Water-Soluble Adamantane-Terminated Dendrimers Possessing a Rhenium Core

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A novel type of radiometal-containing dendrimer with potential radiotherapeutical applications is described. Different generations of this adamantane-terminated, Fréchet-type dendrimer (**28**, **29**, **30**), each consisting of two dendritic wedge ligands around a rhenium core, have been synthesized in organic solvent via reaction with $ReO(PPh_3)_2Cl_3$. Through complexation of their adamantane groups by β-cyclodextrins (β-CDs), these dendrimers were made water soluble (9.6, 0.4, and 0.2 mM, respectively). β-CD-induced solubilization of the wedges in water allowed the complexes to be made under aqueous conditions, via reaction with rhenium gluconate. Not only does this strategy enable the facile synthesis of the radioactive analogue, the yields for these complex-formation reactions in water also turned out to be far higher than those observed for the reactions in organic solvents.

Introduction

Since the first articles on dendrimers by Vögtle,[1] and later by Tomalia[2] and Newkome,[3] research on these branched molecules has resulted in a variety of structures and fields of applications.[4] Among the latter is medicinal chemistry, which looks at dendrimers for their enhanced substrate binding,[5] their potential to transfer biomolecules into cells,[6] and their applications in the fields of imaging (Gd^{III} complexes),[7] and cancer treatment.[8,9] Metallodendrimers[10] might be of specific interest for the treatment of cancer, since a variety of radiometals[11] can be incorporated into, or bound to, the dendrimer. However, only few examples exist of radiometal-containing dendrimers for therapeutic applications.[12]

Examples of dendrimers constructed through reaction of several dendritic wedges with, or self-assembly of these wedges around, a central metal core (M) typically involve the use of *N*-heteroaromatics[13] (M = Cu, Fe, Ru) or carboxylates[14] (M = Ln) as focal points. However, to the best of our knowledge, no examples of dendrimers possessing a radiometal core have been described. We set about to investigate the synthesis of dendrimers possessing rhenium as a radiometal core. The chemistry of technetium and rhenium has developed rapidly due to the importance of the metastable γ-emitting isomer ^{99m}Tc in the field of diagnostic nuclear medicine and the more recent introduction of β^- emitting isotopes ^{188}Re and ^{186}Re in radiotherapy.[15] Although rhenium is widely used as a nonradioactive model for technetium, rhenium itself also has potential to serve as a nuclide in radiotherapy[16] since its isotopes ^{186}Re and ^{188}Re emit β radiation. From an application (i.e., medical) point of view, the dendritic

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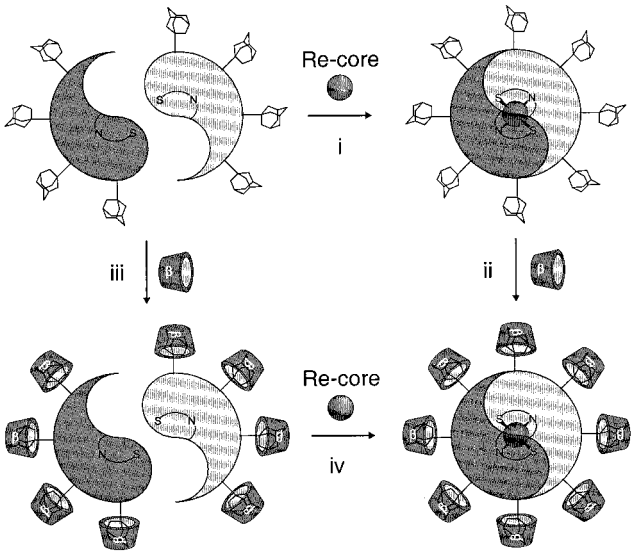
Scheme 1. Synthetic Routes toward a Water-Soluble Dendrimer

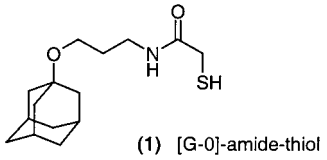


structures would require a certain water solubility in order to be injected into the human body.

Strategies toward Water-Soluble Rhenium Dendrimers. Present strategies to obtain water-soluble dendrimers consist of introducing highly hydrophilic moieties at the periphery of the dendrimers. Among the most commonly used hydrophilic moieties are poly(ethylene glycol),[17] carboxylic acids,[18] ammonium groups,[19] and various types of carbohydrates.[20] Especially when using convergent dendritic growth strategies, water-solubility, already present in the precursors, may result in difficulties during reactions and workup. Ideally, the water solubility should not be introduced until the last step of the synthesis.

Our approach to introduce the water solubility at the end of the synthetic route is by complexing the dendrimer with β-cyclodextrins (β-CDs).[21] Since β-CDs are known to form strong inclusion complexes with adamantanes, thus making them water soluble, dendrimers with an adamantane periphery were synthesized. Two different strategies for the synthesis of β-CD-solubilized dendrimers have been investigated (Scheme 1): (A) synthesis of the dendritic wedges, followed by complex formation in organic solvent (**i**) and subsequent solubilization (**ii**) of the complex in water by β-CD; (B) synthesis of the dendritic wedges, followed by solubilization (**iii**) of the wedges in water by β-CD and subsequent complex formation (**iv**) in water.

Chart 1. Structure of [G-0]-Amide-thiol (1)



(1) [G-0]-amide-thiol

This paper describes the synthesis and characterization of a new class of dendrimers, which may have potential applications as radiopharmaceuticals. Complex formation in organic solvent (strategy A) as well as in water (strategy B) has been achieved. The β-CD-induced water solubility of the different dendrimer generations has been investigated. This work presents a novel method for the synthesis of larger, inherently lipophilic radiometal complexes.

Results and Discussion

Synthesis of the Dendritic Wedges. The starting point for the synthesis of all wedge generations was 1-bromoadamantane (**2**), which is known to be highly reactive in nucleophilic substitutions.[22] The dendritic wedges were synthesized via a convergent growth strategy, i.e., starting from the adamantane periphery and working inward toward what is to become the amide-thiol ligand part. In this way, the number of synthetic steps involving the radiometal can be reduced to a minimum.[23] Apart from the adamantane end groups, the dendrimers are of the classical Fréchet-type,[24] leading to relatively stiff[25] and hydrophobic interiors. To allow the multiple complexation by β-CD to take place, even of the higher generation wedges and dendrimers, a flexible spacer was introduced between the adamantane and the actual dendrimer part. The amide-thiol ligand was chosen since it is known to form strong bis(bidentate) complexes with oxorhenium cores.[26] In the discussion below, the various generations dendritic molecules will be designated by use of the following notation [G-x]−f, in which [G-x] refers to generation number (x = 0, 1, ...) and f refers to the functional group located at the focal point. The notation [G-x]$_2$−Re will be used to designate the rhenium complexes of different generations, which consist of two dendritic wedges coordinated to an oxorhenium core.

The 0th generation dendritic wedge **1** (Chart 1) was synthesized previously,[27] the key step being the nucleophilic substitution reaction of 3-amino-1-propanol with

