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Diastereomeric Oxathia[n](1,1′)ferrocenophanes[1]

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Novel oxathiaferrocenophanes have been synthesized by the reaction of 1,1′-bis(hydroxymethyl)ferrocene with dithiols bearing oxygen in chains. The reactions of 1,1′-bis(α-hydroxyethyl)ferrocenes with dithiols afforded mixtures of diastereomeric products from which pure stereoisomers were isolated and characterized. Some aspects concerning a stereochemical course of the reactions described are discussed.

[Keywords: 1,1′-Bis(α-hydroxyalkyl)ferrocenes, reactions with dithiols; Diastereomers; Ferrocene polyoxathiaethers; Oxathiaferrocenophanes]

Diastereomere Oxathia[n](1,1′)ferrocenophane[1]

Neue Oxathiaferrocenophane wurden durch Umsetzung von 1,1′-Bis(hydroxymethyl)ferrocen mit Dithiolen dargestellt, welche Sauerstoff in den Alkylketten enthalten. Die Reaktion von 1,1′-Bis(α-hydroxyethyl)ferrocenen mit Dithiolen führte zu Mischungen von Diastereomeren, aus welchen reine Stereoisomere isoliert und charakterisiert wurden. Einige Aspekte des stereochemischen Verlaufes dieser Reaktionen werden diskutiert.

Introduction

Until now only few syntheses of macrocycles incorporating the ferrocene unit were reported[2–7]. The general approach in a preparation of these compounds was based either on reactions of ferrocene diols with dithiols[2,4,5] or dichlorides[7], or 1,1′-ferrocenedicarboxylic acid chloride with diamines[3,6] or diols[3] (also diphenols).

In the course of studies on the synthesis of thiaferrocenophanes and macrocyclic ferrocene polyoxathiaethers and polythiaethers, we found that in some cases reactions of 1,1′-bis(α-hydroxylalkyl)ferrocenes with

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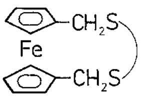
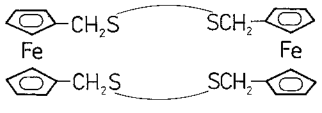
aliphatic dithiols afforded macrocycles bearing two ferrocene subunits (B) in high yields, whereas most of them gave mainly mononuclear products (A).

Recently, we have made an effort to complete the data concerning a structural dependence of the cyclization reaction product on the chain length of an alkane dithiol[8].



A



B

The present work was centred on the reactions of 1,1′-bis(hydroxymethyl)ferrocene and 1,1′-bis(α-hydroxyethyl)ferrocenes with aliphatic dithiols containing oxygen atoms in chains, namely 1,2-bis(2-mercaptoethoxy)ethane or bis-2-(2-mercaptoethoxy)ethyl ether.

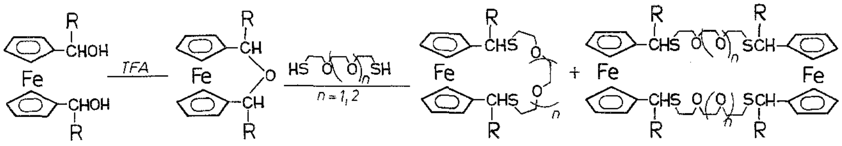
Results and Discussion

All reactions were carried out in high dilution in methylene chloride which appeared to be a solvent of choice, and in the presence of a catalytic amount of trifluoroacetic acid (*TFA*).

Reactions of 1,1′-bis(hydroxymethyl)ferrocene with the dithiols mentioned above cleanly afforded mononuclear polyoxathiaferrocenophanes, i.e., 2,11-dithia-5,8-dioxa[12](1,1′)ferrocenophane (**1**) and 2,14-dithia-5,8,11-trioxa[15](1,1′)ferrocenophane (**2**) in yields of 83%. The reactions can easily be followed by *TLC* since in the presence of *TFA* the starting diol very quickly converts to a readily detectable intermediate cyclic ether, i.e., 2-oxa[3](1,1′)ferrocenophane (cf. Scheme 1).

