Supramolecular Chemistry

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Porous Capsules Allow Pore Opening and Closing That Results in Cation Uptake**

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Dedicated to Prof. Herbert W. Roesky on the occasion of his 70th birthday

Structurally well-defined spherical porous molybdenum oxide based nanocapsules of the type $\{Pentagon\}_{12}\{Linker\}_{30}$[1,2] can be described as artificial cells as they allow the modeling—in solution studies—of passive biological ion transport[3a,b] as well as cell response to stimuli[3c] (see also ref. [4]); for biochemically related literature, see ref. [5a]. Specifically we refer herein to spherical, nanoscale, porous capsules/artificial cells of the type $[\{(Mo)Mo_5O_{21}(H_2O)_6\}_{12}\{Mo_2O_4(ligand)\}_{30}]^{n-}$,[1,2] the overall charges and internal surfaces of which can be fine-tuned by changing the ligands, thus allowing the type and structure of encapsulates to be influenced.[4] Most important, the 20 $\{Mo_9O_9\}$-type pores have crown-ether-like function and can be opened and closed with noncovalently bonded guests in a supramolecular fashion.[6a] Herein we will refer to the special situation of (protonated) urea molecules as guest species,[6b] which are found in all 20 of the capsule pores. Interestingly, after exposition of a solution of this type of capsule to Ca^{2+} ions the Ca^{2+} ions are incorporated, however, in the final precipitated product all 20 pores are again closed with the urea-type guests. This situation is not only of some interest regarding modeling of cell environment interactions but fundamentally shows in an example that supramolecular chemistry is, according to J.-M. Lehn,[5b] a "dynamic chemistry/science": the interaction between the parts, that is, the capsule pores and the "corks"/guests, is based on lability, which allows an easy exchange corresponding to the reversibility of noncovalent interactions. Furthermore, we should note that "*calcium probably fulfills a greater variety of biological functions than any other cation*";[6c] this includes for instance the special role of Ca^{2+} ions in information mediation in connection with the ubiquitous presence of Ca^{2+} channels in excitable cells.[5a] In the present case, the up-taken Ca^{2+} ions influence/direct the structure of the capsule encapsulates, that is, of the water-molecule-based assembly.

Exposition of an aqueous solution of **1**[6d]—where the 20 pores are closed with protonated urea molecules—to Ca^{2+} ions leads finally to the precipitation of **2** which was characterized by elemental analysis, thermogravimetry (to determine the number of crystal water molecules), redox titration (to determine the number of Mo^V centers), bond valence sum (BVS) calculations,[7] spectroscopic methods (IR, Raman), and single-crystal X-ray structure analysis.[8,9]

$$(H^+ \cdot OC(NH_2)_2)_{23}(NH_4)_{29-n}[\{(H^+ \cdot OC(NH_2)_2)_{20} + (H_2O)_{81-n} + (NH_4)_n\} \subset \{(Mo^{VI})Mo^{VI}{}_5O_{21}(H_2O)_6\}_{12}\{Mo^V{}_2O_4(SO_4)\}_{30}] \cdot \approx 100\,H_2O \equiv (H^+ \cdot OC(NH_2)_2)_{23}(NH_4)_{29-n}\mathbf{1a} \cdot \approx 100\,H_2O \quad \mathbf{1}^{[10]}$$

$$(H^+ \cdot OC(NH_2)_2)_{15}(NH_4)_{21-n}[\{(H^+ \cdot OC(NH_2)_2)_{20} + Ca_8 + (H_2O)_{60} + (NH_4)_n\} \subset \{(Mo^{VI})\,Mo^{VI}{}_5O_{21}(H_2O)_6\}_{12}\{Mo^V{}_2O_4(SO_4)\}_{30}] \cdot \approx 150\,H_2O \equiv (H^+ \cdot OC(NH_2)_2)_{15}(NH_4)_{21-n}\mathbf{2a} \cdot \approx 150\,H_2O \quad \mathbf{2}$$

