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Valentin A. Chebanov[a]; Claudia Reidlinger[a]; Hussein Kanaani[b]; Curt Wentrup[b]; C. Oliver Kappe[a]; Gert Kollenz[a]
[a] Organic and Bioorganic Division, Institute of Chemistry, KF-University of Graz, Graz, Austria [b] Department of Chemistry, The University of Queensland, Brisbane, Australia

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Macrocyclic Systems Containing 2,6,9-Trioxabicyclo[3.3.1]-nona-3,7-dienes as Chiral Spacer Groups: Synthesis, Stereochemical Features and Preliminary Complexation Properties

VALENTIN A. CHEBANOV[a], CLAUDIA REIDLINGER[a], HUSSEIN KANAANI[b], CURT WENTRUP[b], C. OLIVER KAPPE[a] and GERT KOLLENZ[a,*]

[a]*Institute of Chemistry, Organic and Bioorganic Division, KF-University of Graz, A-8010 Graz, Austria;* [b]*Department of Chemistry, The University of Queensland, Brisbane Qld 4072, Australia*

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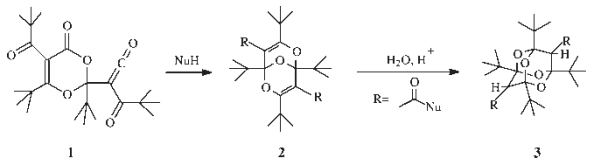
Novel 2:2-macrocycles bearing bridged concave 2,6,9-trioxabicyclo[3.3.1]nona-3,7-dienes as chiral spacer units were obtained by cyclocondensation reaction of the chiral bisacid chloride and the corresponding diols, while use of methylene diamines instead of diols afforded 1:1 macrocycles only. Applying the same, but now template-assisted, experimental procedure to the reaction of the bisacid chloride with triethylene glycol brought about a significant increase in yield as well as a suitable simplification of the work-up during preparation and separation of the corresponding 1:1 as well as 2:2 macrocycles, when compared to results reported previously. HPLC separation on chiral columns revealed the presence of diastereoisomers [*R*,*R*(*S*,*S*)- and *R*,*S*-(*meso*)-forms] for all 2:2 macrocycles, which was further evidenced by the CD spectrum of one of those species as an example. Preliminary ESI-MS experiments indicated strong complexation abilities of the sulphur-containing ligand towards Ag(I), Cu(II) and Au(III) ions.

Keywords: Macrocycles; Bridged bisdioxine spacer; Template experiments; HPLC; CD spectra; Metal ion complexation

INTRODUCTION

Mono- and bifunctionalized 2,6,9-trioxabicyclo-[3.3.1]nona-3,7-dienes **2** ("bridged bisdioxines") are readily formed from reactions of dimeric dipivaloylketene **1** and nucleophiles [1–3]. Dimeric dipivaloylketene, itself a remarkably stable α-oxoketene, could be obtained in quantitative yield by dimerization of the monomeric dipivaloylketene, which is generated by flash vacuum pyrolysis of the corresponding furan-2,3-dione [4,5]. Furthermore, these bridged bisdioxines **2** can be readily converted into tetraoxaadamantanes **3** by acid hydrolysis [6].



1 2 3

Recently, these unusual and chiral heterocyclic systems were incorporated into a variety of macrocyclic polyethers in a 1:1 and/or 2:2 ratio of spacer to chain (e.g. **4**, **6**), in an attempt to investigate their abilities to serve as novel host systems [7]. Incorporation of the chiral spacer was achieved successfully by use of the corresponding bisacid chloride (**8**), where the through-space angle between the two carbonyl chloride groups is very similar to the widely used isophthaloyl dichloride [8–11], 2,6-pyridine dicarbonyl dichloride [12] or even 1,3-adamantane dicarbonyl dichloride [13]. Molecules having aryl groups within the chains (e.g. **5**) successfully bind Hg(II) as 1:1 complexes in extraction experiments [14].