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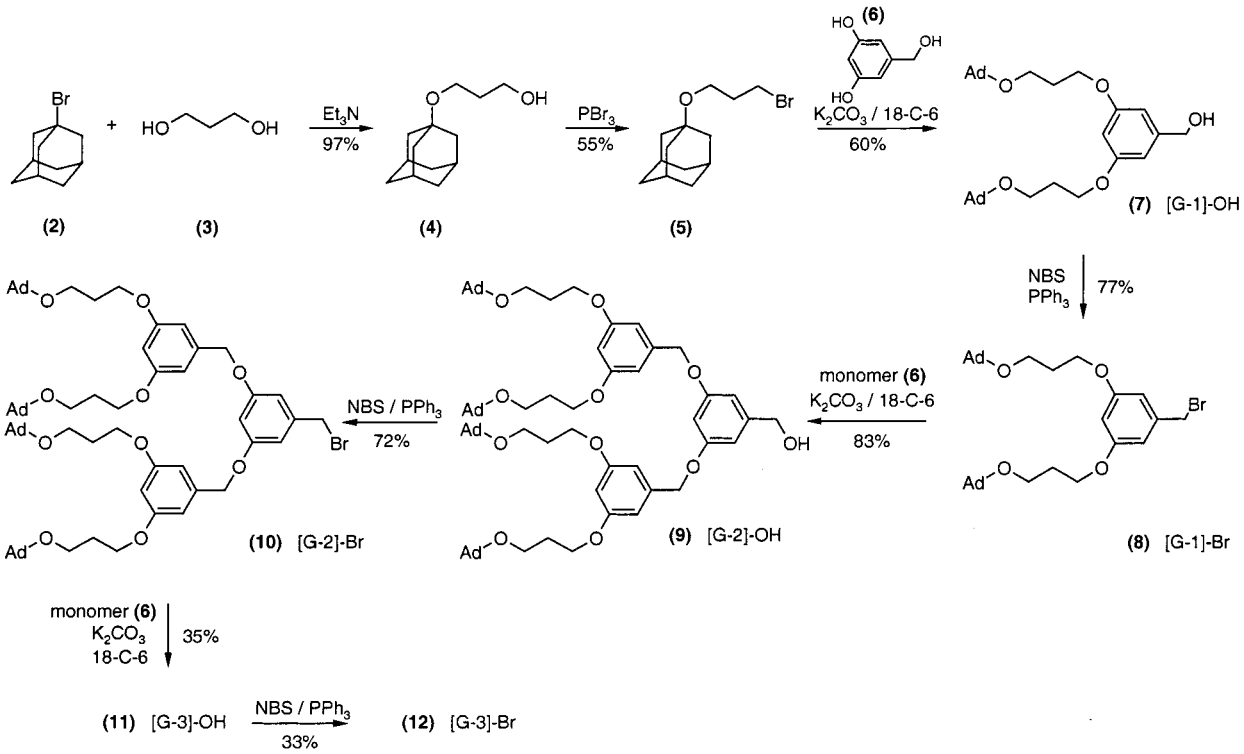
Scheme 2. Synthesis of [G-*x*]-Br (*x* = 1, 2, 3)[a]



[a] Ad = adamantane.

1-bromoadamantane, resulting in the preferential formation of the ether, over the secondary amine in a ratio of 3:1.[28]

The first step in the synthesis of the wedges of higher generations was the nucleophilic substitution reaction of 1,3-propanediol (**3**) with 1-bromoadamantane (**2**) in the presence of triethylamine to give 3-(adamantan-1-yloxy)-propan-1-ol (**4**) in 97% yield (Scheme 2). Subsequent conversion of the remaining hydroxyl functionality to a bromide, using PBr_3 in toluene, gave **5** in 55% yield. Reaction of the bromine **5** with 3,5-dihydroxybenzyl alcohol (**6**) under conditions as used by Hawker and Fréchet,[24] i.e., acetone, K_2CO_3, and 18-crown-6, gave [G-1]-OH (**7**) in 60% yield. For the conversion of the hydroxyl functionality of **7** into the corresponding bromide, a number of brominating agents were examined (CBr_4/PPh_3, PBr_3, NBS/PPh_3). The best results were obtained by performing the reaction using *N*-bromosuccinimide (NBS) and PPh_3 in a minimal amount of DMF.[29] Bromide [G-1]-Br (**8**), which was obtained in 77% yield, was reacted with 3,5-dihydroxybenzyl alcohol (**6**), again under Fréchet conditions, to afford [G-2]-OH (**9**). Subsequent bromination to [G-2]-Br (**10**) (yield 72%), followed by reaction with **6**, to give [G-3]-OH (**11**) and finally bromination (yield 33%) gave [G-3]-Br (**12**).

With increasing dendrimer generations, longer reaction times were required for the brominations of the wedges with a hydroxyl focal point. This difference is most likely due to the increasing bulk of the dendrimer hindering the focal point in undergoing functional group transformation. All OH to Br transformations were easily confirmed by ^{1}H NMR. The observed signals for the benzylic methylene protons showed the expected triplet in the case of the hydroxyl-terminated wedges (**7**, **9**, and **11**) and a singlet in the case of the corresponding bromo-terminated wedges (**8**, **10**, and **12**). The formation of higher generation dendrimeric wedges could be confirmed by integration of the aromatic regions and the appearance of more signals corresponding to the benzylic methylene protons in the ^{1}H NMR spectra. All values were in good correspondence with those observed for dendritic wedges without adamantane end groups by Hawker and Fréchet.[24]

The first step for the introduction of the amide-thiol ligand part was the conversion of the bromides [G-1]-Br (**8**), [G-2]-Br (**10**), and [G-3]-Br (**12**) to their corresponding amines. Classical Gabriel synthesis, introduction of the phthalimide followed by deprotection of the amine using hydrazine, resulted in the amines [G-1]-NH_2 (**16**), [G-2]-NH_2 (**17**), and [G-3]-NH_2 (**18**) in yields as shown in Scheme 3. These yields are in good agreement with the yields for bromine to amine conversion in Fréchet-type wedges, as described by Vögtle et al.[30]

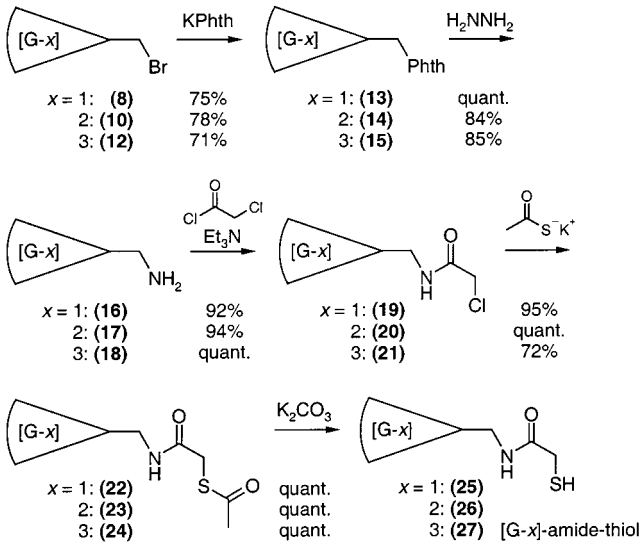
From the amine, further functionalization toward the amide-thiol focal point was performed according to procedures established for the synthesis of the [G-0]-amide-thiol ligand **1**.[27] Reaction of the amines [G-*x*]-NH_2 (*x* = 1, 2, 3) with chloroacetyl chloride in CH_2Cl_2 in the presence of triethylamine gave the corresponding chloroacetamides [G-*x*]-NHC(O)CH_2Cl (*x* = 1: **19**, 2: **20**, 3: **21**)

(28) This reaction was performed according to a literature procedure: Chakrabarti, J. K.; Foulis, M. J.; Szinai, S. S. *Tetrahedron Lett.* **1968**, 6249. However, the preferential substitution on oxygen rather than nitrogen did not result in the described 90% yield (after distillation) of the ether.

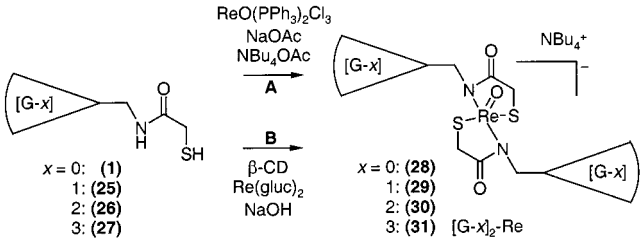
(29) In our hands the CBr_4/PPh_3 bromination method used by Hawker and Fréchet, (ref 24) gave unsatisfactory results for the adamantane-terminated dendrimers, since it often leads to the formation of the bisbrominated product ($ArCHBr_2$), which could not be separated from the desired monobrominated product ($ArCH_2Br$).

(30) Vögtle, F.; Plevoets, M.; Nachtsheim, G.; Wörsdörfer, U. *J. Prakt. Chem.* **1998**, *340*, 112.

Scheme 3. Synthesis of [G-*x*]-Amide-thiol (*x* = 1, 2, 3)



Scheme 4. Synthesis of [G-*x*]$_2$-Re (*x* = 0, 1, 2, 3) in Organic Solvent and in Water[a]



[a] Yields are summarized in Table 2.

in yields of 92%, 94%, and 100%, respectively. The presence of a broad singlet for the amide in the ^{1}H NMR spectra (δ ~6.8 for all generations) clearly proved their formation. The chloro atoms of the chloroacetamide-functionalized wedges were converted into thioesters by reaction with potassium thioacetate in DMF (yields 95%, 100%, and 72% for [G-1], [G-2], and [G-3], respectively). Subsequent basic hydrolysis gave the amide-thiol functionalized wedges **25**, **26**, and **27**, all in quantitative yields. Thiol formation was proven by their ^{1}H NMR spectra, displaying the splitting of the CH_2S signal upon going from the thioester to the free thiol. In all cases, a doublet was observed at δ ~3.3.

