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A Highly Enantiomerically Enriched α-Thiobenzyl Derivative with Unusual Configurational Stability**

Dieter Hoppe,* Bernd Kaiser, Oliver Stratmann, and Roland Fröhlich

Dedicated to Professor Waldemar Adam on the occasion of his 60th birthday

 α -Heterosubstituted, enantiomerically enriched alkyllithium compounds 1 have gained importance in the field of enantioselective synthesis.^[1-4] Electrophilic reagents react with retention of configuration (R¹, R² = alkyl, H), whereas inversion of configuration takes place at the benzylic position.^[2n-p.3h] The configurational stability reaches a synthetically useful level and provides the possibility of handling 1 or *ent*-1 without racemization for only a few α -oxy-^[2] or α amino-substituted^[3] species (1a-1e) and for lithiated alkyl trifluoromethyl sulfones^[4] (1f) between -80 and -30 °C (Scheme 1).



Scheme 1. Inversion of the configuration of alkyllithium compounds 1.

However, α -thio-substituted alkyllithium derivatives **1g** are characterized by a notorious lability of configuration.^[5] As far as we know, the only exception is the lithiated *S*-(α -trimethylsilylalkyl) thiocarbamate **3b**.^[6] It can be kept in diethyl ether at -78 °C for several hours without noticeable racemization, whereas non-silylated **3a** shows configurational



lability under these conditions (TMEDA = N, N, N', N'-tetramethylethylenediamine).^[7] Based on work by H. J. Reich et al.^[5a-e] and R. W. Hoffmann et al.,^[5f-I] this is caused by a different mechanism of racemization. Neither formation of a solvent-separated ion pair nor inversion of configuration at the carbanionic center but rotation of the hyperconjugated S–C bond seems to be the rate-determining step (Scheme 2). In this case the barrier of racemization should be enhanced by

[*] Prof. Dr. D. Hoppe, Dr. B. Kaiser, Dipl.-Chem. O. Stratmann, Dr. R. Fröhlich⁽⁺⁾ Organisch-chemisches Institut der Universität Corrensstrasse 40, D-48149 Münster (Germany) Fax: Int. code + (251)83-39772



Scheme 2. Proposed mechanism for the inversion of configuration in 2g.

bulky substituents R at the sulfur atom (as for 4)^[5k-1] and by branching at the carbanionic center.

With respect to these results we investigated the lithium compound (S)-8, which can be expected to have a larger tendency to form solvent-separated ion pairs than 3a because of the additional resonance stabilization of the anion. Thiocarbamate (S)-7^[8] (>99% ee)^[9] was synthesized from (R)-1-phenylethanol^[10] [(R)-6, Scheme 3], which was ob-



Scheme 3. Synthesis of (S)-8, 9, and ent-9. a) 1. Diisopropyl azodicarboxylate (DIAD)/Ph₃P/MeCOSH (THF), 70%; 2. LiAlH₄ (Et₂O), 99%; 3. NaH/ClCONR₂ (THF) 92%; b) sec-BuLi/TMEDA (Et₂O, -78 °C; c) sec-BuLi/TMEDA (Et₂O, -78 °C; c) sec-BuLi/TMEDA (Et₂O, -78 °C; d) ElX.

tained by the classical method of resolution. Deprotonation^[11] was achieved by adding *sec*-butyllithium/TMEDA to a solution of (S)-7 in diethyl ether at -78 °C. At this temperature the solution was quenched with several electrophilic reagents (method A). We obtained the substitution products (S)-7 (reprotonation with MeOH or AcOH), 9a, and *ent*-9b-*ent*-9e with 97% to greater than 99% *ee* (Table 1).

Table 1. Lithiation and substitution of (S)-7.

Electrophile (ELX)	Method	Product [a]	Yield [%]	ee [%]	[α] ⁷ _D [b]
HOMe	Α	(S)- 7	95	99	- 127.2
HOMe	в	(S)-7	91	≥ 9 9	- 128.6
HOAc	Α	(S)- 7	98	> 99	- 133.5
DOMe	Α	9a[c]	94	98	- 129.1
MeO(CO)Cl	Α	ent-9b	98	\geq 99	- 24.6
MeO(CO)Cl	в	ent-9b	98	\geq 99	-25.5
$CO_2[d]$	Α	ent- 9b	90	99	- 22.5
Ph(CO)Cl	А	ent-9c	82	99	+116.5
Me ₃ SiCl	А	ent-9d	93	≥ 97	- 90.7
Me(CO)Cl	Α	ent- 9e	95	\geq 99	- 22.5
Me(CO)Cl	в	ent- 9e	98	≥99	- 21.8
AcOAc	А	9e	75	57	+12.3

[a] All products were obtained analytically pure (C±0.4%, H±0.3%, N 0.3%). [b] T=20-27°C, c=1.06-1.93 g(100 mL)⁻¹ in CH₂Cl₂. [c] Degree of deuteration 86%. [d] Without deacidification, followed by esterification of the carboxylic acid with diazomethane.

