{NB} + \Sigma\sigma_N^{RC} \qquad (1)$$

σ_N^{dia} represents the interaction of the local diamagnetic electronic current at the nucleus N. σ_N^{para} is caused by the non spherical electronic circulations. The term σ_N^{NB} describes the magnetic fields at the nucleus N, that are caused by electronic currents due to neighbouring atoms or functional groups. σ_N^{RC} represents the shielding effects caused by intramolecular electronic ring currents. One of the most important intermolecular effects to the shielding is the shift caused by LSR, which is handled in chapter III.2.

1. The local diamagnetic shielding term, σ_N^{dia}

The local diamagnetic term describes the isotropic electron rotation around the nucleus. The rotation is prependicular to the stationary field H_o and causes a secondary field H_N^{loc} (dia) which is opposite to the stationary field. The greater the electron density at the nucleus the greater will the diamagnetic effect be and at the higher field will the resonance exist.

2. The local paramagnetic shielding term, σ_N^{para}

Because σ_N^{para} is dependent on the low energy excited electronic states the portion of this term in ^1H NMR is of little importance; the proton does not have low energy excited states.

3. The anisotropic shielding term of the neighbour atom, σ_N^{NB}

σ_N^{NB} describes rotation effects of the local electrons around the atoms B which are neighbours of the atom N under observation and of interatomic electron currents (i.e. currents due to the bonding electrons) between atoms B_1, $B_2 \ldots B_N$. McConnel and Pople derived a simple expression σ_N^{NB} which is based on the assumption that these electron currents may be approximated by point magnetic dipoles for which the atom magnet susceptibilities χ_B^i (i = x, y, z) can be defined. For the case in which the susceptibility tensor χ_B is axially symmetrical, i.e. $\chi^x = \chi^y \neq \chi^z$ the anisotropy term can be expressed as[34]

$$\sigma_N^{NB} = \frac{1}{12\pi N_a} R_{NB}^{-3} \Delta\chi_B (1 - 3\cos^2\Theta_B), \text{ where} \qquad (2)$$

N_a is the number of molecules per unit volume in the sample

and R_{NB} is the distance between nucleus N and dipole B.

$\Delta\chi_B = (\chi_B^z - \chi_B^{xy})$ is the anisotropy of the magnetic suscepti-

bility of the dipole B. Θ_B is the angle between the symmetryaxis of B and the distance vector NB.

It is evident from equation 2 that neighbour anisotropy term depends only on the nature and geometry of B. It is independent of the nature of the observed nucleus N.

4. The ring current term, σ_N^{RC}

The fourth shielding constant σ_N^{RC} is caused by intramolecular currents. Such effects occur especially in aromatic compounds where Π-electrons are free to move in the molecule in an orbital which is not associated with any single atom.

III LANTHANIDE SHIFT REAGENTS (LSR)

1. The structure of the LSR

The first tripositive rare earth β-diketonate complexes were prepared already in 1896.[27] Studies on the chelating tendency with various multidentate ligands have shown that rare earth ions can expand their coordination beyond six and even up to eight or nine

as in the case of $Nd(OH_2)_9(BrO_3)_3$.[28] The best paramagnetic shift reagents are at present complexes of tris-β-diketones and tripositive rare earth metalions.

The common structure of these lanthanide shift reagents is illustrated in Figure 1. As mentioned above Hinckley in 1969 reported for the first time large low field shifts for the protons of cholesterol.[1] The shift reagent he used was $Eu(DPM)_3 \cdot 2$ pyridine. However, unsolvated shift reagent ($Eu(DPM)_3$), was very soon found to be more effective.[8]

Because the solubility of $Eu(DPM)_3$ to the usual solvents is relative poor and slow, more soluble shift reagents were developed, e.g. by changing some of the hydrogens to fluorine atoms at the sidechain of the ligand which very much improved the Lewis acid properties of the shift reagent.[9] Although DPM and FOD complexes of Eu^{3+} and Pr^{3+} have been the most popular lanthanide shift reagents to simplify ^1H NMR spectra of organic molecules numerous other β-diketone complexes have been synthesized. Table 1 lists some β-diketones which have been used and the common abbreviations for them.

Figure 1. The common structure of usual lanthanide shift reagents (LSR).

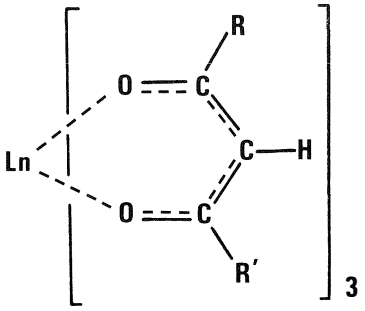


Table 1. β-Diketones employed in LSR of the type $Ln(R\text{-}CO\text{-}CH\text{-}CO\text{-}R')_3$ 1-10 and optically active diketones 11-13 See Figure 1.

	R	R'	parent diketone	abbreviation of diketonate	reference
1	$C(CH_3)_3$	$C(CH_3)_3$	2,2,6,6-tetramethyl-3,5-heptanedione (dipivalomethane)	DPM, THD, TMHD	1, 8
2	$C(CH_3)_3$	$n\text{-}C_3F_7$	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione	FOD	9, 29
3	$C(CH_3)_3$	C_2F_7	1,1,1,2,2-pentafluoro-6,6-dimethyl-3,5-heptanedione	PFD	30
4	$C(CH_3)_3$	CF_3	1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedione	PTA, FHD	30,31
5	CF_3	CF_3	1,1,1,5,5,5-hexafluoro-2,4-pentanedione	HFA	32
6	CF_3	$n\text{-}C_3F_7$	1,1,1,2,2,3,3,7,7,7-decafluoro-4,6-heptanedione	DFHD	32
7	$n\text{-}C_3F_7$	$n\text{-}C_3F_7$	1,1,1,2,2,3,3,7,7,8,8,9,9,9,-tetradecafluoro-4,6-nonanedione	TFN	33
8	C_2F_5	C_2F_5	1,1,1,2,2,6,6,7,7,7-decafluoro-3,5-heptanedione	FHD	10
9	CH_3	CH_3	2,4-pentadione (acetyl acetone)	ACAC	35,36
10	C_6H_5	C_6H_5	1,3-diphenyl-1,3-propanedione (dibenzoylmethane)	DBM	36
11			(+)-3-(2,2,2-trifluoro-1-hydroxymethylene)-camphor	TFC,FACAM	37,39
12			(+)-3-(2,2,3,3,4,4,4-heptafluoropropyl-1-hydroxy-methylene)-camphor	HFBC	38,40
13			(+)-3-(1-tert-butyl-1-hydroxymethylene)-camphor	t-BHMC	20,39

2. Lanthanide induced shifts (LIS)

The chemical shift change caused by addition of a paramagnetic species can be divided into three terms.[41-43]

$$\delta_{LIS} = \delta_{PC} + \delta_{FC} + \delta_{DC}, \text{ where} \quad (3)$$

δ_{LIS} = lanthanide induced shift (LIS)
δ_{PC} = pseudocontact shift (PC)
δ_{FC} = Fermi contact shift (FC)
δ_{DC} = diamagnetic shift (DC)

The first two terms δ_{PC} and δ_{FC} will be discussed in the next two chapters. The complex formation shift δ_{DC} (diamagnetic contribution) has been observed to be negligible.[42-44] An estimate of the magnitude of DC can be obtained by measuring the LIS produced by La^{3+}- or Lu^{3+}-shift reagents.[42,44]

a. Fermi contact shift (FC)

Contact or direct nucleus-spin electron-spin interaction requires the presence of finite paired electron-spin density at the site of the resonating nucleus.[45] This can occur either by direct delocalization or by spin polarization. Both π and σ bonds can take

part in this process.[46] This term decreases quickly in the consecutive bonds.[47]

$$\delta_{FC} = -a_i \frac{\gamma_e}{\gamma_N} \cdot \frac{g\beta S(S+1)}{-3\ k\ T} \text{ , were} \qquad (4)$$

γ_e = the magnetogyric ratio of the electron

γ_N = the magnetogyric ratio of the nucleus

g = the spectroscopic splitting constant of the paramagnetic species

S = total electron spin

β = Bohr magneton

k = Boltzmann constant

T = thermodynamical temperature

a_i = isotropic hyperfine coupling constant (interaction constant)

It has been observed that contact shift is especially important in ^{13}C, ^{14}N, ^{31}P and ^{19}F chemical shifts caused by LSR.[4,6,48] There is evidence that LSR could induce a contact contribution to the ^{1}H-shifts, too.[49]

Elucidation of the portion of contact interaction δ_{FC} in the effects caused by LSR has been studied by many different methods.[50]

The method used in the present study is based on the assumption that for the protons which are more than three bonds away from the lanthanide-ion the contact effects are so little that they need not be taken into consideration. The geometry which gives the best

agreement for the calculated PC-shifts and experimental ^1H shifts except those near the coordination site is used to calculate δ_{FC} for the protons probably influenced by the contact effect. The difference between the calculated δ_{PC} and observed shift for ^1H gives the contact shift (δ_{FC}) for the nucleus in question. This method is the same as Gansow et al. used to calculate the FC for ^{13}C using ^1H-shifts caused purely by pseudocontact mechanism.[51] In this method there is no need to use many different shift reagents, to vary the temperature or to use experimental susceptibility values for the single crystal to get the contact shift contribution for the nucleus under study.

