Calix[4]arene Rhenium(V) Complexes as Potential Radiopharmaceuticals

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The calix[4]arene platform was used for the syntheses of novel rhenium(V) complexes, that may have potential applications as radiopharmaceuticals. The reaction of $ReO(PPh_3)_2Cl_3$ with tetradentate N_2O_2-calix[4]arene ligand **8** in ethanol gave the novel mixed-ligand rhenium complex **9** with the structure $ReO(N_2O_2$-calix)OEt. The configuration was elucidated by using a number of ^{1}H NMR techniques. In **9**, the ethoxy ligand could be easily and quantitatively exchanged for another monodentate ligand to give complex **12**. Tetradentate N_2S_2-calix[4]-arene ligand **15** formed the rhenium complex **16** either via reaction with $ReO(PPh_3)_2Cl_3$ in an organic solvent or by reaction with rhenium gluconate in an aqueous solution. Complex **16** showed good stability in phosphate-buffered saline solution (37 °C, 5 d). The crystal structures of a mono- and a bimetallic complex were determined. The bimetallic N_2O_2-calixarene complex dimer **11** crystallized in the monoclinic space group *C*2/*c*, with a = 38.963(5) Å, b = 23.140(6) Å, c = 27.382(6) Å, β = 128.456(10)°, V = 19 333(7) Å^3, Z = 8, and final R = 0.0519. The monometallic N_2S_2 model complex **17** crystallized in the monoclinic space group *Cc*, with a = 15.715(2) Å, b = 12.045(2) Å, c = 20.022(3) Å, β = 94.863(12)°, V = 3776.3(10) Å^3, Z = 4, and final R = 0.0342.

Introduction

The chemistry of technetium and rhenium has developed rapidly owing to the importance of the metastable γ-emitting isomer ^{99m}Tc in diagnostic nuclear medicine and the more recent introduction of β^--emitting isotopes ^{188}Re and ^{186}Re in radiotherapy.[1] A great number of chelates of technetium and rhenium have been prepared in the search for novel, selective, and effective agents for diagnostic imaging and therapy.[2] The most commonly used chelates are the N_2S_2 or N_2O_2 metal(V) oxo systems shown in Chart 1. A large variety of complexes with BAT (bis(aminoethanethiol)) (**1**), DADT (diamide dithiol) (**2**, **3**), MAMA (monoamine monoamide) (**4**), and Schiff-base ligands (**5**, **6**) derived from salicylaldehyde and mono- or diamines have been described in the literature.[3] Recently, we showed that a variety of monodentate ligands can be combined with tetradentate Schiff-base ligands to give mixed-ligand rhenium complexes (compounds **6**, X = OAlk, OAr, SAlk, OC(O)Alk).[4]

Calix[4]arenes are well-established building blocks in supramolecular chemistry,[5] into which a wide range of functional groups can be introduced.[6] We have used calix[4]arenes for a multitude of applications, e.g., for anion as well as cation binding and/or sensing,[7,8] in sensors for neutral molecules,[9] in catalysis,[10] as NLO active materials,[11] for antibody labeling,[12] and recently for the generation of combinatorial libraries.[13]

This paper presents the syntheses and characterizations of novel N_2O_2 (salen) tetradentate calix[4]arene mixed-ligand rhenium complexes. The monodentate ligand (OEt in Scheme 1) can be exchanged quantitatively for other ligands, demonstrating the potential of this system for linking biomolecules directly to the rhenium core. An N_2S_2 (DADT) tetradentate

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Chart 1. Ligand Systems Used for Complexation of Re and Tc

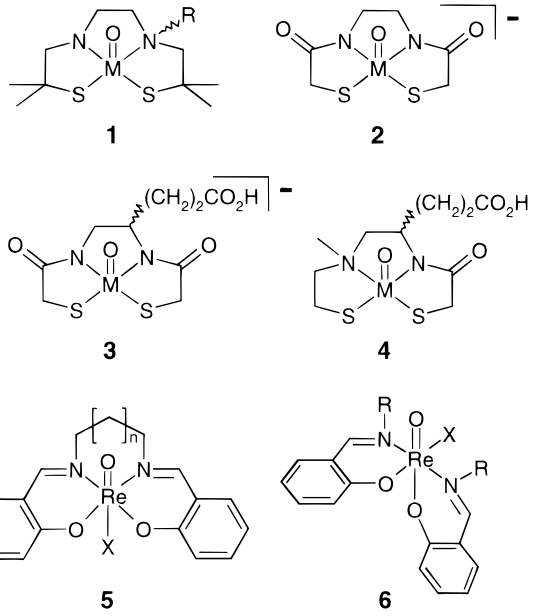
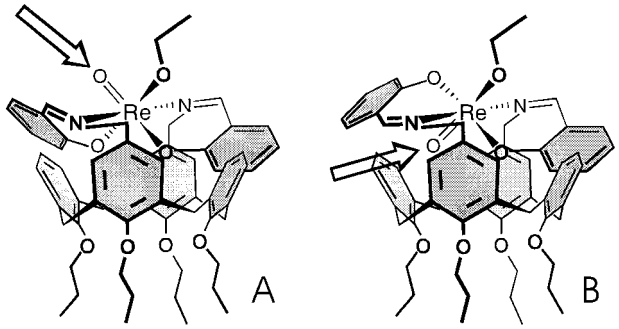


Chart 2. Possible Configurations of Complex **9**



calix[4]arene rhenium complex is synthesized both in organic solvents and in water, and its stability in a phosphorus-buffered saline solution (PBS) is demonstrated.

Results and Discussion

Syntheses and Characterizations of the N_2O_2-calix[4]arene Rhenium Complexes. The N_2O_2-calix[4]arene ligand was synthesized from 1,3-bis(methylamino)tetrapropoxycalix[4]arene (**7**). Addition of 2 equiv of salicylaldehyde gave the bis(Schiff base)calix[4]arene **8** in quantitative yield. In the ^{1}H NMR spectrum of **8**, the (broad) singlet at 13.5 ppm (ArOH), the singlet at 8.30 ppm (CH═N), and the singlet at 4.55 ppm (ArC*H*$_2$N), together with the AB system (methylene protons) that is characteristic for a symmetrically substituted calix[4]arene, clearly proved its formation.

The reaction of **8** with $ReO(PPh_3)_2Cl_3$ in a refluxing mixture of EtOH and $CHCl_3$ in the presence of Et_3N gave complex **9** in a 63% yield after purification by size exclusion chromatography (Sephadex LH-20). The ^{1}H NMR spectrum of **9** clearly proved its formation, showing two anisochronous imine signals at 7.60 and 7.16 ppm. The two double doublets at 5.35 and 4.73 ppm (anisochronous methylene protons) and the double doublet located at 1.32 ppm (methyl protons) showed the presence of the monodentate ethoxy substituent.[14]

Although the presence of two different imine signals indicated the formation of an asymmetric complex, the overall configuration of the complex could not be deduced from the ^{1}H NMR spectrum. CPK molecular models suggested two possible configurations, **A** and **B** (Chart 2), which are both asymmetric but have quite different ligand arrangements, the main difference being the relative positions of the oxo and ethoxy ligands (i.e., *mer* in the case of **A** and *fac* in the case of **B**). To elucidate the correct structure of the complex, a series of NMR experiments were performed.

