Structural Characterisation of Chiral 4-Methoxyphenyl Phenyl Selenoxide

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Crystallisation of 4-methoxyphenyl phenyl selenoxide from aqueous solution leads to a spontaneous resolution of the selenoxide into two enantiomers. The crystal structure determination verified that it is a monohydrate of the selenoxide crystallising in the orthorhombic space group $P2_12_12_1$, $a = 5.3562(6)$, $b = 13.293(2)$ and $c = 16.927(2)$ Å, $Z = 4$, $R_1 = 0.021$ for 2474 reflections. In the crystal the selenoxide molecules are linked by hydrogen bonds to chains of hydrogen-bonded water molecules. The properties of the enantiomeric pure 4-methylphenyl phenyl selenoxide were studied by different spectroscopic techniques. The circular dichroism of a water containing acetonitrile solution of a single crystal remained unchanged for weeks. Racemisation of the selenoxide is not initiated by the presence of water, but only after addition of a small amount of acid.

Selenoxides are readily prepared by oxidation of the corresponding selenides, and though their chemistry has been thoroughly investigated over the last two decades, only a few reports that describe the structures of these compounds are to be found.[1–5] A selenoxide group with two different substituents constitutes a chiral structural element. Davis and coworkers concluded from their investigations of a series of chiral selenoxides that the activation energy for inversion at the selenium atom is sufficiently high to prevent racemisation at ambient temperature. However, in the presence of water the selenoxides racemise readily via symmetric dihydroxy selenuranes.[6,7] According to Paetzold the latter species were unobservable by IR spectroscopy.[8] Therefore the dihydroxy selenuranes must be formed in a very low, but rapidly established equilibrium concentration.

During an investigation of diaryl selenoxides unexpected properties were encountered for the compound 4-methoxyphenyl phenyl selenoxide. The crystalline material analysed for $C_{13}H_{14}O_3Se$; this formula could agree with a dihydroxy selenurane or a selenoxide which has one water molecule incorporated in the crystal structure. Furthermore, the bulk material had a melting range of more than 10 °C (48–59 °C), whereas any single crystal melted sharply. All these observations called for further investigations that could elucidate the structure of this material.

Experimental

Preparation of 4-methoxyphenyl phenyl selenoxide (**1**). To a stirred solution of 4-(phenylseleno)anisole (**2**)[9] (13.2 g, 0.05 mol) and *p*-toluenesulfonic acid monohydrate* (25 mg) in warm methanol (150 ml) was added 35% hydrogen peroxide† (6 g, 0.06 mol) during a 10 min period. The reaction mixture was stirred for 1 h. Water (150 ml) was added, and methanol was removed by distillation *in vacuo*. The residue was placed in a refrigerator (5 °C) overnight and the product was filtered off. Recrystallisation from water (130 ml) and drying over concentrated sulfuric acid gave the monohydrate of **1** (12.5 g, 84%) as white needles. The melting point of one crystal picked up with a pair of tweezers was 52–54 °C, while the bulk material melted in the interval 48–59 °C. $C_{13}H_{14}O_3Se$: found C 52.52%, H 4.61%; calc. C 52.54%, H 4.75%.

Spectroscopic measurements

NMR spectra. A JEOL FX 90Q instrument was used to record ^1H (90 MHz) and ^{77}Se (17.1 MHz) NMR spectra in DMSO-d_6. The conditions for recording of the ^{77}Se-NMR spectra were as described previously.[10] ^1H NMR (DMSO-d_6): δ 3.36 (3 H, s), 3.76 (2 H, s), 7.06 (2 H, d,

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* Addition of the sulfonic acid speeds up the oxidation.
† It was found that aromatic selenoxides cleave an excess of hydrogen peroxide producing oxygen.

J 8.9 Hz), 7.45–7.54 (3 H, m), 7.71 (2 H, d), 7.75–7.79 (2 H, m) ppm. ^{77}Se-NMR (DMSO-d_6): δ 858 ppm. Two of the ^{77}Se-NMR experiments were carried out with the sample in 10 mm NMR-tubes. After a reference spectrum in dry methanol-d_4 (864 ppm) had been recorded, an equivalent measurement was performed for the sample after addition of one equivalent of p-toluenesulfonic acid and 10 equiv. of water (865 ppm).