b. Pseudocontact shift (PC)

Electron-nucleus dipolar interaction is a magnet field phenomen which influences through space rather than through bonds. This effect causes so called pseudo-contact or dipolar shift (PC).[22]

The pseudocontact shift arises from the magnet field caused by paramagnetism at the site of the nucleus. The magnitude of PC can be exposed by R_i, Θ_i and molecular magnetic susceptibilities χ_x, χ_y, and χ_z for the case where $1/\tau_m << (ZAE)$. (ZAE) is the Zeeman anisotropy energy and τ_m is the correlation time for

thumbling in solution.[52] The fractional change in the nuclear frequency is

$$\delta_{PC} = \frac{\Delta\nu}{\nu_o} = D_1 \left\langle \frac{3\cos^2 \Theta_i - 1}{R_i^3} \right\rangle + D_2 \left\langle \frac{\sin^2 \Theta_i \cos 2\phi_i}{R_i^3} \right\rangle \qquad (5)$$

where D_1 and D_2 are functions of the magnetic anisotropy of the complex. For definitions of R_i, Θ_i and ϕ_i see Figure 2.

$$D_1 = \frac{1}{3N_A}\left(\chi_z - \frac{\chi_x}{2} - \frac{\chi_y}{2}\right) \quad \text{and} \quad D_2 = \frac{1}{2N_A}(\chi_x - \chi_y)$$

N_A = Avogadro constant

For the axially symmetric case $\chi_x = \chi_y \neq \chi_z$, $\chi_x = \chi_y = \chi_\perp$ and $\chi_z = \chi_\parallel$. Then in equation (5) the term $\chi_x - \chi_y = 0$ and it becomes

$$\delta_{PC} = \frac{\Delta\nu}{\nu_o} = D_1 \left\langle \frac{3\cos^2 \Theta_i - 1}{R_i^3} \right\rangle \qquad (6)$$

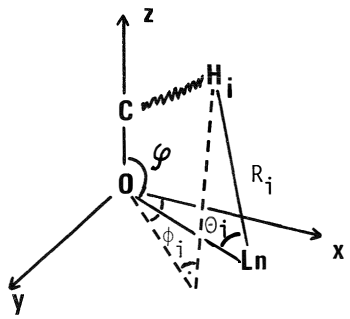


Figure 2. Coordinate system for calculating dipolar shifts. The main magnetic axis is along the Ln-donor bond.

3. The equilibrium and chemical shift

a. Lanthanide shift reagents

In solutions of lanthanide shift reagent L and substrate S different dynamic equilibrium reactions can occur.

NOTE: Lanthanide shift reagent is denoted only in this chapter also by L, otherwise only by LSR.

$$L + S \rightleftharpoons LS \qquad [LS] / [L][S] = K_{B1} \qquad (7)$$

$$LS + S \rightleftharpoons LS_2 \qquad [LS_2] / [LS][S] = K_{B2} \qquad (8)$$

$$L + L \rightleftharpoons L_2 \qquad [L_2] / [L]^2 = K_{B3} \qquad (9)$$

$$L_2 + S \rightleftharpoons L_2S \qquad [L_2S] / [L_2][S] = K_{B4} \qquad (10)$$

In the present study equation (7) is applied because the results in diluted CCl_4-solutions indicate that $Eu(DPM)_3$-alcohol complex ($[L] : [S] = 1:1$) dominates.[55-57] Electronic spectra and molecular weight studies support the statement that $Ln(DPM)_3$ reagents form mainly 1:1 adducts especially in dilute CCl_4 solutions with alcohols and less basic substrates.[58] Complexes $[L] : [S] = 1:2$ appear especially in cases were ligands are fluorinated e.g. with $Ln(FOD)_3$-salts.[59]

The chemical shift of the substrate nucleus can be calculated as weighed average over all magnetic environments where the substrate appears if the concentrations of the different complexes are known. If the reaction (equation (7))

is fast on the NMR time scale then there will be a single resonance centered at[13]

$$\delta_{OBS} = x_S\delta_S + x_{LS}\delta_{LS}, \qquad (11)$$

where x_S and x_{LS} are molar fractions of free substrate and substrate bond to L. δ_S is the chemical shift of free substrate and δ_{LS} is the chemical shift of 1:1 complex (LSR:substrate). Because $x_S = 1 - x_{LS}$ the induced chemical shift δ may be defined as

$$\delta = \delta_{OBS} - \delta_S = x_{LS}(\delta_{LS} - \delta_S) = x_{LS}\Delta_B \qquad (12)$$

where Δ_B is the chemical shift for the LS complex relative to the chemical shift for free S.

Experimentally the observation of a single resonance whose chemical shift varies linearly with the fraction of substrate present as complex is direct evidence that fast-exchange limit is valid.

The present study employs a method where the amount of the LSR L_o is varied at constant S_o. This makes a complete study at low substrate concentrations possible.

For the case where $[S_o] << [L_o]$ ($[S_o]$ and $[L_o]$ are the initial concentrations of LSR and substrate) it can be derived from the equation (12) that[13]

$$\delta = d_i \frac{[L_o]}{[S_o]} \text{ , where } d_i \text{ is a constant} \qquad (13)$$

In calculating the relative DLn-values (equation (14)) for protons in the substrate molecule a method discovered by Paasivirta

is used.[17] First the coefficient d_i (in equation (13)) is determined by regression analysis of experimental data for each proton. The the different DLn-values are calculated by dividing each d_i by the d_α of the α-proton (in relation to OH-group).

$$DLn = \frac{d_i}{d_\alpha} \cdot 100 \qquad (14)$$

The relative shifts are independent of the substrate concentration as quoted by Horrocks.[15] The impurities, which can bind the LSR, are in many cases a disturbing factor, when determining the magnitude of the shift, for instance by using bound shifts (Δ_B).[13] In the present method impurities do not affect the DLn-values. Different shifts caused by LSR can be compared easily if relative shifts like DLn values are used.

b. Optically active lanthanide shift reagents

The diastereomers can be formed by covalent bonds or by coulombic forces between anion and cation or sometimes even by hydrogen bonds.[60,61] A pair of enantiomers can react with an optically active reagent to form two diastereomeric complexes which usually differ from each other in all physical and chemical charasteristic features.

Optically active lanthanide shift reagent (LSR*) forms with the enantiomer pair diastereomeric pairs of associates as illustrated in Figure 3 on page 19 where 1:1

association of (RS)-enantiomer pair ((R) and (S) are the optical antipodes) of a nitrosamine and LSR* complex is shown.[62] Association with LSR* can cause the enantiomeric protons of the nitrosamine to have inequal chemical shifts:

$$\delta_{obs}(R) = x_{S(RS)}\delta_{S(RS)} + x_{L^*S(R)}\delta_{L^*S(R)} \quad (15)$$

$$\delta_{obs}(S) = x_{S(RS)}\delta_{S(RS)} + x_{L^*S(S)}\delta_{L^*S(S)}, \text{ where} \quad (16)$$

$x_{S(RS)}$ is the molar fraction of the substrate
$x_{L^*S(R)}$ is the molar fraction of one diastereomeric pair
L^* denotes LSR* in this chapter
$\delta_{S(RS)}$ is the chemical shift of the racemic mixture (substrate)
$\delta_{L^*S(R)}$ is the chemical shift of one diastereomeric pair

For the systems studied at present, only one splitting of the substrate resonances is observed, if there is no process which could convert each enantiomer to the other, i.e. (R) $\rightleftarrows$ (S) enantiomerization does not occur or the enantiomerization is slow enough for the NMR measurement.

The relative intensities of the corresponding NMR signals of the two enantiomers give a direct measure of the (R)/(S) ratio. Consequently, no preparative separation of the enantiomers from each other is needed for determination of optical purity P.[63]

