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LANTHANIDE(III) SALTS OF (S)-CARBOXYMETHYLOXYSUCCINIC ACID: CHIRAL LANTHANIDE SHIFT REAGENTS FOR AQUEOUS SOLUTION

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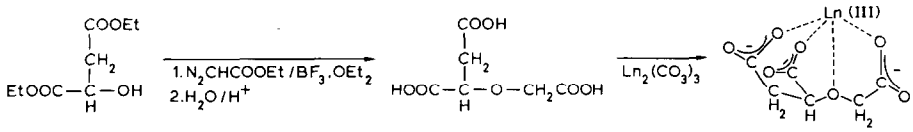
The use of lanthanide(III) salts of (S)-carboxymethyloxysuccinic acid for the NMR separation of enantiomeric mixtures of amino acids and (oxy)carboxylic acids in aqueous solution is described.

Chiral lanthanide shift reagents have found widespread use in the NMR resolution of enantiomeric mixtures and of enantiotopic nuclei in organic solutions.[1] For a large number of optically active compounds, particularly those of natural origin water is the solvent of choice. Chiral lanthanide shift reagents for use in this medium, however, are not well-developed. Pioneering work in this field has been done by Reuben,[2,3] who described the use of in situ prepared lanthanoid complexes with chiral α-hydroxycarboxylate ligands.

We here report on an investigation of the applicability of Eu(III) and Yb(III) complexes of (S)-carboxymethyloxysuccinate (CMOS) as chiral shift reagents in aqueous medium. H_3(CMOS) (**2**) can readily be obtained by reaction of diethyl (S)-malate (**1**) with ethyl diazoacetate, followed by hydrolysis. The solid Ln(III) salts (**3**) can be obtained by neutralization of the acid with $Ln_2(CO_3)_3$.



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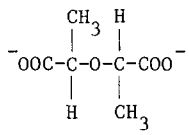
In aqueous solution CMOS can form 1:1 as well as 1:2 Ln(III)-CMOS complexes with high stability constants (log $K_1 \simeq 8$ and log $K_2 \simeq 4$), in which CMOS behaves largely as a tetradentate ligand.[4] Usually, Ln(III) cations have a coordination number of nine in water. So in the 1:1 Ln(III)-CMOS complex about five positions are available for coordination with other ligands. In addition, the Ln(III)-CMOS complex is stable over a large pH range (3-10).

With the use of Eu(III)(S)-CMOS complexes we were able to observe ^{1}H NMR spectral resolution of the two enantiomers in racemic oxydilactate (**4**) and of the enantiotopic CH_2-protons of oxydiacetate (**5**) and nitrilotriacetate (**6**) (see Table 1). The geminal coupling constants in **5** and **6** were determined to be -16.5 and -14.6 Hz, respectively. Moreover,



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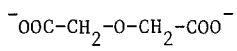

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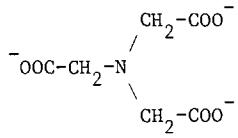

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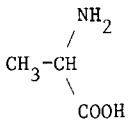

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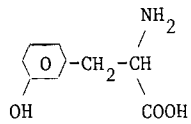

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Table 1. Spectral resolution ΔΔδ (^{1}H NMR, 200 MHz) in mixtures[a] of Ln(III), (S)-CMOS, and a substrate ligand in D_2O

Ln(III)	Substrate ligand[b]	Nucleus	ΔΔδ (ppm)[c]
Eu	(R)-CMOS	-O-C*H*$_2$-COO$^-$	0.02
			0.16
		C*H*-CH$_2$-COO$^-$	0.04
		CH-C*H*$_2$-COO$^-$	0.03
			0.02
Eu	oxydiacetate (**5**)	C*H*$_2$	0.10
Eu	(RR)/(SS)-oxydilactate (**4**)	C*H*$_3$	0.07
		C*H*	0.22
Eu	nitrilotriacetate (**6**)	C*H*$_2$	0.08
Yb	(R)/(S)-alanine[d] (**7**)	C*H*	0.06
		C*H*$_3$	0.04
Yb	(R)/(S)-3-hydroxyphenylalanine[e] (**8**)	C*H*	0.06
		C*H*$_2$	0.03
			0.06