According to the X-ray crystallographic results, the capsule **2a** (Figure 1) shows the characteristic basic polyoxomolybdate skeleton[1,2]—the artificial cell's "inorganic membrane"[4b]—that is present in **1a**,[10] and which also occurs in other spherical capsules.[1,2,4] However, in **2a** there are additionally 20 protonated urea guests closing the 20 $\{Mo_9O_9\}$ pores/rings through noncovalent (that is, hydrogen-bond) interactions[6ab], and, encapsulated Ca^{2+} ions; furthermore, the structure of the encapsulated water-molecule assembly is different in **2a** from that of **1a**. (The presence of Ca^{2+} can also be demonstrated by IR spectroscopy by the shift of a specific sulfate band from 1036 in **1** to 1057 cm^{-1} in **2**; see ref. [3a].) The eight calcium cations found in **2a** are disordered over 20 equivalent positions below the $\{Mo_9O_9\}$ pore openings at the end of the channels (Figure 1), that is, on the C_3 axes, and exhibit the expected octahedral coordination environment which is formed by three oxygen atoms of three sulfate ligands and three oxygen atoms belonging to the encapsulated water shell/assembly (see below and ref. [4]). Whereas **1a** shows the known structure of the NH_4^+/H_2O assembly within a capsule containing SO_4^{2-} ligands,[4a] in **2a** a

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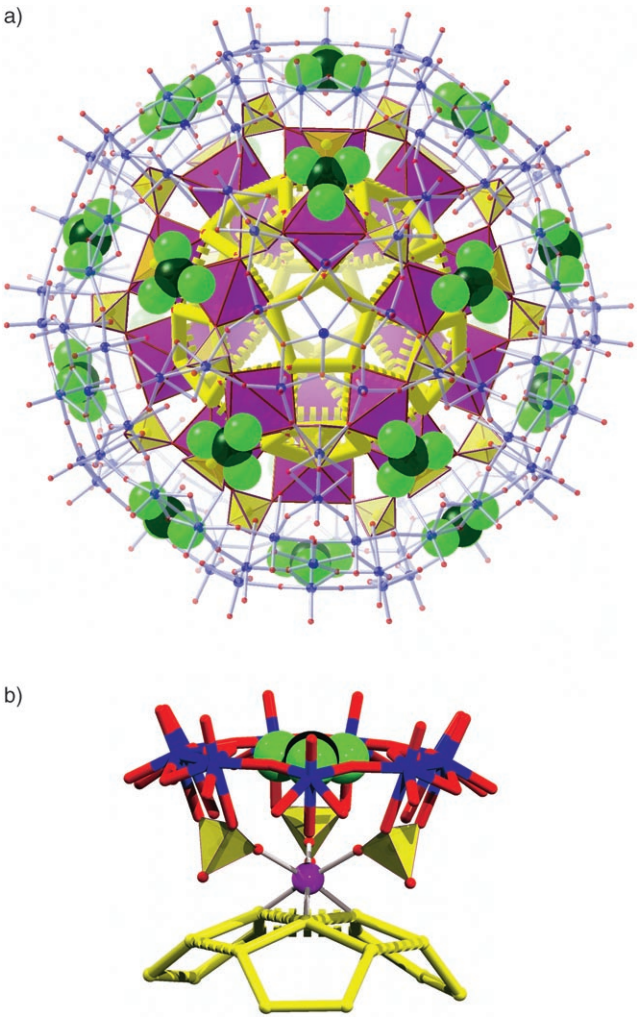

Figure 1. a) Structure of the capsule **2a** with the skeleton in ball-and-stick representation (Mo blue, O red), sulfate ligands (yellow tetrahedra), Ca^{2+} ions in the octahedral coordination of oxygen atoms (pink octahedra), the rhombicosidodecahedral $(H_2O)_{60}$ water assembly inside the capsule (yellow wire-frame representation, solid and dotted lines), and the protonated urea corks (space-filling representation, C dark green, N/O (urea) green). b) For clarity one segment of **2a** is shown separately (same color code as in (a)).