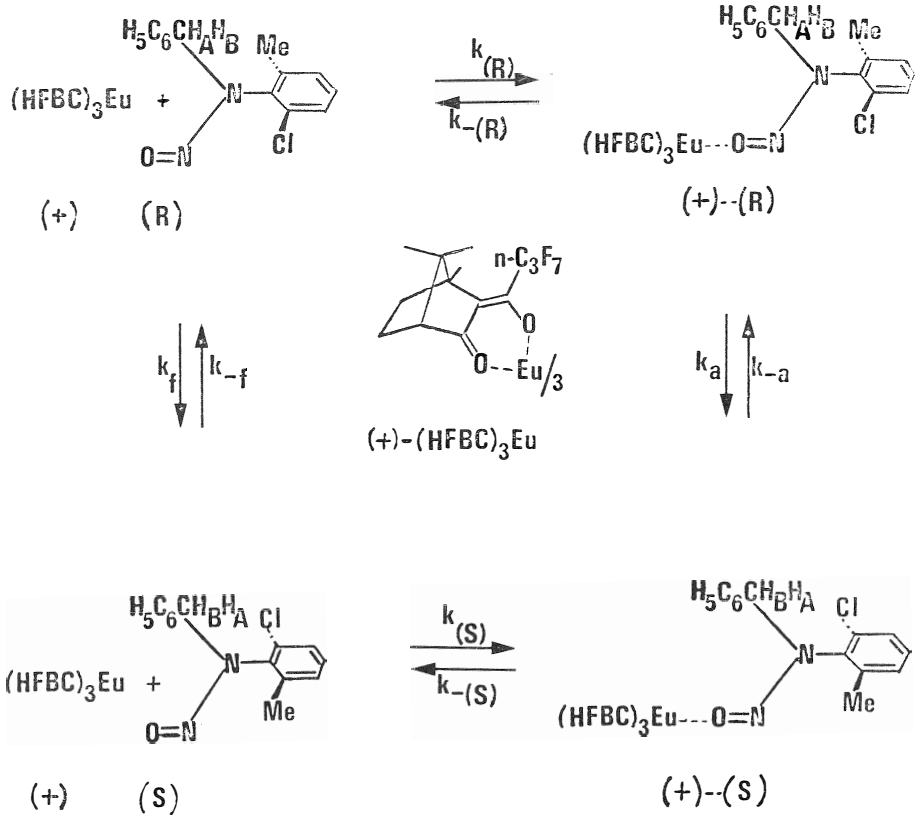


Figure 3. Association equilibrium of both enantiomers of a (RS)-nitrosamine with (+)-Eu(HFBC)$_3$ as optically active shift reagent.[62]

4. The dependence of the induced shifts on the geometric factors

One of the most important uses of chemical shift reagents is the application of the dipolar equation to

determine the structural parameters of the complexes formed by lanthanide shift reagents and substrates.[44,53] There exist few other methods which could give such detailed structural information in solution.

The chemical shift caused by an anisotropic magnetic field of LSR can be calculated explicitly using equation (5). The second term can be neglected despite the fact that the X-ray measurement results from solid LSR-substrate samples usually indicate the existence of nonaxial symmetry. Namely, the rotation about the bond of lanthanide-donor in solution is sufficiently fast compared with Δ_B. Consequently, the effective field at the nucleus averages axial symmetry.[53,54] The complex itself may actually have higher symmetry in solution than in the solid state.[53] The true axially symmetric case has not been directly proven in solution but there are many examples where effectively axial symmetry is achieved for lanthanide shift reagent-substrate complex.[3,15,44]

$$\frac{\Delta\nu}{\nu_o} = D_1(3\cos^2\theta_i - 1)/R_i^3 + D_2(\sin^2\theta_i\cos 2\phi_i)/R_i^3 \qquad (5)$$

For notations of D_1, D_2, θ_i, R_i and ϕ_i see chapter III.2.b.

The fast internal rotation around the lanthanide-donor bond causes the second term to become zero. Therefore, equation (5) becomes simpler:

$$\frac{\Delta\nu}{\nu_o} = D_1(3\cos^2\theta_i - 1)/R_i^3 \qquad (6)$$

Equation (28) can be used to solve the geometric parameters in the following conditions:

1. The observed shifts are purely dipolar in origin.
2. Only one shift reagent-substrate complex (1:1) dominates. The substrate and LSR are in fast dynamic equilibrium.
3. An effectively magnetic axial symmetry appears in the complex resulting in the fact that the shifts depend only on geometric factors, at least for this type of compounds investigated in this study.

There have been some attempts to apply the full equation (27) to the structure determination but the success is limited only to pyridine and related compounds.[64,65]

5. Study of the intramolecular dynamic equilibria by optically active lanthanide shift reagents

Enantiomeric internal processes can be studied with NMR either when the molecule has diastereotopic groups or when an optically active auxiliary compound is added. The latter treatment leads to diastereomeric associates, which have in each case unequal chemical shifts. In this case the enantiomerization by intramolecular processes can be followed provided that the lifetime of the enantiomers is large enough for the NMR-

measurement. The difference between the shifts depends to a great extent on the temperature of the measurements. When the temperature rises the enantiomerization becomes faster, original singlets of isomers broaden, coalesce and form one peak with narrowing linewidth. For different temperatures k-values (rate constants) can be determined by complete lineshape analysis[66] or calculated by different approximations from NMR theory.[67]

In many cases, however, the coalescence temperature is too high to be measured in the presence of the LSR or the lifetimes are too long at lower temperatures. Then one could monitor the racemization from a solution of enriched enantiomer. At the proper temperature samples are taken during a period, say 1.5 halflives, at certain time intervals and analyzed by NMR after addition of a suitable optically active auxiliary reagent. The relative intensities of the NMR signals of enantiomers are measured.

The kinetic intramolecular motion can be calculated from the results. The Gibbs energy of activation $\Delta G^{\ddagger}$ is calculated from the Eyring-equation (17)

$$\Delta G^{\ddagger} = 2.3026\ RT\ (\log \frac{kT}{h} - \log k_1(T)), \text{ where} \qquad (17)$$

T = temperature

k_1 = rate constant

h = Plank constant

k = Boltzmann constant

R = gas constant

The same kinetics can normally be satisfactorily obtained by polarimetry. The present procedure might be useful in monitoring racemizations.

IV COMPUTER PROGRAM FOR THE STRUCTURE DETERMINATION OF THE LANTHANIDE SHIFT REAGENT-SUBSTRATE COMPLEX

For the computer program LASHIFT made for the present study following assumptions were made:

1. The chemical shift caused in NMR by the parametric lanthanide-ion is pseudocontact (dipolar) in origin except for the protons near the coordination site.
2. The complex formed is 1:1 (substrate: lanthanide shift reagent).
3. The main magnetic axis is along the L-O bond.
4. The formed complex is "static" in the sense that the lanthanide approaches the substrate molecule on average from the same direction.

To use the pseudocontact equation (6) one has to know the distance R_i between the paramagnetic nucleus Ln and the nucleus N under observation and the angle Θ_i between the vector R_i and the main magnetic axis. (For definitions see Fig. 2, p. 14). They can be calculated from the cartesian coordinates of the protons and the hetero-

atom in the substrate molecule, the coordinates of the lanthanide and the relative DLn-values. The program calculates also the angle between the main magnetic axis and the vector heteroatom - the carbon atom to which it is bonded (φ) and the distance Ln-heteroatom (r).

Results between calculated (called in program "estimated") and observed relative shifts are controlled by standard errors (b).

V MATERIALS AND METHODS

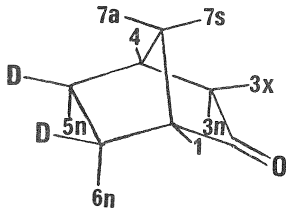
1. For structure determination by $Eu(DPM)_3$

The Figure 4. lists the compounds for which the spatial structures were determined in the $Eu(DPM)_3$-substrate complex.

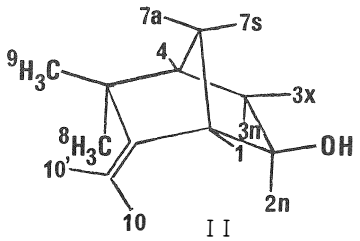
Norcamphor-5-*exo*-6-*exo*-d_2 (I) was prepared by the catalytic deuterization of dehydronorcamphor.[68] The structure of the compound was determined by its NMR spectra.

The 5,5-dimethyl-6-methylenenorbornan-2-*exo*-ol (II) was isolated from Crysanthemum vulgare (L.) Bernh.[69] The alcohol was purified by gas chromatography and led from the outlet of the column directly into a solution of carbon tetrachloride. The structure of the compound was determined by its IR and NMR spectra.

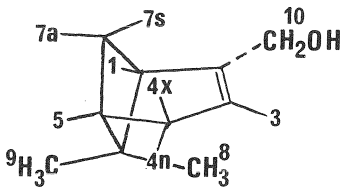
(-)-Myrtenol (III) was isolated from the essential oil of Valeriana Officinalis (L).[70] The alcohol was purified



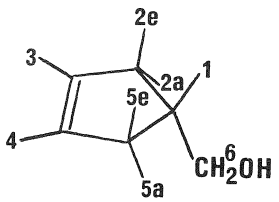
I



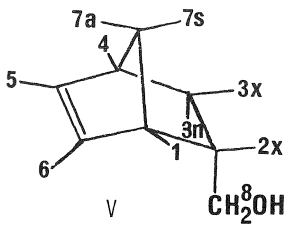
II



III



IV



V

Figure 4. (I) norcamphor-5-*exo*-6-*exo*-d_2, (II) 5,5-dimethyl-6- methylenenorbornan-2-*exo*-ol, (III) (-)-myrtenol, (IV) 3-cyclopentene-1-methanol and (V) 5-norbornene-2-*endo*-methanol

by column chromatography. The structure of the compound was determined by its IR and NMR spectra.

3-Cyclopentene-1-methanol (IV) was prepared by $LiAlH_4$ reduction of the ester of 3-cyclopentene-1-carboxylic acid. The structure of the compound was determined by its IR and NMR spectra.[70]

5-Norbornene-2-*endo*-methanol (V) is a product of the Diels-Alder addition of allyl alcohol to cyclopentadiene. The structure of the compound was determined by its IR and NMR spectra.[70]

The paramagnetic shift reagent $Eu(DPM)_3$ was prepared by the method of Sievers and Rondeau.[9] The compound was purified by crystallization from n-pentane and stored in a vacuum desiccator over silicagel: m.p. = 189°.

