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Short Communication

Synthesis, Stereochemical Characterisation and Absolute Configuration of Enantiomerically Pure Complexes of Sexidentate Ligands

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Summary. The optically active sexidentate Schiff bases [H_3L^5] and [H_3L^6] were prepared from tris[(*S*)-2-aminopropyl]amine and 5-chlor- and 5-isopropylsalicylaldehyde, respectively. Reaction of rhodium trichloride with [H_3L^6] gave an enantiomerically pure [RhL^6] complex with an absolute configuration of Λ for the octahedral arrangement. The chiroptical properties are given.

Keywords. Chelate complexes; Diastereoselective synthesis; Optical activity; Chiroptical properties.

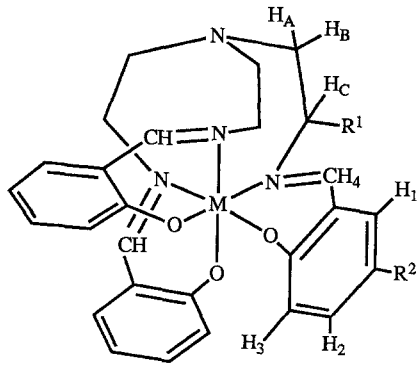
Synthese, stereochemische Charakterisierung und Absolutkonfiguration enantiomerenreiner Komplexe sechszähniger Liganden (Kurze Mitt.)

Zusammenfassung. Ausgehend von Tris[(*S*)-2-aminopropyl]amin und 5-Chlor- beziehungsweise 5-Isopropylsalicylaldehyd wurden die optisch aktiven sechszähnigen Schiffschen Basen [H_3L^5] und [H_3L^6] hergestellt. Die Umsetzung von Rhodiumtrichlorid mit [H_3L^6] ergab einen enantiomerenreinen Komplex [RhL^6] mit einer Absolutkonfiguration von Λ für die oktaedrische Anordnung des Liganden. Die chiroptischen Eigenschaften werden angegeben.

Introduction

Methods to visualize the human heart are of great interest for medical diagnosis. Today, ^{201}Tl is used worldwide as diagnostic radiopharmaceutical for such purposes but a major objective is to replace this isotope by ^{99m}Tc which has superior nuclear characteristics [1]. Following the approach of Deutsch et al. [2], who found that monocationic complexes accumulate in myocardial tissue, several technetium(I) complexes such as $[Tc(CNR)_6]^+$ and $[Tc(dmpe)_3]^+$ (*dmpe*: $Me_2PCh_2CH_2PMe_2$) and technetium(III) complexes such as $[Tc(pdma)_2Cl_2]^+$ [*dpma*: *o*-phenylen-bis(dimethylarsine)] and $[Tc(dmpe)_2Cl_2]^+$ and several others have been extensively investigated as potential heart imaging agents [1].

Currently being investigated are ^{99m}Tc(IV) chelate complexes of sexidentate Schiff bases (Fig. 1) [3]. These complexes preferentially accumulate in normal heart tissue. They are chiral and biodistribution studies have so far been undertaken only with racemic mixtures. Although the bioreceptors are described as "nonspecific",



	R^1	R^2
L^1	H_D	H
L^2	H_D	Cl
L^3	H_D	iso-prop.
L^4	H_D	SO_3^-
L^5	CH_3	Cl
L^6	CH_3	iso-prop.

Fig. 1. Numbering scheme of complexes [*ML*] used in Table 1 and in the experimental section

to our knowledge, biodistribution studies using enantiomerically pure ^{99m}Tc complexes have never been attempted, except for radiolabeled macrocycle-antibody conjugates [4]. The investigated ^{99m}Tc complexes of tris[2-(2-hydroxybenzylidenimino)ethyl]-amine (saltren) and its substituted derivatives could, in principle, be potential candidates for an optical resolution. However, for two reasons, it is very unlikely that such a resolution could be attempted successfully: firstly, the short half life of ^{99m}Tc ($\tau_{1/2} = 6.02$ h) and secondly the fact that such complexes are believed to be fluxional. A barrier to enantiomer interconversion of $\Delta G^{\neq}_{218} \approx 46\,\mathrm{kJ\,mol^{-1}}$ has been found for the [Rh(III)L^2] complex [3], a barrier much too low to support optical activity.

