BINDING AND EXTRACTION OF PERTECHNETATE AND PERRHENATE BY AZACAGES

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1. INTRODUCTION

The design and synthesis of anion receptors of technical and biochemical significance is receiving more and more attention.[1-8] Currently, effective binding and selective phase transfer of the oxoanions pertechnetate and perrhenate is of considerable interest from different point of view. Due to its long half-life and environmental mobility, the radioactive pertechnetate is one of the most hazardous contaminants. In this context, effective and selective separation processes are of utmost importance.[9-12] On the other hand, there are some emerging possibilities for the application of the radiochemically active oxoanions pertechnetate and perrhenate in nuclear medicine.[13,14] The most commonly used isotope in diagnostic nuclear medicine ^{99m}Tc is readily available from a ^{99}Mo/^{99m}Tc generator system.[15-19] Likewise, the β-emitting ^{188}Re – discussed as one of the most interesting radionuclides for specific therapeutic applications – is conveniently produced by a ^{188}W/^{188}Re generator.[20-22] In both cases the radionuclides are available as oxoanions in isotonic solution, and it appears highly desirable to directly complex $^{99m}TcO_4^-$ and $^{188}ReO_4^-$ as they exist in the generator eluate itself. But, the binding of such large, lowly charged anions is a difficult venture. The enthalpic contribution for complexation is rather small. Hence, host compounds being capable to encapsulate these oxoanions are of great interest.

For both directions discussed above, some different requirements have to be fulfilled for the design of ligands. The essential properties of ligands serving as extractants and imaging/therapeutic agents are summarized in Table 1.

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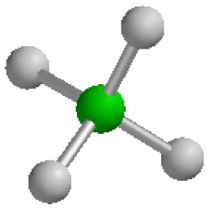
Table 1. Requirements for the design of ligands capable of serving as extractant and imaging/therapeutic agent.

EXTRACTANTS	IMAGING/THERAPEUTIC AGENTS
The receptor has to interact reversibly with the anion in a specific way. This should overcome the solvation energy.	The receptor should form an inclusion compound with the oxoanion in isotonic solution.
The host and the complex formed should display high lipophilicity to avoid leakage of the extractant into the aqueous phase.	The receptor/anion complex should have a well-balanced lipophilicity (LogP: 1-2.5)
The receptor should allow a rapid complexation/decomplexation across phase boundary.	No exchange reaction with endogenous species should happen in physiological environment.



TcO_4^-	ReO_4^-
r = 252 pm	r = 260 pm
pK_a ($HTcO_4$) = 0.033	pK_a ($HReO_4$) = -0.28
$E^0_{TcO4-/TcO2}$ = 0.74 V	$E^0_{ReO4-/ReO2}$ = 0.51 V
ΔG_{hydr} = - 251 kJ·mol^{-1}	ΔG_{hydr} = - 330 kJ·mol^{-1}

Figure 1. Properties of pertechnetate and perrhenate.[23-26]

Figure 1 presents the primary properties of the tetrahedral anions pertechnetate and perrhenate. Cage compounds having the size and binding centers required for anions may be very promising for the molecular encapsulation of these oxoanions. Azacryptands in the protonated state represent such a kind of receptor and are well-known to bind different oxoanions in the interior.[27] Some solid anion cryptates were isolated, and the encapsulation of nitrate,[28] perchlorate,[29,30] chromate, selenate, and thiosulfate[31] was demonstrated. The cage structures of the above mentioned anion cryptates have similarities. In all cases, the azacryptands are fully protonated, and as a result of

electrostatic repulsion, the cavity is expanded. In particular, at low pH these cryptands serve as good anion receptors because of the geometric complementarity of H-bonding and electrostatic interaction between host and guest.[32] In contrast to this, the environment is completely different if the binding of pertechnetate and perrhenate in the generator eluate is considered. At physiological pH, the azacryptands are only partially protonated, and consequently the binding strength and the shape of the cages should differ remarkably in comparison to the strongly acidic media.

We are especially interested to characterize the binding and distribution behavior of selected cage compounds towards pertechnetate and perrhenate at neutral pH. Azacryptands of different size possessing nitrogen atoms as binding centers have been chosen (cf. Fig. 2). Aromatic spacer elements and amide groups were introduced in order to improve the lipophilicity, to lower the flexibility, and to vary the binding mode of the molecules.

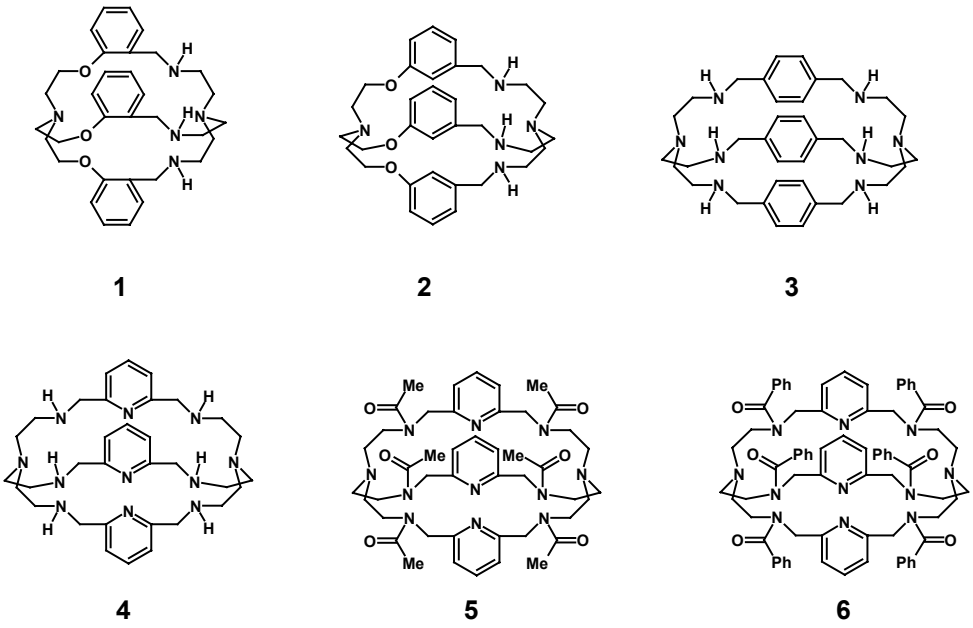


Figure 2. Structures of azacages investigated.

