Recl. Trav. Chim. Pays-Bas **111**, 421–426 (1992) 0165–0513/92/10421–06$2.00

Molecular recognition of barbiturates by a metalloreceptor

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(Received March 10th, 1992)

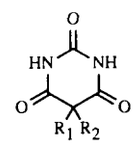
Abstract. Metallomacrocycle **2**, possessing an immobilized Lewis-acidic uranyl cation, was synthesized by reaction of aldehyde **9** with 1,2-*cis*-cyclohexanediamine in the presence of Ba^{2+} as a template cation and subsequent transmetallation with UO_2^{2+}. Docking experiments with barbituric acid revealed that a $-(CH_2)_6-$ spacer between the salen–uranyl and 2,6-diamidopyridine moieties of **2** is optimal. According to ^1H NMR titration experiments, the barbituric acid complex of **2** is up to 2.7 kcal · mol^{-1} more stable than the complexes with five disubstituted derivatives. The flux of barbituric acid through a supported liquid membrane is enhanced 3.7 times by carrier **2** mediated transport.

Introduction

Recently, we have demonstrated that *metalloreceptors* with a Lewis-acidic uranyl cation complexed in a salen or salophene* moiety represent an important class of hosts for the complexation of *neutral organic molecules*[1,2]. The immobilized uranyl cation prefers a pentagonal-bipyramidal coordination with the four ligating sites of the salen/salophene and the neutral molecule in the equatorial positions, and the oxygen atoms at the apical positions.

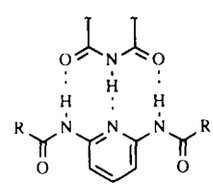
Barbiturates** are attractive neutral guest species because of the possibility of their polytopic interactions with receptor molecules. *Feibush* and *Karger* et al.[3] were the first to recognize the complementarity between barbiturates (Chart 1) and 2,6-diamidopyridines (Chart 2). The formation of three H bonds was shown by X-ray analysis[3] and is in agreement with the stability of the complex in $CDCl_3$[4]. *Hamilton* et al. exploited this complementarity further by incorporation of two 2,6-diamidopyridine units separated by an isophthalic moiety both in an acyclic and a cyclic receptor, to give a complementary array of H bonds[5]. *Rebek* et al. reported barbiturate receptors based on two Kemp's acid derivatives connected by 2,6- or 2,7-disubstituted naphthalene spacers, the latter being receptors superior because of their better shape and size complementarity[6].

All reported barbiturate receptors are based on *multiple-H-bond formation*. In this paper, a barbiturate receptor with both an immobilized uranyl cation and a 2,6-diamidopyridine moiety is presented. The synthesis of receptor **2** is discussed and its complexation properties are assessed by molecular modeling, ^1H NMR spectroscopy, and transport measurements (supported liquid membranes).



1a $R_1 = H, R_2 = H$
1b $R_1 = R_2 = CH_3$
1c $R_1 = R_2 = CH_2CH_3$
1d $R_1 = Phenyl, R_2 = CH_2CH_3$

Chart 1



R = Alkyl chain

Chart 2

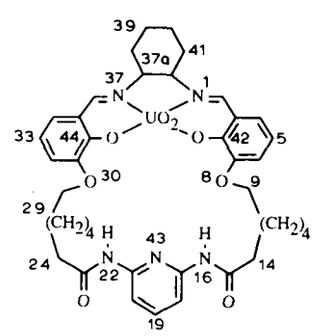


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Chart 3

* Salen = *N,N'*-ethylenebis(salicylideneiminate)
Salophene = *N,N'*-phenylene(salicylideneiminate)
** Barbituric acid = 2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione.

Results and discussion

Design and calculations

Metallomacrocycle **2**, which consists of a salen-uranyl and a 2,6-diamidopyridine moiety connected by flexible spacers, was designed to complex barbiturates. In order to investigate the potential complexation properties of this receptor, molecular mechanics calculations were performed[7].

For the Schiff-base moiety and the uranyl cation, all parameters were not available. Therefore, the salen moiety of a related structure was taken and was regarded as fixed[1d]. The non-bonded parameters of the uranyl cation were determined in order to reproduce the experimental hydration geometry and enthalpy[8].

Docking experiments with barbituric acid (**1a**) revealed that a $-(CH_2)_6-$ spacer seems to be the optimum for complexation. Barbituric acid has the possibility to coordinate via two different oxygens to the uranyl. In both modes of complexation, additional stabilization by H-bond formation can be expected. The calculated structures of the complexes (**3** and **4**) are depicted in Figure 1 and the relevant distances and bond angles of the complexes are summarized in Table I.