pure, well-defined water assembly/shell $\{H_2O\}_{60} \approx 12\{H_2O\}_5$ (radius 6.81–7.12 Å; occupation factor 1 for the O atoms) acting as ligand to the Ca^{2+} ions is observed,[11a] the formation and positioning of which is directed by the abundance of the fixed Ca^{2+} ions. (Though the exact NH_4^+ and H_2O positions in **1a** cannot be distinguished by X-ray crystallography because of a related disorder, there is clear evidence that NH_4^+ ions are involved in the formation of the central $\{X_{20}\}$ dodecahedron.[11a]) The $(H_2O)_{60}$ shell of **2a** corresponds to a distorted rhombicosidodecahedron which might be regarded as an unprecedented polydentate/macrocyclic ligand for the calcium ions or other cations.

Recall that we start with a capsule **1a** closed by the protonated urea "corks" and detect Ca^{2+} ions afterwards in the capsule **2a**, the pores of which are again closed by the same corks. The inorganic membrane pores are definitely not permanently closed, and in solution only a fraction of the pores is always (statistically) open (Figure 2). This problem related to the "behavior" of the corks in solution cannot of

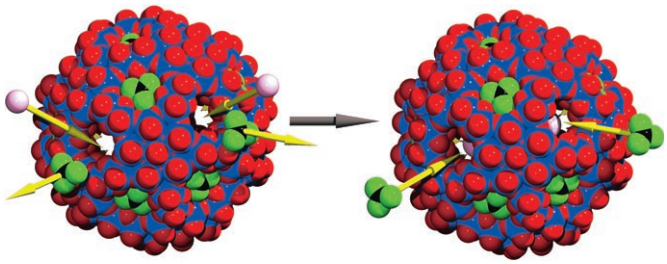

Figure 2. Space-filling representation demonstrating a simplified view of the Ca^{2+} ion uptake based on the capsule **1a**. In the anions of **1** the pores are closed. Treating a solution of **1** with Ca^{2+} ions leads to cation uptake (left) while in the final product **2** the pores again are closed (right; Mo blue, O red, C black, N/O(urea) green, Ca^{2+} pink, yellow arrows indicate direction of motion).

course be solved by an X-ray crystallography study. On the other hand, preliminary ^1H NMR spectra of solutions of **2** in DMF at room temperature clearly indicate the abundance of oxygen-protonated urea species in the pores.[11b] (Oxygen protonation would agree with earlier results for the protonation sites of urea determined by IR and ^{17}O NMR spectroscopy.[6b]) In this case, the peak-intensity analysis reveals that approximately a third of the capsule pores are occupied.[11c] Interesting, in this context, is the possibility of stabilizing the OH-type protonated urea species by integration into the pores. Furthermore, a well-defined temperature-dependent equilibrium can—in the case of guest cations exhibiting a much higher affinity[6a] for the pores than protonated urea—be easily studied by NMR spectroscopy in different solvents.[11d] With such guests the remarkable situation arises in which all the 20 pores are completely closed at lower temperatures and can be (reversibly) opened on heating with the consequence that uptake of different types of cations only occurs at higher temperatures (temperature gating). This process can be demonstrated nicely by ^1H- and metal-NMR spectroscopy studies including EXSY data.[11d]

Under the conditions employed the Ca^{2+} ions cannot pass through the pores with their hydrate coat: for an effective trafficking the comparably large Ca^{2+} complexes must release their water ligands and some of these ligands are "taken up" again inside the artificial cell. (Note: the inorganic membrane pores are semipermeable allowing uptake and release of water but not of organic solvents such as DMF or DMSO.[3b,11d]) A condition for the uptake is therefore that the affinity of Ca^{2+} ions for the H_2O ligands is not too strong. This condition is met in this case as the water ligand "mean residence time" is of the order around 10^{-8} s at room temperature,[12] which is comparable to the published water exchange rate constant of $6–9 \cdot 10^8\ s^{-1}$.[13ab,14] As $[Ca(H_2O)_6]^{2+}$ shows a much greater lability compared to the related Be^{2+} and Mg^{2+} hydrate complexes, Be^{2+} and Mg^{2+} should therefore both show a different behavior with respect to their inter-