Since it is known that enantiomerically pure chelate complexes can be synthesized starting from optically active ligands, especially from bidentate ligands [5], it was challenging to adopt this method to optically active sexidentate ligands. This paper now describes the synthesis and stereochemical analysis of enantiomerically pure chelate complexes starting from optically active substituted saltren ligands.

Results and Discussion

Structure and Fluxionality

Saltren type ligands [H_3L] ($L = L^1 - L^4$) are easily prepared from tris(aminoethyl)amine (*tren*) and salicylaldehyde or substituted aldehydes. Numerous complexes of such ligands have been reported. X-ray crystallographic studies of neutral metal(III) complexes [ML^2] (M = Fe[6], Cr, Mn[7]) show that in the solid state such complexes adopt an overall molecular C_3 symmetry with the C_3 axis passing through the metal and the apical nitrogen.

Table 1. Selected ^{1}H-NMR data of the ligands $[H_3L^5]$, $[H_3L^6]$ and of the complexes $[GaL^3]$ and $[RhL^6]$

	δ (ppm)				^{3}J (Hz)	
	H_A	H_B	H_C	H_D	H_AH_C	H_BH_C
$[H_3L^5]$	2.42	2.70	3.29	–	<1.4	10.4
$[H_3L^6]$	2.50	2.77	3.39	–	2.7	9.3
$[GaL^3]$	3.31	2.82	3.81	3.02	3.1	12.8
$[RhL^6]$	3.30	2.61	3.77	–	3.2	11.6

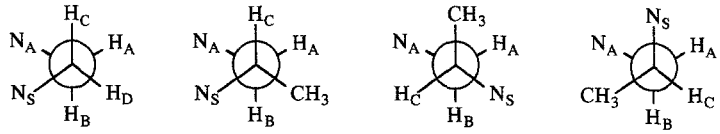
In solution, the $[InL^4]$ and $[ScL^4]$ complexes have been found to be rigid on the NMR time scale at ambient temperatures whereas complexes $[CdL^4]^-$ and $[RhL^3]$ are fluxional [8]. Fluxionality in complexes $[ML]$ $(L = L^1 - L^4)$ results into enantiomer interconversion which is easily monitored by proton NMR spectroscopy. Whereas in rigid complexes (here, rigid means at the slow exchange limit of the NMR time scale) protons H_A and H_B (Fig. 1) as well as H_C and H_D are found at different chemical shifts, but are symmetry equivalent in fluxional complexes. In $[ML^3]$ complexes such as $[RhL^3]$, the isopropylmethyl carbons can be used to monitor fluxionality in the $^{13}C\{^1H\}$ NMR spectra. At the slow exchange limit these carbons are diastereotopic but become symmetry equivalent in fluxional complexes. This can be seen very nicely in the $[GaL^3]$ complex. The ^{1}H-NMR spectrum shows the protons H_A, H_B, H_C, and H_D at different chemical shifts, indicating a rigid structure. The isopropylmethyl groups are accidentally isochronous in the proton spectrum but diastereotopic in the ^{13}C spectrum (δ = 23.98 and 24.06 ppm). The spin system analysis of the proton signals $H_A - H_D$ give proton-proton coupling constants (Table 1) consistent with the conformation found by X-ray crystal structure analysis of the $[FeL^2]$ complex with a dihedral angle N_A-CH_2-CH_2-N_S of ≈ 60 degrees [N_A: apical nitrogen, N_S: Schiff base nitrogen, Fig. 2)].

Optically Active Ligands and Complexes

As for $[RhL]$ $(L = L^1 - L^4)$ complexes it is very unlikely that related ^{99m}Tc complexes can be resolved into enantiomers by any practical method. However, reaction of metal ions with enantiomerically pure ligands can be anticipated to give diastereoselectively optically pure complexes.