Strategy A: Synthesis of the Complexes in Organic Solvent. Complex [G-0]$_2$-Re (**28**) was synthesized previously and was obtained in 11% yield.[27] Following the same procedure, i.e., refluxing a deoxygenated methanolic solution of dendritic wedges [G-*x*]-amide-thiol (*x* = 1, 2), NaOAc, NBu_4OAc, and $ReO(PPh_3)_2Cl_3$ for 2 h, [G-1]$_2$-Re (**29**) and [G-2]$_2$-Re (**30**) were obtained in 13% and 7% yield, respectively, after laborious column chromatography (Scheme 4). The third-generation complex [G-3]$_2$-Re (**31**) could not be obtained (Table 2).

Clear evidence for the formation of the Re complexes was given by their ^{1}H NMR and FAB-MS spectra. All complexes showed similar ^{1}H NMR spectra, each displaying signals for the two AB systems, belonging to the $SCH_2C(O)N$ and $ArCH_2N$ protons, which are anisochronous due to the presence of the oxo ligand on only one side of the complex. Figure 1 shows a representative ^{1}H NMR spectrum of one of the dendrimer complexes (**29**), clearly displaying the anisochronous signals.[31] Signal integration confirmed the presence of 1 equiv of the NBu_4^+ counterion. FAB-MS spectra of the three complex generations showed peaks for $[M - NBu_4]^-$ at *m*/*z* 765.6, 1392.7, and 2651.3, respectively, all showing the correct Re pattern.

Table 1. Water Solubility of the β-CD Complexes of [G-*x*]$_2$-Re (*x* = 0, 1, 2) as Determined by ^{1}H NMR

x	compd	no. of Ad[a]	no. of Ar[b]	solubility (mM)
0	**28**	2	0	9.6
1	**29**	4	2	0.4
2	**30**	8	6	0.2

[a] No. of Ad = number of adamantane moieties. [b] No. of Ar = number of aromatic rings.

Table 2. Comparison of the Yields of Complex Formation [G-*x*]$_2$-Re (*x* = 0, 1, 2, 3) Following Strategies A and B

x	compd	A: yield[a] (%)	B: yield[b] (%)
0	**28**	11	95
1	**29**	13	93
2	**30**	7	68
3	**31**	not isolated	not isolated

[a] Yield after chromatography. [b] Yield after extraction to $CHCl_3$.

Solubilization of the Complexes in Water by β-CD. The water solubility of the β-CD complexes of the obtained dendrimeric rhenium complexes of three different generations (0, 1, 2) was investigated. To saturated solutions of the β-CD/rhenium-complex mixtures was added an internal standard (*t*-BuOH) of known concentration in order to determine the solubilities of the complexes based on the integration of their ^{1}H NMR integrals. The results of these experiments are shown in Table 1.

The relatively high water solubility (9.6 mM) found for [G-0]$_2$-Re (**28**) is most likely due to the absence of the hydrophobic aromatic rings that are present in [G-1]$_2$-Re (**29**) and [G-2]$_2$-Re (**30**). The increase in hydrophobic volume of the macromolecule on going from [G-1]$_2$-Re to [G-2]$_2$-Re is noticeable in the decrease in water solubility from 0.4 to 0.2 mM, respectively.

Strategy B: Synthesis of the Complexes in Water. Complex formations in water were performed, starting from the rhenium precursor complex rhenium gluconate,[32] which was made directly from sodium perrhenate. This rhenium source was used since in order to be useful in nuclear medicine, complexes must be synthesizable in aqueous conditions, starting from sodium perrhenate.[33] However, the aqueous character of the solutions in which these exchange reactions must be performed limits the choice of ligands that can be used, since a certain degree of water solubility must always be present in the ligands for complex formation to take place.[34] This water solubility can be provided by β-CD, as was shown by the

(31) Comparison of the ^{1}H NMR spectra of the dendritic complexes to that of a previously synthesized rhenium complex helped in the assignment of the signals belonging to the hydrogen pairs a and b. Van Bommel, K. J. C.; Verboom, W.; Hulst, R.; Kooijman, H.; Spek, A. L.; Reinhoudt, D. N. *Inorg. Chem.* **2000**, *39*, 4099.

(32) Noll, B.; Kniess, T.; Freibe, M.; Spies, H.; Johannsen, B. *Isotopes Environ. Health Stud.* **1996**, *32*, 21. For the synthesis described here, $NaReO_4$ was used instead of NBu_4ReO_4.

(33) Radioactive rhenium is obtainable as a solution of sodium perrhenate in water. To synthesize rhenium complexes, the perrhenate is usually reduced in situ, using $SnCl_2$, after which the oxorhenium complex can be formed, either directly, or via the formation of a precursor complex.

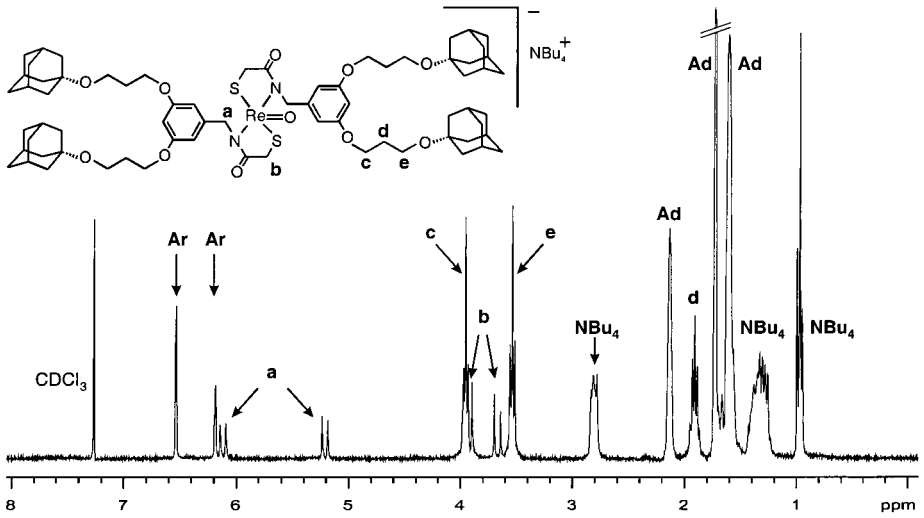


Figure 1. ^{1}H NMR spectrum of [G-1]$_2$-Re (**29**) in $CDCl_3$. Notice the anisochronicity in the signals of **a** and **b**, caused by the oxo ligand.

excellent yields obtained in the β-CD-facilitated synthesis of various small rhenium complexes.[27] Therefore, we decided to synthesize the dendrimeric rhenium complexes in a similar fashion, using the precursor complex rhenium(V) gluconate, and using β-CD to solubilize the dendritic ligands. To avoid the formation of a mixture of cis and trans products, the dendrimeric complex formation reactions were performed for 5 h at 55 °C.[35]

Complex formation (Scheme 4) was performed by first dissolving the ligand [G-*x*]-amide-thiol (x = 0, 1, 2, 3) in a minimal amount of THF, which was added to a solution of β-CD in water. This mixture was then added to a solution of rhenium(V) gluconate, which was brought to pH = 10 by the addition of a NaOH solution. The reaction mixture was stirred at 55 °C for 5 h, during which time a color change from blue to red-brown indicated formation of the dendrimeric complex. The previously determined water solubilities of the β-CD complexes of [G-*x*]$_2$-Re were used to calculate the amounts of water needed in the complex formation reactions, to prevent the complexes from precipitating out of the reaction mixture. After the reaction, 1 equiv of NBu_4OAc was added and the product was extracted into $CHCl_3$ in order to determine the yields. Complexes of generations 0 (**28**, previously synthesized), 1 (**29**), and 2 (**30**) were obtained in yields of 95%, 93%, and 68%, respectively (Table 2), without any further need for purification. Again the third generation complex [G-3]$_2$-Re (**31**) could not be isolated.