Mass spectrometry. A JMS-HX/HX110 instrument was used to record a FAB MS spectrum. FAB MS $m/z = 280$ (M^+) (^{80}Se).

Circular dichroism. A Jasco J-710 spectropolarimeter was used to record the circular dichroism (CD). Measurements were performed at ambient temperature in the wavelength region 350–210 nm for solutions made from individual single crystals dissolved in 0.2 ml dry CH_3CN.

Thermogravimetry. A PL-TGA-1000 thermogravimetric balance calibrated with Ni was used for the thermogravimetric measurement in the range 25–150 °C. The heating rate was 2 °C min^{-1} with a flow of nitrogen over the sample. Sampling was made every 1.25 s. The sample weight was 2.934(1) mg.

X-Ray crystallography. A Stoe Stadi P powder diffractometer was used to record the diagram of the bulk material. Cu $K\alpha_1$ ($\lambda = 1.5406$ Å) radiation selected by a curved germanium monochromator was used for the experiment. The diffraction pattern from the sample in transmission mode was recorded with a position-sensitive detector covering 7° in 2θ. The software[11] Visual X^{POW} provided with the instrument was used to analyse the diffraction pattern employing the result obtained from the single-crystal X-ray diffraction study.

An Enraf-Nonius CAD4 diffractometer was used for collection of X-ray diffraction data on a single crystal cooled to 122.0(3) K. Cu $K\alpha$ radiation obtained from a graphite monochromator was employed. The cell parameters were determined from 25 reflections with θ ranging from 39.30 to 40.44°. An analysis of reflection profiles provided the basis for the selection of the scan range and type. Further details on the data collection are given in Table 1.

The data reduction was performed with the program package DREADD.[12] All reflections were corrected for background, Lorentz and polarization effects. Analysis of the intensities of the five standard reflections revealed an overall decrease of 3.8% within exposure time. The intensities were used to obtain a third-order polynomial that was used as a rescale function for the measured intensities. Correction for absorption was performed using the Gaussian Integration method, the transmission factors were in the range between 0.521 and 0.798. Analysis of the diffraction pattern with respect to symmetry and the systematic absences showed that the crystals belong to the orthorhombic space group

Table 1. Crystal data, data collection and refinement.

Formula	$C_{13}H_{12}O_2Se \cdot H_2O$
M_r	297.21
Crystal size/mm	$0.28 \times 0.07 \times 0.06$
Crystal form	Needle
Crystal colour	Colourless
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Cell dimensions/Å	$a = 5.3562(6)$
	$b = 13.293(2)$
	$c = 16.927(2)$
Volume/Å^3	1205.2(2)
Z	4
D_{calc}/g cm^{-3}	1.638
Radiation	Cu $K\alpha$ ($\lambda = 1.54184$ Å)
T/K	122.0(3)
Scan mode	ω–2θ
Scan range θ/°	4.23–74.92
Index ranges	$-6 \leftarrow h \leftarrow 5$, $0 \leftarrow k \leftarrow 16$, $-21 \leftarrow l \leftarrow 21$
Reflections collected	4998
Independent reflections	2474 ($R_{int} = 0.0217$)
Intensity average decay	3.8%
μ/mm^{-1}	4.178
Absorption correction	Gaussian integration method
Max. and min. transmission	0.798 and 0.521
Refinement method	Full-matrix least-squares on F^2
Data/parameters	2474/210
Goodness of fit on F^2	2.346
Weights	$w = 1/[\sigma^2(F_o^2)]$
Final R-indices [$I > 2\sigma(I)$]	$R_1 = 0.0205$, $wR_2 = 0.0478$
Absolute structure parameter	$-0.03(2)$
Largest diff. peak and hole/e Å^{-3}	0.567 and -0.453

$P2_12_12_1$. Reflections were averaged according to the symmetry of the crystal class, 222.