*Corresponding author. E-mail: kollenz@kfunigraz.ac.at

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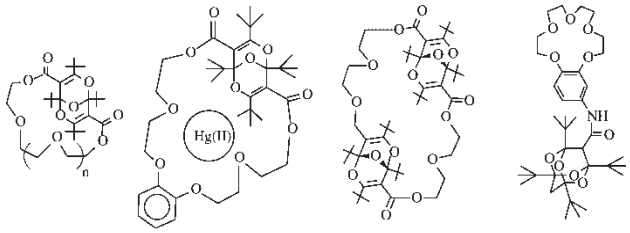
Heterocycles **2** and **3** may also be attached to aminobenzo-crown ethers of various sizes (e.g. **7**), which can significantly increase the complexation ability towards metal ions in extraction experiments [15].



4 5 6 7

Our intention was to exchange the crown ether-like ethylene glycol chains for, for example, hydrocarbon chains as found in cryptophanes, in order to examine their specific stereochemical features as well as to increase the lipophilicity and possibly enhance the ability of these macrocycles to interact with suitable guest molecules.

RESULTS AND DISCUSSION

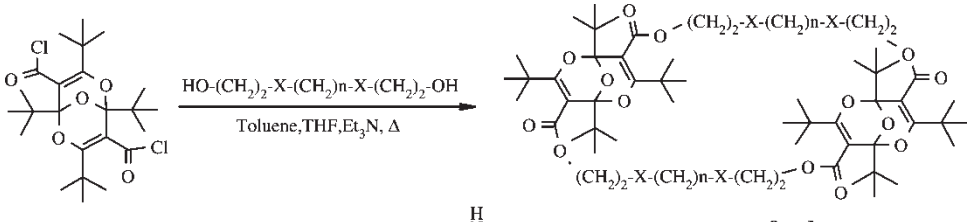
Polymethylenedioxy, Thiapolymethylenedioxy and Polymethylenediamino-bridged Compounds

Hydrolysis of the oxoketene dimer **1** affords the bridged bisacid **2** (R = COOH) [2], which can easily be converted into the corresponding bisacid chloride **8** [2]. The novel macrocyclic systems **9a–d** were obtained by reaction of the bisacid dichloride **8** with diols **9a–c** and dithiaoctanediol **9d** in a boiling mixture of toluene and THF under a nitrogen atmosphere, thus following a slightly improved known procedure [16] (Scheme 1).

The addition of 4-dimethylaminopyridine as a base led to product mixtures that required purification by column chromatography, but the addition of triethylamine gave rise to compounds **9** and **10** of sufficient purity with significantly improved yields.

The structural analysis of compounds **9a–d** is based on detailed ^{1}H and ^{13}C NMR measurements. Comparison of the ^{13}C NMR spectra of **9a–d** with those of several other macrocycles containing bisdioxines as spacer units [1,2,7] allowed the unambiguous identification of these moieties, in particular using the signals at 98.0–98.2 (C1/C5), 102.1–102.7 (C4/C8) and 162.6–163.2 (C3/C7) ppm for the ring carbons of the trioxabicyclo[3.3.1]nona-3,7-diene moiety. The ^{1}H NMR spectra exhibited signals for *tert*-Bu and CH_2 groups only and indicated a significant downfield shift for the OCH_2 protons as expected (see the Experimental section for details). FAB mass spectral data were useful for the determination of the exact size of the macrocycle (1:1, 2:2 or 3:3 ratios of spacer to chain). It became evident that under the reaction conditions used, only macrocyles assembled from two molecules of bisdioxine and two molecules of diols were obtained (**9a–d**). All attempts to isolate any other compounds with different stoichiometries were unsuccessful.