2. RESULTS AND DISCUSSION

2.1. **Liquid-liquid extraction experiments**

Liquid-liquid extraction studies were selected to characterize the binding and distribution behavior of the complexes formed by different azacages with pertechnetate and perrhenate. Using $^{99m}TcO_4^-$ and $^{188}ReO_4^-$ radiotracer, it is easy to get reliable and

precise information about the extraction efficiency and the complex composition in the organic phase. Figure 3 shows the structural influence of the azacryptands **1**–**6** on the extractability of pertechnetate and perrhenate in neutral medium. The most effective extraction of pertechnetate and perrhenate is obtained by cage compound **1** having both triethanolamine and tris(2-aminoethyl)amine (tren) caps bridged with a tolyl spacer in the ortho-position. Amazingly, the structure related compound **2** connected in the meta-position gives significant lower extraction. Also the double tren-capped azacryptands **3** and **4** show a drastically reduced extraction efficiency. In all these cases, a rapid attainment (within some minutes) of both the extraction and back extraction (by lowering the pH) equilibrium was observed. Using the amidocryptands **5** and **6**, no transfer of pertechnetate and perrhenate into the organic phase was found under the experimentally chosen conditions.

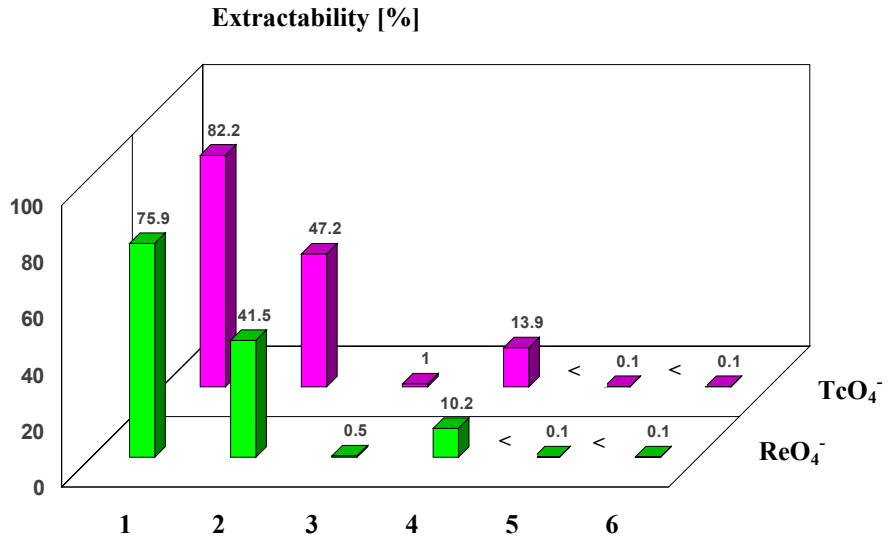


Figure 3. Extractability of pertechnetate and perrhenate by azacryptands **1**–**6**.
[$NaTcO_4$] or [$NaReO_4$] = $1 \cdot 10^{-4}$ M; pH = 7.4 (HEPES/NaOH buffer); [ligand] = $1 \cdot 10^{-3}$ M in $CHCl_3$.

It is worth mentioning here that in all cases pertechnetate is slightly better extracted in comparison to perrhenate. This is a general trend not only for these azacages but also for guanidinium[33] and ammonium[34] compounds, dendrimers[35,36] and bimetallic cyclotriveratrylene hosts.[37] Differences in hydration state are likely responsible for this behavior. Regrettably, there are only estimated thermodynamic data available for pertechnetate, revealing a lower hydration energy (ΔG^0_{hydr} = -251 kJ/mol) than for perrhenate (ΔG^0_{hydr} = -330 kJ/mol).[24] Charge-density calculations[38] corroborate this finding. The partial negative charge of oxygen atoms of perrhenate (-0.755) is clearly increased compared to pertechnetate (-0.739). This fact should lead to a significant stronger hydration, and consequently to a more difficult perrhenate transfer into an organic solvent.

In order to obtain a deeper insight into the extraction equilibrium, the influence of pH on the extraction of pertechnetate was studied. The results determined for azacages **1** and **2** are summarized in Figure 4. The extractability increases with rising pH , reaching a maximum at the pH range between 7 and 8 and decreases in the more basic medium. It can be clearly concluded that this extraction behavior corresponds to the different protonation state of the azacages in aqueous solution.[39] Under acidic conditions, the cage compounds are highly protonated, and as a result become really hydrophilic. This explains their rather poor extraction ability from aqueous into organic solution. The extraction efficiency is only slightly different for **1** and **2** in the pH range between 2 and 7. But, at higher pH azacage **1** is superior to **2**. This fact corresponds to the dominating formation of the LH_2^{2+} species of **1** between pH 7 and 8. In this range, **2** forms mainly the LH_3^{3+} species.