Comparison of Strategies A and B. The yields of complex formation [G-*x*]$_2$-Re (x = 0, 1, 2, 3), following strategies A and B, are shown in Table 2. Clearly, strategy B results in yields far better than those obtained following strategy A. This difference is partially due to the purification (i.e., flash column chromatography) necessary to obtain the complexes synthesized following strategy A. Careful chromatography still results in considerable amounts of impure fractions; i.e., actual yields might be higher. However, ^{1}H NMR spectra of the crude reaction mixtures of these complexes show no indication for yields above 20%. The fact that the complexes can be obtained without any purification, combined with the superior yields, makes strategy B far more attractive.

It is striking that both methods fail to give [G-3]$_2$-Re. A possible explanation might be that the focal point is too sterically hindered for the ligand to undergo complex formation.[36]

Conclusions

It has been shown that dendrimeric complexes of generations 0, 1, and 2 can be synthesized in organic solvent and subsequently solubilized in water by β-CD. The water solubilities of the β-CD adducts of the complexes proved to be 9.6, 0.4, and 0.2 mM for [G-0]$_2$Re, [G-1]$_2$Re, and [G-2]$_2$Re, respectively. By making the adamantane containing dendritic ligands water-soluble, through the addition of β-CD, the same complexes could be synthesized in water in much higher yields, starting from sodium perrhenate.

Therefore it has been shown that β-CD facilitated complex formation is a promising new approach to the synthesis of large lipophilic radiometal complexes, which may have potential applications as radiopharmaceuticals.

Experimental Section

General Methods. All reagents and solvents were obtained from Aldrich, Acros, or Fluka. 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 unless otherwise indicated. NaRe(gluc)$_2$ solution was prepared according to a modified literature procedure[32] and was frozen

(34) This requirement limits the synthesis of lipophilic and intrinsically nonwater-soluble radioactive rhenium complexes to organic solvents, thus requiring more lipophilic radioactive rhenium precursor complexes, available only via laborious syntheses, therefore resulting in an undesired loss of radioactivity.

(35) In the synthesis of small bis(bidentate) rhenium complexes, it was observed that both a cis as well as a trans complex could be formed. Performing the reaction at elevated temperatures for several hours resulted in the exclusive formation of the trans complex; ref 27.

(36) The steric crowding at the periphery of the dendrimer, due to the adamantyl moieties (be they free or complexed by β-CD) may induce a backfolding of the dendrimer backbone thus rendering the focal point inaccessible. Other examples of complex formation failure due to this type of crowding have been reported: (a) Issberner, J.; Vögtle, F.; De Cola, L.; Balzani, V. *Chem. Eur. J.* **1997**, *3*, 706. (b) Enomoto, M.; Aida, T. *J. Am. Chem. Soc.* **1999**, *121*, 874.

directly after preparation. It was stored for no longer than 1 week before use.

Reaction progress was monitored by analytical thin-layer chromatography (Merck aluminum TLC sheets, silica gel 60 F_{254}). Silica gel used in flash chromatography was 0.040−0.063 mm. Preparative thin-layer chromatography was performed using Merck glass PTC plates (20 × 20 cm, silicagel 60 F_{254}, 2 mm). TLC plates were visualized using short-wave UV light (254 nm) or iodine.

^{1}H and ^{13}C NMR spectra were obtained at 300 and 75.5 MHz, respectively, and are reported in parts per million relative to the incomplete deuteration signal of the NMR solvent ($CDCl_3$). Fast atom bombardment (FAB) mass spectra were measured using *m*-nitrobenzyl alcohol (NBA) as a matrix. The presence of solvent in the analytical samples was confirmed by ^{1}H NMR spectroscopy. Melting points are uncorrected.

3-(Adamantane-1-yloxy)propan-1-ol (4). A solution of 1-bromoadamantane (**2**) (15.00 g, 69.8 mmol), triethylamine (30.00 mL, 216 mmol), and 1,3-propanediol (**3**) (110 mL) was refluxed overnight. The mixture was allowed to cool to rt, 100 mL of CH_2Cl_2 was added, and the solution was washed with 2 N HCl solution (5 × 100 mL), water (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give **4** as a light yellow oil. Yield: 97%. ^{1}H NMR: δ 3.78 (m, 2 H), 3.65 (t, 2 H, J = 5.5 Hz), 3.02 (t, 1 H, J = 5.5 Hz), 2.15 (m, 3 H), 1.79 (m, 2 H), 1.76 (m, 6 H), 1.62 (m, 6 H). ^{13}C NMR: δ 72.5, 63.1, 60.0, 41.4, 36.4, 32.2, 30.4. FAB-MS *m*/*z* 209.2 ([M − H]$^-$, calcd for $C_{13}H_{21}O_2$ 209.2).

1-(3-Bromopropoxy)adamantane (5). To a cooled (0 °C) solution of **4** (7.00 g, 33.3 mmol) in toluene (250 mL) was added dropwise a solution of phosphorus tribromide (1.13 g, 12.1 mmol) in toluene (50 mL). After the addition was complete, the mixture was allowed to come to rt and stirred overnight. After removal of the solvent under reduced pressure, the residue was partitioned between CH_2Cl_2 (250 mL) and H_2O (100 mL). The organic layer was washed with water (3 × 50 mL) and brine (50 mL), after which it was dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave a light brown oil, which was purified by column chromatography (CH_2Cl_2) to give **5** as a colorless oil. Yield: 55%. ^{1}H NMR: δ 3.56 (t, 2 H, J = 5.5 Hz), 3.55 (t, 2 H, J = 6.2 Hz), 2.17 (m, 3 H), 2.07 (m, 2 H), 1.77 (m, 6 H), 1.65 (m, 6 H). ^{13}C NMR: δ 57.1, 41.6, 36.5, 33.5, 31.3, 30.5. FAB-MS *m*/*z* 273.1 ([M + H]$^+$, calcd for $C_{13}H_{22}BrO$ 273.1).

[G-1]-OH (7). A suspension of **5** (7.83 g, 28.7 mmol), 3,5-dihydroxybenzyl alcohol (**6**) (1.92 g, 13.7 mmol), dried K_2CO_3 (4.73 g, 34.3 mmol), and 18-crown-6 (0.72 g, 2.7 mmol) in dry acetone (250 mL) was refluxed overnight. After evaporation of the solvent under reduced pressure, the residue was partitioned between water (250 mL) and diethyl ether (250 mL). After extraction of the aqueous layer with diethyl ether (3 × 50 mL), the combined extracts were subsequently dried with $MgSO_4$ and evaporated to dryness under reduced pressure. The crude oil was purified by column chromatography (CH_2Cl_2/MeOH, 99/1) to give **7** as a colorless oil. Yield: 60%. ^{1}H NMR: δ 6.52 (d, 2 H, J = 2.6 Hz), 6.41 (t, 1 H, J = 2.2 Hz), 4.63 (d, 2 H, J = 5.9 Hz), 4.02 (t, 4 H, J = 6.2 Hz), 3.59 (t, 4 H, J = 6.2 Hz), 2.64 (s, 1 H), 2.14 (m, 6 H), 1.98 (m, 4 H), 1.74 (m, 12 H), 1.62 (m, 12 H). ^{13}C NMR: δ 160.5, 143.1, 105.2, 100.6, 72.0, 65.1, 56.2, 41.5, 36.5, 33.4, 30.5. FAB-MS *m*/*z* 525.0 ([M + H]$^+$, calcd for $C_{33}H_{49}O_5$ 525.4).