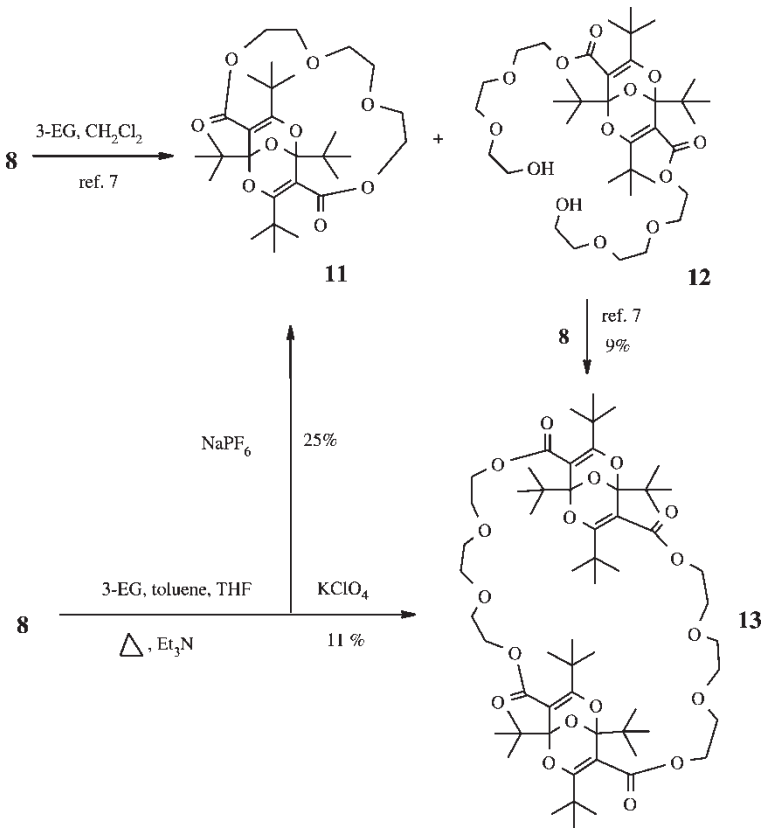
It is interesting to note that under identical conditions, the reaction of **8** with 1,10 (12)-diamines afforded macrocycles **10a,b** with a 1:1 ratio of components only. This again was established by means of FAB mass spectrometry. The structures of **10** were confirmed by the IR and NMR spectra. The ^{13}C NMR spectra again exhibited signals attributed to the carbons of the bridged bisdioxine unit (see above) as well as the diamino-polymethylene parts (27.7–29.9, 39.9–40.0 ppm). In the ^{1}H NMR spectra, in addition to signals due to the *tert*-butyl and CH_2 groups, the NH protons at 5.3 and 5.40 ppm appear as doublets [$J = 4.8$ (**10a**) and 5.5 Hz (**10b**) due to coupling with one of the NCH_2 protons at 3.62 (**10a**)



9	n	X	yield (%)
a	0	-(CH$_2$)-	26
b	4	-(CH$_2$)-	38
c	6	-(CH2)-	40
d	2	-S-	11

10	n	yield (%)
a	10	21
b	12	30

SCHEME 1



SCHEME 2

and 3.69 ppm (**10b**), respectively]. The NH signals collapse to singlets in a decoupling experiment. Furthermore, as an example, the exchange reaction of **10a** with D_2O causes a distinct decrease in the intensity of the corresponding NH signal at 5.3 ppm, but the rate of this exchange process is remarkably slow. Presumably this is due to the strong lipophilic nature of those macrocycles.

Crown Ether-type Compounds

In a previous publication [7] we reported a two-step procedure for obtaining macrocycles with a 2:2 ratio of spacer to chain (e.g. **13**, Scheme 2). In the first step the open-chain compound **12** (in admixture with **11** and other products) was isolated from reaction of, for example, triethylene glycol and the bisacid dichloride **8**. The bisester **12** reacted with the second molecule of **8** to afford macrocycle **13**. The separation and purification of all reaction products required extensive application of dry-flash column chromatography.

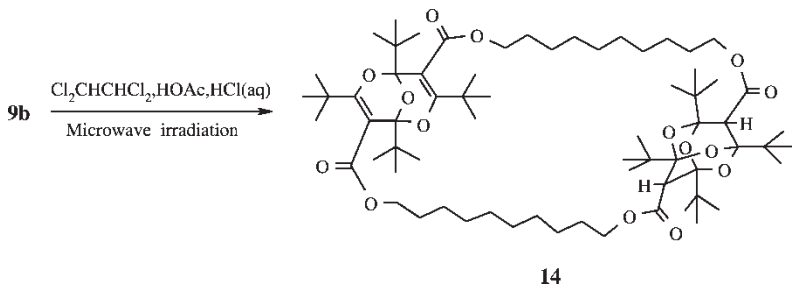
We now report an improved method of preparation of 2:2 macrocycles such as **13**. First, it was found that reaction of **8** with triethylene glycol (3-EG) in a boiling mixture of toluene and THF in the presence of Et_3N afforded compounds **11** and **13** (8% each) in one step. The mixture of **11** and **13** could be separated by fractional recrystallization from methanol without application of chromatographic methods. To increase the yields of the desired 2:2 macrocycles the use of template-assisted synthesis was envisaged: in the presence of sodium hexfluorophosphate as template the yield of **11** increased to 25%, while compound **13** was found in only trace amounts. When selecting a cation with a larger ionic radius as template (e.g. K^+), both macrocycles **11** and **13** were isolated in slightly increased yields (18% and 11%, respectively).