It seems as if a participation of the starting diol in the reaction with the dithiol can be neglected because of the intermediate cyclic oxaphane the disappearance of which marks the end of the reaction. It should be pointed out that the cyclization reactions of ferrocene diols with dithiols, although being of a nucleophilic substitution type, are different from the most frequently applied reactions of dihalides with dithiols, which are carried out under basic conditions. The reactions described here are much faster since they proceed via the extraordinary stable α-ferrocenylalkyl carbenium ions[8,9]. The presence of oxygen atoms in the dithiol chains make them more flexible, which is not the case with alkane dithiols. Hence, the yields of **1** and **2** are relatively high (83%), whereas for example the reaction of 1,1′-bis(hydroxymethyl)-

Scheme 1



R = H, CH_3

Cmpd	R	n	%
1	H	1	83
2	H	2	83
3a + 3b	CH_3	1	50
4a + 4b	CH_3	2	48

Cmpd	R	n	%
1a	H	1	7
2a	H	2	5

ferrocene with 1,8-octanedithiol yields only 36% of the expected 2,10-dithia[12](1,1')ferrocenophane[10].

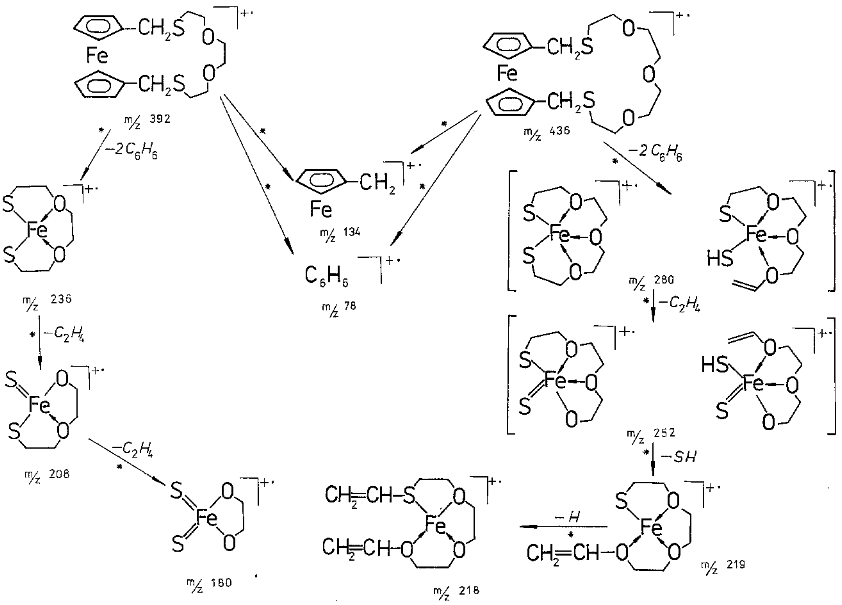
In order to obtain also binuclear macrocyclic compounds we changed the reaction conditions by placing both substrates into a reaction flask without simultaneous addition as required when a classical high dilution technique is applied. Earlier, such tactics had resulted in an almost exclusive formation (80%) of a binuclear macrocyclic ferrocene tetrathiaether when 1,1'-bis(hydroxymethyl)ferrocene was reacted with 1,3-propanedithiol[11]. For the reactions described only small amounts (5-7%) of the dimers were isolated, whilst the mononuclear products (**1** and **2**) were formed in somewhat lower yields (71%). Less diluted reaction mixtures gave mixtures of products which could not be separated.

The structures proposed for the new oxathia[n](1,1')ferrocenophanes are consistent with NMR, IR and mass spectra, molecular weights and elemental analyses (cf. Experimental). The ^{1}H-NMR spectra of **1** and **2** differ somewhat since a distinct triplet of CH_2-S protons of **1** changes in **2** to a multiplet being typical for an ABXY type spectrum. Similar difference can be seen between **1** and **1 a** in their ^{1}H-NMR spectra. Also the ^{13}C-NMR spectra of **1** and **2** are very similar though the difference of chemical shifts between carbons next to a sulphur atom is four times larger for **2** as compared with **1**.

The mass spectra of both **1** and **2** are very clear and the proposed fragmentation pathways, confirmed by the appropriate metastables are shown in Scheme 2. In both compounds the molecular ions are the most intense peaks. Peaks at *m*/z 134 and 78 are present in both mass spectra.

Although *Vögtle* and *Oepen* had already used the reaction between 1,1'-bis(α-hydroxyethyl)ferrocenes and dithiols to prepare oxathiaferrocenophanes[3], we have repeated this reaction under improved conditions (CH_2Cl_2, *TFA*) in order to separate and characterise the stereoisomers.