[G-1]-Br (8). *N*-Bromosuccinimide (0.75 g, 4.2 mmol) was added in small portions to a solution of **7** (2.00 g, 3.82 mmol) and triphenylphosphine (1.10 g, 4.20 mmol) in a minimal amount of DMF (∼10 mL) at 0 °C. After the addition was complete, the solution was heated to 50 °C for 30 min and subsequently allowed to cool to rt. Methanol (5 mL) was added to neutralize the excess NBS, and the mixture was stirred for an additional 5 min, after which time diethyl ether (100 mL) was added. The organic phase was washed with water (100 mL), saturated sodium carbonate (100 mL), and brine (100 mL). After evaporation of the solvent under reduced pressure, the crude product was extracted into hexane (3 × 50 mL), leaving a residue of triphenylphosphine oxide. After evaporation of the hexane under reduced pressure, the remaining crude colorless oil was purified by flash column chromatography (CH_2Cl_2) to yield **8** as a colorless oil. Yield: 77%. ^{1}H NMR: δ 6.54 (d, 2 H, J = 2.2 Hz), 6.43 (t, 1 H, J = 2.2 Hz), 4.42 (s, 2 H), 4.05 (t, 4 H, J = 6.2 Hz), 3.60 (t, 4 H, J = 6.2 Hz), 2.15 (m, 6 H), 1.99 (m, 4 H), 1.76 (m, 12 H), 1.63 (m, 12 H). ^{13}C NMR: δ 160.3, 139.4, 107.5, 101.5, 71.9, 65.1, 56.1, 41.5, 36.4, 33.7, 30.4. FAB-MS *m*/*z* 586.2 (M$^+$, calcd for $C_{33}H_{47}BrO_4$ 586.3).

[G-2]-OH (9) was synthesized analogously to [G-1]-OH (**7**), starting from [G-1]-Br (**12**) (4.04 g, 7.45 mmol). The crude light brown oil was purified by column chromatography (CH_2Cl_2, gradually increased to CH_2Cl_2/MeOH, 98/2) to give [G-2]-OH (**13**) as a white solid. Yield: 83%. Mp: 61 °C. ^{1}H NMR: δ 6.62 (d, 2 H, J = 2.2 Hz), 6.57 (d, 4 H, J = 2.2 Hz), 6.55 (t, 1 H, J = 2.2 Hz), 6.43 (t, 2 H, J = 2.2 Hz), 4.97 (s, 4 H), 4.64 (d, 2 H, J = 5.9 Hz), 4.05 (t, 8 H, J = 6.2 Hz), 3.59 (t, 8 H, J = 6.2 Hz), 2.64 (s, 1 H), 2.13 (m, 12 H), 1.98 (m, 8 H), 1.75 (m, 24 H), 1.63 (m, 24 H). ^{13}C NMR: δ 160.4, 160.1, 142.9, 138.2, 106.0, 105.6, 101.8, 101.1, 72.0, 70.5, 65.1, 56.2, 41.5, 36.5, 33.6, 30.4. FAB-MS *m*/*z* 1153.0 (M$^+$, calcd 1152.7). Anal. Calcd for $C_{73}H_{100}O_{11}\cdot 1.5H_2O$: C, 74.27; H, 8.79. Found: C, 74.43; H, 8.61.

[G-2]-Br (10) was synthesized analogously to [G-1]-Br (**8**), starting from [G-2]-OH (**9**) (4.15 g, 3.87 mmol), except the reaction mixture was heated over a period of 90 min instead of 30 min. The crude colorless oil was purified by column chromatography (CH_2Cl_2) to yield **10** as a colorless oil. Yield: 72%. ^{1}H NMR: δ 6.64 (d, 2 H, J = 2.2 Hz), 6.58 (d, 4 H, J = 2.2 Hz), 6.57 (t, 1 H, J = 2.2 Hz), 6.45 (t, 2 H, J = 2.2 Hz), 4.95 (s, 4 H), 4.42 (s, 2 H), 4.05 (t, 8 H, J = 6.2 Hz), 3.59 (t, 8 H, J = 6.2 Hz), 2.13 (m, 12 H), 1.99 (m, 8 H), 1.75 (m, 24 H), 1.61 (m, 24 H). ^{13}C NMR: δ 160.4, 160.0, 139.7, 138.6, 108.2, 106.0, 102.2, 101.1, 72.0, 70.2, 65.1, 56.2, 41.5, 36.5, 33.6, 30.5. FAB-MS *m*/*z* 1216.0 ([M + H]$^+$, calcd for $C_{73}H_{100}BrO_{10}$ 1215.6).

[G-3]-OH (11) was synthesized analogously to [G-1]-OH (**7**), starting from [G-2]-Br (**10**) (2.39 g, 1.97 mmol). Purification by column chromatography (toluene/ethyl acetate 9/1) gave **11** as a colorless oil. Yield: 35%. ^{1}H NMR: δ 6.68 (d, 4 H, J = 2.2 Hz), 6.61 (t, 2 H, J = 2.2 Hz), 6.58 (d, 8 H, J = 2.2 Hz), 6.43 (t, 4 H, J = 2.2 Hz), 4.96 (s, 12 H), 4.62 (s, 2 H), 4.04 (t, 16 H, J = 6.2 Hz), 3.58 (t, 16 H, J = 6.2 Hz), 2.13 (m, 24 H), 1.97 (m, 16 H), 1.74 (m, 48 H), 1.61 (m, 48 H). ^{13}C NMR: δ 160.4, 160.1, 143.1, 139.0, 138.7, 106.1, 105.8, 105.7, 102.3, 102.2, 102.1, 101.1, 72.0, 70.1, 65.1, 56.2, 41.5, 36.6, 33.6, 30.5. FAB-MS *m*/*z* 2408.4 ([M − H]$^-$, calcd for $C_{153}H_{203}O_{23}$ 2408.5).

[G-3]-Br (12) was synthesized analogously to [G-1]-Br (**8**), starting from [G-3]-OH (**11**) (1.65 g, 0.68 mmol). The reaction was performed for 72 h at 40 °C. Purification by column chromatography (CH_2Cl_2/MeOH = 99/1) gave **12** as a colorless oil. Yield: 33%. ^{1}H NMR: δ 6.68 (d, 4 H, J = 2.2 Hz), 6.64 (d, 2 H, J = 2.2 Hz), 6.61 (t, 1 H, J = 2.2 Hz), 6.58 (d, 8 H, J = 2.2 Hz), 6.56 (t, 2 H, J = 2.2 Hz), 6.44 (t, 4 H, J = 2.2 Hz), 4.97 (s, 12 H), 4.42 (s, 2 H), 4.05 (t, 16 H, J = 6.2 Hz), 3.59 (t, 16 H, J = 6.2 Hz), 2.13 (m, 24 H), 1.98 (m, 16 H), 1.74 (m, 48 H), 1.60 (m, 48 H). ^{13}C NMR: δ 160.4, 160.0, 139.7, 138.6, 106.2, 105.8, 105.7, 102.3, 102.1, 101.9, 101.1, 72.0, 70.2, 65.1, 56.2, 41.5, 36.5, 33.6, 30.5. FAB-MS *m*/*z* 2471.4 (M$^+$, calcd for $C_{153}H_{203}BrO_{22}$ 2471.4).

[G-1]-Phth (13). A solution of [G-1]-Br (**8**) (710 mg, 1.21 mmol) and potassium phthalimide (404 mg, 2.18 mmol) in a minimal amount of dry DMF (∼10 mL) was heated at 80 °C for 2 h, after which time it was allowed to cool to rt and water (100 mL) was added. The water layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined extracts were washed with 2 N HCl solution (5 × 100 mL). The organic layer was dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The residual light brown oil was purified by column chromatography (ethyl acetate/hexane, 50/50 increasing slowly to 75/25) to give **13** as a colorless oil. Yield: 75%. ^{1}H NMR: δ 7.78 (m, 2 H), 7.65 (m, 2 H), 6.48 (d, 2 H, J = 2.2 Hz), 6.30 (t, 1 H, J = 2.2 Hz), 4.69 (s, 2 H), 3.93 (t, 4 H, J = 6.2 Hz), 3.49 (t, 4 H, J = 6.2 Hz), 2.05 (m, 6 H), 1.88 (m, 4 H), 1.65 (m, 12 H), 1.53 (m, 12 H). ^{13}C NMR: δ 168.3, 160.5, 143.1, 134.5,

132.4, 123.7, 105.1, 100.6, 72.0, 65.4, 65.1, 56.2, 41.5, 36.5, 33.5, 30.5. FAB-MS *m/z* 654.3 ($[M + H]^+$, calcd for $C_{41}H_{52}NO_6$ 654.4).