Thus, the template-assisted one-step procedure offers a more convenient method to synthesize the 2:2 macrocycles in particular, without the application of dry-flash chromatography and with slightly increased yields compared with the two-step procedure.

Tetraoxaadamantanes

Acidic hydrolysis of bridged bisdioxines leads to functionalized 2,4,6,8-tetraoxaadamantanes **3** [6,7,15]. With macrocycles containing two trioxabicyclononandiene spacer units (e.g. **9**) only the conversion of one bisdioxine unit has been observed so far [7] (Scheme 3).

Attempts to carry out this conversion with macrocycle **9b** as an example under a variety of conditions (change of reaction time and solvents, heating, addition of gaseous HCl) were unsuccessful. As the first step of the transformation is the addition of water



14

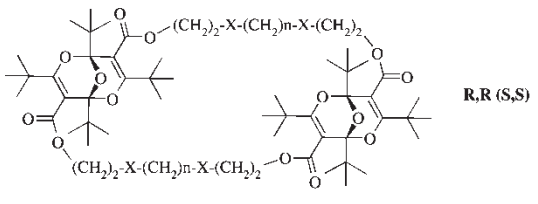
SCHEME 3

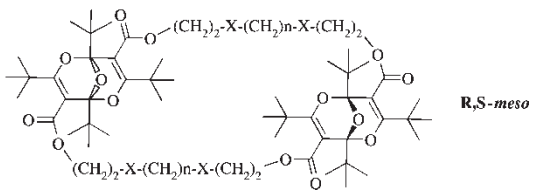
to the double bond of the bisdioxine unit, this failure may correspond to the higher hydrophobic and lipophilic properties of **9** compared to the crown ether-like macrocycles investigated earlier [7].

However, when the reaction was carried out under controlled microwave irradiation, the desired product **14** was obtained in 35% yield. The structure of **14** was established from the ^{1}H NMR spectrum, which, besides signals of *tert*-butyl groups of the bisdioxine (δ 1.05 and 1.21) and the adamantane units (δ 0.96, 0.97, 1.09, 1.11 ppm), exhibited two singlets for the highly characteristic tetraoxaadamantyl methine protons at δ 2.84 and 2.97 ppm [3,6,7]. In the ^{13}C NMR spectrum of **14** signals characteristic of both the bridged bisdioxine [98.13 (C1/C5); 102.70 (C4/C8); 162.8 (C3/C7)] and adamantyl moieties [47.86 (CH), 100.1, 100.9, quaternary ring sp^3 carbons] and 168.67, 169.90, 172.2 ppm for the carbonyl groups could be unambiguously assigned [2,3,6,7].

HPLC Measurements and CD Spectra

Because of the axial chirality of the bridged bisdioxine unit, macrocycles **9a–d** containing two spacer molecules should be present as equimolar mixtures of diastereoisomers: a pair of *R,R*-and *S,S*-enantiomers and the *R,S-meso* form. This was confirmed by HPLC measurements applying a chiral stationary phase.





By using the Chiralpak AD column, a split into three signals was observed. Integration established a 1:1:2 ratio. Furthermore, in the case of **9b**, the fractions were collected separately, and the CD spectra allowed the assignment of two of the fractions to the *R,R* and *S,S* enantiomers, respectively, with a 1:1 ratio of integrated intensity. The last fraction was inactive in the CD and represents the *R,S*-(*meso*)-form. HPLC separation of **9a–d** using a column with a nonchiral stationary phase gave rise to one broad signal with a shoulder. For compounds **10**, as expected, only two signals for the two enantiomers could be detected on the chiral column (Fig. 1).