Instead of *tren*, *tris*[(*S*)-2-aminopropyl]amine was reacted with 5-chloro- and 5-isopropyl salicylaldehyde to give enantiomerically pure ligands $[H_3L^5]$ and $[H_3L^6]$. The proton NMR spectra of both ligands are, of course, consistent with molecular C_3 symmetry. The vicinal coupling constants $^3J(H_AH_C)$ and $^3J(H_BH_C)$ are constistent only with two (A and B) of the three possible staggered conformations of the N_A-CH_2-CH_2-N_S fragment (Fig. 2).

Reaction of $RhCl_3 \cdot 3\,H_2O$ with $[H_3L^6]$ resulted in a $[RhL^6]$ complex, again with molecular C_3-symmetry as indicated by the $^{13}C\{^1H\}$ spectrum. In principle, two diastereomeric complexes are reasonable products of such a reaction: a complex



N_A: apical nitrogen
N_S: schiff base nitrogen

Fig. 2. Staggered conformation of the N_A-CH_2-CH_2-N_S fragments found in the X-ray structures $[ML^2]$ (M = Fe, Cr, Mn) (left) and possible eclipsed conformations A, B, and C of the N_A-CH_2-$CH(CH_3)$-N_S fragments of ligands $[H_3L^5]$ and $[H_3L^6]$ (N_A: apical nitrogen, N_S: Schiff base nitrogen)

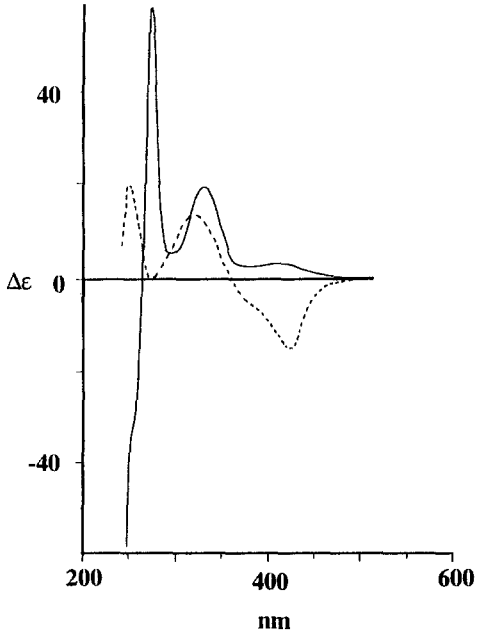


Fig. 3. Circular dichroism of $[H_3L^6]$ (———) and $[RhL^6]$ (- - - - -)

with a ligand of *S*, *S*, *S*-configuration combined with an octahedral arrangement of the ligand $[N_3O_3]$ atoms about the metal of either Λ or Δ configuration. Since both diastereomers are expected to adopt C_3 molecular symmetry, the $^{13}C\{^1H\}$ spectrum is also consistent with a mixture of fast interconverting C_3 symmetrical diastereomers. However, the proton spectrum conclusively shows that just one diastereomer is present in solution to a significant amount. The vicinal coupling constants $^3J(H_AH_C)$ and $^3J(H_BH_C)$ are consistent only with the eclipsed conformers A and B (Fig. 2) but not with C. From the X-ray structure of the $[ML^2]$ complexes (M = Fe[6], Cr, Mn[7]) it follows that, within an octahedral environment, the dihedral angle N_A-CH_2-CH_2-N_S must be approximately ±60 degrees; hence, conformation B can also be excluded.

Furthermore, the vicinal coupling constants of the $[RhL^6]$ complex and those of the $[GaL^3]$ complex are almost identical, showing that the conformation of the

N_A-CH_2-CH_2-N_S fragments must be similar in both complexes. This can only be if the [RhL^6] diastereomer with the amine in conformation A is present almost exclusively, otherwise mixed coupling constants are expected as a result of the interconverting conformers A and C.