The structure was solved by Patterson and Fourier methods using SHELXS86.[13] The structure was refined by full matrix least-squares SHELXL93[14] minimising $\Sigma w(|F_o|^2 - |F_c|^2)^2$. All reflections were used in the refinement. The non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were refined without restraints on the positional and isotropic displacement parameters. The structure determination revealed the presence of one independent water molecule in the structure. The absolute structure of the crystal was established by refinement of the Flack parameter. The final residuals are listed in Table 1 and the final atomic parameters in Table 2.
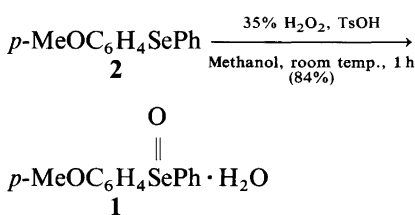
Results

4-Methoxyphenyl phenyl selenoxide (**1**) was prepared from 4-(phenylseleno)anisole (**2**)[9] by oxidation with 35% hydrogen peroxide in methanol at room temperature in the presence of a catalytic amount of p-toluenesulfonic acid followed by addition of water and removal of methanol by distillation. The reaction proceeds without

*Table 2.* Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2).

Atom	x	y	z	$U_{eq}{}^a$
Se1	0.069 76(5)	0.079 99(2)	0.871 69(1)	0.020 19(6)
O1	0.3772(3)	0.1046(1)	0.8676(1)	0.0311(4)
O2	−0.0136(3)	−0.2209(1)	1.1382(1)	0.0202(3)
C11	0.0339(5)	−0.0128(2)	0.7836(1)	0.0163(4)
C12	−0.1683(4)	−0.0771(2)	0.7790(1)	0.0204(4)
C13	−0.1890(5)	−0.1399(2)	0.7136(1)	0.0221(5)
C14	−0.0110(4)	−0.1363(2)	0.6539(1)	0.0182(5)
C15	0.1876(4)	−0.0712(2)	0.6592(1)	0.0199(4)
C16	0.2123(5)	−0.0078(2)	0.7243(1)	0.0184(4)
C21	0.0359(5)	−0.0176(2)	0.9555(1)	0.0168(4)
C22	−0.1636(3)	−0.0091(2)	1.0066(1)	0.0178(4)
C23	−0.1875(4)	−0.0768(2)	1.0689(1)	0.0177(4)
C24	−0.0085(4)	−0.1508(2)	1.0792(1)	0.0153(5)
C25	0.1935(4)	−0.1583(2)	1.0278(1)	0.0178(4)
C26	0.2163(4)	−0.0918(2)	0.9655(1)	0.0193(4)
C31	−0.2235(5)	−0.2193(2)	1.1905(1)	0.0255(5)
O3	0.0222(3)	0.2450(1)	0.0316(1)	0.0252(4)

$^aU_{eq} = 1/3\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* a_i \cdot a_j.$

side-reactions and the yield appears only to be limited by the solubility of 1 in water.

$$p\text{-MeOC}_6\text{H}_4\text{SePh} \xrightarrow[\substack{\text{Methanol, room temp., 1 h} \\ (84\%)}]{35\% \text{ H}_2\text{O}_2, \text{ TsOH}}$$

2

$$\begin{array}{c} \text{O} \\ \| \\ p\text{-MeOC}_6\text{H}_4\text{SePh} \cdot \text{H}_2\text{O} \end{array}$$

1

The X-ray crystal structure determination revealed that the product 1 is a monohydrate of 4-methoxyphenyl phenyl selenoxide, which molecular structure and atomic labeling is shown in Fig. 1. The presence of isolated water molecules in the structure was supported by the TGA measurement, which showed that the solid looses one molecule of water per selenoxide during heating from 40 to 90 °C. These solvent molecules appear to play an important role for the stability of the crystals and thereby their good diffraction quality. The two entities in the crystal are connected by hydrogen bonds forming infinite chains as shown in Fig. 2. The geometrical details of these intermolecular interactions are listed in Table 3.
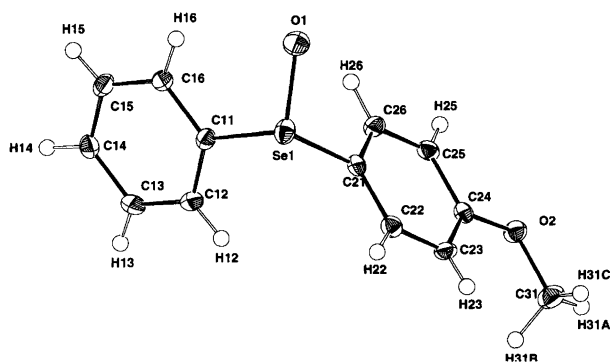
Fig. 1. ORTEPII drawing showing the atomic labeling.
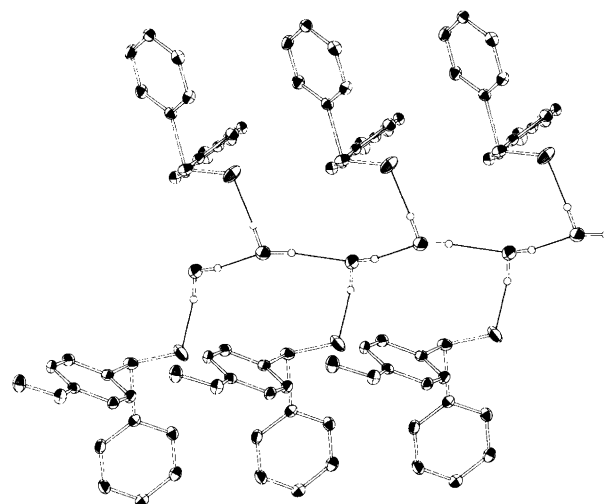
Fig. 2. The packing drawing shows the hydrogen-bond pattern in the structure.