actions with the capsule(s).[14] In this context there is another attractive aspect which is related to the possibility of trapping complete hydrate complexes above the capsules' pores based on hydrogen-bond interactions between the O atoms of the $\{Mo_9O_9\}$ pores/rings and the H_2O ligands. But this type of trapping only occurs for the present type of hydrate complex, which has a low stability-constant value, with less negatively charged capsules, for example, those with linkers containing less negatively charged ligands, such as acetates (instead of sulfates), where the capsule–cation interaction is weaker.[15] Interesting in this context is that the coordination environment of calcium ions in water is not very well defined, and correspondingly different coordination numbers for Ca^{2+} ions are reported in the literature.[13a] This gives, in principle, the option to trap different hydrate complexes in this or in related metal complexes at the capsule surface sites under different conditions,[13c] including different capsule charges (so called "Sphere Surface Chemistry").

An aspect of more general interest in this context is the chance to carry out systematic studies on the interaction between the capsules/artificial cells—the pores of which are partially or temporarily closed with different kinds of complementary guests—and a series of different hydrated cations present in solution; this would allow information to be obtained on the properties and behavior of hydrate complexes. The entrance of appropriate cations can nicely be studied in solution with NMR spectroscopy.[3a,b] Importantly, most of the biological ion pores/channels are not continuously open (note: the K^+ ion leak channels are) they are gated, that is, they can open and then close again.[5a] The opening is due to a response to specific stimuli, for example, corresponding to a change in the voltage across the membrane (leading to the channel protein conformational changes), a mechanical stress, or binding of a ligand.[5a] Referring to the present situation, the abundance of a large number of added cations, such as Ca^{2+}, in the vicinity or at the surface of the highly charged capsule decreases the capsule's charge, that is, diminishes the formal electrochemical gradient.[5a] This can 1) facilitate the release of guests such as protonated (even comparably strongly bonded) organic bases complementary to the $\{Mo_9O_9\}$ pores, and 2) allow subsequent entering of the cations (voltage gating of channels[5a]). In the case of more strongly bonded guests (see above and ref. [6]), this leads to complete pore closing at lower temperatures and cation uptake is observed only at higher temperatures (temperature gating (see above)). Once the cations are encapsulated the charge distribution changes, which might again influence the gating of the pores.

In the present system cation entrance is interesting because of the following facts: Voltage-gated calcium channels—ubiquitous in excitable cells in which Ca^{2+} functions as the ubiquitous intracellular messenger—play a key role in various physiological processes, such as muscle contraction, hormone and neurotransmitter secretion, and neuronal excitability. Several extracellular signals can induce an increase in the cytosolic Ca^{2+} ion concentration by 10–20-fold, which triggers the response.[5a,16,17] An interesting result of the present study is also that the uptake of Ca^{2+} ions leads to a "response in the cavity" in the form of a change in the structure of the encapsulates, that is, of the water/electrolyte based assembly.

Experimental Section

Synthesis of **1** (see also ref. [10]): A mixture of $(NH_4)_{42}[\{(Mo)Mo_5O_{21}(H_2O)_6\}_{12}\{Mo_2O_4(CH_3COO)\}_{30}]\cdot\approx[10\,CH_3COONH_4+300\,H_2O]$ (1.0 g, 0.04 mmol),[2d] ammonium sulfate (4.0 g, 30 mmol), urea (3.0 g, 50 mmol), and water (100 mL) was acidified with 16% HCl (8 mL) in a 250-mL conical flask (covered with a watch-glass) and stirred for 45 min at room temperature. The solution was kept in an open 250-mL beaker at around 23 °C for 10 days. Then the precipitated brown rhombohedral crystals of **1** were collected by filtration and dried in air. Yield: 0.35 g (35% based on Mo); elemental analyses (%) calcd N 5.69, H 2.62, C 1.82; found: N 5.6, H 2.7, C 1.8.