According to molecular mechanics calculations, using the CHARMm force field parameters, complex **3** is favored over complex **4** by 3.5 kcal · mol^{-1}. The calculated distances between the donor and acceptor heteroatoms in complex **3** (2.8–3.1 Å) are similar to the values that *Feibush*[3] (2.9–3.1 Å) and *Hamilton*[5] (2.9–3.2 Å) measured in solid-state barbiturate complexes. Several factors contribute to the preferred binding mode of complex **3**. Complex **3** has one H bond more than complex **4** and, in complex **3**, the hydrogen bonds are shorter than in complex **4** (2.00–2.35 Å *vs* 2.18–2.83 Å); the bond angles are comparable (133–166° *vs* 147–170°). One of the three H bonds in complex **4** must be weak or does not exist because of the great distance (2.83 Å) between O-12 and H-13.

Consequently, according to molecular-mechanics calculations, metallomacrocycle **2** has the appropriate cavity dimensions and **3** is the most likely complex to be formed.

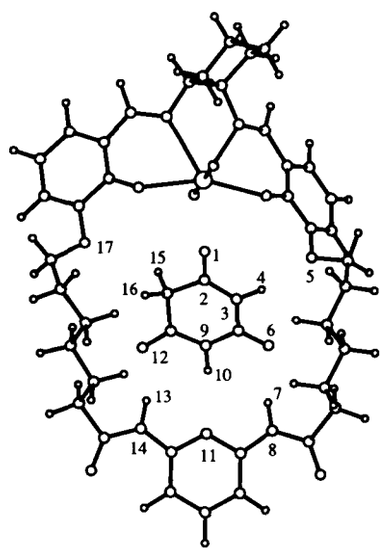
Table I Results of molecular-mechanics calculations.

Complex	Distance (Å)[a]		Bond angle (deg)[a]	
3	$U \cdot\cdot O^1$	2.50	$U \cdot\cdot O^1 \cdot\cdot C^2$	148
	$H^4 \cdot\cdot O^5$	2.07	$N^3 \cdot\cdot H^4 \cdot\cdot O^5$	159
	$O^6 \cdot\cdot H^7$	2.03	$O^6 \cdot\cdot H^7 \cdot\cdot N^8$	166
	$H^{10} \cdot\cdot N^{11}$	2.35	$N^9 \cdot\cdot H^{10} \cdot\cdot N^{11}$	133
	$O^{12} \cdot\cdot H^{13}$	2.01	$O^{12} \cdot\cdot H^{13} \cdot\cdot H^{14}$	155
	$H^{15} \cdot\cdot O^{17}$	2.90		×
	$H^{16} \cdot\cdot O^{17}$	3.57		×
4	$U \cdot\cdot O^1$	2.42	$U \cdot\cdot O^1 \cdot\cdot C^2$	140
	$H^4 \cdot\cdot O^5$	3.68	$N^3 \cdot\cdot H^4 \cdot\cdot O^5$	147
	$O^6 \cdot\cdot H^7$	2.18	$O^6 \cdot\cdot H^7 \cdot\cdot N^8$	170
	$H^9 \cdot\cdot N^{11}$	2.72		×
	$H^{10} \cdot\cdot N^{11}$	2.74		×
	$O^{12} \cdot\cdot H^{13}$	2.83	$O^{12} \cdot\cdot H^{13} \cdot\cdot N^{14}$	160
	$H^{16} \cdot\cdot O^{17}$	2.35	$N^{15} \cdot\cdot H^{16} \cdot\cdot O^{17}$	177

[a] Numbering of atoms is according to Figure 1.

Synthesis

The synthesis of metallomacrocycle **2** was performed in four steps starting from 2,6-pyridinediamine (Scheme 1). Heptanoyl chloride (**5**), prepared from the corresponding acid[9,10] and $SOCl_2$, was reacted with 2,6-pyridinediamine in $CHCl_3$ in the presence of NEt_3 as a base at room temperature to give dibromide **6** in 67% yield. Coupling of dibromide **6** with 3-hydroxy-2-(2-propenoxy)benzaldehyde (**7**)[2b], using K_2CO_3 in CH_3CN as a base, gave dialdehyde **8** in 67% yield[11]. The signals of the CHO and $OC\underline{H}_2CH_2$ protons in the ^{1}H NMR spectrum at 10.46 and 4.03 ppm, respectively, are indicative for the formation of **8**. Deallylation with $Pd(OAc)_2$ and PPh_3 in 80% aqueous ethanol gave the dialdehyde **9** in 87% yield[12]. The signals of the CHO group in the ^{1}H NMR (9.91 ppm) and ^{13}C NMR (196.7 ppm) spectra are present at characteristic positions. Macrocyclization of dialdehyde **9** with *cis*-1,2-cyclohexanediamine (**10**)[13] was achieved by the addition of both a solu-



