The First Liquid-Chromatographic Separation of the (R)- and (S)-Enantiomers of a Chiral Silanol, Silane and Germane

Reinhold Tacke*, Dirk Reichel, Kurt Günther, Stefan Merget

* Institut für Anorganische Chemie, Universität Karlsruhe, Engesserstraße, Geb. 30.45, D-76128 Karlsruhe, Germany
b Zentrale Forschungseinrichtungen der Degussa AG, Rodenbacher Chaussee 4, D-63457 Hanau-Wolfgang, Germany

Dedicated to Prof. Dr. H. Schm idbaur on the occasion of his 60th birthday.

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The racemic mixtures of the muscarinic antagonists cyclohexyl(phenyl)(2-pyrrolidino-ethyl)silanol (sila-procyclidine, rac-1), cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)-silane (rac-2) and cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane (rac-3) were resolved by analytical liquid chromatography (HPLC) using chemically modified cellulose (1) or amyllose (2, 3) as the chiral stationary phase. This chromatographic method was used for the quantitative determination of enantiomeric purity of the (R)- and (S)-enantiomers of 1–3, which were obtained by preparative resolution with chiral auxiliary agents. Furthermore, the enantiomeric purity of these samples was established by 13C NMR studies using chiral shift reagents. According to these studies, the resolved antipodes of 1–3 (obtained by preparative resolution) were almost enantiomerically pure [HPLC: >98.2% ee ((R)-3) to 99.4% ee ((R)-1, (S)-1); NMR: 97% ee].

1. Introduction

In recent years, there has been an increasing interest in optically active silicon and germanium compounds of the formula type A [1–3]. The methods used for the preparation of the (R)- and (S)-enantiomers of this particular type of chiral compounds (center of chirality: Si, Ge) are based on (i) classical resolutions of the respective racemic mixtures via fractional crystallization of appropriate diastereomeric derivatives, (ii) stereoselective chemical transformations of the optically active compounds obtained by the aforementioned method and, more recently, (iii) stereoselective biotransformations of suitable racemic or prochiral organosilicon and organogermanium substrates. To the best of our knowledge, preparative chromatographic resolutions of racemic silicon and germanium compounds of type A have not yet been reported in the literature. However, an analytical gas-chromatographic resolution of a series of racemic silanes and silanols has recently been described [4]. Here we report on the first liquid-chromatographic resolution of a racemic silanol, silane and germane.

2. Results and Discussion

The muscarinic antagonists rac-cyclohexyl-(phenyl)(2-pyrrolidinoethyl)silanol (rac-sila-procyclidine, rac-1), rac-cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)silane (rac-2) and rac-cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane (rac-3) were resolved by analytical liquid chromatography (HPLC). As shown by pharmacological studies on various muscarinic receptor subtypes, the (R)-enantiomers of 1–3 are significantly more potent than the corresponding (S)-antipodes, and the pharmacological receptor selectivity of these drugs is dependent on their absolute configuration [2.d,m].

For the liquid-chromatographic separation of the (R)- and (S)-enantiomers of 1–3, chemically

* Reprint requests to Prof. Dr. R. Tacke.
modified cellulose (1) or amylose (2, 3) was used as the chiral stationary phase [5], and the antipodes of 1–3 were eluted with a mixture consisting of n-hexane, 2-propanol and diethylamine (980:20:0.2, v/v/v). Detection of the respective enantiomers was performed with a UV-VIS detector at 215 nm. Further details of the experimental conditions used for these chromatographic separations are given in the experimental section. Representative chromatograms obtained in these studies are shown in Fig. 1; the retention times of the (R)- and (S)-enantiomers of 1–3 are listed in Table I.

The separation achieved for the racemic samples of rac-1, rac-2 and rac-3 was sufficient for quantification of the resolved enantiomers. We took advantage of this for the quantitative determination of enantiomeric purity of the respective (R)- and (S)-enantiomers obtained by preparative resolution with the antipodes of tartaric acid (1 or O,O′-di-p-toluoyltartaric acid (2 [2m], 3 [4]). The enantiomeric purities (% ee) and retention times of the resolved antipodes of 1–3 determined in these experiments are listed in Table I.