A close inspection of the X-ray structure of the [FeL^2] complex shows that the octahedral configuration is correlated to the dihedral angle of the N_A-CH_2-CH_2-N_S fragment. A positive sign for the dihedral angle is found in complexes with an octahedral Λ configuration and vice versa. This correlation allows the assignment of the absolute configuration of the [RhL^6] complex. Since in conformation A the sign of the dihedral angle N_A-CH_2-CH_2-N_S is positive, the absolute configuration of the octahedral [N_3O_3] arrangement must be Λ.

The CD-spectra of ligand [H_3L^6] and of complex [RhL^6] are given in Fig. 3, the optical rotations are listed in the experimental section. As a preliminary result, we report that the [FeL^5] complex shows an almost identical spectrum to the rhodium complex and can also be considered to adopt also an octahedral Λ configuration.

In view of our results it now seems probable that both antipods of enantiomerically pure ^{99m}Tc complexes can be synthesized. Biodistribution studies using enantiomerically pure material might be useful to better characterize the yet unknown receptor sites for such complexes and as a result lead to better imaging agents.

Experimental

NMR spectra were recorded on a Bruker AM 400-WB or on a Bruker WM 250, CD spectra were obtained on a Jobin Yvon dichrograph MARK III. Optical rotations were measured on a Perkin Elmer 241 polarimeter. All reaction were performed under argon atmosphere.

Tris[(2-hydroxy-5-isopropyl-benzylidenimino)ethyl]amine, [H_3L^3]

To a cooled (0°C) solution of 2.8 g (20 mmol) of tris(2-aminoethyl)amine in diethylether was added a precooled solution of 9.84 g (60 mmol) of 5-isopropylsalicylaldehyde in diethylether. The mixture was stirred at 0°C for 1 h and then additionally at room temperature for 3 h. The solvent was removed under reduced pressure to give 11.6 g of a yellow oil which crystallized partially after standing for 16 h at −15°C. Recrystallization from hexane gave 8.4 g (75%) of [H_3L^3] as yellow crystals, m. p. 56 − 64°C. An analytical sample was recrystallized twice from hexane, m. p. 67 − 69°C. (Found: C 72.32, H 8.34, N 9.64; calc. for $C_{36}H_{48}N_4O_3$: C 73.94, H 8.27, N 9.58%). ^{1}H-NMR ($CDCl_3$): δ 1.20 (CH_3), 2.80 (CH), 2.90 (H_C, H_D), 3.62 (H_A, H_B), 6.88 (H^3), 6.92 (H^1), 7.16 (H^2), 8.22 (H^4).

Tris[(S)-2-(hydroxy-5-chlor-benzylidenimino)propyl]amine, [H_3L^5]

To a cooled (0°C) solution of 0.31 g (1.99 mmol) of 5-chlorsalicylaldehyde in diethylether was added dropwise a precooled solution of 0.125 g (0.67 mmol) of tris[(S)-2-aminopropyl]amine in diethylether. The mixture was kept 3 h at 0°C, yielding 0.27 g (67%) of [H_3L^5] as a yellow precipitate, m. p. 200 − 208°C. (Found: C 59.43, H 5.45, N 9.25; calc. for $C_{30}H_{33}Cl_3N_4O_3$: C 59.66, H 5.51, N 9.28%). ^{1}H-NMR ($CDCl_3$): δ 1.15 (CH_3), 2.42 (H_A), 2.70 (H_B), 3.29 (H_C), 5.83 (H^1), 6.91 (H^3), 7.25 (H^2), 7.70 (H^4). $[\alpha]_D^{20}$ (*Et*OH, $c = 0.0192$): +130.5°; CD[λ (Δε)]: 259 nm (33.4), 283 (−0.6), 325 (10.8), 368 (1.2), 410 (2.1).

Tris[(S)-2-(hydroxy-5-isopropyl-benzylidenimino)propyl]amine, [H_3L^6]

To a cooled (0°C) solution of 0.33 g (2 mmol) of 5-isopropylsalicylaldehyde in diethylether was added dropwise a precooled solution of 0.125 g (0.67 mmol) of tris[(*S*)-2-aminopropyl]amine in diethylether.