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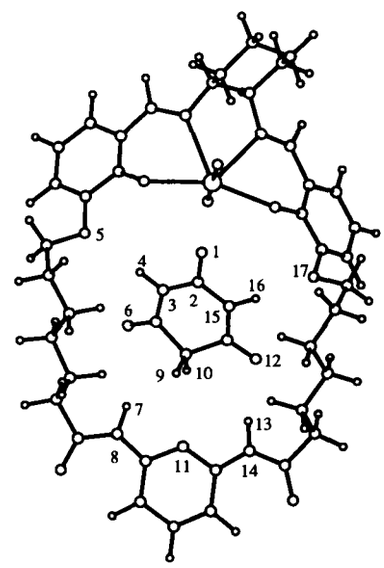

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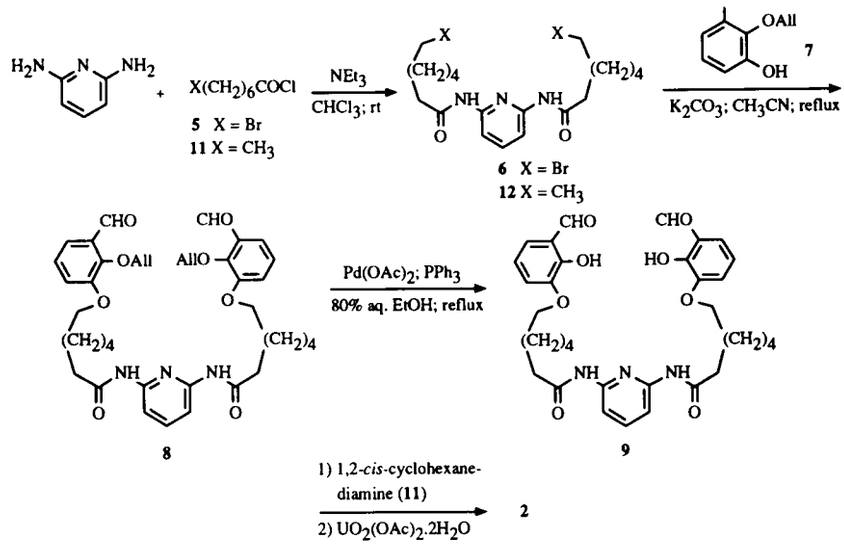
Figure 1. View of calculated structures **3** *and* **4**.



Scheme 1

tion of **9** and diamine **10** to a refluxing solution of $Ba(OTf)_2$[14] in THF. Subsequent addition of $UO_2(OAc)_2 \cdot 2H_2O$ gave metallomacrocycle **2** in 46% yield. In the presence of Ba^{2+}, the yield of **2** is comparable to the yields of the crown ether metallomacrocycles reported previously (47–48%). Obviously, only a few heteroatoms in the cavity are sufficient for Ba^{2+} to act as a template cation. The high-resolution electron-impact mass spectrum showed an intensive M^+ peak, thus proving the macrocyclization and the tight cocomplexation of the UO_2^{2+} cation. Imine-bond formation is indicated by the ^1H NMR (DMSO-d_6), ^{13}C NMR ($CDCl_3$/DMSO-d_6), and IR spectra, with signals at 9.40 ppm (singlet), 167.4 ppm (doublet), and 1614 cm^{-1}, respectively. The cyclohexyl moiety exists in a chair conformation, as discussed previously[2d].

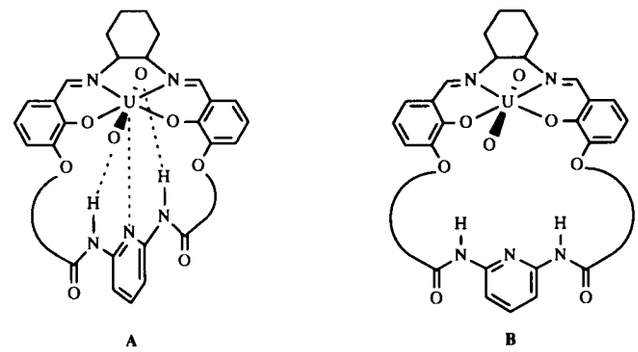


Chart 4

Self-complexation

The ^1H NMR spectrum of metallomacrocycle **2** is dependent on the choice of solvent and temperature. In DMSO-d_6 at 298 K, all signals have the expected pattern and chemical shift (for details, see Experimental), but in $CDCl_3$ the situation is quite different.

At 298 K in dry $CDCl_3$, a concentration-independent signal of the metalloreceptor amide protons is present at 12.83 ppm. In the reference compound **12** (prepared from 2,6-pyridinediamine and acid chloride **11**), the NH signal is present at 7.51 ppm. The extreme downfield shift of the NH signal and its independence of concentration indicate intramolecular H-bond formation. The alkyl protons of the spacer and the pyridine protons in the ^1H NMR spectrum provide further evidence for self-complexation. Compared with dialdehyde **9**, the number of non-equivalent protons in **2** increases; this indicates more rigidification of the alkyl chains. The signals of the pyridine protons appear as a broadened singlet at 8.00 ppm instead of a doublet and a triplet. The significant downfield shift of the pyridine *para*-proton ($\Delta\delta$ 0.27–0.33 ppm, relative to **9** and **12**) suggests coordination to the immobilized uranyl cation. In the CPK model, the uranyl and 2,6-diamidopyridine moiety are complementary; the folded structure **A** depicted in Chart 4 is suggested as the self-complex[15].