Table 3. Hydrogen-bond distances (Å) and angles (°).

D–H$\cdots$A	D$\cdots$A	H$\cdots$A	D–H$\cdots$A	D–H
O3–H3A$\cdots$O3^i	2.887(1)	2.02(3)	171(3)	0.89(3)
O3–H3B$\cdots$O1^{ii}	2.740(2)	1.80(3)	167(3)	0.96(3)

Symmetry codes: ^{i}½ + x, ½ − y, −z; ^{ii}x − ½, ½ − y, 1 − z.

The water molecules related by the twofold screw axis parallel to the short a-axis are connected by hydrogen bonds. The selenoxide molecules related by the same screw axis are linked to these infinite chains of water molecules through another set of hydrogen bonds. Using the graph set method described by Etter,[15] the infinite chain of hydrogen-bonded water molecules has the graph set $C(2)$ and the other hydrogen bond O3–H3B$\cdots$O1 has the graph set D; thus it is possible to describe the entire hydrogen-bond pattern by the unitary graph set $N_1 = C(2)D$.

There is a pronounced difference in the O–O hydrogen bond distance of the two linear hydrogen bonds. O3$\cdots$O3 is significantly longer than O3$\cdots$O1, 2.887(1) Å compared to a 2.740(2) Å. This difference in hydrogen-bond lengths supports the assumption that O1 carries a partial negative charge. In addition to the hydrogen-bond interactions, the packing is influenced by stacking of the phenyl groups as shown in the stereo pair in Fig. 3.

Bond lengths and angles of 1 are presented in Table 4. The tetrahedral arrangement around Se shows that the crystal studied contains the Se atom in a (S)-configuration. The small difference in Se–C11 and the Se–C21 distances could be due a small increase of the double bond character of the Se–C21 bond, induced by the methoxy group.

The geometry of the two benzene rings in 1 are distorted by their substituents from the idealized hexagonal symmetry. Substituent effects on the geometry of
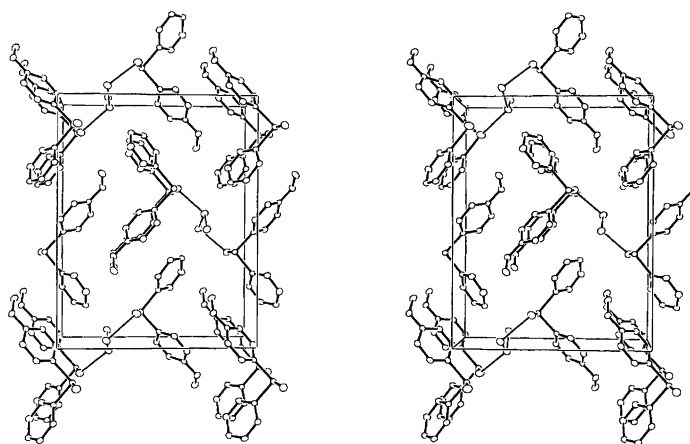
Fig. 3. Stereo pair of the packing in the unit cell seen along the crystallographic *a*-axis.

Table 4. Selected geometric parameters.