After the mixture had been kept at 0°C for 3 h, 10 ml of pentane were added. The volume of the solvent was reduced to 5 ml by blowing argon through the reaction mixture. This procedure was repeated three to four times until yellow crystals were formed. Yield: 0.21 – 0.25 g (50 – 60%) of $[H_3L^6]$, m.p. 138 – 145°C. (Found: C 74.43, H 8.45, N 9.15; calc. for $C_{39}H_{54}N_4O_3$: C 74.72, H 8.68, N 8.94%). ^{1}H-NMR ($CDCl_3$): δ 1.00 (CH_3), 1.11 (CH_3), 1.14 (CH_3), 2.50 (H_A), 2.57 (CH), 2.77 (H_B), 3.39 (H_C), 6.26 (H^1), 6.85 (H^3), 7.08 (H^2), 7.98 (H^4). $[\alpha]_D^{20}$ (*Et*OH, $c = 0.0132$): +288°; CD [λ (Δε)]: 261 nm (59.7), 282 (5.2), 325 (19.4), 365 (2.3), 404 (3.2).

Complexes

$[GaL^3]$: To a solution of 0.29 g (0.5 mmol) of $[H_3L^3]$ and 0.167 g (2 mmol) sodium acetate in 30 ml ethanol was added 0.29 g (0.5 mmol) of $Ga(NO_3)_3 \cdot 9\,H_2O$ in 10 ml ethanol. The mixture was heated 3 h under reflux. After the volume of the solvent had been reduced to 5 ml, the suspension was kept 16 h at 5°C. The formed precipitate was filtered off to give 0.20 g (61%) of $[GaL^3]$ as yellow crystals. ^{1}H-NMR ($CDCl_3$): δ 1.20 (CH_3), 2.77 (CH), 2.82 (H_B), 3.02 (H_D), 3.31 (H_A), 3.81 (H_C), 6.69 (H^3), 6.83 (H^1), 7.17 (H^2), 8.06 (H^4). $^{13}C\{^1H\}$NMR ($CDCl_3$): δ 23.98 and 24.06 (CH_3), 37.73 (CH), 57.21 and 61.81 (CH_2); 116.50, 123.02, 130.88, 133.75, 167.68 (aromatic carbons); 170.61 (C=N).

$[RhL^6]$: To a solution of 0.08 g $RhCl_3 \cdot 3\,H_2O$ (0.3 mmol) and 0.07 g sodium acetate in ethanol was added dropwise a solution of 0.063 g (0.1 mmol) $[H_3L^6]$ in 20 ml ethanol. The mixture was heated under reflux for 3 h. The solvent was removed under reduced pressure. To the residue was added 10 ml dichloromethane and the resulting suspension was filtered. The volume of the filtrate was reduced to 2 ml and 10 ml diethylether was added. A brown precipitate was formed immediately and was removed by filtration. The filtrate was evaporated and finally suspended in diethylether. After filtration and solvent evaporation 0.017 g (23%) of $[RhL^6]$ was isolated as an orange brown glassy oil. ^{1}H-NMR ($CDCl_3$): δ 1.14, 1.20 (CH_3), 2.61 (H_B), 2.76 (CH), 3.30 (H_A), 3.77 (H_C), 6.85, 7.03 ($H^{2,3}$), 6.92 (H^1), 7.73 (H^4). $^{13}C\{^1H\}$NMR ($CDCl_3$): δ 17.60 (amine-CH_3), 23.96 and 24.04 (isoprop-CH_3), 32.65 (isoprop-CH), 64.44 (CHN), 65.16 (CH_2), 122.38, 131.27, 133.49 (aromatic carbons, quaternary carbons were not detected); 159.98 (C=N). $[\alpha]_D^{20}$ (*Et*OH, $c = 0.024$): −281 ±3°; CD [λ (Δε)]: 250 nm (18.8), 272 (0.8), 320 (12.8), 420 (−13.8).

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