The imine proton signal at 7.16 ppm served as the starting point for further structural assignments. Scalar (long-range) couplings as indicated by COSY/TOCSY techniques afforded the neighboring ortho aromatic proton signal at 6.93 ppm, as well as the imine−methylene proton signals resonating upfield at 3.75 and 3.60 ppm. COSY and TOCSY walks yielded also the entire spin system of the imine- and oxygen-substituted aromatic moiety (6.70, 7.44, and 7.28 ppm) starting from the signal at 6.93 ppm.

Long-range contacts (TOCSY) were found for the imine−methylene protons and the ortho aromatic protons, located at 5.71 and 5.30 ppm. The large upfield shifts suggest a strong (electronic) influence of the Re nucleus on this side of the molecule, also found for the corresponding imine−methylene protons. Through-space contacts (ROESY) were found for the imine−methylene protons and the proton resonating at 5.71 ppm *only*, indicating that the imine substituent is pointing in the direction of the proton residing at 5.30 ppm and providing the "sense" of the substituted structure. The imine−methylene protons also showed through-space contacts with one of the ethoxy protons (5.35 ppm), proving the presence of the ethoxy group on this side of the molecule. The COSY spectrum (Figure 1) clearly shows the two anisochronous ethoxy protons (Et1 and Et2; see Chart 3 for the numbering scheme of **9**) and their

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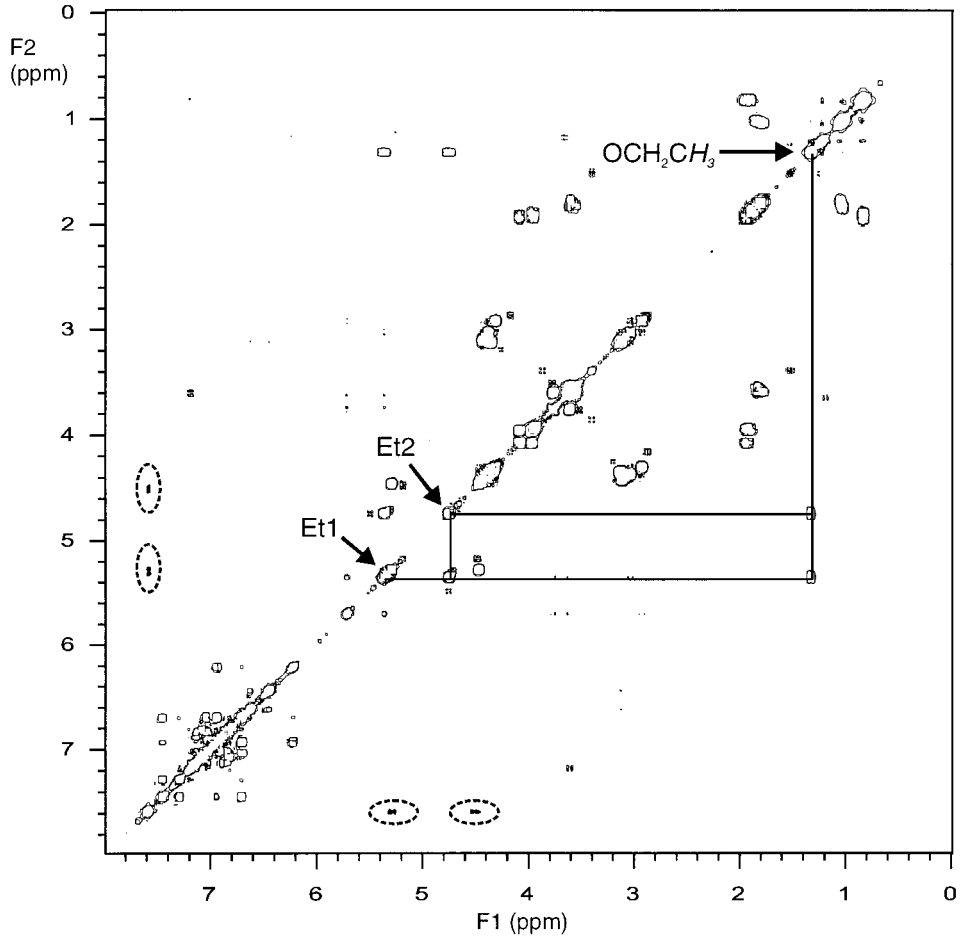
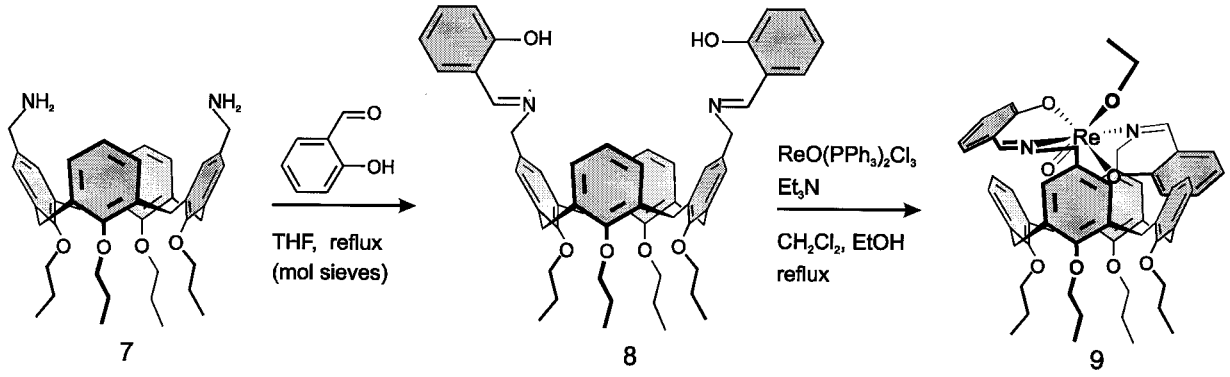


Figure 1. COSY spectrum of **9**. Note the strong contacts found for the imine protons and the corresponding methylene protons (encircled signals).