Rebek et al. introduced an NMR-spectroscopic method to determine constants of self-complexation (K_{sc})[16]. In principle, the equilibrium constant (**A** $\rightleftharpoons$ **B**) can be extracted from equation 1, where δ_{obs} represents the observed chemical shift, δ_c the chemical shift of the self-complexed molecule (**A**), and δ_f the chemical shift of the open form (**B**).

$$K_{sc} = [A]/[B] = (\delta_{obs} - \delta_f)/(\delta_c - \delta_{obs}) \quad (1)$$

The chemical shifts δ_f and δ_c cannot be determined experimentally and approximated values must be used. The chemical shift δ_c was taken from low-temperature ($-50\,^\circ C$) ^1H NMR spectra (equilibrium shifts to the self-complexed form), and δ_f was taken from a related reference compound, diamide **12**. Using the chemical shifts of the amide protons (δ_{obs} 12.83 ppm, δ_c 13.18 ppm, and δ_f 7.51 ppm), a self-complexation constant K_{sc} of 15.2 was calculated.

Rebek et al.[6] observed self-complexation of both diimide and dilactam receptors connected by flexible spacers [e.g., $(CH_2)_n$ with n = 2–5] and *Gellman* et al.[17] studied the self-complexation of flexible α,ω-diamides. They obtained values for the intramolecular self-complexation constant of the same order or magnitude (K_{sc} 0.2 to 24) as in this study.

Complexation and membrane transport

The complexation properties of receptor **2** were studied by solid–liquid extractions in $CDCl_3$ of the almost insoluble barbituric acid (**1a**) and receptor **2**. The insoluble **2**-barbituric acid complex [m/z of $(M + H)^+$ 1080] precipitated from $CDCl_3$ during the experiment. Consequently, it was

not possible to determine the amount of solubilized barbituric acid complex formed.

^{1}H NMR-spectroscopic-titration experiments were performed with the metalloreceptor **2** and the complementary barbiturates **1a–d** (Chart 1). The amide proton of **2** was used as a probe. Mixtures of solvents were necessary because of the insolubility of **1a–b** in $CDCl_3$[18]. The results of the titration experiments are summarized in Table II.

Table II Association constants (M^{-1}) in different solvent systems determined with ^{1}H NMR titration experiments at 298 K.

Guest	$CDCl_3$ (5% DMSO-d_6)	$CDCl_3$ (20% DMSO-d_6)
1a	n.p.[a]	102
1b	112	< 1
1c	97	< 1
1d	45	< 1

[a] Not performed due to low solubility of guest.

From Table II, it is clear that in $CDCl_3$ (20% DMSO-d_6) the barbituric acid complex is at least two orders of magnitude ($\Delta\Delta G = -2.7$ kcal · mol^{-1}) more stable than the complexes with the substituted barbiturates **1b–d**. A correlation in $CDCl_3$ (5% DMSO-d_6) between the size of the substituent and the stability of the complex is observed; a barbiturate with smaller substituents gives a more stable complex. During the titration experiment, no shift of the substituent signals is observed. We assume that they are not close to the pyridine ring.

The first example of carrier-mediated transport of a neutral molecule (urea) through a supported liquid membrane was discussed by *Nijenhuis* et al.[19]. Subsequently, metallomacrocycle-mediated membrane transport of barbituric acid (**1a**) by receptor **2** was investigated, as described in the Experimental. A flux of $1.75 \cdot 10^{-8}$ mol · cm^{-2} · h^{-1}, 3.7 times higher than that of the blank flux ($0.47 \cdot 10^{-8}$ mol · cm^{-2} · h^{-1}) was found.

Experimental

General methods

NMR spectra were recorded on Bruker AC-250 spectrometer in $CDCl_3$ with TMS as internal standard, if not stated otherwise. DEPT* polarization transfer from ^{1}H to C nuclei in refocused ^{1}H-coupled spectra was used to determine the multiplicities of the carbon signals in the ^{13}C NMR spectra. Mass spectra were obtained with a Finnigan MAT 90 spectrometer. Positive-ion fast-atom bombardment (FAB) mass spectra were obtained with *m*-nitrobenzyl alcohol as a matrix. IR spectra were recorded with a Nicolet 5 SCX FT spectrophotometer. Melting points were determined with a Reichert melting point apparatus and are uncorrected. Elemental analyses were carried out by a Model 1106 Carlo Erba Strumentazione Elemental Analyzer. Petroleum ether, $CDCl_3$, and H_2Cl_2 were distilled before use. Petroleum ether (PE) refers to the fraction with b.p. 40–60°C. THF was freshly distilled from sodium/benzophenone. CH_3CN and DMF were stored over molecular sieves (4 Å). Other chemicals and solvents were of reagent grade and were used without purification. Column chromatography was performed with silica gel (Merck; 0.015–0.040 mm; 230–400 ASTM). All reactions were carried out in a static nitrogen atmosphere. Heptanoic acid[9,10] and 3-hydroxy-2-(2-propenoxy)benzaldehyde[2b] were prepared according to published procedures.