Scheme 2



The mixture of diastereomeric 1,1′-bis(α-hydroxyethyl)ferrocenes (meso + rac.) was reacted with the dithiols already mentioned and the reactions were followed by *TLC*/Al_2O_3 (hexane-ether-chloroform, 10:2:1). It was noted, that the diastereomeric diols are converted into the mixture of intermediate cyclic ethers, i.e., *trans*- and *cis*-1,3-dimethyl-2-oxa[3](1,1′)ferrocenophanes during the first minutes of the reaction; then after one hour an almost exclusive formation of one stereomeric oxathiaphane was observed. At the same time the more reactive intermediate, i.e., *cis*-1,3-dimethyl-2-oxa[3](1,1′)ferrocenophane began to disappear and after 4–5 h it was completely consumed. On the basis of the chromatographic similarity to *trans* (rac.)- and *cis* (meso)-1,3-dimethyl-2-oxa[3](1,1′)ferrocenophanes, where R_F(meso) < R_F(rac.)[12], it may be assumed that the faster migrating stereoisomers (**3 b** and **4 b**) are racemic forms, and **3 a** and **4 a** which are formed in higher yields are meso forms. The molar ratios of the diastereomers isolated by preparative *TLC* (alumina, benzene-ether, 10:1) were in both cases meso:rac. ~ 1.7:1. This result is in agreement with a difference in the reactivity of intermediate cyclic ethers. It can be assumed that the *cis* intermediate, being more reactive than its *trans* counterpart, reacts with a dithiol affording in a relatively short time the meso product. The less reactive *trans* isomer reacts with the dithiol with a lower rate, thus the competitive polymerization reaction decreases the yield of the second diastereomer. This assumption was partly confirmed by the results of separate experiments in which pure *trans*- or *cis*-1,3-dimethyl-2-oxa[3](1,1')ferrocenophanes were employed instead of the diastereomeric mixture of 1,1'-di(α-hydroxyethyl)ferrocenes, as substrates in reactions with dithiols.

If *trans*-1,3-dimethyl-2-oxa[3](1,1')ferrocenophane was used as a substrate, a highly efficient ($> 90\%$) and stereoselective formation of only the faster migrating product was observed in each reaction. Surprisingly, the amount of polymer formed was smaller than expected. In contrast, with *cis*-1,3-dimethyl-2-oxa[3](1,1')ferrocenophane partial isomerization took place and the meso product obtained was contaminated with the racemic form.

Thus, the assumption made at the beginning, that the role of the starting diols in the reactions in question could be neglected, may not be fully justified.

The ^{1}H-NMR spectra of the stereoisomers **3a** and **3b**, or **4a** and **4b** at 60 MHz are indistinguishable, however a slight difference (0.04 ppm) of the chemical shifts of the methyl protons for the **3a** and **3b** pair was observed at 100 MHz.

The mass spectra are quite similar within pairs of the stereoisomers and proposed fragmentations are generally similar to those shown in Scheme 2, differing only in the ferrocene part. In the case of the **3a** and **3b** pair the most abundant ion peaks (m/z 236) result via $C_6H_5CH_3$ elimination from the parent ions, while the mass spectra of **4a** and **4b** show molecular ions as the most intense peaks.

An additional indication as to the stereochemistry of the compounds, assumed as meso, is provided by their pronounced tendency to polymerize during prolonged storage. An examination of *Dreiding* models indicates that the meso are more "sterically crowded" than the racemic forms and therefore may tend to decompose easier. A final answer is expected from an X-ay study which is now in progress.

Acknowledgement

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Experimental

The ^{1}H-NMR-spectra were obtained on JEOL JNM-C-6OH, Tesla BS 492 C-80 and Varian XL-100 MHz spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C-NMR spectra were obtained on a Bruker 90 MHz spectrometer at 22.63 MHz. All infrared (IR) spectra were recorded on a UR-20 spectrometer (Carl Zeiss, Jena). The mass spectra (MS) were measured on a LKB 9000 S instrument with direct inlet system at 70 eV electron energies. The molecular weight determinations were performed by isothermal distillation method on a MICROMOL OX-103 apparatus (Budapest). Melting points were determined on a *Böetius* apparatus and are uncorrected. The elemental analyses were performed by the Laboratory of Microanalysis and Automatization of Analytical Methods, CBM i M PAN (Łódź). Reagent grade solvents were used without further purification. 1,1'-Bis(hydroxymethyl)ferrocene[13], 1,1'-bis(α-hydroxyethyl)ferrocenes[14], *trans*- and *cis*-1,3-dimethyl-2-oxa[3](1,1')ferrocenophanes[12] and both dithiols[15] were prepared in our laboratory according to published methods.