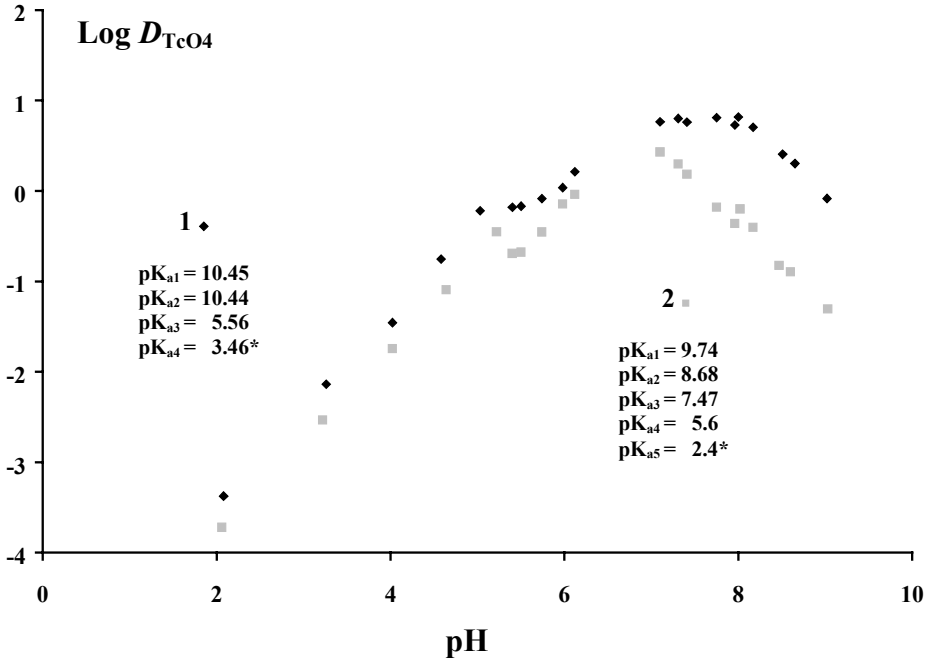


Figure 4. Extraction of pertechnetate with azacryptands 1 and 2 as a function of pH. [$NaTcO_4$] = $1 \cdot 10^{-4}$ M; pH = 2.0-5.2 (NaOAc/HCl buffer); pH = 5.4-6.1(MES/NaOH); pH = 7.1-8.0 (HEPES/NaOH); pH = 8.0-9.0 (TAPS/NaOH); [ligand] = $1 \cdot 10^{-3}$ M in $CHCl_3$; * pK_a (H_2O, 0.1 M $[(CH_3)_4N]NO_3$) from Ref. 39.

Extraction of pertechnetate and perrhenate was also examined at different concentrations of cage compounds. The results, shown in Fig. 5, reveal an essentially linear relationship between the distribution ratio and the azacryptand concentration. The slopes of the lines in the log $D_{TcO4/ReO4}$/log c_{ligand} diagram were unity, indicating a clean 1:1 composition of the extracted complexes. Loading experiments of the organic phase at

the same experimental conditions give a maximum ratio of ligand to anion of 1:2. It follows that the cage compounds can be transferred into the organic phase in the mono- and diprotonated form with one or two bound pertechnetate/perrhenate anions. It seems to be plausible because the extraction of higher charged species should be energetically disfavored.

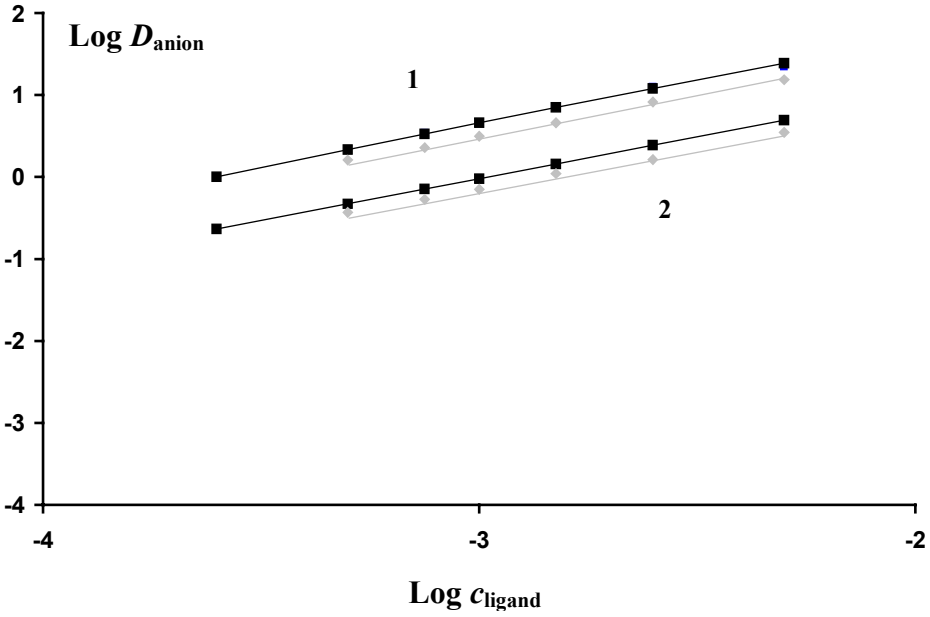


Figure 5. Extraction of pertechnetate and perrhenate with azacryptands **1** and **2** as function of ligand concentration. [$NaTcO_4$ ■, $NaReO_4$ ◆] = $1 \cdot 10^{-4}$ M; pH = 7.4 (HEPES/NaOH buffer); [ligand] = $2.5 \cdot 10^{-4}$-$5 \cdot 10^{-3}$ M in $CHCl_3$.

Generally, the penetration of anions into the cavity of azacages **1** and **2** may be hindered by encapsulated water molecules.[41,42] Furthermore, derived from the size relation and molecular modeling calculations, the cage cavity of these azacryptands seems to be too small in particular for the large pertechnetate and perrhenate oxoanions.

On the other hand, the cryptands **3**–**6** have a more suitable size for the encapsulation of these large anions. This was also shown by molecular modeling.[38] Unfortunately, these compounds show a poor extraction for pertechnetate and perrhenate in the neutral media (cf. Fig. 3).

Regarding the extraction as function of pH, the double tren-capped cryptands **3** and **4** (cf. Fig.6) follow the same trend as obtained for **1** and **2** (cf. Fig.4). That can be also explained on the basis of the different protonation state in dependence on pH.[43,44] The lower extraction efficiency of **3** and **4** in comparison to **1** and **2** should lie in the higher overall basicity connected with a greater number of secondary nitrogen atoms, and consequently the complexes formed should have a lower lipophilicity in the acidic and

the neutral media. This can be illustrated by a high proportion of the higher charged species LH_5^{5+}, LH_4^{4+} and LH_3^{3+} of **3** and **4** present at the pH range between 7 and 8.

As shown in Fig. 6, the extraction power of **6** is significantly stronger in comparison to **1**–**4** in the acidic pH range. Because in the case of **6**, only the two bridgehead nitrogen atoms can be protonated and favor the anion transfer. Therefore, between pH 2 and 3 the pertechnetate extractabilities are in the same order of magnitude as for **1** and **2** at neutral conditions. Only slight differences of pertechnetate and perrhenate extraction were obtained for **5** and **6**, apparently caused by the change in the lipophilicity in going from the acetylated compound **5** to the benzoylated derivative **6**.