Care was taken when handling uranyl containing compounds because of their toxicity and radioactivity[20].

General procedure for synthesis of diamides **6** *and* **12**

7-Bromoheptanoic acid or heptanoic acid (62.5 mmol) was refluxed in $SOCl_2$ (50 ml) for 2 h to yield, after concentration *in vacuo*, the corresponding acid chlorides **5** or **11**, respectively. 2,6-Pyridinediamine (1.36 g, 12.50 mmol) and NEt_3 (3.29 g, 32.6 mmol) were added to a solution of acid chloride **5** or **11** in $CDCl_3$ (100 ml), whereupon the mixture was stirred for 45 min at room temperature. Subsequently, water (100 ml) was added and the pH was adjusted to 10 with diluted NaOH. The $CHCl_3$ layer was separated and the remaining aqueous layer was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield after flash chromatography (SiO_2; EtOAc/PE 1 : 1) pure diamides **6** and **12**.

N,N′-*2,6-Pyridinediylbisheptanamide* (**12**). Yield 70%; m.p. 111–115°C (EtOAc/PE). Anal. calcd. for $C_{19}H_{31}N_3O_2$ (333.473): C 68.43, H 9.37, N 12.60; found: C 68.36, H 9.78, N 12.30%. ^{1}H NMR: δ 7.90 (d, *J* 8.0 Hz, 2H, H-3/6); 7.73 (t, *J* 8.0 Hz, 1H, H-4); 7.51 (s, 2H, NH); 2.37 [t, *J* 7.5 Hz, 4H, C(O)CH_2]; 1.72 [t, *J* 7.5 Hz, 4H, C(O)$CH_2C\underline{H}_2$]; 1.43–1.13 [m, 12H, $(CH_2)_3$]; 0.89 (t, *J* 6.6 Hz, 6H, CH_3). ^{13}C NMR: δ 171.4 (s, CO); 149.3 (s, C-2/6); 140.6 (d, C-4); 109.2 (d, C-3/5); 37.6 [t, C(O)CH_2]; 31.3, 28.6, 25.2, 22.7 [t, $(CH_2)_4$]; 13.8 (q, CH_3). IR (KBr): 1670 cm^{-1} (C=O). UV ($CHCl_3$) λ_{max}: 300 nm. Ms (EI) *m/z*: 333.242 (M^+, calcd. 333.242).

N,N′-*2,6-Pyridinediylbis(7-bromoheptanamide)* (**6**). Yield 67%; m.p. 75–78°C (EtOAc/PE). Anal. calcd. for $C_{19}H_{29}Br_2N_3O_2$ (491.265): C 46.45, H 5.95, N 8.55; found: C 46.62, H 6.18, N 8.43%. ^{1}H NMR: δ 7.88 (d, *J* 8.0 Hz, 2H, H-3/5); 7.68 (t, *J* 8.0 Hz, 1H, H-4); 7.54 (s, 2H, NH); 3.40 (t, *J* 6.7 Hz, 4H, OCH_2); 2.37 [t, *J* 7.4 Hz, 4H, C(O)CH_2]; 1.91–1.79 (m, 4H, CH_2); 1.76–1.67 (m, 4H, CH_2); 1.51–1.37 [m, 8H, $(CH_2)_2$]. ^{13}C NMR: δ 171.3 (s, CO); 149.4 (s, C-2/6); 140.7 (d, C-4); 109.4 (d, C-3/5); 37.5 [t, C(O)CH_2]; 33.7, 32.4, 28.2, 27.8, 25.0 [t, $(CH_2)_5$]. IR (KBr) 1661 cm^{-1} (C=O). Ms (EI) *m/z* 489.064 (M^+, calcd. 489.063).