Determination of the relative paramagnetic chemical shifts (DEu-values):[17] The ^1H-NMR spectrum of the compound was run without LSR in carbon tetrachloride. Then a known amount of $Eu(DPM)_3$ was added to the solution and the spectrum was run again. The addition of $Eu(DPM)_3$ was usually done in 8 to 10 portions. The addition of $Eu(DPM)_3$ caused a little negative shift in reference TMS compared to pure TMS in CCl_4. The origin of the shift is unknown. The substrate concentration was kept as low as possible to avoid the formation of the other than 1:1 complexes (substrate:shift reagent). The chemical shifts of each proton were plotted against the added $Eu(DPM)_3$ and the linear part of the plot was used in the determination of the coefficients d_i (equation 13) by linear regression analysis. For compounds which did not have the α-proton the most shifted proton was

used as the reference d_i.

The coordinates of the norbornane skeleton for the computation were taken from the publication of Willcox and coworkers.[71] For the other molecule skeletons the coordinates were measured from the Dreiding molecular models. The carbon oxygen distance in a C-OH group was taken to be 1.46 Å and in a C=O group 1.22 Å.[72,73]

Structure analysis of the substrate-lanthanide shift reagent complex was performed on a computer program LASHIFT using a Honeywell 1642 computer system. It operates as follows: The predetermined first point in the lanthanide lattice (x lower limit, y lower limit, z lower limit) is taken for first calculation of φ, Θ_i, R_i and r. (See Figure 7, p.39) for each point (i) observed:

$$C_i = (3\cos^2 \Theta_i - 1)/R_i^3$$

The "best" line for the group of points (i) is determined by regression. For each C_i the corresponding $DEu_{Estimated}$ is taken from the regression line. The results including the standard error of the regression are stored into the memory. The program automatically performs an addition (x addition) determined in advance to x lower limit. After that the procedure described above is repeated. If $\Sigma(DEu_{Obs.} - DEu_{Estim.})^2 = c$ is smaller than in the previous case it is valid and the previous result is deleted. Then y addition is added

to the y lower limit and the calculations are performed again. If the c is now smaller than in the preceding case it is stored. The same procedure is done for z lower limit and then back to x and so on, until the previously set upper limits (x upper limit, y upper limit, z upper limit) are reached. When all the points in the lattice have been examined and the "best" point hase been found the results are plotted on the terminal. Next the lattice vectors and the steps (x addition, y addition, z addition) are bisected and this new lattice is set around the optimum point ("best" point) found in the previous iteration phase and a new iteration round takes place. The same procedure, if desired, is done simultaneously for the two other lattices, namely for the heteroatom and one point in the substrate molecule. The iteration continues until the optimum point no longer changes noticeably. Then the iteration is broken at the terminal.

The ^{1}H-NMR spectra were recorded on a 60 MHz Perkin-Elmer Model R 12 B spectrometer in CCl_4 as solvent. The gas chromatograph used was Perkin-Elmer Model 800. Melting points were determined on a Büchi "Tottoli" instrument and are not corrected.

2. For enantiomeric purity measurements and intramolecular dynamics by $Eu(HFBC)_3$

Liquid chromatography on triacetylcellulose:[74] The separation of enantiomers was performed by column chromatography on swollen microcrystalline triacetylcellulose as a sorbent (particle sizes 0.056 to 0.071 mm) and ethanol/H_2O (96:4) as an eluent. The chromatographic equipment consisted of two glass columns of 2.5 cm internal diameter and 30 cm length (Serva G.m.b.H., Heidelberg), UV analyser LKB 8300 Uvicord II, polarimeter Perkin-Elmer 141, fraction collector LKB 2112 Redirac, twochannel recorder Servogord 2S (Goerz Electro G.m.b.H., Wien), membrane pump ProMinet electronic (Chemia und Filter G.m.b.H., Heidelberg, pressure 10 to 11 atm).

Analytical chromatograms were obtained by passing a racemate through the system including one or two triacetylcellulose columns. Absorbance and angle of rotation of the eluate were recorded continuously (see Fig. 5, p. 30).

For preparative chromatography two equal columns were used and the final eluate was divided into different parts by means of the fraction collector. The recycling procedure was applied by performing several passages of the solution through the columns. This was achieved with a manual gauge (Dreh-Probenaufgabe-Ventil, Latek G.m.b.H., Heidelberg) which, in addition, removed a

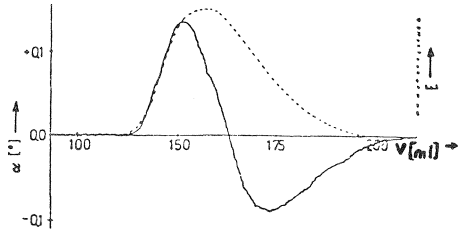


Figure 5. Analytical chromatogramm of 50 mg of (±)-VI in ethanol/H_2O (96:4) after passage through a triacetylcellulose column (cf. text): α: Rotation angle (––) at 365 nm. measured by flow through a polarimeter. E: Extinction (---) at 254 nm. measured by flow through a photometer. V: Volume of the eluate (injection at V = 0).[74]

smaller first part of the solution ("early eluate") from the system (cutting), whereas a larger second part was led through the other column.

Determination of enantiomeric purity P:[75] The relative intensities of two suitable ^1H NMR signals of the enantiomers in the presence of an optically active auxiliary compound served for the measurement of P (Table 2, p. 45). Spectrum copies were repeatedly cut out and divided into the two components which were weighed. (+)-Tris(3-heptafluorobutyryl-D-camphorato)europium-(III) or (+)-Eu(HFBC)$_3$ was available from Regis Chemical Co., Morton Grove, Ill., USA.

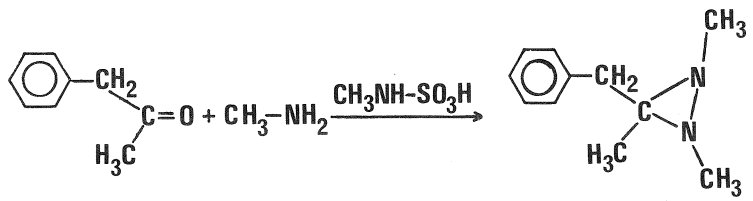
Racemization monitored by ^{1}H NMR:[75] A stoppered tube (internal diameter 1 cm) containing the solvent (1.5 ml for (-)-benzyl-1,2,3-trimethyldiaziridine (-)-VI) was warmed in the ultrathermostat (Colora U3-S8, $\Delta T = \pm 0.1^{o}$) at the desired temperatures (Table 3, p.46) The reaction was started by adding a solution (689 mmol of (-)-VI in 1.5 ml) of an enriched enantiomer in the same solvent. Portions of 0.3 ml were drawn out of the solution at suitable time intervals and cooled to 0^{o}C. After addition of (+)-Eu(HFBC)$_3$ ^{1}H NMR spectra (Fig. 8 and 9, p. 42) of the 3-Me signals were recorded, cut and weighed, as above.

Racemization monitored by polarimetry:[74] 0.025 M solution containing enriched (-)-VI were set into the 5 cm cell of a Perkin-Elmer 241 electronic polarimeter. The rate was measured directly by plotting the rotation angle versus time (determined by chart speed). The temperature ($\Delta T = \pm 0.1^{o}$) of the thermostated cell was read at its inlet and outlet, the mean value being taken as the actual cell temperature. The evaluation of first order rate constants and $\Delta G^{\ddagger}$-values (Table 3) for both types of racemization was carried out with the program[76] KIN 3 using the least squares procedure. The calculations were performed on the Siemens TR 440 computer.

Melting points were determined on a Büchi SMP 20 instrument and are not corrected. ^{1}H NMR spectra were recorded on a Varian T-60 (CW mode, 60 MHz) and a Bruker

WH-90 (PFT mode, 8K data points, 90 MHz) spectrometer in $CDCl_3$ unless indicated otherwise. ^{13}C NMR spectra were recorded in the PFT mode at 22.63 MHz on a Bruker WH-90 spectrometer (8K data points). Specific rotations were measured by means of a Perkin-Elmer 241 electronic polarimeter, CD spectra on a Jasco J-40A instrument at 22 °C. Low and high resolution mass spectra were obtained with a Varian MAT-CH5 spectrometer, respectively, operating at 70 eV by direct insertion probes. The fractionations under reduced pressure were carried out on a Spaltrohr column (Fischer, Labor- und Verfahrenstechnik, Bonn-Bad Godesberg).

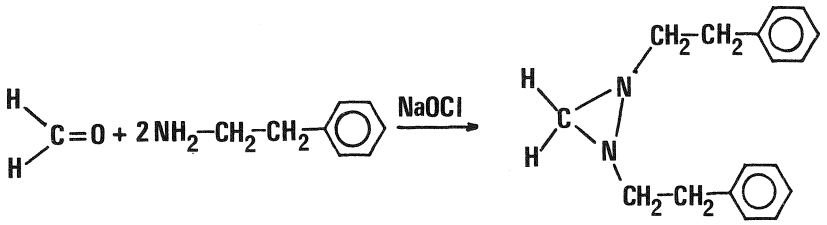
(±)-3-Benzyl-1,2,3-trimethyldiaziridine (VI) was prepared from benzyl methyl ketone, methylamine and N-methyl-hydroxylamine-O-sulfonic acid according to the general procedure given by Schmitz and coworkers.[77] Colorless crystals from n-pentane: m.p. 23-26 °C, n_D^{20} 1.5138.