Characteristic IR bands: (KBr pellet, some characteristic bands for the range 1700–500 cm^{-1}): $\tilde{\nu}=1703$ [w, $\delta(ureaH^+)$], 1622 [s, $\delta(H_2O)$], 1555 [w, $\delta(ureaH^+)$], 1402 [m, $\delta(NH_4)$], 1196 (w), 1140 (m), 1036 (w) [all $\nu_{as}(SO_4)$], 972 [s, ν(Mo=O)], 852 (m), 795 (s), 723 (s), 630 (w), 569 cm^{-1} (s). (The $ureaH^+$ bands are influenced by the hydrogen bonds in the pores and are rather different from those of urea itself.)

Characteristic Raman bands: (solid state, KBr dilution, $\lambda_e\approx1064$ nm): $\tilde{\nu}=950$ [m, ν(Mo=O)], 880 [ν_s ($O_{bridging}$ breathing/A_{1g})], 372 (m), 303 cm^{-1} (w).

2: A mixture of **1** (2.0 g, 0.07 mmol), $CaCl_2\cdot2H_2O$ (0.5 g, 3.40 mmol), and water (50 mL; pH < 2) was stirred for 2 h at room temperature. The solution was then kept in an open 250-mL beaker at about 23 °C and after one week the precipitated brown rhombohedral crystals were collected by filtration through a glass frit (D2) and dried in air. Yield: 0.6 g (30% based on Mo); elemental analyses (%) calcd N 4.47, C 1.47, H 2.55, Ca 1.12; found: N 4.5, C 1.5, H 2.4, Ca 1.1.

Characteristic IR bands: (KBr pellet, some characteristic bands for the range 1700–500 cm^{-1}): $\tilde{\nu}=1703$ [w, $\delta(ureaH^+)$], 1624 [s, $\delta(H_2O)$], 1555 [w, $\delta(ureaH^+)$], 1402 [s, $\delta(NH_4)$], ≈1200 (sh), 1143 (m-s), 1057 (w) [all $\nu_{as}(SO_4)$], 976 (s), 947 (w) [both ν(Mo=O)], 854 (m), 796 (s), 725 (s), 632 (w), 573 cm^{-1} (s).

Characteristic Raman bands: (solid state, KBr dilution, $\lambda_e\approx1064$ nm): $\tilde{\nu}=950$ [m, ν(Mo=O)], 879 [ν_s ($O_{bridging}$ breathing/A_{1g})], 372 (m), 302 cm^{-1} (w).

The chemical formulae of **1** and **2** refer to the maximum possible number of crystal water molecules which correspond to the related volume calculated from the cell volume and the sum of volumes of all cell ingredients excluding those of the crystal water molecules. The given calculated values for C, N, Ca are related to a formula with 50 crystal water molecules less than given (note: **1** and **2** as all similar compounds show slow weathering, that is, loss of crystal water).

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heim, **2004**, pp. 452 – 475; f) N. Hall, *Chem. Commun.* **2003**, 803 – 806.