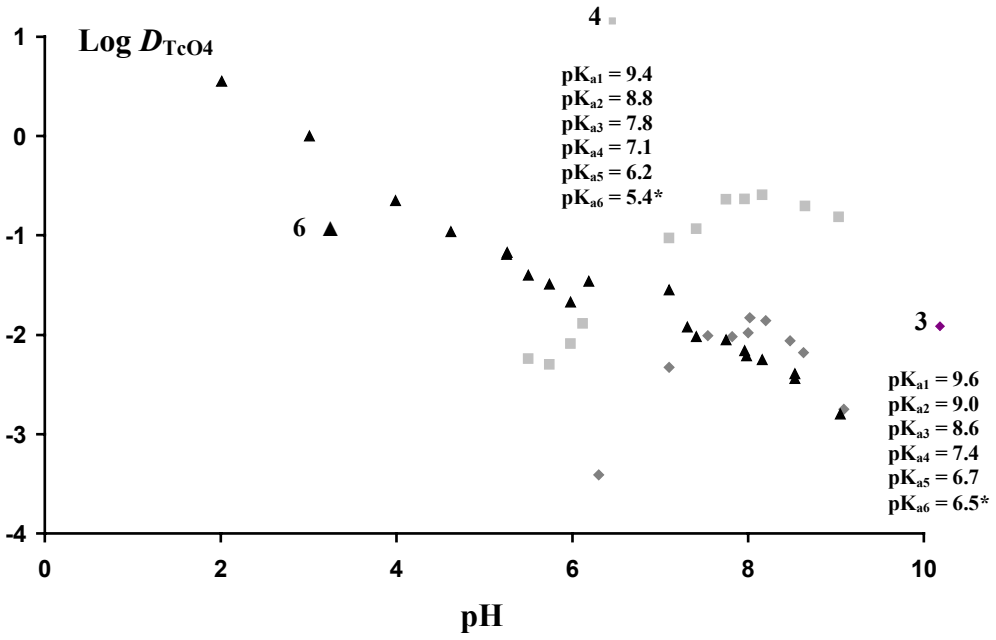


Figure 6. Extraction of pertechnetate with cryptands **3, 4** and **6** as function of pH. (experimental conditions are the same as in Fig. 4) [**3**, **4**] = $1 \cdot 10^{-3}$ M in $CHCl_3$; [**6**] = $5 \cdot 10^{-3}$ M in $CHCl_3$; * pK_a (H_2O, 0.1 M $[(C_2H_5)_4N]ClO_4$ from Ref. 43.

In order to obtain information about the lipophilicity of the cages, we have determined the partition of **1**–**4**, and **6** between water and 1-octanol. The concentrations of azacryptands in the organic and aqueous phase were determined by UV measurements. At pH = 7.4 more than 96% of **1, 3** and **4** remains in the aqueous phase. On the other hand, 70% of **2** and 95% of the amidocryptand **6** are preferentially located in the organic phase. The partition behavior of **6** can be explained on the basis of low basicity and increasing lipophilicity caused by the nonprotonable amidofunction compared to aminocages, and it is in good agreement with the results obtained by mass spectrometry.[45] Also, the aminocages **1**, **3** and **4** are preferentially located in the organic

phase after complete deprotonation. Accordingly, 98% of **1** is transferred into 1-octanol at pH > 10. It is true that amidocages have the appropriate lipophilicity to act as an extractant, but owing to the loss of the protonable secondary amine groups as binding centers, the ability to transfer the oxoanions pertechnetate and perrhenate disappears in particular in the neutral media. Knowing that pyridine nitrogen[43] should also not protonate at pH > 2, we assume that the extraction behaviour of amidocages **5** and **6** is caused only by the protonation of the bridging tertiary amine nitrogens at low pH.

Information about the overall stoichiometry of complexes extracted was also obtained by measuring the distribution ratios of anions between the organic and aqueous phase as a function of the ligand concentration (cf. Fig. 7). The data determined with slopes of unity were consistent with preferential 1:1 complex formation of pertechnetate and perrhenate with the cryptands **3**–**6**. In case of **3** and **4** the maximum loading of the organic phase by pertechnetate or perrhenate is characterized by a ligand to anion ratio of 1:2.

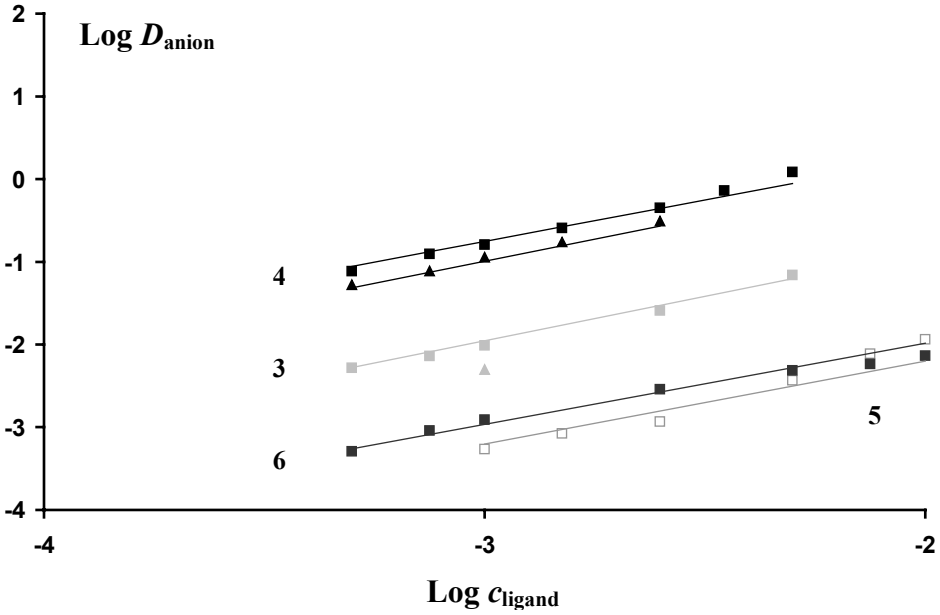


Figure 7. Extraction of pertechnetate and perrhenate with cryptands **3 - 6** as function of ligand concentration. (experimental conditions are the same as in Fig. 5).

2.2. Structural Considerations

Unfortunately, solvent extraction studies reveal no information about the complex structure. The anion can be arranged inside and outside the cavity. The formation of anion cryptates is mainly influenced by the host/guest complementarity of size and

binding mode, the protonation and solvation state of the cage compounds, but also by charge and solvation of the anion. Taking into account the large size of pertechnetate and perrhenate, there is only the possibility to bind one anion inside the cavity of the cryptands investigated.