^[+] X-ray structure analyses

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The absolute configuration of compounds *ent-9b* to *ent-9d* was confirmed by single-crystal X-ray diffraction analysis with anomalous dispersion.^[12]

In further experiments a solution of (S)-8 was maintained at -2 to 0°C for ten minutes and then cooled again to -78°C before the electrophile was added (method B). The products (S)-7, ent-9b, and ent-9e still had the high enantiomeric purity of $\geq 99\% \ ee^{[13]}$ Therefore, the half-life of racemization of 8 can be extrapolated to several hours.^[14] As observed for the corresponding benzylcarbamate (O instead of S in 8), substitution mainly takes place with inversion of configuration.^[2n-p] Only electrophilic reagents that tend to coordinate the lithium cation react suprafacially with retention of configuration; examples are protonic acids or acid anhydrides as shown for 9e in Table 1. The combination of effective kinetic acidification of the optically active precursor 7 by an S-carbamoyl group with hindrance of rotation of the adjacent C-S bond in the ion pair provided the first, and probably generalizable, access to highly enantiomerically enriched α -thiocarbanions.

Experimental Section

Method A: Salt-free sec-butyllithium (1.25 mmol, $\approx 1.3 \text{ M}$ in isopentane/cyclohexane) was added to a solution of TMEDA (174 mg, 1.50 mmol) and (S)-7 (293 mg, 1.00 mmol) in diethyl ether (10.0 mL) at -78° C. After 2 h of stirring the electrophile was injected, and the reaction mixture stirred for a further 2–5 h. The cool solution was poured into a mixture of diethyl ether (10 mL) and 2 \times HCl (10 mL). The aqueous phase was extracted three times with diethyl ether. After the combined organic phases were dried and deacidified with Na₂SO₄/NaHCO₃, the crude product was purified by flash chromatography on silica gel.

Method B: After lithiation and 1 h of stirring at -78 °C the reaction mixture was warmed to -2 to 0 °C (internal thermometer) in an ice/water bath within 2–5 min, kept at this temperature for 10 min, and cooled to -78 °C with a dry ice/ acetone bath within about 10 min. The electrophile was added, and the reaction mixture treated as described for method A.