N,N′-*2,6-Pyridinediylbis[7-[3-formyl-2-(2-propenyloxy)phenoxy]heptanamide]* (**8**). A mixture of dibromide **6** (4.91 g, 10 mmol), 3-hydroxy-2-(2-propenoxy)benzaldehyde (**7**) (3.56 g, 20 mmol) and K_2CO_3 (5.52 g, 40 mmol) in CH_3CN (200 ml) was refluxed till completion (approximately 15 h; TLC; SiO_2; EtOAc/PE 2 : 3). The solvent was evaporated, water (250 ml) was added and, to avoid the formation of an emulsion, the pH was adjusted to pH 2 with concentrated HCl. Extraction with CH_2Cl_2 (3 × 250 ml), followed by drying over $MgSO_4$, concentration *in vacuo*, and purification by flash chromatography (SiO_2; EtOAc/PE 2 : 3) gave pure **8**: yield 67%; m.p. 91–94°C (EtOAc/PE). Anal. calcd. for $C_{39}H_{47}N_3O_8$ (685.816): C 68.30, H 6.91, N 6.13; found: C 68.43, H 6.85, N 5.90%. ^{1}H NMR: δ 10.46 (s, CHO); 7.88 (d, *J* 8.0 Hz, 2H, H′-3/5); 7.67 (t, *J* 8.0 Hz, 1H, H′-4); 7.64 (s, 2H, NH); 7.42–7.38 (m, 2H, Ar H); 7.14–7.06 (m, 4H, Ar H); 6.15–5.99 (m, 2H, $OCH_2C\underline{H}CH_2$); 5.38–5.24 (m, 4H, $OCH_2CHC\underline{H}_2$); 4.69–4.65 (m, 4H, $OC\underline{H}_2CHCH_2$); 4.03 (t, *J* 6.5 Hz, 4H, OCH_2); 2.41 [t, *J* 7.4 Hz, 4H, C(O)CH_2]; 1.89–1.70 [m, 8H, $(CH_2)_2$]; 1.59–1.47 [m, 8H, $(CH_2)_2$]. ^{13}C NMR: δ 190.0 (s, CHO); 171.6 (s, CO); 152.4, 152.3 (s, C-2, C-3); 149.6 (s, C′-2/6); 140.7 (d, C′-4); 133.1 (d, $OCH_2\underline{C}HCH_2$); 130.1 (s, C-1); 124.2, 119.1, 118.9 (d, C-4, C-5, C-6); 119.0 (t, $OCH_2C\underline{H}CH_2$); 109.3 (d, C′-3/5), 75.1 (t, $O\underline{C}H_2CHCH_2$); 60.4 (t, $O\underline{C}H_2CH_2$); 37.4 [t, C(O)CH_2]; 28.9, 28.7, 25.8, 25.0 [t, $(CH_2)_4$]. IR (KBr): 1703 (C=O), 1684 (CHO) cm^{-1}. Ms (EI) *m/z* 685.332 (M^+, calcd. 685.336).

N,N′-*2,6-Pyridinediylbis[7-(3-formyl-2-hydroxyphenoxy)heptanamide]* (**9**). A mixture of diallyl compound **8** (4.22 g, 6.16 mmol), $Pd(OAc)_2$ (28 mg, 0.13 mmol), PPh_3 (133 mg, 0.51 mmol), NEt_3 (5.05 g, 50 mmol), and HCOOH (2.25 g, 50 mmol) in 80% aqueous EtOH (150 ml) was refluxed for 90 min. The ethanol was evaporated and the total water volume was adjusted at 100 ml. The mixture was extracted with CH_2Cl_2 (3 × 100 ml). The combined CH_2Cl_2 layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (SiO_2; CH_2Cl_2/MeOH 25 : 1) to give pure aldehyde **9**: yield 87%; m.p. 141–142°C (EtOAc/PE). Anal. calcd.

* DEPT = Distorionless Enhancement by Polarization Transfer

for $C_{33}H_{39}N_3O_8$ (605.684): C 65.44, H 6.49, N 6.94; found: C 65.25, H 6.61, N 6.74%. ^{1}H NMR: δ 11.14 (s, 2H, OH); 9.91 (s, 2H, CHO); 8.39 (s, 2H, NH); 7.91 (d, *J* 8.0 Hz, 2H, H'-3/5); 7.67 (t, *J* 8.0 Hz, 1H, H'-4); 7.19–7.09 (m, 4H, H-4, H-6); 6.94 (t, *J* 7.9 Hz, 2H, H-5); 4.02 (t, *J* 6.1 Hz, 4H, OCH_2); 2.43 [t, *J* 7.5 Hz, 4H, $C(O)CH_2$]; 1.90–1.74 [m, 8H, $(CH_2)_2$]; 1.62–1.45 [m, 8H, $(CH_2)_2$]. ^{13}C NMR: δ 196.7 (s, CHO); 171.8 (s, CO); 151.6 (s, C-2); 149.8 (s, C'-2/6); 147.8 (s, C-3); 140.7 (d, C'-4); 124.7, 119.7, 119.4 (d, C-4, C-5, C-6); 120.9 (s, C-1); 109.2 (d, C'-3/5); 69.2 (t, OCH_2); 37.2 [t, $C(O)CH_2$]; 28.2, 28.0, 25.1, 24.6 [t, $(CH_2)_4$]. IR (KBr): 1687 (CO), 1654 (CHO) cm^{-1}. Ms (EI) *m/z* 605.278 (M^+, calcd. 605.274).