ESI-MS Experiments

The ability of several of the previously synthesized crown ether-type molecules [7] to extract metal ions from solutions was examined by electrospray mass spectrometry following the procedure reported by Moeder *et al.* [17]. None of them showed any marked affinity except for Na^+ and K^+, as is commonly observed in ESI-MS. By contrast, the sulphur-containing host **9d** exhibited a strong affinity for Ag^+, Cu^{2+} and Au^{3+}. Macrocycles containing sulphur atoms within a polyether chain are known to offer good complexation properties towards Ag^+ ions in general [18–20]. The affinity for Ag^+ is so great that **9d** is useful for cleaning the mass spectrometer inlet system of residual silver remaining after injecting other Ag^+ complexes. If any silver ions remain in the system, injecting the Cu^{2+} or Au^{3+} complexes of **9d** will result in ion exchange, so that only the Ag^+ complex is observed. Quantitative complexation studies are under way, and the results will be reported elsewhere.

EXPERIMENTAL

General

^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 360 (360 MHz) and Bruker DRX Avance (500 MHz) spectrometers. IR spectra were recorded on a Perkin Elmer 298 spectrometer. FAB mass spectra were obtained on a VGZAB-2sEQ spectrometer. ESI-MS was run on a Finnigan MAT 900 XL-Trap System with Finnigan ESI-3 Electrospray Source and Interface. The samples were introduced in solution at 5 μl min^{-1} via an injection valve with a 20 μl loop. The ESI

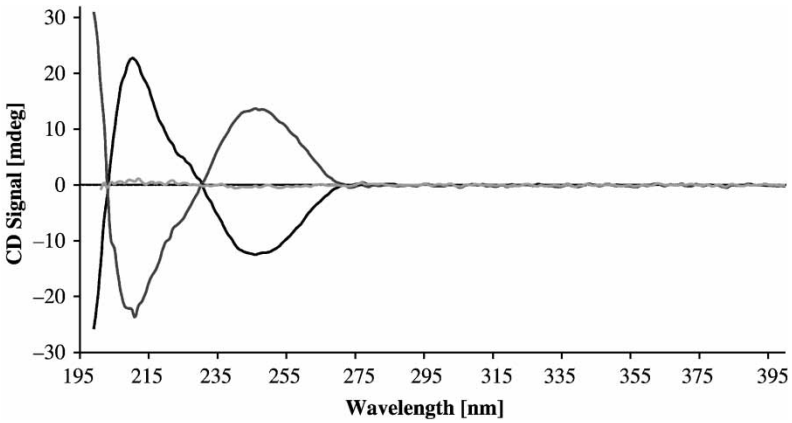


FIGURE 1 CD spectrum of the *R,R*(*S,S*)-isomers and the *meso*-form of **9b** after HPLC separation.

spray voltage was 3.3 kV. Elemental analyses were performed on a C,H,N automate Carlo Erba 1106. HPLC measurements were recorded on a Hewlett-Packard 1050 apparatus. CD spectra were measured on a Jasco J-715 spectrometer. Microwave irradiations were carried out with an Emrys-Synthesizer (mono mode, Personal Chemistry AB). Melting points are uncorrected.

The bisacid dichloride **8** was prepared according to the literature [2]. All other starting materials were purchased from Sigma-Aldrich Chemical Co. and used without further purification. Triethylene glycol was dried over molecular sieves (4 Å). The stationary phase (Silica Gel 60H, Merck) and solvents used as eluants in dry-flash chromatography (DFC) were purchased in a high quality grade.

General Procedure for the Reaction of the Bisacid Dichloride 8 with Diols

The procedure is a slight improvement on a published method of macrocycle preparation [16]. A solution of the bisacid dichloride **8** (0.5 g; 1.05 mmol) in 25 ml of dry toluene and a solution of the corresponding diol (1.1 mmol) and Et_3N (1 ml) in a mixture of dry toluene (8 ml) and dry THF (17 ml) were simultaneously added dropwise to 80 ml of vigorously stirred boiling dry toluene under nitrogen over 3 h. The reaction mixture was then heated with stirring for 20 h and filtered. The solvents were evaporated and the residue was triturated with hot methanol. The precipitate formed on cooling was separated by suction filtration and recrystallized from ethyl acetate.