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- [9] All experiments were also carried out with the racemic starting material rac-7. The enantiomeric excesses were determined with ¹H NMR spectroscopy (300 MHz) by addition of (+)-Eu(hfc)₃ or (+)-Pr(hfc)₃ (11-56 mol%) in CDCl₃ (0.8 mL) and comparison with corresponding spectra of the racemic compounds. Usually the highly enantiomerically enriched products showed only the signal for one enantiomer. In these cases the given enantiomeric excesses and detection limits were confirmed by addition of the racemic compounds.
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- [12] X-ray structure analyses: a) ent-9b: $C_{18}H_{25}NO_4S$, $M_r = 351.45$, $0.5 \times 0.35 \times$ 0.25 mm³, a = 6.225(1), b = 12.754(1), c = 23.029(1) Å, V = 1828.4(3) Å³, $\rho_{\text{calcd}} = 1.277 \text{ g cm}^{-3}, \ \mu = 17.49 \text{ cm}^{-1}, \ Z = 4, \text{ orthorhombic. space group}$ $P2_12_12_1$ (no. 19), $\lambda = 1.54178$ Å, T = 223 K, $\omega/2\theta$ scans, 2220 reflections collected (+h, -k, -l), $(\sin\theta)/\lambda = 0.62 \text{ Å}^{-1}$, 2220 independent and 2172 observed reflections with $I \ge 2\sigma(I)$, 224 refined parameters, R = 0.043, $wR^2 = 0.121$, max./min. residual electron density $0.57/ - 0.27 \text{ e} \text{ Å}^{-3}$, Flack parameter -0.03(3); hydrogen atoms were calculated and refined as riding. b) ent-9c: C₂₃H₂₇NO₃S, $M_r = 397.52$, $0.6 \times 0.3 \times 0.2$ mm, a = 9.931(1), c = 18.842(2) Å, V = 1609.3(3) Å³, $\rho_{calcd} = 1.231$ g cm⁻³, $\mu = 15.17$ cm⁻¹, empirical absorption correction with φ -scan data (0.895 $\leq C \leq$ 0.999), Z = 3, trigonal, space group P3₁ (no. 144), $\lambda = 1.54178$ Å, T = 223 K, $\omega/2\theta$ scans, 6770 reflections collected ($\pm h$, $\pm k$, -l), (sin θ)/ $\lambda = 0.62$ Å⁻¹, 2263 independent and 2188 observed reflections with $I \ge 2\sigma(I)$, 259 refined parameters, R =0.041, $wR^2 = 0.107$, max/min. residual electron density $0.34/ - 0.25 \text{ e} \text{ Å}^{-3}$, Flack parameter 0.02(2); hydrogen atoms were calculated and refined as riding. c) ent-9d: $C_{19}H_{31}NO_2SSi$, $M_r = 365.60$, $0.70 \times 0.50 \times 0.20$ mm, a =11.501(2), b = 7.914(2), c = 11.599(2) Å, $\beta = 96.21(2)$, V = 1045.9(4) Å³, $\rho_{\text{calcd}} = 1.161 \text{ g cm}^{-3}, \ \mu = 19.98 \text{ cm}^{-1}, \text{ empirical absorption correction with}$ φ -scan data (0.831 $\leq C \leq 0.999$), Z = 2, monoclinic, space group $P2_1$ (no. 4), $\lambda = 1.54178$ Å, T = 223 K, $\omega/2\theta$ scans, 4574 reflections collected ($\pm h$, -k, $\pm l$), $(\sin \theta)/\lambda = 0.62$ Å⁻¹, 2294 independent and 1964 observed reflections with $I \ge 2\sigma(I)$, 225 refined parameters, R = 0.065, $wR^2 = 0.147$, max/min. residual electron density $0.60/-0.44 \text{ e} \text{ Å}^{-3}$, Flack parameter -0.01(3); hydrogen atoms were calculated and refined as riding. All data were collected on an Enraf Nonius CAD4 diffractometer. Programs used: data reduction MolEN, structure solution SHELXS-86, structure refinement SHELXL-93. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-

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100446. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: int. code + (1223)336-033; e-mail: deposit@chemcrys.cam.ac.uk).

- [13] Reproduction of these results requires salt-free sec-butyllithium and highly pure, and in particular disulfide-free, 7; otherwise lower yields and enantiomeric excesses are registered.
- [14] An experiment in which (S)-8 is warmed to -2 to 0°C for 1 h and quenching with methyl chloroformate leads to *ent-9b* in 58% yield with 73% *ee.* A longer reaction time at 0°C causes severe decomposition.

A Highly Stable Silver(t) Complex of a Macrocycle Derived from Tetraazatetrathiacyclen**

Thomas Gyr, Helmut R. Mäcke,* and Michael Hennig

The chemistry of the coinage metals is of special interest in many diverse fields; one notable example is the medical application of gold(1) complexes for treating rheumatoid arthritis and as cytotoxic agents.^[1] Another promising application is the use of the β -ray-emittig radionuclides ¹¹¹Ag^[2] and ¹⁹⁸Au^[3] in selective internal radiotherapy of tumors as radiometal-based bioconjugates. To reach their biological target intact, the radiometal is generally immobilized with a chelating ligand to withstand attack of the metal ions from body fluids and to avoid transfer of these metals to proteins. There has been great progress along these lines with other metallic radionuclides for radiotherapy, for example with ⁶⁷Cu^[4] and ⁹⁰Y.^[5] However, the considerable efforts expended in synthesizing complexes of silver(1) with sufficient stability to allow their use in vivo^[2,6] have not been successful.

Here we describe the initial results of a study directed at synthesizing stable Ag(1) complexes. Preliminary results indicated that the macrocyclic chelating ligand 1,4,7,10-tetrakis[2-methylsulfanyl)ethyl]-1,4,7,10-tetraazacyclododecane (dotete, 1; the letters A - E identify carbon atoms whose



resonances appear in the ¹³C NMR spectra in Figure 3) shows a very high affinity for Ag^+ , which is strongly preferred over Pb^{2+} ; the two ions are found together in nature.^[7] Moreover, it was of interest to ascertain if the coordination number for Ag^+ could be extended to eight by a strong electronic interaction between Ag^+ and the thioether functional groups,^[8] utilizing the conformational rigidity and potential preorganization of cyclen-like macrocycles with side chains (cyclen = 1,4,7,10tetraazacyclododecane).^[9] Despite the preference of Ag^+ for coordination numbers two and four,^[10] the use of crown thioether ligands produced complexes with coordination number six.^[11] We report here the synthesis, characterization, and X-ray crystal structure of a novel N4S4 macrocycle as well as the crystal and solution structures of its new extraordinarily stable Ag⁺ complex. Its stability is also compared to that of the Pb²⁺ complex.