*[9,10,11,12,13,14,15,16,22,23,24,25,26,27,28,29,37a,38,39,40,41,-41a-Docosahydro-15,23-dioxo-16*H,*22*H*-3,7:31,35-dimetheno-17,-21-nitrilo-8,30,1,16,22,37-benzodioxatetraazacyclononatriacontine-42,-44-diolato(2-)-*N^1,N^{37},O^{42},O^{44}*]dioxouranium* (**2**). Separate solutions of dialdehyde **9** (0.97 g, 1.6 mmol in 75 ml of THF) and 1,2-*cis*-cyclohexanediamine (**10**) (0.18 g, 1.6 mmol in 25 ml of MeOH) were added to a refluxing solution of $Ba(OTf)_2$ (0.70 g, 16 mmol) in THF (150 ml) in 45 min. $UO_2(OAc)_2 \cdot 2H_2O$ (0.72 g, 1.7 mmol) was introduced after 20 min and reflux was maintained for another 30 min. The reaction mixture was cooled to room temperature and stirred for 2 h with water (100 ml). Subsequently, the organic solvents were evaporated and saturated solutions of Na_2SO_4 (100 ml) and 0.1M NaOH (100 ml) were added. The mixture was extracted with CH_2Cl_2 (1 × 600 ml; 2 × 200 ml). The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was taken up in approximately twice the minimal amount of $CHCl_3$ needed to dissolve and by dropwise addition of PE pure metallomacrocycle **2** precipitated as an orange solid performing the procedure twice: yield 46%; m.p. 236°C (dec.). Anal. calcd. for $C_{39}H_{47}N_5O_8U \cdot 5H_2O$ (1041.933)[21]: C 44.95, H 4.55, N 6.72; found: C 44.92, H 4.87, N 6.47%. ^{1}H NMR (DMSO-d_6): δ 10.12 (s, 2H, NH); 9.40 (s, 2H, CH=N); 7.75–7.67 (m, 3H, H'-3/5, H'-4); 7.25–7.20 (m, 4H, H-4, H-6); 6.59 (dd, *J* 7.8 Hz, 2H, H-5); 4.62–4.52 (m, 2H, H_{cy}-1); 4.13 (t, *J* 6.8 Hz, 4H, OCH_2); 2.45 [t, *J* 6.5 Hz, 4H, $C(O)CH_2$]; 2.40–2.27 (m, 2H, H_{cy}-2_{eq}); 1.95–1.37 (m, 24H, CH_2, H_{cy}-2_{ax}, H_{cy}-3). ^{1}H NMR ($CDCl_3$ dried over P_2O_5): δ 12.83 (br s, 2H, NH); 9.33 (s, 2H, CH=N); 8.01 (br s, 3H, H'-3/5, H'-4); 7.13 (d, *J* 7.2 Hz, 4H, H-4, H-6); 6.72 (m, 2H, H-5); 4.90–4.15 (m, 6H, H_{cy}-1, OCH_2); 2.9–1.2 [m, 26H, $(CH_2)_5$, H_{cy}-2, H_{cy}-3]. ^{13}C NMR ($CDCl_3$/DMSO-d_6 4:1): δ 172.5 (s, CO); 167.4 (d, CH=N); 160.2 (s, C-2); 150.2, 150.0 (s, C-3, C'-2); 139.8 (d, C'-4); 126.4, 118.0, 115.9 (d, C-4, C-5, C-6); 123.8 (s, C-1); 109.3 (d, C'-3); 71.3 (t, C''-1); 69.2 (t, OCH_2); 37.4 [t, $C(O)CH_2$]; 29.3, 28.4, 27.7, 25.6, 25.3 [t, $(CH_2)_4$, C''-2]; 21.5 (t, C''-3). IR (KBr): 1692 (C=O), 1614 (C=N), 895 (O–U–O) cm^{-1}. UV ($CHCl_3$) λ_{max}: 287 nm. Ms (EI) *m/z* 951.394 (M^+, calcd. 951.392).