General procedure

The oxathiaferrocenophanes were prepared by simultaneous dropwise addition of 1,1'-bis(α-hydroalkyl)ferrocene (4 mmol) dissolved in 50 ml of CH_2Cl_2-benzene, 1:1 and the dithiol (4 mmol) dissolved in 50 ml of CH_2Cl_2 into 350 ml of vigorously stirred and refluxing CH_2Cl_2 containing 5 drops of trifluoroacetic acid. The reaction was monitored by *TLC* (DC, Aluminiumoxid 60 F-254 neutral, Merck, benzene) and carried out until complete disappearance of a cyclic intermediate ether (ca. 24 h). The reaction mixture was washed with 5% aqueous ammonia and water, dried over anh. $MgSO_4$. The solvent was evaporated and the crude product was chromatographed (column or preparative *TLC*). Specific details and characteristics are given for each compound.

2,11-Dithia-5,8-dioxa[12](1,1')ferrocenophane (**1**)

The crude product was chromatographed on an alumina column (basic, deactivated) with benzene to yield 1.3 g (83%) of orange crystals, mp. 125-127 °C. IR (CCl_4): 3070, 2860 (br), 1400, 1360 and 1350 (d), 1065, 1035, 1025 cm^{-1}. ^1H-NMR (δ): 2.80 (t, 4 H, SCH_2), 3.78 (s, 4 H, *Fc*$\mathbf{CH_2}$), 3.85 (s, 4 H, OCH_2CH_2O), 3.92 (t, 4 H, CH_2O), 4.21 (br. s, 8 H, *Fc*). ^{13}C-NMR ($CDCl_3$, δ): 31.57 and 31.78 (CH_2S), 67.93, 69.57 and 85.29 (C_{Fc}), 70.67 (CH_2O), 73.20 (OCH_2CH_2O). MS (*m*/z, I.): M^+—392 (100), 236 (91), 208 (29), 180 (23), 134 (20), 78 (25). Anal. calcd. for $C_{18}H_{24}FeO_2S_2$: C 55.10; H 6.16; S 16.34; mol wt. 392.3. Found: C 55.43; H 6.53; S 15.90; mol wt. 408.

2,11,24,33-Tetrathia-5,8,27,30-tetraoxa[12,12](1,1')ferrocenophane (**1 a**)

Brown viscous oil, 0.11 g (7%). ^1H-NMR (δ): 2.75 (m, 8 H, SCH_2), 3.4-3.9 (multiplet overlapping with two singlets, 24 H, OCH_2 + *Fc*$\mathbf{CH_2}$ + OCH_2CH_2O), 4.12 (br. s, 16 H, *Fc*). The IR (CCl_4) spectrum is superimposable onto that of **1**. Anal. calcd. for $C_{36}H_{48}Fe_2O_4S_4$: C 55.10; H 6.16; S 16.34; mol. wt. 784.6. Found C 54.74; H 6.30; S 16.01; mol wt. 828.

2,14-Dithia-5,8,11-trioxa[15](1,1')ferrocenophane (**2**)

The pure product 1.45 g (83%) which was obtained by column chromatography as described for **1** crystallized as brown crystals, mp. 77-78.5 °C. IR (CCl_4): 3060, 2840 (br), 1400, 1360 and 1350 (d), 1285, 1245, 1120 (br), 1035 and 1020 cm^{-1}. ^1H-NMR (δ): 2.5-3.2 (m, 4 H, SCH_2), 3.70 and 3.78 (m + br. s, 4 H, OCH_2 + 4 H, *Fc*$\mathbf{CH_2}$ + 8 H, OCH_2CH_2O), 4.20 (br. s, 8 H, *Fc*). ^{13}C-NMR ($CDCl_3$, δ): 31.46 and 32.31 (CH_2S), 68.12, 69.68 and 85.80 (C_{Fc}), 71.05 and 71.24 (OCH_2CH_2O), 73.13 (CH_2O). MS (*m*/z, I.): M^+—436 (100), 280 (21), 252 (31), 219 (38), 218 (32), 134 (26), 78 (30). Anal. calcd. for $C_{20}H_{28}FeO_3S_2$: C 55.04; H 6.47; S 14.69; mol wt. 436.4. Found: C 55.19; H 6.48; S 14.81; mol wt. 470.