Scheme 1. Synthesis of N_2O_2-calix Rhenium Complex **9**



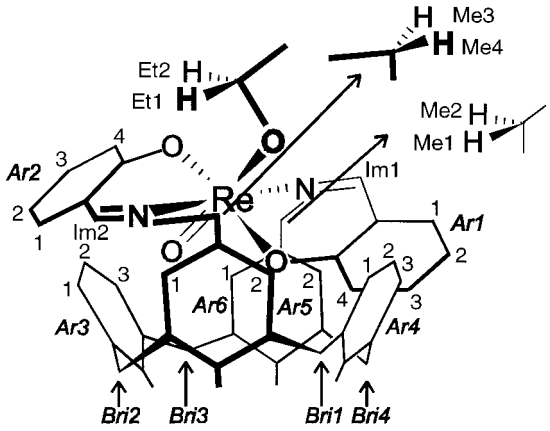
contacts with the OCH_2CH_3 protons. By using long-range contacts (COSY/TOCSY), the ortho aromatic protons at 5.71 and 5.30 ppm also provided the bridging methylene protons: the bridging protons afforded the neighboring ortho protons of the adjacent aromatic systems. ROESY/NOESY contacts provided the neighboring aromatic protons as well, whereas COSY and TOCSY walks yielded the other aromatic protons. From the other imine proton resonance at 7.60 ppm, the corresponding imine−methylene group, which is directed toward the Re═O group, could be assigned (5.29 and 4.44 ppm, COSY/TOCSY; see encircled signals in Figure 1). Long-range contacts identified the ortho aromatic proton at 7.04 ppm, whereas COSY/TOCSY walks yielded the other aromatic protons at 6.70, 6.93, and 6.20 ppm, respectively. By combining this information, we could assign all the resonances unambiguously.

Although the proposed structure (**B**) has all four donor atoms (i.e., N_2O_2) of the calix in a square planar arrangement around the oxorhenium core, the overall structure lacks any symmetry. This in contrast to structures known for simple N_2O_2 tetradentate salen rhenium complexes, which all possess a plane of symmetry (through the Re═O axis). However, the Re═O core is no longer aligned with the symmetry axis of the calix[4]arene part, thereby desymmetrizing the overall structure.

Attempts to crystallize **9** resulted in the formation of the dimeric structure **11** (Figure 2). In **11**, the Re═O, or rather the O═Re−O−Re═O axis, is now aligned with the symmetry axis of the calix[4]arene. This, combined with the 90° rotation angle between the halves that form the dimer (Figure 3), results in a complex with local S_4 symmetry in the crystal structure.

The μ-oxo bond most likely forms because the alkoxy

Chart 3. Numbering Scheme for Complex **9**[a]



[a] Aromatic bonds and propoxy substituents have been omitted for clarity. Ar(1...6) = aromatic rings 1 to 6 (e.g., Ar2-3 is hydrogen 3 of aromatic ring 2); Bri(1...4) = methylene bridges 1 to 4 (two hydrogens each); Im(1,2) = imine hydrogens 1 and 2; Me(1...4) = methylene hydrogens 1 to 4; Et(1,2) = ethoxy hydrogens 1 and 2.

moieties exchange with water from the air, after which they dimerize with elimination of a water molecule (Scheme 2), similar to reactions found for oxorhenium porphyrins[15] and rhenium dithioether complexes.[16] Although rhenium salen complexes are stable in the solid state and in a variety of solvents, previous work has shown that attempts to crystallize these complexes often result in the isolation of crystals of their corresponding dimers.[3k,17]

Previously we showed that the alkoxy ligand of rhenium salen alkoxy complexes can be quantitatively exchanged for a variety of other ligands (OAlk, OPh, SAlk, OC(O)Alk).[4] Similarly, the ethoxy ligand of **9** could be easily exchanged for another alkoxy ligand (Scheme 3). When **9** was refluxed in CH_2Cl_2 in the presence of an excess of MeOH, the methoxy complex **12** was isolated quantitatively. We plan to employ this ligand exchange reaction for the linkage of antibodies (ABs) via the SH or COOH moieties present in the constant region of antibodies.

Synthesis and Characterization of the N_2S_2-calix[4]arene Rhenium Complex. The synthesis of the DADT-type calix[4]-arene began with calix[4]arene **13** (Scheme 4), functionalized with two ethoxyethoxy substituents, to achieve some water solubility, and two (chloroacetamido)methyl moieties, which were introduced via a Tscherniac−Einhorn amidomethylation reaction.[18] The chloro moieties were converted into thiols, via reaction with potassium thiolacetate and subsequent hydrolysis of the thioesters to give **15** in nearly quantitative yield based on the initial amount of **13**. Reaction of **15** with $ReO(PPh_3)_2Cl_3$ in refluxing MeOH in the presence of Bu_4NOAc gave a red-brown precipitate, which was filtered off and washed with cold MeOH and diethyl ether to give analytically pure **16**.

The formation of rhenium complex **16** was proved by a combination of techniques. ^1H NMR showed a very broad spectrum, most likely due to the paramagnetic character of the complex. However, it did exhibit all the signals in the expected positions. A satisfactory elemental analysis, combined with FAB-MS peaks at *m*/*z* 973 (isotope pattern Re) for $[M - NBu_4]^-$ (negative mode) and *m*/*z* 1215 for M^+ (positive mode) and an IR signal at 976 cm^{-1} corresponding to $\nu_{Re=O}$, verified the molecular constitution of the complex. A CPK molecular model of the N_2S_2-calix[4]arene ligand shows that the two bidentate ligand arms can only coordinate in a trans rather than a cis fashion. This is also the preferred mode for binding of bidentate ligands that are not covalently connected, as can be clearly seen in the X-ray crystal structure of model N_2S_2 complex **17** (Figure 4), which was synthesized in the same way as the calix[4]arene rhenium complex **16**. On the basis of these observations, we expect **16** to have the configuration shown in Scheme 4.

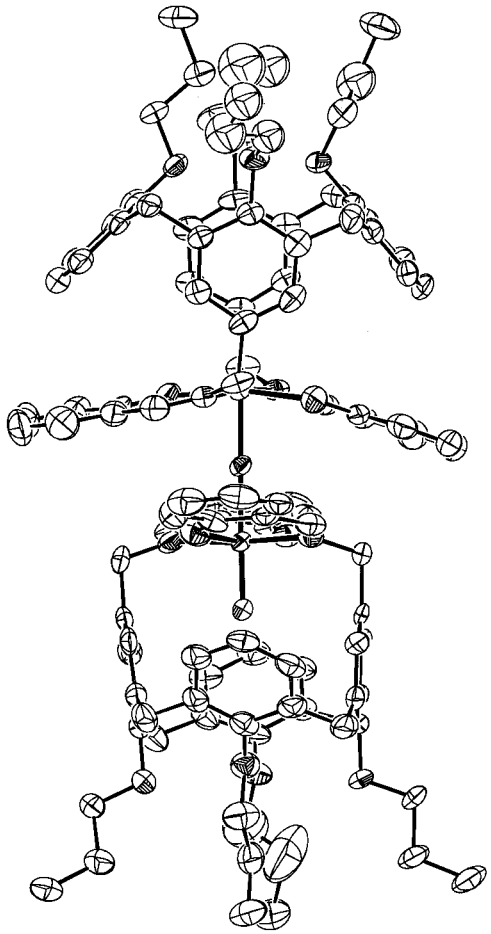


Figure 2. Atomic displacement ellipsoid plot[33] of calix dimer **11** drawn at the 50% probability level. Hydrogen atoms and the minor disorder component have been omitted for clarity.