As can be seen from Fig. 8, generally some different coordination patterns are possible. Considering the monoprotonated form of a host with an adequate size, the mononegative oxoanion may be bound inside of the cavity. But this desired binding mode is often prevented by unfavorable ligand conformation. Furthermore, the cavity can be blocked by bound solvent molecules, in particular water. Consequently, the penetration of the oxoanion should be complicated. Nevertheless, the first perrhenate inclusion complex with a hexaprotonated aminocage could be isolated.[46]

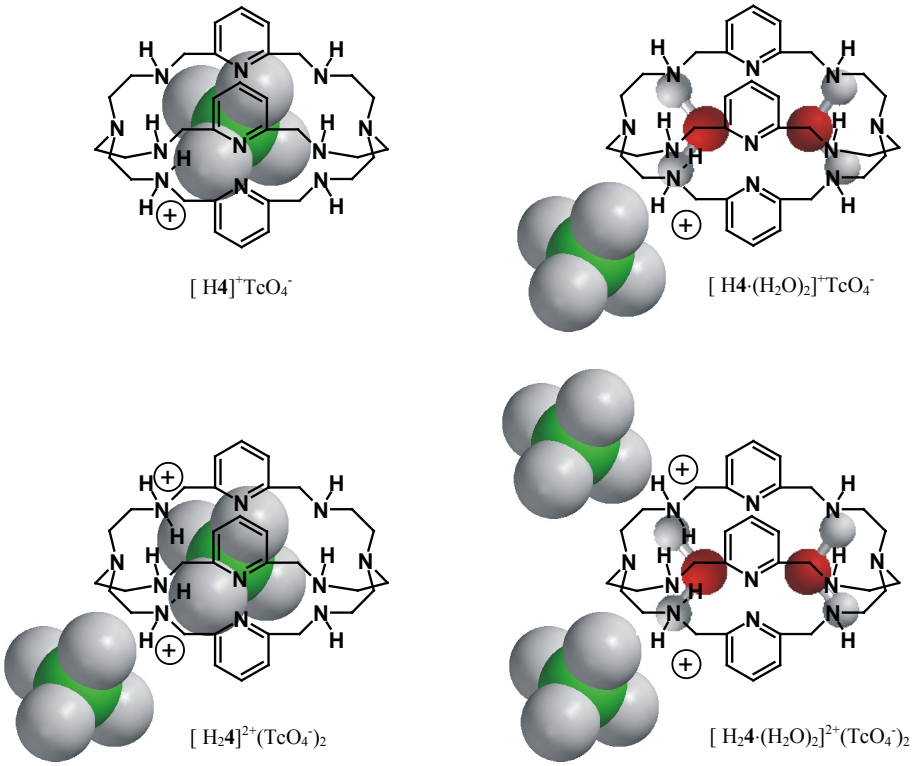


Figure 8. Possible coordination patterns for binding pertechnetate and perrhenate by azacage **4** in mono and diprotonated form.

In order to find more detailed information about the structural arrangement of the anion with regard to the above questions, we have generated some solid crystals of perrhenate complexes with azacages. In contrast to the usual procedure of applying strongly acidic solutions to azacryptands[27-30], we started from cage monohydrochlorides

dissolved in methanol. Such a solution was passed through a column loaded with a strong basic anion exchanger in the perrhenate form. This procedure was chosen because we are especially interested to get more information about the binding mode of azacages with perrhenate in the neutral media. In the case of azacryptand **1**, single crystals of sufficient X-ray diffraction quality were isolated. The structure of the complex formed with perrhenate is shown in Fig. 9.

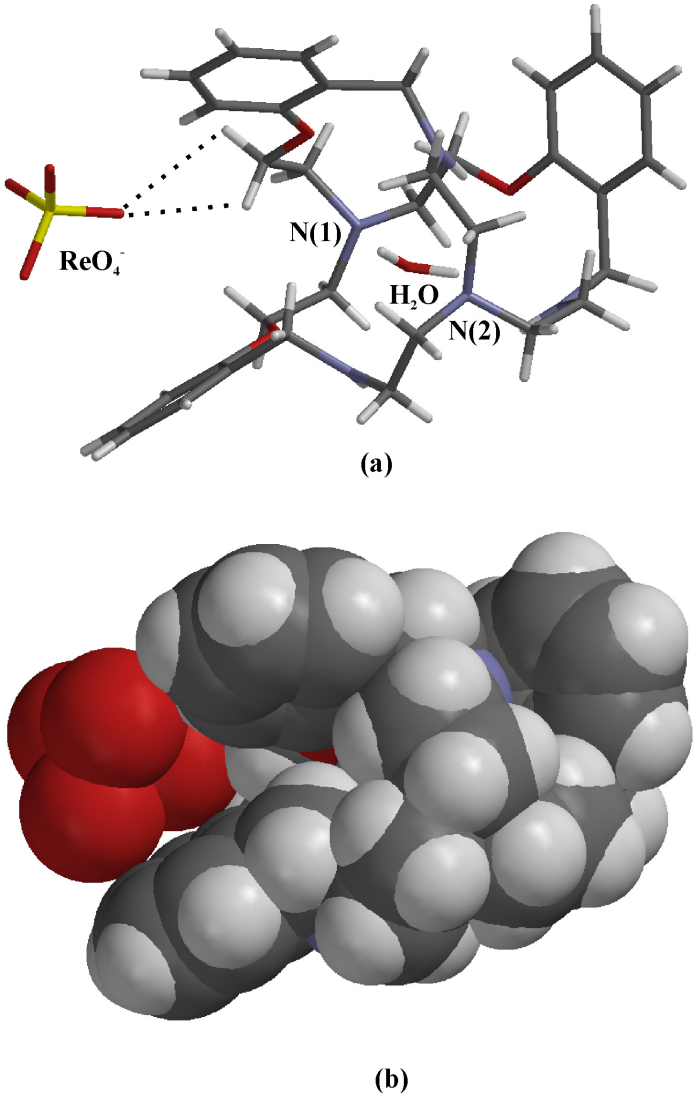


Figure 9. X-ray structure of azacryptand **1** with perrhenate [perspective views: (a) tube (b) space filling].

