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CHIRAL RELAXATION REAGENTS (CRR) IN ^{13}C NMR SPECTROSCOPY: FIRST DETERMINATION OF ENANTIOMERIC EXCESS

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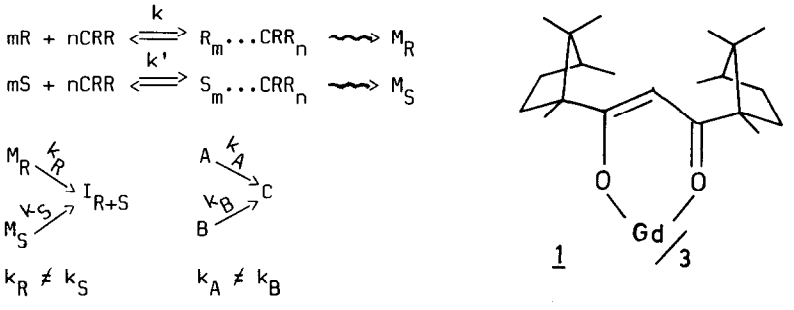
Summary: A simple method is described for determination of enantiomeric excess by the use of chiral relaxation reagents in ^{13}C NMR spectroscopy.

Optically active gadolinium(III) compounds, like the well known chiral shift reagents, form diastereomeric complexes with enantiomers. For (+) and (-)methylephedrine we recently demonstrated that these diastereomeric complexes give identical chemical shift values but differ substantially in their carbon-13 relaxation rates.[1] We now report that these differing relaxation rates can be used quantitatively, e.g. for the determination of enantiomeric excess.

Scheme 1



Enantiomers R and S and chiral relaxation reagent CRR form diastereomeric complexes R_m... CRR_n and S_m...CRR_n in a first reversible step (Scheme 1). The 180° pulse of the inversion recovery sequence builds up net magnetizations M_R and M_S, which relaxe to thermal equilibrium with the rate constants k_R and k_S ($k_R \neq k_S$). The analytical 90° pulse, applied at variable time intervals t_1, causes time dependent ^{13}C NMR signal intensities I_{R+S} for all carbon atoms with identical chemical shifts for both enantiomers. The intensity I_{R+S} depends on the rate constants k_R and k_S and the concentration of enantiomers R and S. Formally this is an analogy to first order reactions of two compounds A and B, forming a common product C. Here, the integrated rate law is given by $\log([C_\infty]-[C]) = \log([A_0]e^{-k_A t} + [B_0]e^{-k_B t})$ and the rate constants k_A and k_B and the initial concentrations of A and B may be calculated by a simple graphical method.[2] In our case the intensity I_{R+S} represents the common product C. Therefore, a plot of $\log(I_\infty - I_t)$ versus time does not yield a straight line, if $k_R \neq k_S$. After the enantiomer with the higher relaxation rate has relaxed, the semilogarithmic plot now defines a straight line, allowing extrapolation to $t_1 = 0$. The intercept with the y axis gives the

value of I_{to} for one enantiomer. Thus the enantiomeric composition, and hence the enantiomeric excess ee, may be calculated from the values of I_∞ and I_{to}.

To check our method we prepared enantiomeric mixtures of (+) and (-)methylephedrine and also of (+) and (-)camphor by weight and performed ^{13}C inversion recovery experiments[3] in the presence of chiral relaxation reagent $Gd(dcm)_3$ 1 with each mixture. Figure 1 gives the semilogarithmic T_1 plot for the signal at δ = 72.4 ppm of methylephedrine. The plot clearly shows the deviation from a straight line for short time intervals t_1. The plotted straight line reflects the final linear portion and is used for extrapolating to t_1 = 0. The calculated enantiomeric compositions are given in Table 1 and are in good agreement with the prepared compositions.

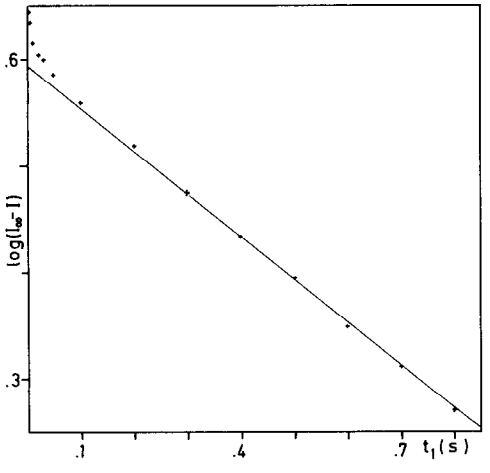


Figure 1. Plot of log $(I_\infty - I_t)_4$ versus time for methylephedrine (shown are the intensities of the signal at δ = 72.4 ppm).

Table 1.

Determination of Enantiomeric Composition

Compound	Proportion of Enantiomers by weight [mg] /[%]	calculated [%]	$Gd(dcm)_3$/ Solvent [mg]
(+)Methyl-ephedrine	407.7/80.3	78.8	2.83/
(-)Methyl-ephedrine	101.0/19.7	-	$CDCl_3$
(+)Methyl-ephedrine	346.5/69.8	69.2	2.83/
(-)Methyl-ephedrine	150.0/30.2	-	$CDCl_3$
(+)Methyl-ephedrine	300.0/59.8	57.3	2.83/
(-)Methyl-ephedrine	201.4/40.2	-	$CDCl_3$
(-)Camphor	319.0/62.9	63.9	0.94/
(+)Camphor	188.0/37.1	-	C_6H_{12}+C_6D_6

Note that the enantiomeric composition may be determined in one experiment by carbon-13 T_1 measurements without knowing the spin lattice relaxation times of the pure enantiomers or their difference. On the other hand the relaxation rates k_R and k_S of the diastereomeric complexes must differ substantially for reasonable accurate determinations of enantiomeric excess. Our results show that this is fullfilled even for substrates like camphor.

References and Notes

1. Hofer, E., Keuper, R., and Renken, H., Tetrahedron Lett., 25, 1141 (1984).
2. Brown, H.C. and Fletcher, R.S., J.Am.Chem.Soc., 71, 1845 (1949).
3. Inversion recovery $(180°\text{-}t_1 - 90°\text{-}t_2)_n$ experiments were performed on a Bruker WP 80.
4. Experimental condition: 1.21 M (+)methylephedrine (69.8%); 0.52 M (-)methylephedrine; 1.58×10^{-3} M $Gd(dcm)_3$; Solvent: $CDCl_3$.

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