Bond lengths (Å)

Se1–O1	1.683(2)	C14–C15	1.374(3)
Se1–C21	1.931(2)	C15–C16	1.394(3)
Se1–C11	1.945(2)	C21–C22	1.379(3)
O2–C24	1.366(3)	C21–C26	1.390(4)
O2–C31	1.430(3)	C22–C23	1.393(3)
C11–C12	1.383(4)	C23–C24	1.385(3)
C11–C16	1.388(3)	C24–C25	1.391(3)
C12–C13	1.390(3)	C25–C26	1.382(3)
C13–C14	1.389(4)		

Bond angles (°)

O1–Se1–C21	104.6(1)	C22–C21–Se1	118.6(2)
O1–Se1–C11	100.9(1)	C26–C21–Se1	120.0(2)
C21–Se1–C11	97.36(8)	O2–C24–C23	124.3(2)
C12–C11–Se1	120.8(2)	O2–C24–C25	115.1(2)
C16–C11–Se1	117.2(2)	C22–C21–C26	121.3(2)
C12–C11–C16	121.9(2)	C24–C23–C22	119.4(2)
C11–C12–C13	118.6(2)	C26–C25–C24	120.0(2)
C11–C16–C15	118.5(2)	C21–C22–C23	119.6(2)
C14–C13–C12	120.2(2)	C25–C26–C21	119.0(2)
C14–C15–C16	120.4(2)	C23–C24–C25	120.7(2)
C15–C14–C13	120.4(2)		

Torsion angles (°)

O1–Se1–C11–C12	159.5(2)	O1–Se1–C21–C22	139.7(2)
O1–Se1–C11–C16	−23.7(2)	O1–Se1–C21–C26	−37.6(2)
C21–Se1–C11–C12	52.9(2)	C11–Se1–C21–C22	−116.9(2)
C21–Se1–C11–C16	−130.2(2)	C11–Se1–C21–C26	65.8(2)

the benzene ring have been investigated by Domenicano and Murray-Rust.[16] They found that these effects appear to be additive. One of the phenyl groups attached to the selenoxide has a methoxy group in *para* substitution. Using the distortions reported for the methoxy group[16] we calculate the angle distortions exerted by the selenoxide on the 4-methoxyphenyl group to be $\Delta\alpha = 1.9°$, $\Delta\beta = -1.5°$, $\Delta\gamma = 0.3°$ and $\Delta\delta = 0.4°$. Apart from the $\Delta\alpha$ value, these values compare well with the angle distortions caused by the selenoxide group on the mono-substituted phenyl group, $\Delta\alpha = 2.4°$, $\Delta\beta = -1.8°$, $\Delta\gamma = 0.3°$ and $\Delta\delta = 0.5°$.

Very limited structural information is available on substituted selenoxides. A search for the fragment C–Se(O)–C in the Cambridge Structural Database CSD (version 5.12)[17] resulted only in five structures with $R < 8\%$, that all had a phenyl group as one of the substituents on the Se–O group.[1–5] The bond distances and angles around the selenium atom were analysed with the program VISTA.[17] An overview of these results are shown in Table 5. The compounds were divided into two groups, one group where the other substituent is a sp^3-carbon and another group where it is a sp^2-carbon. The Se–C(Ph) bonds are generally longer in the latter group

Table 5. Results of the CSD search.

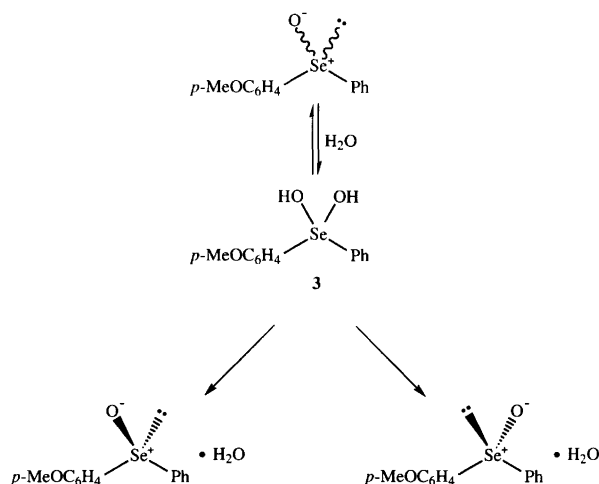| Refcode	Se–O/Å	Se–C(ph)/Å	Se–C/Å	C(ph)–Se–C/°	O–Se–C(ph)/°	O–Se–C/°
2IPh–Se(O)–C(sp³)						
JEKTAU	1.678	1.926	1.970	97.0	103.5	102.3
LICRIY	1.676	1.928	1.955	96.9	102.8	103.4
Ph–Se(O)–C(sp²)						
YIBYIR	1.648	1.942	1.956	95.7	100.8	103.4
YIHFIE	1.690	1.952	1.958	96.6	101.8	102.8
YULWUX	1.647	1.938	1.949	96.0	103.1	103.3