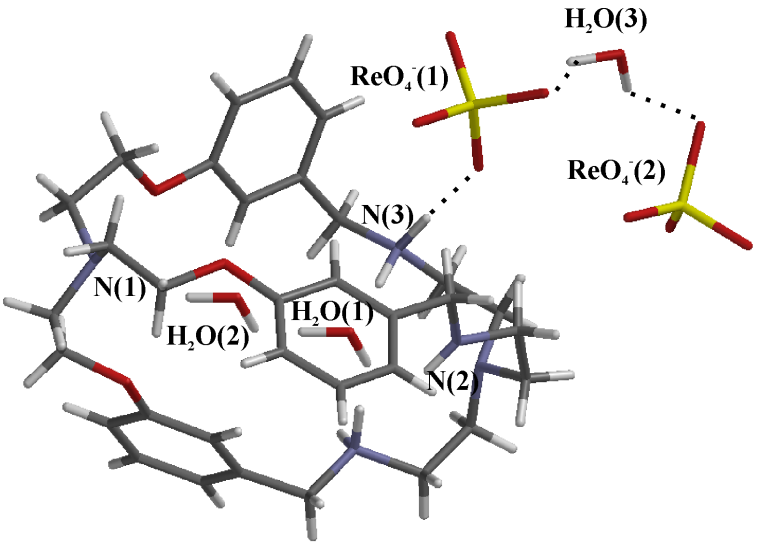
In the same way as found by solvent extraction, 1:1 complex formation in the solid state was observed. The perrhenate anion is arranged outside the cavity, partially embedded between two benzene rings. This structure leads to a shortening of the distance between the bridgehead nitrogens [N(1)–N(2): 5.812 Å] compared to the free ligand (6.249 Å).[38] Weak hydrogen bonding is observed between one perrhenate oxygen atom and the two methylene hydrogen atoms of the tolyl spacer unit [$O(ReO_4^-)$–$H(CH_2)$: 2.575 and 2.658 Å]. Such weak hydrogen bonding of the perrhenate anion with methylene hydrogen atoms is also known for crown compounds.[47,48] We found that one water molecule is encapsulated by the cryptand. That is very similar to a rhodanide complex of **1**.[41] In this case, the cavity is also blocked by water, and the anions are arranged outside of a diprotonated host. On the other hand, a crystal structure of perchlorate with **1** shows that even if the cage is fully protonated, the anions are bound at the periphery.[37] Molecular modeling calculations[38] confirm the preferential arrangement of anions outside the cavity of **1**.

Also for azacage **2** a complex structure was found where the perrhenate anion is arranged at the periphery of the ligand molecule (cf. Fig. 10). In contrast to **1**, the azacage **2** is diprotonated, and it results in a 2:1 complex (perrhenate:**2**) in the solid state, which is in agreement with the maximum loading in solvent extraction experiments. The structure of the perrhenate complex is very similar to the corresponding perchlorate complex[42] isolated. Accordingly, the distances between the bridgehead nitrogens [N(1), N(2)] of 9.003 Å and 9.052 Å are almost the same for the perrhenate und perchlorate complex. Likewise, two water molecules are bound inside the cavity. In the case of the perrhenate complex, one perrhenate anion forms a strong hydrogen bond to the protonated secondary nitrogen N(3). The distance from one oxygen atom of ReO_4^- (1) to N(3) is 2.77 Å. Moreover, the two perrhenate molecules are bridged by water, forming two additional hydrogen bonds (2.72 Å and 2.96 Å).

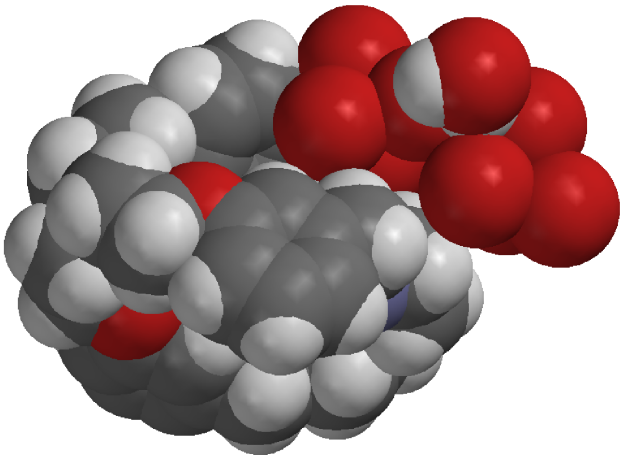
In the case of azacryptand **3**, the X-ray crystal structure analysis led to a further different structure arrangement (cf. Fig. 11). The asymmetric unit contains two independent, but very similar molecules. There is no indication of any interactions between these molecules. That is comparable to a structure of a bistren capped azacage bridged with xylyl spacers in the meta-position recently described.[43] In the case of the perrhenate complex, the cage structure is stabilized in a rather flat arrangement. The distances between the bridgehead nitrogen atoms are 10.224 and 10.072 Å, respectively. The formation of two intramolecular hydrogen bonds between secondary amine nitrogen atoms of each cage molecule should be responsible for that (N-H–N: 2.86, 2.96 Å; 2.87, 2.96 Å). The resulting long and narrow structure of the azacage leads once again to an arrangement where the perrhenate anions are bound outside the cavity. Each cage molecule is surrounded with two perrhenate and three water molecules.

To sum up, the occupation of cryptands by water molecules as found for azacages **1** and **2** as well as the formation of intramolecular hydrogen bonds evidenced for **3** hamper the penetration of anions into the cavity. Furthermore, a low state of protonation seems to favor complex structures where the anions are bound outside the cavity. Nevertheless, in particular bistren capped azacages are very promising in view of the encapsulation of large anions. As evidenced in the solid state, the pyridine-containing bistren cryptand **4** is able to accommodate the hexafluorosilicate anion.[29] The SiF_6^{2-} anion has a radius of 2.59 Å that is very similar to ReO_4^- (2.60 Å). Likewise, the bistren capped azacage bridged with xylyl spacers in the meta-position encapsulates the large dinegative oxoanions

chromate (2.40 Å), selenate (2.43 Å), and thiosulfate (2.50 Å).[31] Further studies using this compound as anion receptor have shown, that oxalate can be included with distinctive stability.[49] In case of the fluoride ion, three different complex structures with similar cages were found. Among them the first anion-based cascade complex, in which a water molecule bridges two fluoride ions inside the cage **3**.[50]



(a)



(b)

Figure 10. X-ray structure of azacryptand **2** with perrhenate [perspective views: (a) tube (b) space filling].