[a] Concentration ratios (S)-CMOS/other ligand = 2; Eu(III)/total ligand = 0.5; [b] As their Na salts except for the amino acids; total ligand concentration 0.14 M; [c] Measurements with Eu(III) at 81 °C, those with Yb(III) at 20 °C; [d] Concentration ratio Yb(III)(S)-CMOS/alanine = 0.63; R/S = 2; pH = 3.3; [e] Concentration ratio Yb(III)(S)-CMOS/3-hydroxylphenylalanine = 1.81; R/S = 1; substrate ligand concentration 0.05 M; pH = 3.1.

self-resolution occurs in the $Eu(CMOS)_2^{3-}$ complex[5] as appeared by the addition of Eu(III) to mixtures of (R)- and (S)-CMOS. The exchange of both CMOS and substrate ligands, except **6**, was rapid with respect to the ^1H NMR time scale. In the case of nitrilotriacetate (NTA), slow exchange (of **6**) was observed between the mixed complexes $Eu(NTA)((S)\text{-}CMOS)^{3-}$ and $Eu(NTA)_2^{3-}$.

Upon stepwise addition of Yb(S)-CMOS to an aqueous solution of an (R)/(S)-mixture of alanine (**7**) at pH 3.3 resolution of the enantiomers was obtained. At a ratio of Yb(S)-CMOS/alanine of 0.63 in the 200 MHz ^1H NMR spectrum separations of 11 and 7 Hz were obtained for the *CH* and CH_3 signals, respectively (see Figure 1). Yb(S)-CMOS is the first

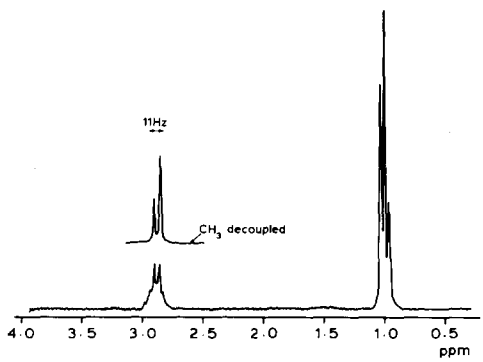

Figure 1. 200 MHz ^1H NMR spectrum of 13.2 mg alanine (R:S = 1:2) in D_2O in the presence of 35.2 mg Yb(S)-CMOS at pH 3.3 (20 °C).

lanthanide shift reagent that is capable to accomplish NMR resolution of enantiomers of an amino acid. The signals of Yb(S)-CMOS were not observable due to strong broadening as a result of slow exchange with respect to the ^1H NMR time scale, whereas the exchange of alanine was still rapid. At increasing pH's the NMR separation of the enantiomers decreases and at pH 7 no separation was observable. Possibly, in the mixed Yb(S)-CMOS/alanine complexes at pH < 7 there is some interaction between one of the (S)-CMOS carboxylate groups and the NH_3^+ group of alanine. In this way a rather rigid orientation of the alanine ligand with respect to the chiral environment may be achieved, which might be favorable for spectral resolution.[3,5] In connection with a study of structure-activity relationships of pharmacological compounds,[6] the Yb(S)-CMOS shift reagent was applied to determine the optical purity (≥ 98%) of the synthetic amino acids (R)- and (S)-3-hydroxyphenylalanine (**8**), since other methods proved to be rather insufficient. In addition a comparison of the relative Yb-induced shifts of the enantiomers with those of alanine, supported the assignments of the absolute configurations.

It may be concluded that Ln(III)(S)-CMOS complexes are readily accessible and useful chiral shift reagents for aqueous solution bringing about spectral resolution in compounds varying from the weakly coordinating amino acids to very strongly coordinating compounds like **6**. Particularly, Yb(S)-CMOS seems promising, since the extensively broadened ^1H signals of (S)-CMOS do not interfere with the substrate ^1H signals. With the stable and solid Ln(S)-CMOS salts the procedure to obtain spectral resolution is analogous to that commonly used with chiral shift reagents in organic solvents, *viz.* stepwise addition of the shift

reagent to the NMR sample until optimal separation of the signals under consideration is obtained.

Acknowledgements

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2. J. Reuben, *J. Chem. Soc., Chem. Commun.* **1979**, 68.
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4. C.A.M. Vijverberg, J.A. Peters, W.M.M.J. Bovée, H. Vroon, A.P.G. Kieboom, and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas*, in press.
5. It should be noted that application of (diamagnetic) $LaCl_3$ under the same conditions did not result in NMR resolution of the enantiomers. So, the use of a paramagnetic lanthanide ion seems to be a requirement for spectral resolution.
6. H.C. Beyerman, A.M. van Leersum, and L. Maat, to be published.

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