[G-2]-Phth (14) was synthesized analogously to [G-1]-Phth (**13**), starting from [G-2]-Br (**10**) (1.77 g, 1.49 mmol). The reaction mixture was heated to 70 °C and stirred overnight. The residual light brown oil was purified by column chromatography (CH_2Cl_2/MeOH, 99/1) to give **14** as a colorless oil. Yield: 78%. ^{1}H NMR: δ 7.84 (m, 2 H), 7.73 (m, 2 H), 6.67 (d, 2 H, J = 2.2 Hz), 6.55 (d, 4 H, J = 2.2 Hz), 6.53 (t, 1 H, J = 2.2 Hz), 6.42 (t, 2 H, J = 2.2 Hz), 4.92 (s, 4 H), 4.79 (s, 2 H), 4.03 (t, 8 H, J = 6.2 Hz), 3.59 (t, 8 H, J = 6.2 Hz), 2.13 (m, 12 H), 1.98 (m, 8 H), 1.75 (m, 24 H), 1.61 (m, 24 H). ^{13}C NMR: δ 167.6, 160.4, 160.1, 139.6, 138.7, 108.1, 108.0, 106.1, 105.7, 102.3, 102.1, 101.1, 100.9, 72.0, 70.1, 65.1, 56.2, 41.5, 36.5, 30.4. FAB-MS *m/z* 1281.0 ($[M - H]^-$, calcd for $C_{81}H_{102}NO_{12}$ 1280.7).

[G-3]-Phth (15) was synthesized analogously to [G-1]-Phth (**13**), starting from [G-3]-Br (**12**) (0.56 g, 0.23 mmol). The crude reaction mixture was purified by column chromatography (CH_2Cl_2, gradually changed to CH_2Cl_2/MeOH = 99/1) to yield **15** as a colorless oil. Yield: 71%. ^{1}H NMR: δ 7.85−7.70 (m, 4 H), 6.68 (d, 4 H, J = 1.8 Hz), 6.58 (d, 8 H, J = 2.2 Hz), 6.54 (t, 3 H, J = 2.2 Hz), 4.95 (s, 12 H), 4.79 (s, 2 H), 4.05 (t, 16 H, J = 6.2 Hz), 3.59 (t, 16 H, J = 6.2 Hz), 2.12 (m, 24 H), 1.98 (m, 16 H), 1.74 (m, 48 H), 1.60 (m, 48 H). ^{13}C NMR: δ 167.8, 160.4, 160.0, 138.9, 138.8, 138.5, 134.0, 133.9, 132.0, 123.3, 107.4, 106.3, 105.8, 101.6, 100.9, 71.9, 70.1, 65.0, 56.1, 41.5, 36.4, 30.4. FAB-MS *m/z* 2538.5 (M^+, calcd for $C_{161}H_{207}NO_{24}$ 2538.5).

[G-1]-NH$_2$ (16). A suspension of [G-1]-Phth (**13**) (500 mg, 0.77 mmol) in ethanol (25 mL) was heated to reflux. When all had dissolved, hydrazine hydrate (99%) (0.63 mL) was added to the reaction mixture, after which the mixture was stirred for 1.5 h (after 30 min a white substance precipitated). The reaction mixture was allowed to cool to rt and was partitioned between a 20% KOH solution (50 mL) and CH_2Cl_2 (50 mL). The water phase was extracted with CH_2Cl_2 (3 × 50 mL), and the combined extracts were washed with water (150 mL) and brine (150 mL). The solution was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give pure **16** as a colorless oil in quantitative yield. ^{1}H NMR: δ 6.39 (d, 2 H, J = 2.2 Hz), 6.29 (t, 1 H, J = 2.2 Hz), 3.97 (t, 4 H, J = 6.2 Hz), 3.72 (s, 2 H), 3.51 (t, 4 H, J = 6.2 Hz), 2.06 (m, 6 H), 1.91 (m, 4 H), 1.67 (m, 12 H), 1.54 (m, 12 H). ^{13}C NMR: δ 160.5, 146.0, 105.4, 100.6, 72.0, 65.1, 56.4, 46.5, 41.5, 36.5, 30.5. FAB-MS *m/z* 525.0 ($[M + H]^+$, calcd for $C_{33}H_{50}NO_4$ 524.4).

[G-2]-NH$_2$ (17) was synthesized analogously to [G-1]-NH$_2$ (**16**), starting from [G-2]-Phth (**14**) (1.00 g, 0.78 mmol). Workup gave **17** as a colorless oil. Yield: 84%.[37] ^{1}H NMR: δ 6.59 (m, 6 H), 6.52 (t, 1 H, J = 2.2 Hz), 6.44 (t, 2 H, J = 2.2 Hz), 4.97 (s, 4 H), 4.05 (t, 8 H, J = 6.2 Hz), 3.81 (s, 2 H), 3.59 (t, 8 H, J = 6.2 Hz), 2.13 (m, 12 H), 1.99 (m, 8 H), 1.75 (m, 24 H), 1.62 (m, 24 H). ^{13}C NMR: δ 160.4, 160.1, 145.8, 138.9, 106.0, 105.8, 100.9, 100.3, 71.9, 70.0, 65.1, 56.2, 46.6, 41.5, 36.4, 30.4. FAB-MS *m/z* 1153.0 ($[M + H]^+$, calcd for $C_{73}H_{102}NO_{10}$ 1152.7).

[G-3]-NH$_2$ (18) was synthesized analogously to [G-1]-NH$_2$ (**16**), starting from [G-3]-Phth (**15**) (0.41 g, 0.16 mmol). The reaction time was 2 h, after which time workup gave **18** as a colorless oil. Yield: 85%.[37] ^{1}H NMR: δ 6.69 (m, 5 H), 6.58 (m, 10 H), 6.44 (t, 6 H, J = 2.2 Hz), 4.95 (s, 12 H), 4.05 (t, 16 H, J = 6.2 Hz), 3.82 (s, 2 H), 3.58 (t, 16 H, J = 6.2 Hz), 2.12 (m, 48 H), 1.98 (m, 16 H), 1.74 (m, 48 H), 1.60 (m, 48 H). ^{13}C NMR: δ 160.4, 160.1, 156.0, 145.7, 139.2, 138.8, 106.3, 105.9, 101.5, 100.9, 100.3, 71.9, 70.1, 69.9, 65.1, 56.1, 46.5, 41.5, 36.4, 30.3. FAB-MS *m/z* 2409.3 ($[M + H]^+$, calcd for $C_{153}H_{206}NO_{22}$ 2409.5).

[G-1]-NHC(O)CH$_2$Cl (19). To a cooled solution (0 °C) of [G-1]-NH$_2$ (**16**) (400 mg, 0.76 mmol) and Et_3N (0.14 mL, 1.00 mmol) in CH_2Cl_2 (25 mL) was added dropwise a solution of chloroacetyl chloride (0.12 mL, 1.00 mmol) in CH_2Cl_2 (25 mL). After the addition was complete, the mixture was stirred for 1 h at rt. Subsequently, 1 N HCl (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with water (150 mL) and brine (150 mL) and dried with $MgSO_4$. The solvent was evaporated under reduced pressure, after which the residue was purified by column chromatography (CH_2Cl_2, gradually shifted to CH_2Cl_2/MeOH, 99/1) to give **19** as an orange/red oil. Yield: 92%. ^{1}H NMR: δ 6.78 (bs, 1 H), 6.35 (m, 3 H), 4.34 (d, 2 H, J = 5.9 Hz), 4.03 (s, 2 H), 3.96 (t, 4 H, J = 6.2 Hz), 3.51 (t, 4 H, J = 6.2 Hz), 2.06 (m, 6 H), 1.91 (m, 4 H), 1.67 (m, 12 H), 1.55 (m, 12 H). ^{13}C NMR: δ 165.7, 160.6, 139.2, 106.3, 100.5, 71.9, 65.1, 56.1, 43.9, 42.6, 41.5, 36.4, 30.4. FAB-MS *m/z* 599.5 (M^+, calcd for $C_{35}H_{50}ClNO_5$ 599.3).