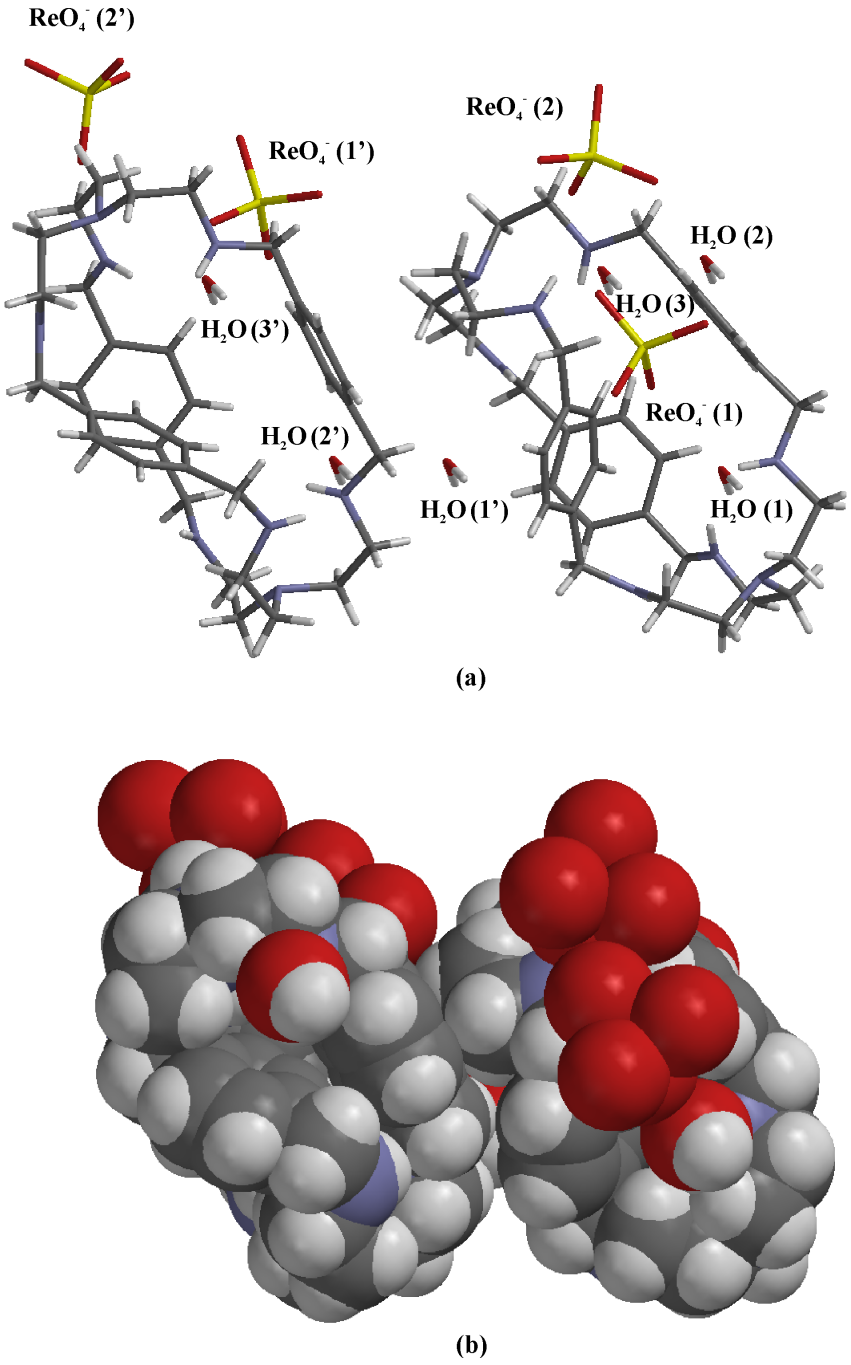


Figure 11. X-ray structure of azacryptand **3** with perrhenate [perspective views: (a) tube (b) space filling].

3. CONCLUSIONS

Aminocages **1**–**4** and amidocages **5** and **6** are capable of extraction of the large oxoanions pertechnetate and perrhenate. Extraction behavior was consistent with clean 1:1 complex formation at an excess of the ligand over the anion concentration. A maximum loading of two anions per ligand molecule was observed at higher anion concentration. In all cases, pertechnetate is slightly better extracted than perrhenate.

The efficiency of oxoanion extraction correlates especially with the acid-base behavior of the cage compounds and the lipophilicity of the anions. In view of the application as extractants, the lipophilicity of aminocages has to be increased. Preliminary results show that both the lipophilicity and extraction efficiency are remarkably enhanced after methylation of secondary amine nitrogen atoms of the cage.[46] The amidocages have the appropriated lipophilicity. But, due to the preferred protonation at low pH, these cryptands only exhibit high extraction of oxoanions in acidic solution. The replacement of tertiary by secondary amide groups seems to be an interesting way to improve the extraction efficiency in the neutral media. In this case the oxoanions can be additionally stabilized by hydrogen bonds.

An another promising approach is based on the use of open-chain counterparts of the cage compounds having the tren unit modified by lipophilic moieties.[46]

The molecular encapsulation of pertechnetate and perrhenate for imaging and therapeutic purposes is a challenging task. To achieve a high stability in vivo the oxoanions have to be mechanically locked into cage compounds.

4. EXPERIMENTAL SECTION

4.1. Synthesis

Reagent-grade chemicals were used as provided. The cryptands **1**–**4** were prepared as described earlier (**1**,[40] **2**,[51] **3**,[27] and **4**[27]). The amidocryptands **5** and **6** were obtained by acetylation and benzoylation, respectively, of pyridine-containing cryptand **4**. In a typical experiment, 3 mmol acetylchloride (benzoylchloride) dissolved in 30 mL dry dichloromethane was added over a period of 1.5 h to a solution of 0.5 mmol **4** and 4 mmol triethylamine in dry dichloromethane (50 mL). After the addition was complete, the solution was heated to reflux for 2 h. The solution was cooled up to room temperature, and was washed with $KHCO_3$ (10% in water) and finally with water. After drying the organic layer with anhydrous Na_2SO_4, the solvent was removed in vacuo. The residue was purified by MPLC (Lichroprep SiO_2, 15-25 µm, CH_2Cl_2/MeOH = 100:25).

Amidocryptand **5**: glassy solid in 55.9 % yield;
FAB MS (matrix: 3-nitrobenzyl alcohol): *m*/*z* (%): 854.5 (100) [M^+];
$C_{45}H_{63}N_{11}O_6$: 854.06.