*[9,10,11,12,13,14,15,16,22,23,24,25,26,27,28,29,37a,38,39,40,41,-41a-Docosahydro-15,23-dioxo-16*H,*22*H*-3,7:31,35-dimetheno-17,-21-nitrilo-8,30,1,16,22,37-benzodioxatetraazacyclononatriacontine-42,-44-diolato(2-)-*N^1,N^{37},O^{42},O^{44}*]dioxouranium · barbituric acid* (**2** · barbituric acid)[21]. A solution of 0.155M barbituric acid (**1a**) in DMSO (320 µl) was added to a solution of receptor **2** in $CHCl_3$ (35 ml). Upon leaving to stand, a solid started to precipitate. To induce further precipitation, 5 ml portions (totally 25 ml) of PE were added over a period of several hours. The fine, orange powder was isolated using a centrifuge (3000–4000 rpm · min^{-1}; 5 min) to yield 40% of the complex: m.p. > 315°C. ^{1}H NMR ($CDCl_3$/DMSO-d_6 3:1): δ 11.24 (br s, 2H, NH_{barb}); 9.72 (br s, 2H, CONH); 9.30 (s, 2H, CH=N); 7.90–7.60 (m, 3H, H'-3/5, H'-4); 7.20–7.10 (m, 4H, H-4, H-6); 6.61 (dd, *J* 7.7 Hz, H-5); 4.62 (m, 2H, H_{cy}-1), 4.18 (t, *J* 6.8 Hz, 4H, OCH_2), 3.47 (s, 2H, barb-CH_2), 2.48 [t, *J* 6.5 Hz, 4H, $C(O)CH_2$], 2.00–1.45 (m, 24H, CH_2, H_{cy}-2_{ax}, H_{cy}-3). ^{13}C NMR: due to low solubility in all tested solvents, not recorded. IR (KBr): 1696 (C=O), 1612 (CH=N), 905 (O–U–O) cm^{-1}. Ms (FAB), *m/z* 1080.7 (M^+, calcd. for ($C_{39}H_{47}N_5O_8U + C_4H_4N_2O_3 + H$) 1080.4. Ms (EI) *m/z* 951.389 (M^+, calcd. for $C_{39}H_{47}N_5O_8U$ 951.393), 128.022 (M^+, calcd. for $C_4H_4N_2O_3$ 128.022).

Calculations

Molecular-mechanics calculations were performed with CHARMm and the graphical QUANTA interface[23]. Force-field parameters were taken from CHARMm, except the non-bonded parameters for the uranyl cation. For the uranyl cation, the non-bonded parameters were determined to reproduce the experimental hydration geometry and enthalpy[8]. For the electrostatic interaction, parameter values of 2.0 e for the charge on the U atom, and of 0.0 e on the O atom were taken. For the van-der-Waals-interaction parameters of the U atom, values of − 1.0 kcal/mol for E_{min} and of 1.50 Å for R_{min} were determined. With these values, the hydration of a uranyl cation in a water box was simulated with molecular-dynamics equilibration runs, to give a reasonable agreement with the experimental hydration data. The coordinates of the Schiff-base moiety were taken from a published structure (Figure 3 in Ref. 1d) and were kept fixed by atom constrains (value − 1, described in the CHARMm users guide) in the calculations.
With molecular mechanics calculations, the steric minima of the complexes and of the isolated guest molecules were determined by variation of all the relevant degrees of freedom: position and orientation of the guest and rotatable bonds in the substituent to the Schiff-base moiety of the host. Minimizations were terminated at RMS < 0.0001.

Solid–liquid-extraction experiments

A 2–5-mM solution of metallomacrocycle **2** in $CDCl_3$ (1 ml) was equilibrated for 20 h with solid guest. Solids were filtered and the organic layer was analyzed with ^{1}H NMR spectroscopy. With **1a** as a guest all receptor precipitated.

^{1}H NMR titrations

Quantitative data were obtained with a 250-MHz ^{1}H NMR spectrometer operating at a digital resolution of 0.001 ppm. Measurements under dynamic exchange conditions were carried out at 298 K in $CDCl_3$ with 5% DMSO-d_6 or $CDCl_3$ with 20% DMSO-d_6 with TMS as an internal standard. Incremental amounts of guests were added to a solution of host **2** of constant concentration. Conditions in different solvents are:

5% DMSO-d_6 in $CDCl_3$	[H] = 1.85–1.86 mM
	[G] = 0.41–18.85 mM
20% DMSO-d_6 in $CDCl_3$	[H] = 2.23 mM
	[G] = 0.91–22.72 mM

For each titration experiment, 10 spectra with varying host/guest ratios were recorded. Data evaluation was performed by non-linear regression as described by *de Boer* et al.[24]. No Δδ was observed for mixtures of dimethylbarbituric (**1b**), diethylbarbituric (**1c**), or ethylphenylbarbituric (**1d**) acid (90 mM) and receptor **2** (9.2 mM) in $CDCl_3$ with 20% DMSO-d_6. The results are summarized in Table II.

Transport through a supported liquid membrane[25]

The transport experiments were carried out in a permeation cell consisting of two identical cylindrical compartments (half-cell volume: 50 ml; effective area 12.4 cm^2) at 298 K. The Accurel membrane (thickness, *d* 100 µm; porosity, Θ 64%) was impregnated with *o*-nitrophenyl *n*-octyl ether (blank experiments) or with *o*-nitrophenyl *n*-octyl ether containing 6.4 mM of carrier **2** (mediated transport). The source phase contained a 50-mM solution of barbituric acid (**1a**) in doubly-distilled water. The concentration of acid (**1a**) in the aqueous receiving phase (doubly-distilled water) was measured after 23 h using UV spectroscopic methods. Absorptions (257 nm) were fitted to a calibration curve.

Acknowledgements

For performing the elemental analyses, we express our gratitude to *A. M. Montanaro–Christenhusz* and for recording the mass spectra we are indebted to *T. W. Stevens*.

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