[G-2]-NHC(O)CH$_2$Cl (20) was synthesized analogously to [G-1]-NC(O)CH$_2$Cl (**19**), starting from [G-2]-NH$_2$ (**17**) (0.81 g, 1.06 mmol). The crude reaction product was purified by column chromatography (CH_2Cl_2/MeOH, 99/1) to give **20** as an orange/red oil. Yield: 94%. ^{1}H NMR: δ 6.82 (bs, 1 H), 6.57 (d, 5 H, J = 2.2 Hz), 6.52 (d, 2 H, J = 2.2 Hz), 6.44 (t, 2 H, J = 2.2 Hz), 4.95 (s, 4 H), 4.43 (d, 2 H, J = 5.9 Hz), 4.11 (s, 2 H), 4.05 (t, 8 H, J = 6.2 Hz), 3.59 (t, 8 H, J = 6.2 Hz), 2.13 (m, 12 H), 2.01 (m, 8 H), 1.75 (m, 24 H), 1.62 (m, 24 H). ^{13}C NMR: δ 160.5, 160.3, 139.5, 138.7, 106.7, 105.8, 101.2, 100.9, 72.0, 70.1, 65.1, 56.2, 43.8, 42.6, 41.5, 36.5, 30.5. FAB-MS *m/z* 1226.3 ($[M - H]^-$, calcd for $C_{75}H_{101}ClNO_{11}$ 1226.4).

[G-3]-NHC(O)CH$_2$Cl (21) was synthesized analogously to [G-1]-NC(O)CH$_2$Cl (**19**) starting from [G-3]-NH$_2$ (**18**) (0.33 g, 0.14 mmol) to give pure **21** as a colorless oil in quantitative yield. Purification by column chromatography was not necessary. ^{1}H NMR: δ 6.80 (s, 1 H), 6.68 (m, 5 H), 6.58 (m, 10 H), 6.56 (m, 2 H), 6.44 (m, 4 H), 4.96 (s, 12 H), 4.43 (d, 2 H, J = 5.9 Hz), 4.07 (s, 2 H), 4.06 (t, 16 H, J = 6.2 Hz), 3.58 (t, 16 H, J = 6.2 Hz), 2.13 (m, 24 H), 1.98 (m, 16 H), 1.74 (m, 48 H), 1.61 (m, 48 H). ^{13}C NMR: δ 165.8, 160.4, 160.2, 139.6, 139.0, 138.8, 106.8, 106.4, 105.9, 101.5, 100.9, 71.9, 70.1, 65.1, 56.2, 43.8, 42.6, 41.5, 36.5, 33.4, 30.5. FAB-MS *m/z* 2483.6 ($[M - H]^-$, calcd for $C_{155}H_{205}ClNO_{23}$ 2483.2).

[G-1]-NHC(O)CH$_2$SC(O)CH$_3$ (22). A solution of [G-1]-NHC(O)CH$_2$Cl (**19**) (0.51 g, 0.85 mmol) in DMF (10 mL) was added dropwise to a solution of potassium thioacetate (0.14 g, 1.25 mmol) in DMF (15 mL) in a darkened round-bottom flask. The reaction mixture was stirred overnight at rt, after which time it was dissolved in CH_2Cl_2 (200 mL), washed with 0.5 N HCl solution (3 × 50 mL) and brine (50 mL), and dried with $MgSO_4$. The solvent was evaporated under reduced pressure, giving a light brown oil. Trace amounts of DMF were removed by repeated azeotropic evaporation with toluene to give pure **22**. Yield: 95%. ^{1}H NMR: δ 6.37 (m, 3 H), 4.34 (d, 2 H, J = 5.9 Hz), 4.01 (t, 4 H, J = 6.2 Hz), 3.58 (s, 2 H), 3.57 (t, 4 H, J = 6.2 Hz), 2.40 (s, 3 H), 2.13 (m, 6 H), 1.97 (m, 4 H), 1.74 (m, 12 H), 1.61 (m, 12 H). ^{13}C NMR: δ 194.6, 167.9, 160.5, 139.8, 106.0, 100.2, 72.0, 65.1, 56.2, 43.9, 41.7, 36.5, 33.1, 30.4. FAB-MS *m/z* 640.3 ($[M + H]^+$, calcd for $C_{37}H_{54}NO_6S$ 640.4).

[G-2]-NHC(O)CH$_2$SC(O)CH$_3$ (23) was synthesized analogously to [G-1]-NHC(O)CH$_2$SC(O)CH$_3$ (**22**) starting from [G-2]-chloroacetamide (**20**) (0.50 g, 0.41 mmol) to give **23** as a colorless oil in quantitative yield. ^{1}H NMR: δ 6.53 (d, 4 H, J = 2.2 Hz), 6.45 (t, 1 H, J = 2.2 Hz), 6.41 (d, 2 H, J = 2.2 Hz), 6.36 (t, 2 H, J = 2.2 Hz), 4.93 (s, 4 H), 4.36 (d, 2 H, J = 5.9 Hz), 4.04 (t, 8 H, J = 6.2 Hz), 3.58 (t, 8 H, J = 6.2 Hz), 3.58 (s, 2 H), 2.39 (s, 3 H), 2.13 (m, 12 H), 1.98 (m, 8 H), 1.74 (m, 24 H), 1.61 (m, 24 H). ^{13}C NMR: δ 194.3, 162.5, 160.4, 160.1, 140.2, 138.8, 129.0, 128.2, 125.3, 106.4, 105.9, 100.9, 72.0, 70.1, 65.1, 56.2, 43.8, 41.5, 36.5, 33.0, 31.4, 30.5. FAB-MS *m/z* 1269.1 ($[M + H]^+$, calcd for $C_{77}H_{106}NO_{12}S$ 1268.8).

[G-3]-NHC(O)CH$_2$SC(O)CH$_3$ (24) was synthesized analogously to [G-1]-NHC(O)CH$_2$SC(O)CH$_3$ (**22**) starting from [G-3]-chloroacetamide (**21**) (0.36 g, 0.15 mmol) to yield **24** as a colorless oil. Yield: 72%. ^{1}H NMR: δ 6.69 (m, 5 H), 6.59 (m, 10 H), 6.49 (m, 2 H), 6.44 (m, 4 H), 4.97 (s, 12 H), 4.38 (d, 2 H, J = 5.9 Hz), 4.05 (t, 16 H, J = 6.2 Hz), 3.59 (t, 16 H, J = 6.2 Hz), 3.59 (s, 2 H), 2.37 (s, 2 H), 2.13 (m, 24 H), 1.99 (m, 16 H), 1.75 (m, 48 H), 1.61 (m, 48 H). ^{13}C NMR: δ 194.4, 160.4, 160.1, 140.2, 139.1, 138.8, 129.0, 128.2, 125.2, 106.4, 105.9, 101.5, 100.9, 71.9, 70.1, 65.1, 56.2, 43.7, 41.5, 36.5, 36.5, 33.0, 30.5. FAB-MS *m/z* 2527.7 ($[M + H]^+$, calcd for $C_{157}H_{212}NO_{24}S$ 2527.4).

(37) Workup of this product resulted in extensive foam formation in the separatory funnel. Therefore, the product could not be obtained in the expected near-quantitative yield.

[G-1]-Amide-thiol (25). To a nitrogen-saturated solution of [G-1]-$NHC(O)CH_2SC(O)CH_3$ **(22)** (350 mg, 0.55 mmol) in methanol (40 mL) was added an aqueous solution of K_2CO_3 (0.5 g in 20 mL of water). The solution was refluxed for 30 min, after which time it was allowed to cool to rt and 1 N HCl solution (50 mL) was added. The water layer was extracted with CH_2Cl_2 (2 × 50 mL), after which the combined extracts were washed with water (100 mL) and brine (100 mL) and dried with $MgSO_4$. The solvent was evaporated under reduced pressure to give **25** as a light yellow oil in quantitative yield. ^{1}H NMR: δ 6.90 (bs, 1 H), 6.43 (m, 3 H), 4.40 (d, 2 H, J = 5.5 Hz), 4.04 (t, 4 H, J = 6.2 Hz), 3.59 (t, 4 H, J = 6.2 Hz), 3.31 (d, 2 H, J = 7.0 Hz), 2.14 (m, 6 H), 1.99 (m, 4 H), 1.90 (t, 1 H, J = 9.2 Hz), 1.75 (m, 12 H), 1.62 (m, 12 H). ^{13}C NMR: δ 160.6, 139.7, 106.3, 100.3, 72.0, 65.2, 56.2, 44.0, 41.5, 36.5, 30.4. FAB-MS m/z 598.3 ($[M + H]^+$, calcd for $C_{35}H_{52}NO_5S$ 598.3).