Fig. 4. Diagram illustrating how racemisation of the selenoxide occurs through a dihydroxy selenurane **3** intermediate.

of compounds. Furthermore there appears to be a correlation between the Se–O bond lengths and the C–Se–C angles, so that a short Se–O bond is associated with a small C–Se–C angle. However, apart from these observations the number of known selenoxide structures is too small to draw further conclusions.

Discussion

The monohydrate of **1** was prepared from symmetrical reagents; this leads to a product that contains the two enantiomers in equal amounts. Crystallization of such a racemic mixture will most frequently lead to the precipitation of a racemic compound, e.g. crystals containing both enantiomers in equal amounts. More rarely a spontaneous resolution may take place, so that a conglomerate of enantiomeric pure crystals are precipitated.[18] The observation that crystals of the monohydrate of **1** belong to the enantiomorphous space group $P2_12_12_1$ shows that it forms a conglomerate. This was further supported by the difference between the properties of the bulk material and a single crystal. Any single crystal melts sharply at 52–54 °C, whereas a mixture of the crystals melts diffusely in the range 48–58 °C, we interpret this as melting of a conglomerate that changes due to the dehydration during melting. This is supported by the

powder diffraction diagram recorded for the bulk material. It agrees perfectly with a diagram calculated from the crystal structure of the enantiomer.

The formation of racemic compounds is thermodynamically favoured by a small entropy term,[18] therefore one would expect that enantiomerically pure crystals must show an energetically favourable packing. It is apparent from an inspection of Fig. 2 that the hydrogen bond interactions could equally well connect molecules of opposite chirality. The spontaneous resolution of the 4-methoxyphenyl phenyl selenoxide is rather related to interactions between the phenyl groups. Figure 3 shows how the stacks of the 4-methoxyphenyl and the phenyl groups are oriented along the *b*-axis to make a very efficient packing. This observation is in line with the results from studies of the crystallisation of racemic mixtures, which showed that the weaker secondary interactions play a significant role in the crystallisation of racemates.[19,20]

The circular dichroism of the solutions made from the bulk material showed no effects of chirality, whereas solutions made in a similar way from a single crystal had a distinct circular dichroism, that only differed in the sign of its Cotton effects, which did not appear to change with time. These latter experiments on solutions made from a single crystal demonstrate that the chirality of the selenoxide is preserved in neutral solution even in the presence of one equivalent of water. Even after adding water to the acetonitrile solution of **1** the circular dichroism remained unchanged for more than a week. The circular dichroism and thereby the 'chirality' of the solution disappeared only after a catalytic amount of hydrochloric acid had been added. The same behavior was observed for the compound (+)-methyl-2,4,6-triisopropylphenyl selenoxide by Davis *et al.*[6] They also investigated (+)-methyl phenyl selenoxide which racemised in less than 10 s in the presence of 1 equiv. of water, and concluded that the difference in racemisation behavior is a consequence of steric hindrance in the formation of the dihydroxy selenurane.

Inspection of the hydrogen bond arrangement in Fig. 2 shows that the monohydroxy intermediate can be formed readily, whereas the side of the selenium atom most prone to nucleophilic appears to be protected by the substituents. This steric hindrance could explain why the

dihydroxy selenurane is not formed in neutral solution. To investigate the possible presence of a dihydroxy intermediate ^{77}Se NMR measurements were performed, but it was not possible to detect the dihydroxy selenurane intermediate by this technique. This supports the conclusion made earlier by Paetzold from IR spectroscopical data, that if the racemisation occur via a dihydroxy selenurane intermediate, it is only present in very small amounts.[8]

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