In nuclear medicine, the source of all radioactive rhenium is a solution of sodium perrhenate in water. Therefore, if a complex is to be used in nuclear medicine, it must be possible to synthesize it under aqueous conditions, starting from this sodium perrhenate. As in the analogous case of technetium(V) gluconate,[19] rhenium(V) gluconate[20] is often used as a precursor for the preparation of rhenium(V) complexes. Exchange reactions with appropriate ligands may be carried out in aqueous or aqueous/organic solutions, and the resulting Re complexes are, as a rule, of high (radiochemical) purity. Rhenium gluconate was synthesized according to an adapted literature procedure,[20] using $NaReO_4$ instead of NBu_4ReO_4. After reaction of the N_2S_2-calix[4]arene ligand **15** with a basic rhenium gluconate solution for 1 h, the aqueous reaction mixture was extracted with

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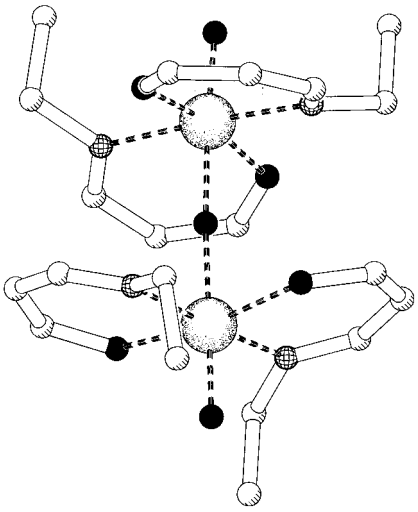


Figure 3. Coordination of Re in calix dimer **11**. Only the chelate rings and the attachment points of the calixarene are shown. Key: Re, dotted circles; O, black circles; N, cross-hatched circles; C, shaded circles.

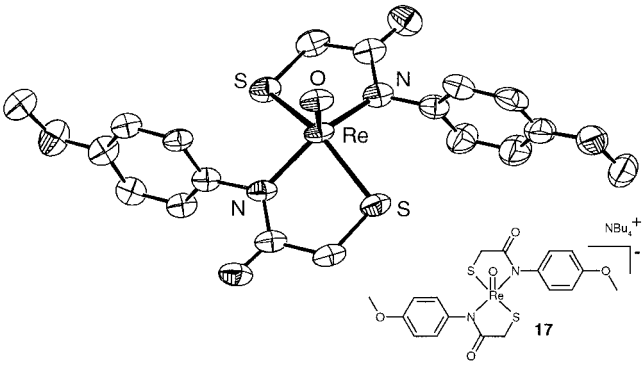


Figure 4. Structure and atomic displacement ellipsoid plot[33] of N_2S_2 model complex **17** drawn at the 50% probability level. Hydrogen atoms and the counterion have been omitted for clarity.

chloroform to give rhenium complex **16** in 93% yield. Analysis of the obtained product proved it to be identical to the complex synthesized in an organic solvent.

To investigate the stability of **16**, it was dissolved in an MeOH/phosphate-buffered saline solution (PBS) (1:99) and the resulting solution was allowed to stand at 37 °C for 5 days, after which it was extracted into chloroform and analyzed. Elemental analyses and FAB-MS and IR spectra showed no significant changes when compared to the original data, suggesting good stability of the complex under physiological conditions.

Conclusion

We conclude that calix[4]arenes are good platforms for the syntheses of novel potential radiopharmaceuticals. Both N_2O_2- and N_2S_2-calix[4]arene rhenium complexes could be synthesized, the latter showing good stability in PBS solution.

Experimental Section[21]

NMR experiments were performed using a Varian Unity 400 WB NMR spectrometer operating at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. ^{1}H and ^{13}C NMR, COSY,[22] clean-TOCSY (MLEV17),[23] NOESY,[24] and HMQC[25] experiments were used for the assignments of the ^{1}H and ^{13}C resonances. All 2D spectra were collected as 2D hypercomplex data.[26] Weighted with shifted sine-bell functions, the COSY data were Fourier transformed in the absolute-value mode while the clean-TOCSY (MLEV17) and HMQC data were transformed in the phase-sensitive mode. All data processing was performed using standard Varian VnmrS/VnmrX software packages. COSY and TOCSY spectra were accumulated with 256 increments and 32 scans per increment, typically. In the clean-TOCSY experiments, the mixing times of the MLEV17 pulse were arrayed between 30 and 100 ms; in the NOESY experiments, mixing times of 30−90 ms were applied. Routine spectra were recorded on a Varian Inova NMR spectrometer operating at 300 and 75.5 MHz for ^{1}H and ^{13}C, respectively. All spectra were recorded in $CDCl_3$ unless otherwise stated. Residual solvent protons were used as internal standards, and chemical shifts are given in ppm relative to tetramethylsilane (TMS). Fast atom bombardment (FAB) mass spectra were recorded on a Finnigan MAT 90 spectrometer using *m*-nitrobenzyl alcohol (NBA) as a matrix. All solvents were purified by standard procedures. All other chemicals were analytically pure and were used without further purification. All reactions were carried out under an inert argon atmosphere. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Melting points (uncorrected) of all compounds were obtained on a Reichert melting point apparatus. The calix[4]arenes **7**[6j] and **13**[18] and 2-chloro-*N*-(4-methoxyphenyl)acetamide[27] were prepared according to literature procedures.