VI

(±)-1,2-Di-(2,2'-phenylethyl)-diaziridine (VII) was obtained by condensation of formaldehyde with 2-phenylethylamine and addition of sodiumhypochlorite following the general procedure of Schmitz and coworkers.[77]

The compound was identified by its NMR spectra.



VII

(+) and (-)-3-Benzyl-1,2,3-trimethyldiaziridine were obtained from 100 mg of (±)-VI which as eluted through two triacetylcellulose columns at flow rate of 135 ml/h. Altogether seven passages took place. The six early eluates contained 46 mg of crystalline (+)-VI, $[\alpha]_{436}^{22}$ = +85 ± 5° (0.350 g/100 ml CCl_4) P = 59 ± 3 %. The last fractions of the final eluate contained 26 mg of crystalline (-)-VI, $[\alpha]_{436}^{22}$ = -141 ± 4° (0.050 g/100 ml CCl_4) P = 97 ± 3 %.

(-)-1,2-Di-(2,2'-phenylethyl)-diaziridine was obtained from (±)-VII which was eluted through two columns at flow rate 135 ml/h. The last fractions of the final eluate contained (-)-VII, $[\alpha]_{436}^{22}$ = -7.3° P = 35 %.

VI RESULTS AND DISCUSSION

1. Structural determinations

Tori et al. have studied deuteration products of

α-pinene using $Eu(DPM)_3$ as shift reagent.[78] They used the corresponding undeuterated compound to find out in which position the deuterium atom stands in the shifted NMR spectra. The application of LS-reagent $Eu(DPM)_3$ on the deuterated product of dehydronorcamphor (compound I, page 25) clearly demonstrates that both deuterium atoms stand at the exo positions (carbons 5 and 6) because the iteratively computerized structure agrees very well with the assumption that the proton chemical shifts caused by $Eu(DPM)_3$ are purely dipolar in origin and that the complex formed is axially symmetric (see Figure 7 p.39). Another possibility that the deuterium atoms could be at the endo positions gives a very poor standard error. The Eu-O (r) distance would be too long and the angle φ too small for a chemically reasonable result. The results for norcamphor-5-*exo*-6-*exo*-d_2 (I) are: Eu-O distance r = 2.5 Å (1 Å = 0.1 nm) and the angle φ = 156°. The values are consistent with the result 2-norbornanon-$Eu(DPM)_3$ complex (r = 2.7 Å and φ = 167°).[79] The linear dependence of the induced chemical shifts for norbornane protons on the LSR concentration and the iteration result for LSR-substrate complex indicates clearly that only one species LS (not LS_2 or any other) dominates.

The $Eu(DPM)_3$ induced spectra for 5,5-dimethyl-6-methylene-norbornan-2-*exo*-ol (II) clearly demonstrate the effectiveness of LSR. In the shifted spectra typical

spin-spin couplings of the norbornane protons can be seen. There still remains, however, uncertainty about the configuration of OH on the carbon atom 2. This problem can be assessed with the LASHIFT computer program. The results obtained are in clear accordance with other structure determinations for secondary alcohols (r = 2.42 Å and φ = 132.8°). One good example from the literature is the structure of hydroxyoxetan-Eu(DPM)$_3$-complex, in which r = 2.7 ± 0.4 Å.[80]

An example of the 2-*exo*-norbornanol configuration is isoborneol. For the latter Hawkes et al. obtained structural parameters in the Eu(FOD)$_3$ complex to be r = 2.51 Å and φ = 129.6°.[81] Compound II is also called nojigiku alcohol[82] and it is the first camphene derivative which has been isolated from nature.[83]

Earlier it has been noticed that the contact shift mechanism plays an unimportant role in the isotropic ^{1}H chemical shifts of norbornanol generated by Pr(DPM)$_3$.[84] In the present study, however, three Eu(DPM)$_3$-primary alcohol complexes with noticeable contact mechanism contribution to the α-protons were found. The substrates were (-)-myrtenol (III), 3-cyclopentene-1-methanol (IV) and 5-norbornene-2-*endo*-methanol (V).[70] The method used was nearly equal to that by Gansow et al. applied to the contact shifts of ^{13}C.[51]

The present method is very easy and very rapid to use in comparison with the other methods suggested. One

method presumes that experimental single crystal susceptibilities have to be known.[50] Usually they are not available for the LSR-substrate system. Another method needs shifts induced by Gd^{3+}-complexes, which do not have pseudocontact effect.[50] However, usually the broadening of the ^1H signals by the relaxation effects of Gd^{3+} makes determination of the exact signal position impossible. In a third method several different shift reagents (with different lanthanide ions) have to be used to identify the contact shift mechanism.[50] Thus we have found that our method is very simple to use and gives results comparable with other methods.

DeBoer predicts for α-methyl protons of dimethylveratrole-$Eu(FOD)_3$ complex a contact contribution of 38 %.[50] Similar contact effects appeared also for alcohols III and V in the present study. The contact shift contribution for the α-protons of compound IV apparently is much higher. Regrettably, the symmetry of the molecule reduces the number of observation points to four, i.e. the structure parameters of the complex could not be obtained with the same accuracy as for III and V.

$Eu(DPM)_3$ increases the shift difference between the diastereotopic 8A and 8B protons in 5-norbornene-2-*endo*-methanol (V). This means that the protons are not geometrically equivalent with regard to the europium atom. The result indicates that the conformation Va is dominant (See Figure 6). The same inequality was also

observed for the diastereotopic α-protons of (-)-myrtenol (III), but the shift difference is not as great as in the former case. Hence the average values of the α-proton shifts to determine the DEu-value were used. The observation is in variance with results of Abraham and coworkers for 3-*exo*-methyl-5-norbornene-2-*endo*-methanol.[85] They did not observe any difference for the DEu-values of the diastereotopic α-protons. The difference between the contact effect values for 8a and 8b protons of V could

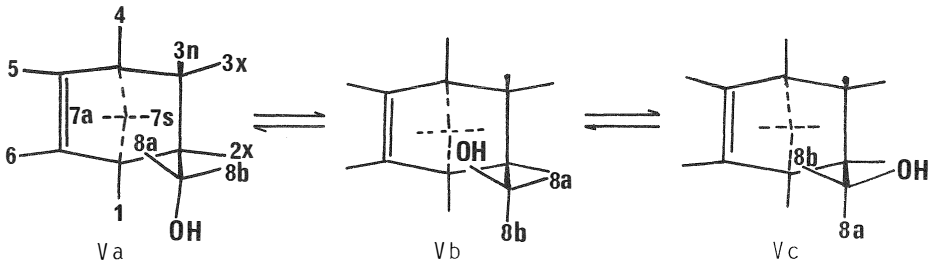


Figure 6. The different conformations of 5-norbornene-2-*endo*-methanol.

arise from the uncertainty in the determination of the coordinates for these protons. A slight change in coordinates causes a big difference for estimated DLn-values near the coordination site. The same is true also for the diastereotopic α-protons of (-)-myrtenol (III). In Figures 4 and 7 both enantiomers of myrtenol are drawn because it is unknown which one of them is

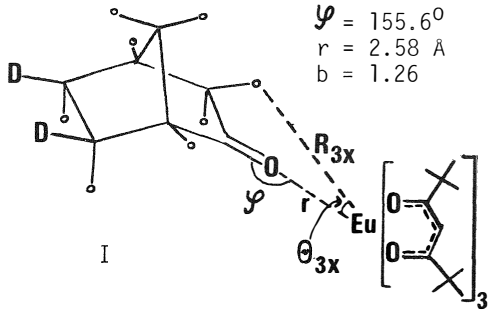
(-)-myrtenol. The present method does not give any solution to this problem.

The errors between the observed and estimated DEu values in the determination of the lanthanide shift reagent substrate complex are partly due to the contact shift mechanism. However, the errors in the observed DEu values and the coordinates of the protons, except near the coordination site, play a minor role in the structure determination.

The computed average structures of $Eu(DPM)_3$-substrate complexes are drawn in Figure 7.