Bis(1,3,5,7-tetra(tert-butyl)-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-diyl)-di(1,10-dioxo-2,9-dioxadecane) (9a)

Colourless solid, yield 26%, mp 286–288°C. IR (KBr): ν (cm^{-1}) 2840–3040 (CH), 1718 (C═O), 1620 (C═C); ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 36H), 1.20 (s, 36H), 1.27–1.40 (m, 8H), 1.62 (m, 8H), 3.77 (m, 4H), 4.28 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 24.6, 28.6 [$C(CH_3)_3$], 37.3, 39.4 [$C(CH_3)_3$], 24.9, 25.2, 27.7, 28.8, 64.4 (CH_2), 98.1 (C1/C5), 102.5 (C4/C8), 162.7 (C3/C7); 169.8 (C = O); m/z (FAB, Noba-matrix): 1042.5 $[M + H]^+$. Anal. Calcd for $C_{60}H_{96}O_{14}$: C, 69.20; H, 9.29. Found: C, 68.80; H, 9.36.

Bis(1,3,5,7-tetra(tert-butyl)-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-diyl)-di(1,14-dioxo-2,13-dioxatetradecane) (9b)

Colourless solid, yield 38%, mp 295–298°C. IR (KBr): ν (cm^{-1}) 2820–3020 (CH), 1716 (C═O), 1620 (C═C); ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 36H), 1.21 (s, 36H), 1.22–1.30 (m, 24H), 1.69 (m, 8H), 3.81 (m, 4H), 4.26 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 24.7, 28.8 [$C(CH_3)_3$], 37.4, 39.5 [$C(CH_3)_3$], 26.2, 28.3, 29.2, 29.5, 64.9 (CH_2), 98.2 (C1/C5), 102.7 (C4/C8), 162.7 (C3/C7); 169.7 (C═O); m/z (FAB, Noba-matrix): 1153.7 $[M + H]^+$. Anal. Calcd for $C_{68}H_{112}O_{14}$: C, 70.80; H, 9.79. Found: C, 70.58; H, 9.91.

Bis(1,3,5,7-tetra(tert-butyl)-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-diyl)-di(1,16-dioxo-2,15-dioxahexadecane) (9c)

Colourless solid, yield 40%, mp 220–222°C. IR (KBr): ν (cm^{-1}) 2820–3040 (CH), 1718 (C═O), 1620 (C═C); ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 36H), 1.21 (s, 36H), 1.24–1.30 (m, 32H), 1.65 (m, 8H), 3.83 (m, 4H), 4.27 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 24.6, 28.8 [$C(CH_3)_3$], 37.3, 39.4 [$C(CH_3)_3$], 26.2, 28.2, 29.4, 29.6, 64.9 (CH_2), 98.0 (C1/C5), 102.6 (C4/C8), 162.6 (C3/C7); 169.8 (C═O); m/z (FAB, Noba-matrix): 1209.7 $[M + H]^+$. Anal. Calcd for $C_{72}H_{120}O_{14}$: C, 71.49; H, 10.00. Found: C, 71.36; H, 10.02.

Bis(1,3,5,7-tetra(tert-butyl)-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene-4,8-diyl)-di(1,12-dioxo-2,11-dioxa-5,8-dithiadodecane) (9d)

Colourless solid, yield 11%, mp 282–284°C. IR (KBr): ν (cm^{-1}) 2850–3000 (CH), 1720 (C═O), 1618 (C═C);

^{1}H NMR ($CDCl_3$): δ 1.03 (s, 36H), 1.22 (s, 36H), 1.72–2.81 (m, 16H), 4.03 (m, 4H), 4.30 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 24.6, 28.9 [$C(CH_3)_3$], 37.5, 39.5 [$C(CH_3)_3$], 30.3, 32.2, 63.4 (CH_2), 98.1 (C1/C5), 102.1 (C4/C8), 163.2 (C3/C7); 169.2 (C=O); *m/z* (FAB, Noba-matrix): 1169.3 $[M + H]^+$. Anal. Calcd for $C_{60}H_{96}O_{14}S_4$: C, 61.64; H, 8.27. Found: C, 62.00; H, 8.46.