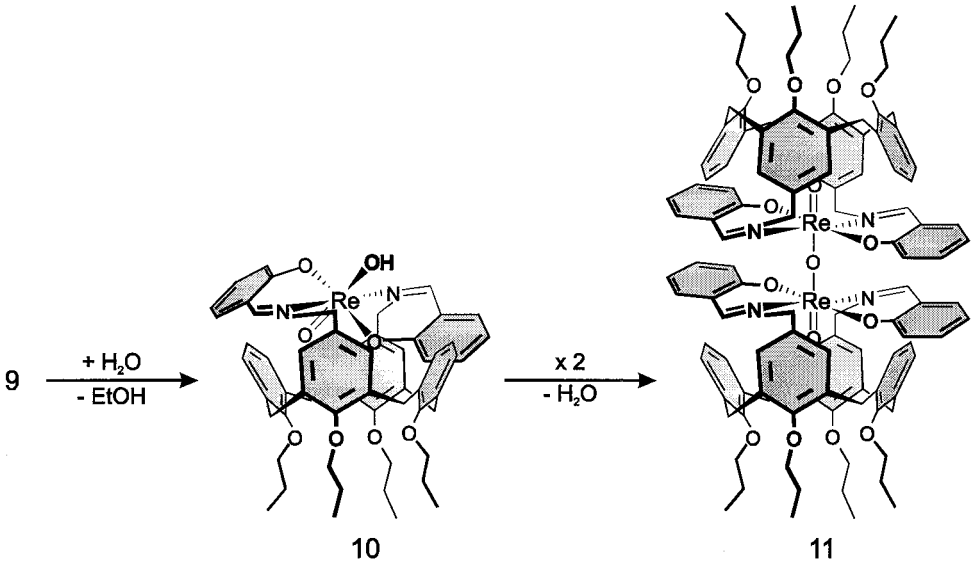
Calix-salen 8. A solution of **7** (0.37 g, 0.57 mmol) and salicylaldehyde (0.74 g, 1.14 mmol) in THF (30 mL) was refluxed over molecular sieves for 2 h, after which removal of the solvent in vacuo gave a yellow oil in quantitative yield. The ^{1}H NMR spectrum of the crude product showed the presence of some minor impurities, but the product was used without any further purification. ^{1}H NMR: δ 13.5 (b s, 2 H, ArOH), 8.30 (s, 2 H, CH═N), 7.31 (t, 2 H, J = 7.2 Hz, sal Ar H), 7.24 (d, 2 H, J = 7.1 Hz, sal Ar H), 6.95 (d, 2 H, J = 7.2 Hz, sal Ar H), 6.89 (t, 2 H, J = 7.2 Hz, sal Ar H), 6.70 (s, 4 H, Ar H), 6.47 (m, 6 H, Ar H), 4.55 (s, 4 H, CH_2N), 4.45 and 3.15 (AB-q, 2 × 4 H, J = 13.1 Hz, ArCH_2Ar), 3.93 (t, 4 H, J = 7.7 Hz, OCH_2), 3.82 (t, 4 H, J = 7.7 Hz, OCH_2), 1.93 (m, 8 H, CH_2CH$_3$), 0.94 (m, 12 H, CH_3).

The Calix-salen Rhenium OEt Complex 9. To a solution of crude **8** (1.08 g, 0.57 mmol) in a mixture of CH_2Cl_2 and EtOH (50 mL each) were added Et_3N (0.13 g, 1.25 mmol) and $ReO(PPh_3)_2Cl_3$ (0.48 g, 0.57 mmol), and the mixture was refluxed for 4 h, during which the reaction mixture turned dark green. Removal of the solvents in vacuo yielded a dark green solid, which was dissolved in CH_2Cl_2 (100 mL). The solution was washed with 1 N HCl (2 × 100 mL), water (100 mL), and brine (100 mL), after which it was dried with $MgSO_4$. The solvent was removed in vacuo to give the crude product. Chromatography using a Sephadex LH-20 column (CH_2Cl_2:MeOH = 1:1) yielded a green solid which was identified as **9**. Yield: 63%. Mp: >200 °C dec. ^{1}H NMR (400 MHz; see Chart 3 for numbering): δ 7.60 (b m, 1 H, CH_{Im1}), 7.44 (m, 1 H, CH_{Ar2-3}), 7.28 (m, 1 H, CH_{Ar2-4}), 7.16 (b m, 1 H, CH_{Im2}), 7.13 (m, 1 H, CH_{Ar3-3}), 7.06 (m, 1 H, CH_{Ar4-1}), 7.04 (m, 1 H, CH_{Ar1-1}), 7.01 (m, 1 H, CH_{Ar3-1}), 6.93 (m, 1 H, CH_{Ar2-1}), 6.93 (m, 1 H, CH_{Ar1-3}), 6.87 (m, 1 H, CH_{Ar3-2}), 6.81 (m, 1 H, CH_{Ar4-3}), 6.81 (m, 1 H, CH_{Ar4-2}), 6.70 (m, 1 H, CH_{Ar2-2}), 6.70 (m, 1 H, CH_{Ar1-2}), 6.63 (m, 1 H, CH_{Ar5-2}), 6.45 (m, 1 H, CH_{Ar5-1}), 6.20 (m, 1 H, CH_{Ar1-4}), 5.71 (m, 1 H, CH_{Ar6-2}), 5.35 (dq, $^2J_{AB}$ = 10.1 Hz, J = 6.8 Hz, 1 H, CH_{Et1}), 5.30 (m, 1 H, CH_{Ar6-1}), 5.29 (d, $^2J_{AB}$ = 13.2 Hz, 1 H, CH_{Me1}), 4.73 (dq, $^2J_{AB}$ = 10.1 Hz, J = 6.8 Hz, 1 H, CH_{Et2}), 4.44 (d, $^2J_{AB}$ = 13.2 Hz, 1 H, CH_{Me2}), 4.42 (m, 1 H, CH_{Bri3}), 4.37 (m, 1 H, CH_{Bri2}), 4.34 (m, 1 H, CH_{Bri4}), 4.30 (m, 1 H, CH_{Bri1}), 4.08 (m, 1 H, OCH_{propyl}), 3.96 (m's, 3 H, OCH_{propyl}), 3.75 (d, $^2J_{AB}$ = 15.2 Hz, 1 H, CH_{Me3}), 3.60 (d, $^2J_{AB}$ = 15.2 Hz, 1 H, CH_{Me4}), 3.58 (m's, 4 H, OCH_{propyl}), 3.12 (m, 1 H, CH_{Bri4}),

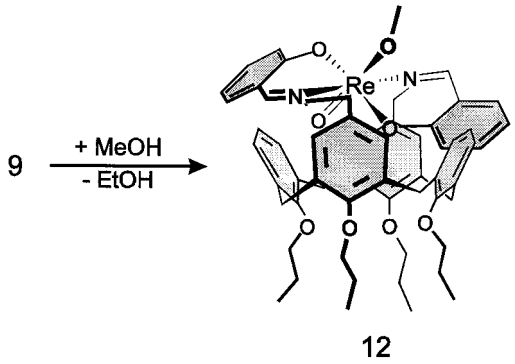
(21) The name calix[4]arene is used instead of the official CA name: pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecene-25,26,27,28-tetrol.

(22) Bax, A.; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542.
(23) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *65*, 355.
(24) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546.
(25) Bax, A.; Griffey, R. H.; Hawkins, B. L. *J. Magn. Reson.* **1983**, *55*, 301.
(26) States, D. J.; Haberkorn, R. A.; Ruben, D. J. *J. Magn. Reson.* **1982**, *48*, 286.
(27) Musser, J. H.; Chakraborty, U.; Bailey, K.; Sciortino, S.; Whyzmuzis, C. *J. Med. Chem.* **1987**, *30*, 62.