Amidocryptand **6**: glassy solid in 61.5 % yield;
FAB MS (matrix: 3-nitrobenzyl alcohol): m/z (%): 1226.5 (100) [M^+];
$C_{75}H_{75}N_{11}O_6$: 1226.49.

Perrhenate complexes of the azacryptands **1**–**3** were prepared on the following way: 10 mg of cryptand was dissolved in 10 mL methanol/acetonitrile (9/1) and the equimolar amount of 0.1 M HCl was added. This solution was passed through a column filled with 2 mL strongly basic anion exchange resin (DOWEX®1XA-200) in the perrhenate form.

After washing the column with 50 mL methanol and finally with 5 mL acetonitrile, the eluate was completely evaporated. The residue obtained was dissolved in CH_2Cl_2, and the solution was dried using anhydrous Na_2SO_4. After complete removal of the solvent, colorless solidified oils were obtained. X-ray-quality crystals were grown by slow evaporation of an acetonitrile solution at room temperature.

4.2. Liquid-Liquid Extraction Procedure

Extraction studies were performed at 25 ± 1 °C in 2 cm^3 microcentrifuge tubes by mechanical shaking. The phase ratio $V_{(org)}$:$V_{(w)}$ was 1:1 (0.5 cm^3 each); the shaking period was 30 min. The extraction equilibrium was achieved during this period. All samples were centrifuged after extraction. The pertechnetate and perrhenate concentration in both phases was determined radiometrically using β-emission ($^{99}TcO_4^-$, $^{188}ReO_4^-$; liquid scintillation counter LS 6000 LL/Beckman). The aqueous solution was adjusted using 0.05 mol·dm^3 NaOAc/HCl (pH 2.0–5.2), 2-[N-morpholino]ethanesulfonic acid (MES)/NaOH, 5.4–6.1), N-[2-hydroxyethyl]piperazine-N′-[2-ethanesulfonic acid] (HEPES)/NaOH, 7.1–8.0), and 3-([2-hydroxy-1,1-bis(hydroxymethyl)ethyl]-amino)-1-propanesulfonic acid, TAPS)/NaOH, 8.0–9.0).

In order to determine the partition coefficients of azacages in the water/1-octanol system, 0.001 M stock solutions of aminocages in buffer, saturated with 1-octanol, were prepared. In the case of amidocage **6**, 0.001 M stock solution in 1-octanol, saturated with buffer, was prepared. Partition experiments were performed with 0.0001 M solution of azacage in aqueous solution (HEPES/NaOH, pH = 7.4; 2-amino-2-methylpropanol/HCl buffer, pH = 10.6), and 0.0001 M amidocage in 1-octanol, respectively. The phase ratio $V_{(org)}$:$V_{(w)}$ was 1:1 (0.8 cm^3 each); the shaking period was 2 h. After separation of both phases by centrifugation, the concentration of azacages in the aqueous and organic phase were analyzed by UV-spectroscopy (Lambda 2, Perkin-Elmer).

4.3. X-ray Crystallography

The X-ray data were collected at room temperature (293 K) on a SMART-CCD diffractometer (SIEMENS), using graphite-monochromatized Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by direct methods using SHELXS-90 and refined with SHELXL-97.[52] An empirical absorption correction (Ψ-scan) was applied. The anisotropic refinement of all non-hydrogen atoms was only possible for the perrhenate complex of azacage **2**. Because of the relatively poor quality obtained for the perrhenate complexes of azacages **1** and **3**, only the heavy atoms could refined anisotropically. This explains the relative high *R*-values of these complexes. Therefore also some restraints for bondlength and angles are applied. The positions of hydrogen atoms were calculated corresponding to their geometrical conditions and refined using the riding model. Atomic positional and thermal parameters, full lists of bond lengths and angles, and F_o/F_c values have been deposited as supporting information at the CCDC. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. **CCDC** 177808, 177809 and 177810. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

[H**1** ⊂ H_2O)] · ReO_4: $C_{33}H_{48}N_5O_8Re$, FW = 828.98, a = 10.535(10), b = 12.661(11), c = 13.870(12) Å, α = 74.19(2)°, β = 75.19(2)°, γ = 76.11(3)°, V = 1692(3) Å^3, triclinic P-1, Z = 2, μ = 3.649 mm^{-1}, 1381 reflections collected, 1369 unique reflections, R_{int} = 0.0688, R1 = 0.1478, wR2 = 0.3050 [$I > 2\sigma(I)$], R1 = 0.1873, wR2 = 0.3228 (all data), GOF = 1.132.

[H_2**2** ⊂ $(H_2O)_2$] · $(ReO_4)_2$ · H_2O: $C_{33}H_{53}N_5O_{14}Re_2$, FW = 1116.22, a = 11.583(4), b = 28.744(9), c = 12.337(4) Å, β = 92.003(6)°, V = 4105(2) Å^3, monoclinic $P2_1/n$, Z = 4, μ = 5.960 mm^{-1}, 12553 reflections collected, 3815 unique reflections, R_{int} = 0.1008, R1 = 0.0427, wR2 = 0.0981 [$I > 2\sigma(I)$], R1 = 0.0726, wR2 = 0.1076 (all data), GOF = 0.789.

{[H_2**3**] · $(ReO_4)_2$ · $(H_2O)_3$}$_2$: $C_{36}H_{62}N_8O_{11}Re_2$, FW = 1155.35, a = 15.05(3), b = 17.42(3), c = 16.97(3) Å, β = 93.77(4)°, V = 4441(14) Å^3, monoclinic $P2_1/n$, Z = 4, μ = 5.509 mm^{-1}, 13586 reflections collected, 7941 unique reflections, R_{int} = 0.1139, R1 = 0.0979, wR2 = 0.2220 [$I > 2\sigma(I)$], R1 = 0.1398, wR2 = 0.2388 (all data), GOF = 1.102.

5. ACKNOWLEDGMENTS

We thank the Sächsisches Ministerium für Wissenschaft und Kunst (project no. 7531-50-03-0370-01/4), the Deutsche Forschungsgemeinschaft, Germany, and the Department of Science and Technology, India, for support of this work. The authors are indebted to Ms. I. Schubert and Ms. U. Stöckgen for their careful experimental assistance, Dr. T. Rambusch for molecular modeling calculations, and Prof. J. Nelson for stimulating discussions.

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