General Procedure for the Reaction of the Bisacid Dichloride 8 with Diamines

A solution of the bisacid dichloride **8** (0.5 g; 1.05 mmol) in dry toluene (25 ml) and a solution of the corresponding diamine (1.1 mmol) and Et_3N (1 ml) in a mixture of dry toluene (8 ml) and dry THF (17 ml) were simultaneously added dropwise to 80 ml of vigorously stirred boiling dry toluene under nitrogen over 3 h. The reaction mixture was then heated with stirring for an additional 20 h and filtered. The solvents were evaporated, and the residue was dissolved in the minimum amount of a mixture of EtOAc and hexane (1:10) and purified by means of DFC. The product was essentially pure as isolated. Analytical samples were obtained by recrystallization from 1:10 EtOAc:hexane.

4,8-(1,14-Dioxo-2,13-diazatetradecane)-1,3,5-7-tetra(tert-butyl)-2,6,9-trioxabicyclo[3.3.1]-nona-3,7-diene (10a)

Yield 21%, mp 225–288°C. IR (KBr): ν (cm^{-1}) 3450 (NH), 2820–3020 (CH), 1665 (C=O), 1618 (C=C); ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 18H), 1.32 (s, 18H), 1.20–1.64 (m, 16H), 2.79 (m, 2H), 3.72 (m, 2H), 5.30 (d, 2H, $J = 4.8$ Hz); ^{13}C NMR ($CDCl_3$): δ 24.7, 29.2 [$C(CH_3)_3$], 37.8, 39.9 [$C(CH_3)_3$], 27.7, 28.1, 28.3, 28.5, 29.9 (CH_2), 98.3 (C1/C5), 106.0 (C4/C8), 160.3 (C3/C7); 167.8 (C=O); *m/z* (FAB, Noba-matrix): 575.4 $[M + H]^+$. Anal. Calcd for $C_{34}H_{58}N_2O_5$: C, 71.04; H, 10.17; N, 4.87. Found: C, 71.10; H, 10.25; N, 4.63.

4,8-(1,16-Dioxo-2,15-diazahexadecane)-1,3,5-7-tetra(tert-butyl)-2,6,9-trioxabicyclo[3.3.1]-nona-3,7-diene (10b)

Yield 30%, mp 220–223°C. IR (KBr): ν (cm^{-1}) 3460 (NH), 2820–3020 (CH), 1665 (C=O), 1618 (C=C); ^{1}H NMR ($CDCl_3$): δ 1.08 (s, 18H), 1.31 (s, 18H), 1.20–1.68 (m, 20H), 1.62 (s, 4H), 2.80 (m, 2H), 3.71 (m, 2H), 5.40 (d, 2H, $J = 5.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 24.8, 29.2 [$C(CH_3)_3$], 37.7, 40.0 [$C(CH_3)_3$], 27.1, 27.7, 28.1, 28.8, 28.9 (CH_2), 98.2 (C1/C5), 106.1 (C4/C8), 160.3 (C3/C7); 168.1 (C=O); *m/z* (FAB, Noba-matrix): 603.3 $[M + H]^+$. Anal. Calcd for $C_{36}H_{62}N_2O_5$: C, 71.72; H, 10.37; N, 4.65. Found: C, 71.63; H, 10.44; N, 4.29.

Reaction of the Bisacid Dichloride 8 with Triethylene Glycol [7]

A solution of the bisacid dichloride **8** (0.5 g; 1.05 mmol) in 25 ml of dry toluene and a solution of triethylene glycol (1.1 mmol) and Et_3N (1 ml) in a mixture of dry toluene (8 ml) and dry THF (17 ml) were simultaneously added dropwise to 80 ml of vigorously stirred boiling dry toluene under nitrogen over 3 h. The reaction mixture was then heated with stirring for 20 h and filtered. The solvents were evaporated and the residue was washed with hot methanol. The precipitate formed (2:2 macrocycle **13**) [7] was separated by suction filtration and recrystallized from MeOH:EtOAc (10:1) in 8% yield.

The methanolic mother liquor was cooled down (−10°C) to precipitate the 1:1 macrocycle **11** [7] (8% yield), which was recrystallized from a mixture of *n*-hexane and ethyl acetate.