The reaction of cyclen with 2-chloroethyl methyl sulfide in CH₃CN and in the presence of K_2CO_3 as base readily yields dotete. A solution of dotete in CH₂CL₂ was mixed with an equimolar amount of silver nitrate in CH₃CN; addition of ammonium hexafluorophosphate gave colorless crystals of [Ag(dotete)]PF₆ (2). The effective encapsulation of Ag⁺ by dotete was confirmed by two qualitative observations: 1) [Ag(dotete)]⁺ is stable in phosphate-buffered saline for 24 h, and 2) a slight excess of dotete readily dissolves AgI.

By using pH titrations and argentometric methods the protonation constants for dotete and complexation constants with Ag⁺ in MeOH/H₂O (1/1) were determined to $pK_{a1} = 11.26$ and $pK_{a2} = 6.02$; the complexation constant is $\lg K_{[Ag(dotete)^+]} = 19.63$. This is by far the highest binding constant reported for silver(1) ions.

The high stability is preserved at lower pH values; the protonated species $[Ag(Hdotete)]^{2+}$ was formed with $\lg K_{[Ag(Hdotete)^{2+}]} = 2.8$. Measurements on the concentration of free silver ion gave values of 0.3% at pH = 2.2, which is consistent with that obtained from pH titrations. The extraordinary stability of $[Ag(dotete)]^+$ was confirmed by a competition experiment with the strong Ag⁺-chelating ligand [18]aneS6 ([18]aneS6 = 1,4,7,10,13,16-hexathiacyclooctadecane). An equimolar amount of Ag⁺ with traces of ^{110m}Ag⁺ was added to a 90% methanolic, neutral, phosphate-buffered solution of [18]aneS6 and dotete [10:1, Eq. (a)]. The mixture was investigated with HPLC and TLC using radiometric detection methods.

$${}^{110\text{m}}\text{Ag}^{+} + \text{dotete (1 equiv)} + [18]\text{aneS6 (10 equiv)} \rightarrow \\ [10\text{m}\text{Ag}(\text{dotete})]^{+} + [18]\text{aneS6}$$
 (a)

Both methods showed exclusive formation of $[^{110m}Ag-(dotete)]^+$, indicating that this complex possesses a stability constant that is at least three orders of magnitude higher than that for $[Ag([18]aneS6)]^+$ under these conditions. For $[Pb(dotete)]^{2+}$ stability constants of $\lg K_{[Pb(dotete)^{2+}]} = 8.8$ and $\lg K_{[Pb(Hdotete)^{3+}]} = 3.0$ were found.

The X-ray structures were determined for the uncomplexed monoprotonated dotete (counter ion $PF_{\overline{6}}$) and for $[Ag(dotete)]PF_6(2)$.^[15] In the case of 2, there are two molecules in the asymmetric unit. They possess similar conformations with the exception of a disordered side chain in one molecule, which was refined for two slightly different conformations. The molecule without disorder is shown in Figure 1. Both independent cations show the same coordination geometry: The Ag⁺ ion is hexacoordinated to the four nitrogen and two of the four possible sulfur donor atoms. The molecules are chemically equivalent but differ in the orientation of the terminal methyl group on the coordinated sulfur atoms. The four nitrogen atoms are nearly coplanar (maximum deviation 0.018 Å), and the silver ion is located 1.346 and 1.329 Å above the best N₄ plane. The Ag-N (av 2.53(3) Å) and Ag-S bond lengths (av 2.72(3) Å) are not unusual. Two opposite noncoordinating sulfur atoms are more than 5.0 Å from Ag. The structure of the free protonated ligand is shown in Figure 2. Its preorganization is clear even in the solid state. The N4 plane is intact (maximum deviation 0.055 Å), and the side chains are all syn to the N4 plane.

 ^[*] Prof. Dr. H. R. Mäcke, Dipl.-Chem. T. Gyr Institut für Nuklearmedizin des Universitätsspitals Petersgraben 4, CH 4031 Basel (Switzerland) Fax: Int. code + (61)265-4897 e-mail: maecke@ubaclu.unibas.ch Dr. M. Hennig Hoffmann-La Roche, Basel

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