2. Enrichment of racemic mixtures

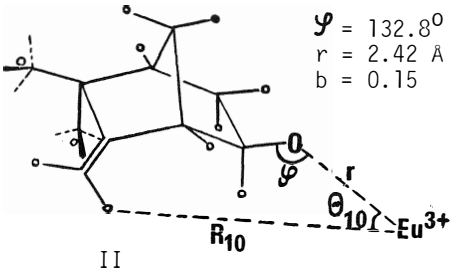
In the study of racemic substances there is always a problem: the question on the separation of the optical antipodes e.g. the enantiomers. In the literature many different methods to separate optical antipodes are given.[63] Kostyanovskii and his group have obtained kinetic enrichments in some cases for diaziridines and also high enantiomeric purity via diastereomeric salts of 3-carboxy-3-methoxy-carbonyl-1-methyldiaziridine with an optically active amine.[86] Both approaches, however, need special functional groups (NH and COOH, respectively) in the diaziridine molecule. Because the enrichement of enantiomers of the present diaziridines via diastereomeric



I

φ = 155.6°
r = 2.58 Å
b = 1.26

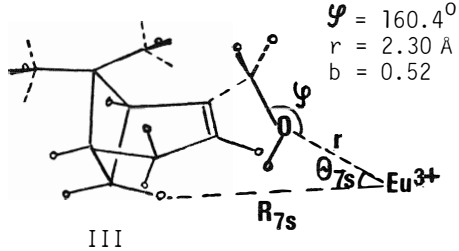
proton i	DEu Observ	DEu Estim	R_i Å	Θ_i °
1	100.0	100.4	4.96	28.2
3x	98.5	97.8	5.36	18.7
3n	100.0	100.9	4.85	30.8
4	34.9	36.9	7.19	16.9
5n	31.9	31.3	5.86	38.2
6n	56.0	56.5	4.48	43.2
7s	66.8	65.1	6.40	6.6
7a	39.1	38.4	7.07	17.8



II

φ = 132.8°
r = 2.42 Å
b = 0.15

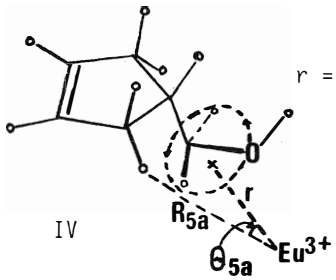
1	63.5	63.5	4.78	24.6
2n	100.0	100.1	3.64	35.3
3x	81.0	80.8	4.23	29.5
3n	38.3	38.3	4.89	35.1
4	26.5	26.6	6.54	16.7
7s	64.5	64.7	5.12	12.8
7a	31.0	30.8	6.51	6.6
8	12.7	12.7	7.02	31.0
9	12.5	12.5	7.94	16.3
10	12.2	12.2	6.40	37.3
10'	10.2	10.2	7.14	33.1



III

φ = 160.4°
r = 2.30 Å
b = 0.52

1	43.2	43.0	5.23	28.8
3	44.7	44.7	5.62	19.3
4x	16.0	16.2	7.17	24.6
4n	16.0	15.8	7.00	11.9
5	12.1	11.0	8.06	21.9
7s	16.4	16.6	5.76	39.6
7a	15.4	15.4	6.57	33.4
8	18.1	18.7	7.54	9.2
9	8.4	8.8	8.10	27.0
10	100.0	a142. b151.	4.01 3.78	17.2 22.8

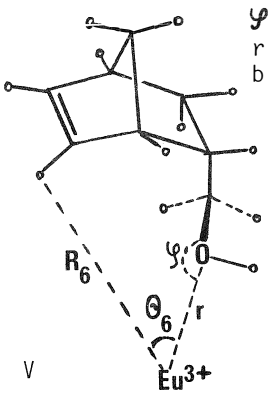


IV

r = 2.41 Å

1	80.2	80.2	5.04	6.6
2a=5a	62.8	62.0	4.70	30.1
2e=5e	41.5	41.5	6.03	17.5
3=4	20.0	20.0	7.01	29.3
6	100.0	396.0	2.69	24.3

Continued on the next page.



V

proton i	DEu Observ	DEu Estim	R_i Å	Θ_i °
1	41.8	41.7	5.74	28.3
2x	60.8	60.8	5.73	13.4
3x	25.9	26.4	7.44	5.3
3n	37.8	37.4	6.59	13.7
4	13.5	13.3	8.66	11.8
5	15.2	15.4	7.13	32.0
6	27.7	27.7	5.68	37.0
7s	17.4	18.1	7.89	16.3
7a	14.3	13.5	8.01	24.1
8a	100.0	130.6	4.51	17.0
8b	94.8	130.3	4.51	17.4

Figure 7. Computed average structures of the 1:1 complex between norcamphor-5-*exo*-6-*exo*-d_2 (I), 5,5-dimethyl-6-methylenenorbornan-2-*exo*-ol (II), (-)-myrtenol (III), 3-cyclopentenyl-1-methanol (IV), 5-norbornene-2-*endo*-methanol (V) and $Eu(DPM)_3$ in CCl_4 solution. For notations of the protons i see Figure 4, p. 27. The difference between the estimated and observed DEu values give the contact contributions for the CH_2O protons of the compounds III 10a 100.0-142.0 = -42, 10b -51 and V 8a -30.6, 8b 35.4 relative DEu units respectively. For IV the contact contribution is equal for both protons and is approximated to -296 relative DEu units.

salts with optically active acids were not possible we chose one of the other most useful methods, namely liquid chromatography. We used and further developed the method discovered by Hesse and Hagel.[87] In the method

optically active triacetylcellulose is used as the stationary phase. The socalled recycling technique was used. It increases the effective column length without increasing the pressure needed. At least some enrichment in solution was attained for each diaziridine enantiomer hitherto tested by us. Apparently, this is a versatile technique which does not depend very strongly upon the presence or absence of special groups, although mono-substituted benzene ring seems to favour the separation.[87,88]

Compound (-)-VI could be enriched to 97 ± 3 % enantiomeric purity. The enantiomeric purities were determined by ^{1}H NMR in the presence of the optically active auxiliary compound Eu(HFBC)$_3$. There are some other methods used to determine the enantiomeric purity but for instance gas chromatographic methods are not suitable because of intramolecular processes in a diaziridine molecule at higher temperatures. The use of (+)-Eu(HFBC)$_3$ is very versatile and rapid. Two suitable signals of the enantiomers, the 3-Me signal of (+)- and (-)-VI (Fig. 8 and 9) were chosen for enantiomer ratio determination.

3. DNMR experiments

The barriers to inversion in diaziridines are of interest for the study of substituent and medium effects.[89]

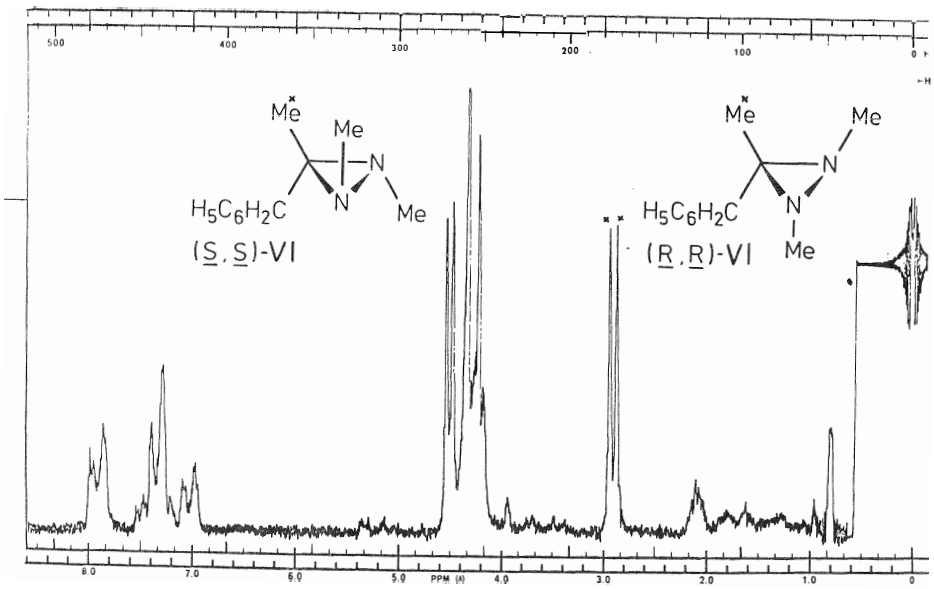


Figure 8. The ^{1}H NMR spectrum of (±)-1,2,3-trimethyl-3-benzyldiaziridin (VI) after addition of 0.27 equivalents of (+)-Eu(HFBC)$_3$ in toluen-d$_8$.

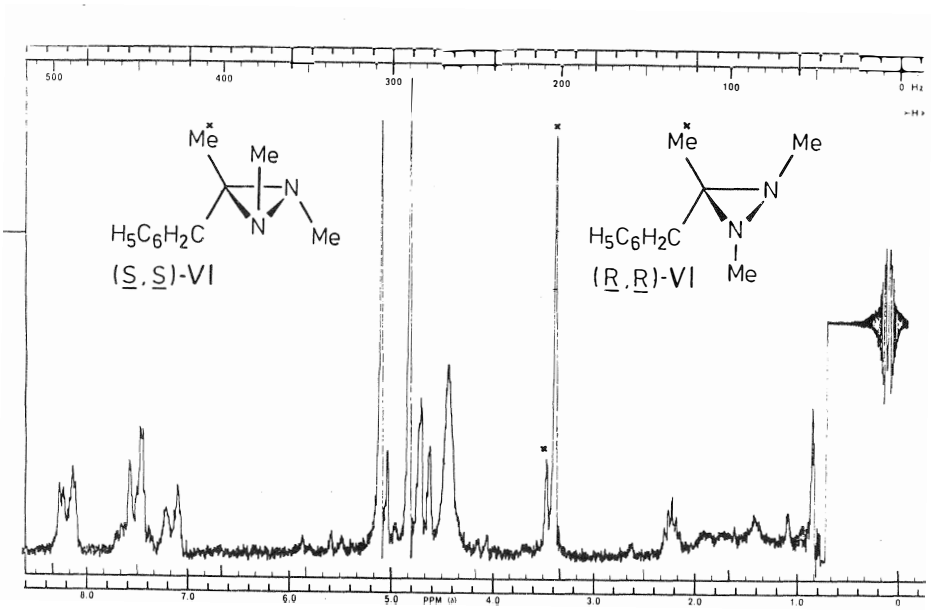


Figure 9. The ^{1}H NMR spectrum of (+)-1,2,3-trimethyl-3-benzyldiaziridin ((+)-VI) after addition of 0.35 equivalents of (+)-Eu(HFBC)$_3$ in toluen-d$_8$.