Scheme 2. Formation of Calix Dimer **11**



Scheme 3. Exchange of the Alkoxy Ligand



3.09 (m, 1 H, CH_{Bri3}), 3.02 (m, 1 H, CH_{Bri2}), 2.91 (m, 1 H, CH_{Bri1}), 1.92 (m's, 4 H, CH_2CH_3), 1.79 (m's, 4 H, CH_2CH_3), 1.32 (dd, $J = 6.8$ Hz, $J = 6.8$ Hz, 3 H, OCH_2CH_3), 1.02 (t, 3 H, CH_3), 1.01 (t, 3 H, CH_3), 0.83 (t, 3 H, CH_3), 0.81 (t, 3 H, CH_3). ^{13}C NMR: δ 171.3, 171.2, 169.9, 167.2, 157.8, 157.4, 155.2, 153.8, 137.6, 136.9, 136.5, 135.7, 135.3, 133.9, 133.6, 133.0, 132.7, 132.2, 130.7, 129.3, 129.2, 128.7, 127.7, 126.7, 125.3, 124.1, 122.8, 122.6, 121.6, 119.8, 119.3, 119.1, 118.3, 116.5, 77.2, 76.3, 71.3, 70.8, 31.1, 29.6, 23.5, 23.0, 22.8, 19.2, 10.9, 10.7, 9.8. FAB-MS (*m*/*z*, ^{187}Re, correct isotope pattern, NBA): 1105.2 $(M + H)^+$, 1060.2 $(M - OEt + H)^+$. Anal. Calcd for $C_{58}H_{65}N_2O_8Re$: C, 63.08; H, 5.93; N, 2.54. Found: C, 63.32; H, 6.08; N, 2.53.

The Calix-salen Rhenium OMe Complex 12. To a solution of **9** (0.15 g, 0.14 mmol) in CH_2Cl_2 (50 mL) was added 5 mL of MeOH. After the solution was refluxed for 2 h, the solvents were removed in vacuo to give **12** as a green solid. Yield: 100%. Mp: >200 °C dec. ^{1}H NMR: the spectrum was identical to that of **9**, but instead of the signals at δ 5.35, 4.73, and 1.32 (belonging to OEt), there was a signal at δ 4.70 (s, 3 H, OCH_3). ^{13}C NMR: δ 171.2, 171.1, 169.8, 167.1, 157.8, 157.4, 155.2, 153.7, 137.5, 137.0, 136.5, 135.6, 135.3, 133.8, 133.6, 133.0, 132.6, 132.2, 130.6, 129.3, 129.2, 128.7, 127.7, 126.7, 126.3, 125.3, 124.1, 122.7, 122.6, 121.6, 119.7, 119.3, 119.2, 118.3, 116.5, 77.4, 76.4, 71.2, 67.3, 31.1, 29.6, 23.5, 23.1, 22.5, 11.0, 10.6, 9.6. FAB-MS (*m*/*z*, ^{187}Re, correct isotope pattern, NBA): 1091.3 $(M + H)^+$, 1060.3 $(M - OMe + H)^+$. Anal. Calcd for $C_{57}H_{63}N_2O_8Re$: C, 62.79; H, 5.82; N, 2.57. Found: C, 63.02; H, 5.98; N, 2.49.

5,17-Bis[((2-acetylthio)acetamido)methyl]-25,27-bis(1-ethoxyethoxy)-26,28-dihydroxycalix[4]arene (14). A mixture of thiolacetic acid (0.17 g, 2.2 mmol) and K_2CO_3 (0.31 g, 2.2 mmol) in DMF (10 mL) was stirred for 15 min. A solution of **13** (0.79 g, 1.0 mmol) in DMF (10 mL) was then added dropwise over a period of 30 min. After the reaction mixture was stirred overnight in the dark, CH_2Cl_2 (200 mL) was added, and the resulting mixture was washed with 1 N HCl (5 × 100 mL), water (100 mL), and brine (100 mL). After the washed mixture was dried with $MgSO_4$, the solvent was removed in vacuo to give **14** as a light brown waxy solid. Yield: 99%. ^{1}H NMR: δ 8.11 (s, 2 H, OH), 6.92 (s, 4 H, Ar H), 6.91 (d, 4 H, $J = 7.3$ Hz, Ar H), 6.78 (t, 2 H, $J = 7.3$ Hz, Ar H), 6.41 (b s, 2 H, NH), 4.43 and 3.38 (AB-q, 2 × 4 H, $J = 13.2$ Hz, $ArCH_2Ar$), 4.25 (d, 4 H, $J = 5.6$ Hz, CH_2N), 4.17 (t, 4 H, $J = 4.4$ Hz, $ArOCH_2$), 3.89 (t, 4 H, $J = 4.4$ Hz, $ArOCH_2CH_2$), 3.68 (q, 4 H, $J = 7.0$ Hz, CH_2CH_3), 3.58 (s, 4 H, CH_2S), 2.21 [s, 6 H, $C(O)CH_3$], 1.28 (t, 6 H, $J = 7.0$ Hz, CH_3). ^{13}C NMR: δ 196.0, 165.6, 152.9, 151.8, 133.3, 128.9, 128.3, 128.2, 127.3, 125.2, 75.4, 69.0, 66.8, 42.8, 33.2, 31.0, 30.2, 15.1. FAB-MS (*m*/*z*, NBA): 859.3 $(M + H)^+$. Anal. Calcd for $C_{46}H_{54}N_2O_{10}S_2$: C, 64.31; H, 6.34; N, 3.26. Found: C, 64.22; H, 6.48; N, 3.29.

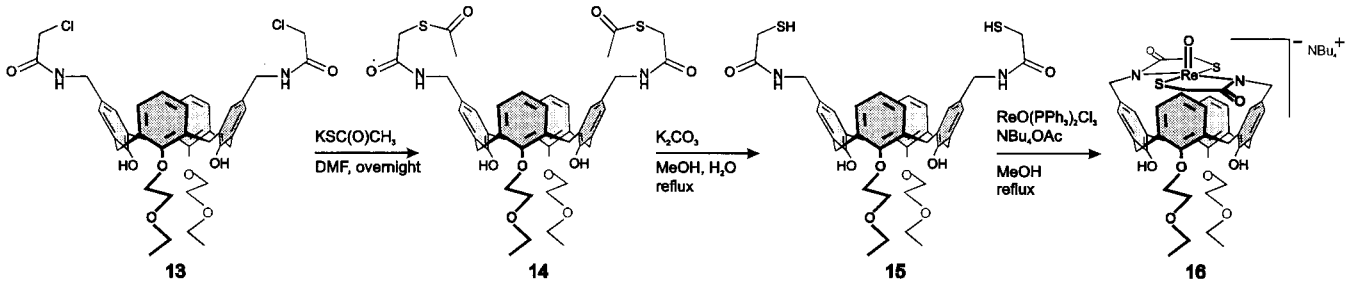
5,17-Bis[(2-mercaptoacetamido)methyl]-25,27-bis(1-ethoxyethoxy)-26,28-dihydroxycalix[4]arene (15). A mixture of **14** (0.75 g, 0.87 mmol) and K_2CO_3 (0.72 g, 5.22 mmol) in MeOH/H_2O (40 and 20 mL) was refluxed for 30 min, after which TLC analysis showed full conversion of the starting material. The reaction mixture was poured into a mixture of ice and 2 N HCl (100 mL each), after which the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), followed by drying with $MgSO_4$. Removal of the solvent in vacuo yielded a yellow oil, which was directly used without further purification.