Template Experiments

Reaction of the Bisacid Dichloride 8 with Triethylene Glycol in Presence of $NaPF_6$

Solutions of **8** (0.4 g; 0.85 mmol) in 20 ml of dry toluene and of triethylene glycol (0.13 g, 0.85 mmol) and Et_3N (1 ml) in a mixture of dry toluene (10 ml) and dry THF (10 ml) were simultaneously added dropwise over 3 h to a vigorously stirred boiling mixture of dry toluene (55 ml), dry THF (15 ml) and $NaPF_6$ (0.3 g) under nitrogen. The reaction mixture was then heated with stirring for 20 h and filtered. The solvents were evaporated, and the residue was dissolved in hot methanol. When the methanolic solution was cooled to −10°C the 1:1 macrocycle **11** was isolated by suction filtration and recrystallized from a mixture of hexane and ethyl acetate (25% yield). Compound **13** was not found in the reaction mixture.

Reaction of the Bisacid Dichloride 8 with Triethylene Glycol in the Presence of $KClO_4$

Using the above procedure but with $KClO_4$ instead of $NaPF_6$ **13** was obtained in 11% yield after recrystallization from MeOH:ethyl acetate 10:1.

The methanol solution was cooled to −10°C and macrocycle **11** was obtained (17%) after recrystallization from a mixture of hexane and ethyl acetate.

HPLC Experiments

Compounds **9a–d** and **10b** were dissolved in a mixture of hexane and 2-propanol 99.75:0.25, which was also applied as the mobile phase, in concentrations of 0.8–1.2 mol l^{-1} (injected volumes 25 μl). UV detection was at 230 and 254 nm. Chiralpak AD (Daicel Comp.) and Zivi I Columns were used.

9a: On Chiralpak AD splitting into three signals [retention time (min): 7.1 *meso*-form; 4.1 and 5.4, enantiomers].

9b: On Chiralpak AD splitting into three signals [retention time (min): 6.2 *meso*-form; 5.4 and 8.2 enantiomers]. On Zivi I there was only one broad signal with a shoulder (retention time 9.0). In this case pure *n*-hexane was used as eluant.

9c: On Chiralpak AD splitting into three signals [retention time (min): 5.8 *meso*-form; 5.4 and 6.8 enantiomers].

9d: On Chiralpak AD splitting into three signals [retention time (min): 13.6 *meso*-form; 10.8 and 19.1 enantiomers].

10b: On Chiralpak AD splitting into two signals [retention time (min): 7.4 and 9.0].

Conversion of 9b into the 2,4,6,8-Tetraoxaadamantane 14

Compound **9b** (0.2 g, 0.17 mmol) was dissolved in a mixture of acetic acid (2 ml), dichloroethane (2 ml) and concentrated hydrochloric acid (0.1 ml). A suitable glass tube was filled with the mixture, sealed and irradiated using controlled microwave irradiation (170°C, 40 min). Then the solvents were evaporated under reduced pressure and the residue was recrystallized from a mixture of CH_3CN and EtOAc. Yield 0.07 g (35%). mp 168–170°C; ^{1}H NMR ($CDCl_3$): δ 0.96, 0.97, 1.05, 1.09, 1.11, 1.21 (6s, 72H), 1.18–1.70 (m, 36H); 2.84, 2.97 (2s, 2H); 3.60–4.32 (m, 8H); m/z (ESI): 1170.8 $[M + H]^+$.

ESI-MS Experiments [17]

Samples were prepared by three methods: (i) 0.2 mg (1.7×10^{-7} mol) of **9d** was dissolved in CH_2Cl_2 and 0.1 mmol of the appropriate salt was added. The mixture was shaken on an orbital shaker for 1 h, and the solution was examined by ESI-MS. (ii) Compound **9d** (0.2 mg) was dissolved in 1 ml of CH_2Cl_2, and the salt (0.1 mmol) dissolved in 1 ml of water and picric acid (5×10^{-3} mol) were added. After shaking for 1 h, the organic phase was examined by ESI-MS. (iii) Compound **9d** and the salt were dissolved in methanol-CH_2Cl_2 (2:1), and after shaking for 1 h the homogeneous mixture was examined by ESI-MS. The first method gave the best results. The salts used for successful complexation were $AgNO_3$, $Cu(NO_3)_2$ and $KAuCl_4$. The corresponding mass spectra showed parent peaks at m/z 1276 and 1278 (**9d**·Ag^+), 1232 and 1234 (**9d**·Cu^+) and 1366 (**9d**·Au^{3+}).

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