Particularly, the influence of a complexing auxiliary compound upon the barrier in a substrate molecule should be tested.[90] Such compounds, if optically active, may be used for the measurement of the relative amount of enantiomers.[60,89] But there is evidence that auxiliary compounds do not have any effect on the barrier[62] or very little as can be seen from the measurements done with polarimetry.[74] Some $\Delta G^{\ddagger}$-values for inversion, measured by NMR of equilibrating of diastereomers, by NMR signal coalescence, or by polarimetry are known.[89,91-93] However, the true inversion barrier for each particular nitrogen atom, *trans-cis* process, in a *trans*-diaziridine molecule could not be given from the overall $\Delta G^{\ddagger}$-value measured.[89]

(1*R*,2*R*)- VI (1*S*,2*S*)- VI

The intramolecular dynamic equilibrium between enantiomeric diaziridines (1R,2R)-VI and (1S,2S)-VI is of the first order and the reaction rate constant could be determined as a function of time.[75] Calculated for the *trans-cis* process $\Delta G^{\ddagger}$ = 115.5 kJ/mol (Table 3.) which closely agrees with the one obtained by polarimetry ($\Delta G^{\ddagger}$ = 115.4 kJ/mol). This is in satisfactory

agreement with the value 27.2 ± 0.1 kcal/mol (= 113.9 kJ/mol C_2Cl_4, 89.9 °C) for an inversion in diastereomeric diaziridine.[89] Polarimetry and racemization monitored by NMR signal intensities are apparently two rasemization methods which serve to study intramolecular processes. The latter method has not been reported earlier in the literature.

Monitoring of the racemization from ^1H NMR signal intensities in the presence of an optically active auxiliary compound is laborious. But we think that in cases where the angle of rotation is small as for the compound (-)-VII ($[\alpha]_{436}^{22}$ = -7.3° and enantiomeric purity P = 35 %) one could achieve more accurate values.[75] The errors of the $\Delta G^{\ddagger}$ values would be smaller than achieved by polarimetry. The present results are collected in Table 3. Monitoring the thermal racemization would become simpler if it could be carried out in the presence of the optically active additive. This was impossible for diaziridine VI because it slowly decomposed in the presence of europium complex at 89.9°.

VII SUMMARY

The structure of the norcamphor-5-*exo*-6-*exo*-d_2-$Eu(DPM)_3$ complex was determined. It was possible to demonstrate that in the deuterization reaction product

Table 2. Separations by liquid chromatography and properties of enantiomeric diaziridines VI

Predominant enantiomer	Number of passages	Eluates used[b]	δ	b Hz	S	m	Solvent	P %	$[\alpha]_{365}^{22}$ CCl_4
(+)-VI	7	6 early eluates	2.87	1.5	3-Me	0.27	toluen-d_8	59±3	+151°
(-)-VI		last fractions of final eluate	2.93	1.5				97±3	-245°

a) See experimental part.

b) See text for different eluates.

δ and b: ^{1}H NMR shift[x] and linewidth for a signal of the predominant enantiomer in the presence of (+)-Eu(HFBC)$_3$:

S: Signal monitored

m: Number of equivalents of optically active auxiliary compound.

P: Enantiomeric purity, determined from ^{1}H NMR intensities.

x) The δ-values in the presence of (+)-Eu(HFBC)$_3$ depend strongly upon the ratio m of the reagent to the substrate.

Table 3: Racemization data of (-)-1,2,3-trimethyl-3-benzyldiaziridin, obtained by simultaneous polarimetry and ^{1}H NMR of sample solutions withdrawn at specific times

	Solvent	T °C	Method	$t_{0.5}$ (min) [a]	10^4 k [a] (s^{-1})	$\Delta G^{\ddagger}$ [b] (kJ/mol)
(-)-VI	toluene	89.9	polarim., 436 nm	56.9	1.01	115.4 ± 0.2
(-)-VI	toluene-d_8	89.9	^{1}H NMR intens. [c]	60	1.0	115.5 [d]

a) For two consecutive nitrogen inversions, interconverting the *trans*-diaziridine into the enantiomeric *trans*-diaziridine via a *cis*-intermediate.[79]

b) Corrected for a single nitrogen inversion, converting the *trans*-diaziridine into a *cis*-intermediate.[79]

c) Two 3-Me signals, generated by subsequent addition of 0.27 equivalents of (+)-Eu(HFBC)$_3$ to each of 11 sample solutions.

d) Final error rougly estimated to amount to ± 0.6 kJ/mol.

of dehydrocamphor the deuterium atoms occupy the *exo*-position on the carbon atoms 5 and 6. Through the 5,5-dimethyl-6-methylenenorbornan-2-*exo*-ol-Eu(DPM)$_3$ complex it was observed that the contact shift mechanism for secondary alcohols in negligible. This was in agreement with earlier findings. The shift effect of the secondary 2n proton fit very well to the McConnell and Robertson equation without assuming any contact shift for this proton. In contrast, noticeable negative (to higher field) contact shift contributions for the α-protons of primary alcohols 3-cyclopentene-1-methanol, 5-norbornene-2-*endo*-methanol and (-)-myrtenol in the Eu(DPM)$_3$-substrate complexes were observed.

An iterative computer program was constructed which takes into account affectial axial symmetry in the substrate-shift reagent complex. The program is able to iterate the coordinates of lanthanide, the atom in coordination point and one point under observation.

The optically active shift reagent Eu(HFBC)$_3$ was shown to be a very powerful auxiliary compound in determining the enantiomeric purity of diaziridines. With the aid of (+)-Eu(HFBC)$_3$ the inversion barrier ($\Delta G^{\ddagger}$) for each particular nitrogen atom in a trans-diaziridine molecule can be determined in enriched diaziridine samples. This method was before unknown and it is comparable in many respects with the polarimetric method. However, this method is not as exact as polarimetry but for compounds

which have a very small angle of rotation it can be the preferable method for determining the molecular dynamics for the optically active molecules of a certain kind.

REFERENCES

1. Hinckley, C.C., *J. Am. Chem. Soc.* 91 (1969) 5160

2. Demarco, P.V., Elzey, T.K., Lewis, R.B. and Wenkert, E., *J. Am. Chem. Soc.* 92 (1970) 5734

3. Briggs, J., Hart, F.A., Moss, G.P. and Randall, E.W., *Chem. Comm.* (1971) 364

4. Witanowski, M., Stefaniak, L., Januszewski, H., Wolkowski, Z.W., *Chem. Comm.* (1971) 1573

5. Wolkowski, Z.W., Beauté, C. and Jantzen, R., *Chem. Comm.* (1972) 619

6. Mandel, F.S., Cox, R.H. and Taylor, R.C., *J. Magn. Res.* 14 (1974) 235

7. Jackson, J.A., Lemons, J. and Taube, H., *J. Chem. Phys.* 32 (1960) 553

8. Sanders, J.K.M. and Williams, D.H., *Chem. Comm.* (1970) 422

9. Rondeau, R.E. and Sievers, R.E., *J. Am. Chem. Soc.* 93 (1971) 1522

10. Burgett, C.A. and Warner, P., *J. Magn. Res.* 8 (1972) 87

11. Reuben, J. and Leigh, Jr.J.S., *J. Am. Chem. Soc.* 94 (1972) 2789

12. Springer, C.S., Meek, D.W. and Sievers, R.E., *Inorg. Chem.* 6 (1967) 1105

13. Armitage, I., Dunsmore, G., Hull, L.D. and Marshall, A.G., *Can. J. Chem.* 50 (1972) 2119

14. Briggs, J., Frost, G.H., Hart, F.A., Moss, G.P. and Staniforth, M.L., *Chem. Comm.* (1970) 749

15. Horrocks, Jr.W.DeW. and Sipe, III J.P., *J. Am. Chem. Soc.* 93 (1971) 6800

16. Liu, K-T, *Tetrahedron Lett.* (1973) 2747

17. Paasivirta, J., *Suomen Kemistil.* B 44 (1971) 131

18. von Ammon, R., Fischer, R.D. and Kanellakopulos, B., *Chem. Ber.* 104 (1971) 1072