The N_2S_2-Calix Rhenium Complex 16. (i) Synthesized in an Organic Solvent. A solution of crude **15** (0.22 g, 0.28 mmol) and Bu_4NOAc (0.37 g, 1.23 mmol) in MeOH (30 mL) was refluxed for 30 min. $ReO(PPh_3)_2Cl_3$ (0.23 g, 0.28 mmol) was added, and refluxing was continued for another 3 h, during which the solution turned red-brown. Cooling the solution to room temperature gave a precipitate, which was filtered off, washed with cold MeOH (5 mL) and diethyl ether (10 mL), and finally dried in vacuo, to give **16** as a red-brown solid. Yield (calculated from **14**): 62%.[28] Mp: >250 °C dec. IR (KBr, cm^{-1}): 976 ($\nu_{Re=O}$). FAB-MS (*m*/*z*, ^{187}Re, correct isotope pattern, NBA): positive mode, 1215.6 $(M)^+$; negative mode, 973.5 $(M - NBu_4)^-$. Anal. Calcd for $C_{58}H_{82}N_3O_9S_2Re$: C, 57.31; H, 6.80; N, 3.46. Found: C, 57.47; H, 6.85; N, 3.44.

(ii) Synthesized in Water. A degassed rhenium(V) gluconate solution (3.3 mL, 224 μmol) was adjusted to pH 10 by 1 N NaOH, and a solution of crude **15** (176 mg, 224 μmol) dissolved in 0.5 mL of degassed MeOH was added. The color rapidly changed to red-brown.

(28) Concentration of the reaction mixture to increase the yields led to precipitation of PPh_3 and thus to an impure product. No further attempts were made to improve this yield.

Scheme 4. Synthesis of N_2S_2-calix Rhenium Complex **16**



After the solution was stirred for 1 h, NBu_4Cl (62 mg, 224 μmol) was added and the solution was extracted with chloroform (3 × 5 mL). The combined extracts were dried with $MgSO_4$. Removal of the solvent in vacuo yielded **16** as a red-brown solid. Yield: 93%. Mp: >250 °C dec. IR (KBr, cm^{-1}): 975 ($\nu_{Re=O}$). FAB-MS (*m*/*z*, ^{187}Re, correct isotope pattern, NBA): positive mode, 1215.5 $(M)^+$; negative mode, 973.4 $(M - NBu_4)^-$. Anal. Calcd for $C_{58}H_{82}N_3O_9S_2Re$: C, 57.31; H, 6.80; N, 3.46. Found: C, 57.21; H, 6.95; N, 3.39.

(2-Acetylmercapto)acetic Acid *p*-Anisidide (18). A mixture of thiolacetic acid (0.17 g, 2.2 mmol) and K_2CO_3 (0.31 g, 2.2 mmol) in DMF (10 mL) was stirred for 15 min. A solution of 2-chloro-*N*-(4-methoxyphenyl)acetamide (0.40 g, 2.0 mmol) in DMF (10 mL) was then added dropwise over a period of 30 min. After the reaction mixture was stirred overnight in the dark, CH_2Cl_2 (200 mL) was added and the resulting mixture was washed with 1 N HCl (5 × 100 mL), water (100 mL), and brine (100 mL). After the washed mixture was dried with $MgSO_4$, the solvent was removed in vacuo to give a light brown waxy solid, which was recrystallized from toluene to give pure **18**. Yield: 75%. Mp >175 dec. ^1H NMR: δ 8.00 (b s, 1 H, NH), 7.41 (d, 2 H, J = 7.8 Hz, Ar H), 6.82 (d, 2 H, J = 7.8 Hz, Ar H), 3.79 (s, 3 H, OCH_3), 3.63 (s, 2 H, CH_2S), 2.42 [s, 3 H, $C(O)CH_3$]. ^{13}C NMR: δ 194.6, 167.1, 155.6, 147.6, 129.4, 112.8, 55.3, 37.5 32.4. FAB-MS (*m*/*z*, NBA): 227.3 $(M)^+$. Anal. Calcd for $C_{11}H_{13}NO_3S \cdot 0.25$toluene: C, 58.38; H, 5.76; N, 5.38. Found: C, 58.28; H, 5.81; N, 5.42.

Mercaptoacetic Acid *p*-Anisidide (19).[29] A mixture of **18** (0.15 g, 0.66 mmol) and K_2CO_3 (0.17 g, 1.32 mmol) in MeOH/H_2O (20 and 10 mL) was refluxed for 30 min, after which TLC analysis showed full conversion of the starting material. The reaction mixture was poured into a mixture of ice and 2 N HCl (100 mL each), and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), after which they were dried with $MgSO_4$. Removal of the solvent in vacuo yielded a yellow oil, which was directly used without further purification. Yield: 95%. ^1H NMR: δ 8.40 (b s, 1 H, NH), 7.43 (d, 2 H, J = 7.8 Hz, Ar H), 6.86 (d, 2 H, J = 7.8 Hz, Ar H), 3.69 (s, 3 H, OCH_3), 3.37 (d, 2 H, J = 9.2 Hz, CH_2S), 2.00 (t, 1 H, J = 9.2 Hz, SH).