Interestingly, even the enantiomers of the silanol 1 could be separated by this particular chromatographic technique without any problems; there were no indications of a significant degree of racemization of (R)-1 and (S)-1 under the experimental conditions used (for the racemization

Table I. Data for the analytical liquid-chromatographic separation (HPLC) of the (R)- and (S)-enantiomers of 1–3.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention time [min]</th>
<th>Enantiomeric purity [% ee]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-1</td>
<td>6.74 (6.71)</td>
<td>≥ 99.4</td>
</tr>
<tr>
<td>(S)-1</td>
<td>8.84 (8.77)</td>
<td>≥ 99.4</td>
</tr>
<tr>
<td>(R)-2</td>
<td>6.27 (6.25)</td>
<td>≥ 98.8</td>
</tr>
<tr>
<td>(S)-2</td>
<td>8.97 (8.95)</td>
<td>≥ 99.0</td>
</tr>
<tr>
<td>(R)-3</td>
<td>5.99 (5.99)</td>
<td>≥ 98.2</td>
</tr>
<tr>
<td>(S)-3</td>
<td>8.53 (8.48)</td>
<td>≥ 99.0</td>
</tr>
</tbody>
</table>

*For details, see experimental section; *b the first value was measured when starting from the racemic mixture; the second value (in brackets) was measured when starting from the pure enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section); *c sample obtained by preparative resolution using a chiral auxiliary agent (see experimental section).
of chiral silanols, see ref. 2d and literature cited
therein).

The chromatographically determined ee values of the resolved (R)- and (S)-enantiomers of 1–3 are in good agreement with the results obtained by NMR-spectroscopic studies. As shown in Fig. 2, the respective enantiomers of 1–3 can be clearly discriminated by $^{13}$C NMR spectroscopy in the presence of the chiral shift reagents (+)-Eu(hfc)$_3$ (for 1) or (−)-TFAE (for 2 and 3) (for details, see experimental section) [(a) racemic mixture; (b): (R)-enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section); (c) (S)-enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section)].

Fig. 2. Characteristic $^{13}$C NMR partial spectra of the (R)- and (S)-enantiomers of 1 (left), 2 (middle) and 3 (right) obtained in the presence of the chiral shift reagents (+)-Eu(hfc)$_3$ (for 1) or (−)-TFAE (for 2 and 3) (for details, see experimental section) [(a) racemic mixture; (b): (R)-enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section); (c) (S)-enantiomer obtained by preparative resolution using a chiral auxiliary agent (see experimental section)].
3. **Experimental Section**

3.1. **Preparation of rac-1, (R)-1 and (S)-1**

The racemate and the (R)- and (S)-enantiomers of cyclohexyl(phenyl)(2-pyrrolidinoethyl)silanol (sila-procyclidine, 1) were prepared according to ref. 2d.

3.2. **Preparation of rac-2, (R)-2 and (S)-2**

The racemate and the (R)- and (S)-enantiomers of cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)silane (2) were prepared according to ref. 2m.

3.3. **Preparation of rac-3, (R)-3 and (S)-3**

The racemate and the (R)- and (S)-enantiomers of cyclohexyl(hydroxymethyl)phenyl(2-piperidinoethyl)germane (3) were prepared by analogy to rac-2, (R)-2 and (S)-2 (synthesis of rac-3 from Cl₃GeCH₂Cl; resolution of rac-3 with the antipodes of O,0'-di-β-toluoyltartaric acid) [6].

3.4. **Chromatographic studies**

HPLC pump: Shimadzu LC6-A. Detector: Soma S-3702 UV-VIS. Integrator: Shimadzu C-R3A. Eluent: n-hexane/2-propanol/diethylamine (980:20:0.2, v/v/v); the HPLC-grade solvents were purchased from Merck. Column: CHIRALCEL OD (1) or CHIRALPAK AS (2, 3) (Daicel Chemical Industries); 4.6 mm i.d. x 250 mm. Flow rate: 0.8 ml/min. Detection: 215 nm. Temperature: 25 °C (1) or 30 °C (2, 3). Injection volume: 20 μl (3 mg of the sample material dissolved in 10 ml of the eluent).

3.5. **NMR-spectroscopic studies**

The ¹³C NMR spectra were recorded at room temperature on a Bruker AC-250 (1) and AM-400 (2, 3) NMR spectrometer operating at 62.9 MHz and 100.6 MHz, respectively. (+)-Tris[3-(2,2,3,3,4,4,4-heptafluoro-1-hydroxybutylidene)<i>-</i>camphorato]europium(III) [(+)-Eu(hfc)₃] and (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol[(-)-TFAE] were purchased from Aldrich and Sigma, respectively. Composition of the samples used for the NMR experiments: 165 μmol 1, 67.0 μmol (+)-Eu(hfc)₃, 0.6 ml CDC₁₃; 30.2 μmol 2, 152 μmol (-)-TFAE, 0.5 ml CDC₁₃; 31.9 μmol 3, 192 μmol (-)-TFAE, 0.5 ml CDC₁₃.

**Acknowledgements**

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