[G-2]-amide-thiol (26) was synthesized analogously to [G-1]-amide-thiol **(25)** starting from [G-2]-$CH_2NHC(O)CH_2SC(O)CH_3$ (**23**) to give **26** as a light yellow oil in quantitative yield. ^{1}H NMR: δ 6.92 (bs, 1 H), 6.57 (d, 4 H, J = 2.2 Hz), 6.52 (t, 1 H, J = 2.2 Hz), 6.44 (d, 2 H, J = 2.2 Hz), 6.30 (t, 2 H, J = 2.2 Hz), 5.01 (s, 4 H), 4.43 (d, 2 H, J = 5.9 Hz), 4.02 (t, 8 H, J = 6.2 Hz), 3.62 (t, 8 H, J = 6.2 Hz), 3.30 (d, 2 H, J = 9.2 Hz), 2.11 (m, 12 H), 1.97 (m, 8 H), 1.75 (m, 24 H), 1.63 (m, 24 H). The crude reaction product was used directly and without further purification in the synthesis of $[G\text{-}2]_2$-Re (**30**).

[G-3]-amide-thiol (27) was synthesized analogously to [G-1]-amide-thiol **(25)** starting from [G-2]-$CH_2NHC(O)CH_2SC(O)CH_3$ (**24**) (0.22 g, 87.1 μmol) to yield **27** as a light yellow oil in quantitative yield. ^{1}H NMR: δ 6.95 (bs, 1 H), 6.69−6.44 (m, 21 H), 4.97 (s, 12 H), 4.40 (d, 2 H, J = 5.9 Hz), 4.05 (t, 16 H, J = 6.2 Hz), 3.59 (t, 16 H, J = 6.2 Hz), 3.27 (d, 2 H, J = 9.2 Hz), 2.13 (m, 24 H), 1.98 (m, 16 H), 1.73 (m, 48 H), 1.60 (m, 48 H). The crude reaction product was used directly and without further purification in the synthesis of $[G\text{-}3]_2$-Re (**31**).

$[G\text{-}1]_2$-Re (29) in MeOH. A nitrogen-saturated solution of [G-1]-amide-thiol (**25**) (0.24 g, 0.40 mmol) in MeOH (25 mL) was heated to reflux. A nitrogen-saturated solution of NBu_4-OAc (60 mg, 0.20 mmol) and NaOAc (66 mg, 0.80 mmol) in MeOH (10 mL) was added to the refluxing solution and refluxing was continued for 15 min. Finally, $ReO(PPh_3)_2Cl_3$ (0.17 g, 0.20 mmol) was added, and the solution was refluxed for an additional 2 h, after which time it was allowed to cool to rt. $CHCl_3$ (75 mL) was added to the mixture, after which the solution was washed with 0.5 N HCl solution (100 mL) and brine (100 mL) and dried with $MgSO_4$. The solvent was evaporated under reduced pressure to give a solid brown material. The crude reaction product was purified by column chromatography (CH_2Cl_2/MeOH, 98/2 to give **29** as a brown solid material. Yield: 13%. Mp > 220 °C dec. ^{1}H NMR: δ 6.54 (d, 4 H, J = 2.2 Hz), 6.19 (d, 2 H, J = 2.2 Hz), 6.16 and 5.21 (d, 2 H, $^2J_{AB}$ = 15.0 Hz), 3.98 (t, 8 H, J = 6.2 Hz), 3.92 and 3.67 (d, 2 H, $^2J_{AB}$ = 17.6 Hz), 3.54 (t, 8 H, J = 6.2 Hz), 2.81 (m, 8 H), 2.14 (m, 12 H), 1.91 (m, 8 H), 1.74 (m, 24 H), 1.60 (m, 24 H), 1.33 (m, 16 H), 0.98 (t, 12 H, J = 7.0 Hz). ^{13}C NMR: δ 195.9, 159.6, 144.4, 107.0, 106.7, 72.0, 65.2, 58.4, 56.5, 41.5, 36.5, 30.4, 23.7, 19.6, 13.7. FAB-MS m/z, correct rhenium isotope pattern = 1393.7 (negative mode, $[M - NBu_4 - H]^-$, calcd 1393.6), 242.2 (positive mode, NBu_4^+, calcd 242.3). Anal. Calcd for $C_{86}H_{134}N_3O_{11}ReS_2$: C, 63.13; H, 8.25; N, 2.57; S, 3.92. Found: C, 62.90; H, 8,14; N, 2.55; S, 4.18.

$[G\text{-}2]_2$-Re (30) in MeOH was synthesized analogously to $[G\text{-}1]_2$-Re **(29)** in MeOH starting from [G-2]-amide-thiol (**26**) (0.62 g, 0.51 mmol). The crude reaction product was purified by column chromatography (CH_2Cl_2/MeOH, 99/1 gradually changed to CH_2Cl_2/MeOH, 9/1), followed by p-TLC (CH_2Cl_2/MeOH, 96/4), to give **30** as a red brown oil. Yield: 7%. ^{1}H NMR: δ 6.71 (d, 4 H, J = 2.2 Hz), 6.54 (d, 8 H, J = 2.2 Hz), 6.41 (t, 4 H, J = 2.2 Hz), 6.16 and 5.29 (d, 2 H, $^2J_{AB}$ = 14.7 Hz), 4.88 (s, 8 H), 4.03 (t, 16 H, J = 6.2 Hz), 3.96 and 3.72 (d, 2 H, $^2J_{AB}$ = 17.6 Hz), 3.58 (t, 16 H, J = 6.2 Hz), 2.68 (m, 8 H), 2.14 (m, 24 H), 1.97 (m, 16 H), 1.74 (m, 48 H), 1.62 (m, 48 H), 1.22 (m, 16 H), 0.90 (t, 12 H, J = 7.0 Hz). ^{13}C NMR: δ 194.9, 160.4, 159.4, 139.2, 138.4, 106.5, 106.1, 101.4 100.7, 72.0, 70.2, 68.0, 65.2, 58.4, 56.2, 41.6, 36.5, 30.5, 25.6, 23.6, 19.5, 13.7. FAB-MS m/z, correct rhenium isotope pattern = 2651.3 (negative mode, $[M - NBu_4]^-$, calcd for $C_{150}H_{202}N_2O_{23}ReS_2$ 2651.4).

$[G\text{-}1]_2$-Re (29) in Water. To a nitrogen-flushed (1 h) solution of β-cyclodextrin (1.14 g, 1.00 mmol) in water (710 mL) was added a solution of [G-1]-amide-thiol (**25**) (0.15 g, 0.25 mmol) dissolved in a minimal amount of MeOH (~5 mL). A freshly prepared $NaRe(gluc)_2$ solution (1.81 mL, 0.125 mmol), adjusted to pH = 10 by the addition of 1 N NaOH solution, was added, and the resulting mixture was flushed with nitrogen for an additional 15 min. After being stirred for 5 h at 55 °C, the solution was allowed to come to rt, and NBu_4-OAc (0.20 g, 0.67 mmol) was added. Stirring was continued for an additional 10 min, after which time the mixture was extracted with $CHCl_3$ (4 × 100 mL). The combined extracts were washed with water (250 mL) and brine (250 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure, giving pure **29** as a brown solid. Yield: 93%. Characterization proved it to be identical to **29** synthesized in MeOH.

$[G\text{-}2]_2$-Re (30) in water was synthesized analogously to $[G\text{-}1]_2$-Re **(29)** in water starting from [G-2]-amide-thiol (**26**) (0.16 g, 0.13 mmol). The water volume was 770 mL. Yield: 68%. Characterization proved it to be identical to **30** synthesized in MeOH.

Determination of the Water Solubilities of 28, 29, and 30. The complexes were dissolved in MeOH or THF (~5 mL), and an aqueous solution (~10 mL) of β-CD was added (2 equiv of β-CD per adamantane moiety). The combined solvents were evaporated under reduced pressure, and D_2O (2 mL) was added to the residue. After sonicating the mixtures overnight, filtration of the samples over a Millipore filter (0.45 μm, Spartan 13/B; Schleicher & Schuell) gave saturated solutions of the β-CD/rhenium-complex mixtures. A D_2O solution containing an internal standard (t-BuOH) of a known concentration was added in order to enable the calculation of the solubilities of the different complexes based on their ^{1}H NMR integrals.

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