The N_2S_2 Model Complex 17. To a degassed, refluxing solution of **19** (0.12 g, 0.61 mmol) in MeOH (35 mL) were added NBu_4OAc (0.55 g, 1.83 mmol) and $ReO(PPh_3)_2Cl_3$ (0.26 g, 0.30 mmol). The reaction mixture was refluxed for 2 h, CH_2Cl_2 (150 mL) was added, and the mixture was washed with H_2O (100 mL) and brine (100 mL), after which it was dried with $MgSO_4$. After evaporation of the solvent, the crude reaction mixture was dissolved in MeOH (10 mL), and diethyl ether (50 mL) was then added to precipitate complex **17**. Yield: 65%. Mp >250 °C dec. ^1H NMR: δ 7.17 (d, 2 H, J = 8.8 Hz, Ar H), 6.90 (d, 2 H, J = 8.8 Hz, Ar H), 3.85 and 3.71 (AB-q, 2 × 2 H, J = 17.6 Hz, CH_2S), 3.82 (s, 3 H, OCH_3), 3.02 (m, 8 H, NCH_2), 1.51 (m, 8 H, NCH_2CH_2), 1.35 (m, 8 H, CH_2CH_3), 0.99 (t, 12 H, J = 7.0 Hz, CH_3). ^{13}C NMR: δ 195.9, 156.6, 147.8, 129.6, 112.7, 58.7, 55.3, 23.8, 19.7, 13.6. FAB-MS (*m*/*z*, ^{187}Re, correct isotope pattern, NBA): positive mode, 836.2 $(M + H)^+$, 1077.5 $(M + NBu_4)^+$; negative mode, 592.7 $(M - NBu_4)^-$. Anal. Calcd for $C_{34}H_{54}N_3O_5S_2Re$: C, 48.90; H, 6.52; N, 5.03. Found: C, 49.02; H, 6.59; N, 5.14.

(29) Mercaptoacetic acid *p*-anisidide was synthesized previously via a variety of synthetic routes, e.g.: (a) Bhandari, C. S.; Mahnot, U. S.; Sogani, N. C. *J. Prakt. Chem.* **1971**, *313*, 849. (b) Bateja, S.; Verma, S.; Bhandari, C. S.; Sogani, N. C. *J. Prakt. Chem.* **1979**, *321*, 134.

Table 1. Crystallographic Data for Calix Dimer **11** and N_2S_2 Model Complex **17**

	11	**17**
formula	$C_{112}H_{120}N_4O_{15}Re_2$	$[C_{18}H_{18}N_2O_5ReS_2]^+$ $[C_{16}H_{36}N]^-$
mol wt	2134.55	835.16
cryst system	monoclinic	monoclinic
space group	*C*2/*c* (No. 15)	*Cc* (No. 9)
Z	8	4
a, Å	38.963(5)	15.715(2)
b, Å	23.140(6)	12.045(2)
c, Å	27.382(6)	20.022(3)
β, deg	128.456(10)	94.863(12)
V, Å^3	19 333(7)	3776.3(10)
D_{calcd}, g cm^{-3}	1.467	1.469
μ_{calcd} (Mo Kα), cm^{-1}	2.6	3.4
R1[a] [$I > 2\sigma(I)$]	0.0519 (13042 reflns)	0.0342 (6831 reflns)
wR2[b]	0.1268	0.0878
GOF	1.025	1.035

[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.

Crystal Structure Determination of Calix[4]arene Dimer 11 and N_2S_2 Model Complex 17. Crystals of **11** were obtained by slow evaporation of a $CDCl_3$ solution of **9**. Crystals of **17** were obtained by vapor diffusion of diethyl ether into a methanolic solution of **17**. Crystals suitable for X-ray structure determination were glued to the tops of glass capillaries and transferred into a cold nitrogen stream on an Enraf-Nonius CAD4-T diffractometer (**11**) or a Nonius Kappa CCD diffractometer (**17**), both on a rotating anode. The unit cell parameters were checked for the presence of higher lattice symmetry.[30] Crystal data and details of the data collections are collected in Table 1. Data were collected at 150 K using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å).

The structures of **11** and **17** were solved by automated direct methods and automated Patterson methods, respectively (SHELXS-86).[31] Refinements on F^2 were carried out using full-matrix least-squares techniques (SHELXL-97).[32] For both compounds, refinements converged with $\Delta/\sigma_{max} \leq 0.005$ and $\Delta/\sigma_{av} < 0.000$. Hydrogen atoms were included in the refinements in calculated positions riding on their carrier atoms. All ordered non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were included in the refinements with fixed isotropic atomic displacement parameters related to the values of the equivalent isotropic displacement parameters of their carrier atoms.

For **11**, 91 292 reflections were measured ($1.6 < \theta < 25.25°$; $-46 < h < 44$, $-27 < k < 23$, $-32 < l < 30$; ϕ and ω area detector scans, with a crystal to detector distance of 40 mm; 21 h X-ray exposure time), 17 479 of which were unique ($R_{int} = 0.0832$, $R_\sigma = 0.0732$) for a crystal of approximate dimensions 0.07 × 0.07 × 0.27 mm. An absorption correction based on multiple measurements of symmetry-related reflections was applied;[33] the transmission range was 0.609−

(30) Spek, A. L. *J. Appl. Crystallogr.* **1988**, *21*, 578.
(31) Sheldrick, G. M. *SHELXS-86: Program for crystal structure determination*; University of Göttingen: Göttingen, Germany, 1986.
(32) Sheldrick, G. M. *SHELXL-97: Program for crystal structure refinement*; University of Göttingen: Göttingen, Germany, 1997.

0.808. Two of the eight crystallographically independent propoxy groups were refined with a two-site disorder model. One isotropic displacement parameter each was refined for the major and the minor site of each disordered atom. A total of 1197 parameters were refined; the final residual density was in the range $-1.30 < \Delta\rho < 1.73$ e Å^{-3} (near Re).

For **17**, 7996 reflections were measured ($1.02 < \theta < 27.50°$; $-20 < h < 17$, $-15 < k < 0$, $-25 < l < 25$; $\omega/2\theta$ scans with $\Delta\omega = (0.84 + 0.35 \tan\theta)°$; 20 h X-ray exposure time), 7374 of which were unique ($R_{int} = 0.0149$, $R_\sigma = 0.0242$) for a crystal of dimensions $0.17 \times 0.38 \times 0.68$ mm. An analytical absorption correction based on measured crystal dimensions was applied;[34] the transmission range was 0.260−0.563. The studied crystal turned out to be a racemic twin, the twin ratio refining to 0.743(8):0.257. A total of 413 parameters were refined; the final residual density was in the range $-0.74 < \Delta\rho < 1.12$ e Å^{-3} (near Re).

Neutral-atom scattering factors and anomalous dispersion corrections were taken from ref 35. Geometrical calculations and productions of the illustrations were performed with PLATON.[33]

Acknowledgment. This work was supported in part (A.L.S.) by the Council for Chemical Sciences, Netherlands Organization for Scientific Research.

Supporting Information Available: X-ray crystallographic files, in CIF format, for **11** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

IC000172X

(33) Spek, A. L. *PLATON: A multi-purpose crystallographic tool*; Utrecht University: Utrecht, The Netherlands, 1999. Internet: http://www.cryst.chem.uu.nl/platon.

(34) De Meulenaer, J.; Tompa, H. *Acta Crystallogr.* **1965**, *19*, 1014.

(35) Wilson, A. J. C., Ed. *International Tables for Crystallography*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992; Vol. C.