2,14,27,39-Tetrathia-5,8,11,30,33,36-hexaoxa[15,15](1,1')ferrocenophane (**2a**)

Brown viscous oil, 0.09 g (5%). ^{1}H-NMR (δ): 2.80 (m, 8 H, SCH_2), 3.3–3.95 (multiplet overlapping with two singlets, 32 H, OCH_2 + *Fc*$\mathbf{CH_2}$ + OCH_2CH_2O), 4.10 (br. s, 16 H, *Fc*). Anal. calcd. for $C_{40}H_{56}Fe_2O_6S_4$: C 55.04; H 6.47; S 14.69; mol wt. 872.8. Found: C 55.52; H 6.18; S 15.04; mol wt. 927.

(meso + rac.)-1,12-Dimethyl-2,11-dithia-5,8-dioxa[12](1,1')ferrocenophanes (**3a** + **3b**)

The crude mixture of the diastereomeric oxathiaphanes, **3a** + **3b** was roughly separated by column chromatography (deact. alumina, neutral, benzene). The pure stereoisomers were obtained on additional purification by preparative *TLC* (Aluminiumoxid F-254T, 1.5 mm; benzene-ether, 10:1). Total yield: 0.80 g (50%). After chromatographic separation 0.47 g of the meso form and 0.28 g of the racemic form was obtained (molar ratio, meso:rac. = 1.68).

3a (meso), yellow crystals, mp. 88–90 °C. ^{1}H-NMR (δ): 1.58 (d, 6 H, CH_3), 2.75 (m, 4 H, SCH_2), 3.70 (br. s, 4 H, OCH_2CH_2O), 3.5–4.5 (m, 4 H, CH_2O + 2 H, CH + 8 H, *Fc*). MS (*m*/z. I.): M^+—420 (85), 236 (100), 208 (25), 180 (19). Anal. calcd. for $C_{20}H_{28}FeO_2S_2$: C 57.15; H 6.71; S 15.25; mol wt. 420.3. Found (for the mixture meso + rac.): C 57.18; H 6.85; S 14.93; mol wt. 442.

3b (rac.), yellow crystals, mp. 96–98 °C. ^{1}H-NMR (δ): 1.58 (d, 6 H, CH_3), 2.75 (m, 4 H, SCH_2), 3.67 (br. s, 4 H, OCH_2CH_2O), 3.5–4.5 (m, 4 H, CH_2O + 2 H, CH + 8 H, *Fc*). MS (*m*/z, I.): M^+—420 (74), 236 (100), 208 (29), 180 (21).

(meso + rac.)-1,15-Dimethyl-2,14-dithia-5,8,11-trioxa[15](1,1')ferrocenophanes (**4a** + **4b**)

The crude mixture was chromatographed as described for **3**. The total yield was 0.90 g (48%). After preparative *TLC* 0.53 g of the meso form and 0.32 g of the racemic form was obtained (molar ratio meso:rac. = 1.66).

4a (meso), brown viscous oil. ^{1}H-NMR (δ): 1.62 (d, 6 H, CH_3), 2.4–3.1 (m, 4 H, SCH_2), 3.5–4.4 (multiplet overlapping with two broad singlets 4 H, OCH_2 + 2 H, CH + 8 H, OCH_2CH_2O + 8 H, *Fc*). MS (*m*/z, I.): M^+—464 (100), 280 (34), 252 (35), 219 (33), 218 (25). Anal. calcd. for $C_{22}H_{34}FeO_3S_2$: C 56.90; H 7.38; S 13.81; mol wt. 464.4. Found (for the mixture meso + rac.): C 57.12; H 7.11; S 13.48; mol wt. 491.

4b (rac.), brown-yellow crystals, mp. 89–91 °C. ^{1}H-NMR (δ): 1.62 (d, 6 H, CH_3), 2.4–3.1 (m, 4 H, SCH_2), 3.4–4.0 (multiplet overlapping with singlet, 4 H, OCH_2 + 2 H, CH + 8 H, OCH_2CH_2O), 4.10 (br. s, 8H, *Fc*). MS (*m*/e, I.): M^+—464 (100), 280 (44), 252 (44), 219 (47), 218 (29), 91 (25).

Reactions of trans- and cis-1,3-dimethyl-2-oxa[3](1,1')ferrocenophanes with the dithiols

The reactions were carried out as described in the general procedure. Instead of appropriate ferrocene diols cyclic ferrocene ethers were used.

The reactions of *trans*-1,3-dimethyl-2-oxa[3](1,1')ferrocenophane with both dithiols were carried out for 48 h. The racemic products were separated from minor impurities by column chromatography (deact. alumina, benzene): **3b** (93%), **4b** (91%).

The reaction mixtures obtained from *cis*-1,3-dimethyl-2-oxa[3](1,1')ferrocenophane were monitored by *TLC* and were not separated.

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