19. Ho, F.F.L., *Polym. Lett.* 9 (1971) 491

20. Whitesides, G.M. and Lewis, D.W., *J. Am. Chem. Soc.* 92 (1970) 6979

21. Cheng, H.N. and Gutowsky, H.S., *J. Am. Chem. Soc.* 94 (1972) 5505

22. McConnell, H.M. and Robertson, R.E., *J. Chem. Phys.* 29 (1958) 1361

23. Flockhart, B.D., *CRC Critical Reviews in Analytical Chemistry* (1976) 69

24. Wehrli, F.W. and Wirthlin, T., *Interpretation of carbon 13 NMR spectra*, Heyden London, 1978, p. 22

25. McConnell, H.M., *J. Chem. Phys.* 27 (1957) 226

26. Emsley, J.W., Feeney, J. and Sutcliffe, L.H., *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Pergamon Press, vol. I, 1968, p. 130

27. Urbain, *Bull. Soc. Chim.* 15 (1896) 347

28. Sinha, S.P., *Complexes of the Rare Earths*, Pergamon Press, Oxford, 1966, p. 18

29. Rondeau, R.E. and Sievers, R.E., *Anal. Chem.* 45 (1973) 2145

30. Francis, H.E. and Wagner, W.F., *Org. Magn. Res.* 4 (1972) 189

31. Sanders, J.K.M., Hanson, S.W. and Williams, D.H., *J. Am. Chem. Soc.* 94 (1972) 5325

32. Richardson, M.F. and Sievers, R.E., *Inorg. Chem.* 10 (1971) 498

33. Morril, T.C., Clark, R.A., Bilobran, D. and Youngs, D.S., *Tetrahedron Lett.* (1975) 397

34. Atkins, P.W., *Molecular quantum mechanics*, Clarendon Press, Oxford, 1970, p. 443

35. Green, R.D. and Sinha, S.P., *Spectroscopy Lett.* 4 (1971) 411

36. Hart, F.A., Moss, G.P. and Staniforth, M.L., *Tetrahedron Lett.* (1971) 3389

37. Georing, H.L., Eikenberg, J.N. and Koemer, G.S., *J. Am. Chem. Soc.* 93 (1971) 5913

38. Fraser, R.R., Petit, M. and Sanders, J.K.M., *J. Chem. Comm.* (1971) 1450

39. Haller, R. and Bruer, H-J., *Arch. Pharm.* 309 (1976) 367

40. Knabe, J. and Gradmann, V., *Arch. Pharm.* 310 (1977) 469

41. Kessler, H. and Molter, H., *Angew. Chem.* 86 (1974) 552 (German)

42. Ajisaka, K. and Kainosho, M., *J. Am. Chem. Soc.* 97 (1975) 330

43. Uebel, J.J., Pacheco, C. and Wing, R.M., *Tetrahedron Lett.* (1973) 4383

44. Welti, D.H., Linder, M. and Ernst, R.R., *J. Am. Chem. Soc.* 100 (1978) 403

45. Reuben, J. and Fiat, D., *Inorg. Chem.* 8 (1969) 1821

46. Morishima, I., Okada, K., Ohashi, M. and Yonezawa, T., *Chem. Comm.* (1971) 33

47. Reuben, J. and Fiat, D., *J. Chem. Phys.* 51 (1969) 4909

48. Kainosho, M. and Ajisaka, K., *Chem. Lett.* (1972) 1061

49. Grotens, A.M. and Smid, J., *Tetrahedron Lett.* (1971) 4863

50. DeBoer, J.W.M., Sakkers, P.J.D., Hilbers, C.W. and DeBoer, E., *J. Magn. Res.* 25 (1977) 455 and references cited therein

51. Gansow, O.A., Loeffler, P.A., Davis, R.E., Willcott III, M.R. and Lenkinski, R.E., *J. Am. Chem. Soc.* 95 (1973) 3389

52. Horrocks, Jr. W.DeW. and Greenberg, E.S., *Inorg. Chem.* 10 (1971) 2190

53. Sievers, R.E., *Nuclear magnetic resonance shift reagents*, Academic Press New York 1973

54. Briggs, J.M., Moss, G.B., Randall, E.W. and Sales, K.D., *Chem. Comm.* (1972) 1180

55. Armitage, I., Dunsmore, G., Hall, L.D. and Marshall, A.G., *Chem. and Ind. London*, (1972) 79

56. Wing, R.M. and Uebel, J.J. and Andersen, K.K., *J. Am. Chem. Soc.* 95 (1973) 6064

57. Sullivan, G.R., *J. Am. Chem. Soc.* 98 (1976) 7162

58. Ghotra, J.S., Hart, F.A., Moss, G.P. and Staniforth, M.L., *Chem. Comm.* (1973) 113

59. Reuben, J., *J. Am. Chem. Soc.* 95 (1973) 3534

60. Pirkle, W.H., *J. Am. Chem. Soc.* 88 (1966) 1837

61. Mannschreck, A., *Nachr. Chem. Techn.* 23 (1973) 295

62. Lefèvre, F., Burgemeister, T., and Mannschreck, A., *Tetrahedron Lett.* (1977) 1125

63. Raban, M. and Mislow, K., in *Topics in Stereochemistry*, Vol.2, N.L. Allinger and E.L. Eliel, Eds., Interscience, New York 1967, p. 199

64. Cramer, R.E., Dubois, R. and Seff, K., *J. Am. Chem. Soc.* 96 (1974) 4125

65. Cramer, R.E. and Maynard, R.B., *J. Magn. Res.* 31 (1978) 295

66. Binch, G., *J. Am. Chem. Soc.* 91 (1969) 1304

67. Rogers, M.T. and Woodbrey, J.C., *J. Phys. Chem.* 66 (1962) 540

68. Korvola, J., Häkli, H and Paasivirta, J., *Finn. Chem. Lett.* 1 (1974) 16

69. Paasivirta, J., Häkli, H. and Forsén, K., *Finn. Chem. Lett.* 1 (1974) 165

70. Paasivirta, J., Häkli, H. and Widen, K-G., *Org. Magn. Res.* 6 (1974) 380

71. Chiang, J.F., Wilcox Jr., C.F. and Bauer, S.H., *J. Am. Chem. Soc.* 90 (1968) 3149

72. Landolt-Börnstein, *Zahlenwerte und Funktionen 1 Band, Atom und Molekularphysik, 3 Teil, Molekeln II,* 6 Auflage, s. 552

73. Fuhrer, H., Kartha, V.B., Kruger, P.J., Mantsch, H.H. and Jones, R.N., *Chem. Rev.* 72 (1972) 441

74. Häkli, H. and Mannschreck, A., *Angew. Chem. Int. Ed. Engl.* 16 (1977) 405

75. Häkli, H., Mintas, M. and Mannscreck, A., *Chem. Ber.* 112 (1979) 2028

76. Kölle, U., Dissertation, Univ. Heidelberg 1969, p. 88

77. Schmitz, E., *Dreiringe mit zwei Heteroatomen*, Springer Verlag, Berlin 1967, p. 75, 82

78. Tori, K., Yoshimura, Y. and Muneyuki, R., *Tetrahedron Lett.* (1971) 333

79. Demarco, P.V., Cerimele, B.J., Crane, R.W. and Thakkar, A.L., *Tetrahedron Lett.* (1972) 3539

80. Farid, S., Ateya, A. and Maggio, M., *Chem. Comm.* (1971) 1285

81. Hawkes, G.E., Leibfritz, D., Roberts, D.W. and Roberts, J.D., *J. Am. Chem. Soc.* 95 (1973) 1659

82. Matsuo, A., Uchio, M., Nakayama, M., Matsubara, Y. and Hayashi, S., *Tetrahedron Lett.* (1974) 4219

83. von Schantz, M. and Forsén, K., *Farm. Aikak.* 80 (1971) 122

84. Briggs, J., Hart, F.A. and Moss, G.P., *Chem. Comm.* (1970) 1506

85. Abraham, R.J., Coppell, S.M. and Ramage, R., *Org. Magn. Res.*, 6 (1974) 658

86. Kostyanovskii, R.G. and Shustov, G.V., *Doklady Chem.* 232 (1977) 71; *Chem. Abstr.* 87 (1977) 23109

87. Hesse, G. and Hagel, R., *Justus Liebigs Ann. Chem.* (1976) 996 and earlier papers

88. Bertsh, K. and Jochims, J.C., *Tetrahedron Lett.* (1977) 4379

89. Mannscreck, A. and Seitz, W., *IUPAC, XXIIIrd, Int. Congr. Pure and Appl. Chem.*, Vol. 2, Butterworths London 1971, p. 309

90. Kessler, H. and Molter, M., *J. Am. Chem. Soc.* 98 (1976) 5970

91. Mannschreck, A. and Seitz, W., *Angew. Chem. Int. Ed. Engl.* 8 (1969) 212

92. Kostyanovskii, R.G., Polyakov, A.E., Shustov, G.V., Zakharov, K.S. and Markov, V.I., *Doklady Chemistry* 219 (1974) 831; *Chem. Abstr.* 82 (1975) 97576

93. Shustov, G.V., D'yachenko, O.A.D., Aldoshin, S.M., Zolotoi, A.B., Isobaev, M.D., Chervin, I.I., Atovmyan, L.O. and Kostyanovskii, R.G., *Doklady Chemistry* 231 (1977) 1972; *Chem. Abstr.* 86 (1977) 155100