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[6] a) The first published example referred to the integration of $20[C(NH_2)_3]^+$ ions into the $20\{Mo_9O_9\}$ pores/rings in the same way as into a crown ether host, that is, the O···H–N bonding is comparable to that in crown ether hosts; for details see ref. [3c]. The pore(host)–guest interactions with other protonated bases such as $H^+{\cdot}OC(NH_2)_2$ (see below) and $HC(NH_2)_2^+$ (unpublished results; see also comments in the text) are as expected weaker, while with the increasing basicity of the corresponding unprotonated base—which is lowest in case of urea—the stability of the protonated species increases (H. R. Christen, F. Vögtle, *Organische Chemie, Vol. 1*, Salle and Sauerländer, Frankfurt am Main, **1992**, p. 452); b) Urea is, apart from its biological (e.g., protein denaturation) and industrial importance (see, for example, J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, Wiley, New York, **2000**, p. 273), especially interesting structurally and chemically: firstly because of the abundance of the (complementary) hydrogen-bonding sites giving rise to the remarkable cage/inclusion structures (see, for example, G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, New York, **1997**, p. 175), and secondly to the (in principle) different sites for protonation, that is, at the N and O atoms. The OH type species is stabilized by the contribution of the mesomeric border structure exhibiting the $C{=}NH_2^+$ fragment (K. P. C. Vollhardt, N. E. Schore, *Organische Chemie*, Wiley-VCH, 3. Aufl, Weinheim, **2000**, p. 956; see also: H. Beyer, W. Walter, *Lehrbuch der Organischen Chemie*, Hirzel, Stuttgart, 21. Aufl., **1988**, p. 356). Important in this case is that O protonation allows hydrogen-bond interactions in the pores in three directions. The problem of protonated sites was controversial for a long time starting from Alfred Werner's opinion: From vibrational spectra of normal urea salts, for example, with the $PtCl_6^{2-}$ ion, it was concluded for the first time that the preferable site of protonation is the O atom (W. Kutzelnigg, R. Mecke, *Chem. Ber.* **1961**, *94*, 1706 – 1716). Also from ^{17}O NMR spectroscopy studies over a wide pH range, from aqueous solution to fluoro sulfonic acid, it was concluded that (the first) protonation takes place at the O atom; in a magic acid even double protonation was observed (B. Valentine, T. E. St. Amour, D. Fiat, *Org. Magn. Reson.* **1984**, *22*, 697–700); c) W. Kaim, B. Schwederski, *Bioinorganic Chemistry: Inorganic Elements in the Chemistry of Life*, Wiley, Chichester, **1994**, p. 293; d) Note: this type of capsules is stable in solution at pH values between 1.5 and 4 and under exclusion of oxygen.

[7] I. D. Brown in *Structure and Bonding in Crystals, Vol. II* (Eds.: M. O'Keeffe, A. Navrotsky), Academic Press, New York, **1981**, pp. 1 – 30.

[8] Crystal data for **2**: $C_{35}H_{823}Ca_8Mo_{132}N_{91}O_{809}S_{30}$, $M_r = 29415.4\ g\,mol^{-1}$, rhombohedral, space group $R\bar{3}$, $a = 32.8169(7)$, $c = 73.921(2)$ Å, $V = 68944(3)$ Å^3, $Z = 3$, $\rho = 2.125\ g\,cm^{-3}$, $\mu = 1.96\ mm^{-1}$, $F(000) = 42978$, crystal size $= 0.40 \times 0.30 \times 0.30\ mm^3$. Crystals of **2** were removed from the mother liquor and immediately cooled to 183(2) K on a Bruker AXS SMART diffractometer (three circle goniometer with 1 K CCD detector, $Mo_{K\alpha}$ radiation, graphite monochromator; hemisphere data collection in ω at 0.3° scan width in three runs with 606, 435, and 230 frames ($\varphi = 0$, 88 and 180°) at a detector distance of 5.00 cm). A total of 115162 reflections ($1.55 < \Theta < 27.01°$) were collected of which 32366 reflections were unique ($R(\mathrm{int}) = 0.0290$). An empirical absorption correction using equivalent reflections was performed with the program SADABS 2.10. The structure was solved with the program SHELXS-97 and refined using SHELXL-97 to $R = 0.0389$ for 27502 reflections with $I > 2\sigma(I)$, $R = 0.0487$ for all reflections; max./min. residual electron density 1.87 and $-1.85\ e\,Å^{-3}$ (SHELXS/L, SADABS from G. M. Sheldrick, University of Göttingen, **1997/2003**; structure graphics with DIAMOND 3.0, http://www.crystalimpact.com/ and with POV-Ray 3.6, http://www.povray.org/).

[9] The basic structure of the educt **1**[10], for which the synthesis is also given (see Experimental Section), corresponds to that of **2**.

[10] a) S. Roy, Thesis, Faculty of Chemistry, University of Bielefeld, **2005**; b) A. Müller, A. Merca, S. Roy, H. Bögge, M. Schmidtmann, unpublished results.

[11] a) The shell system in the cavity of **1a** spanned by $n\,NH_4^+/m\,H_2O = X$ centers with $m \gg n$ is X_{60} (distorted rhombicosidodecahedron) + X_{20} (dodecahedron) + X (in the center) and is also found, for example, in an ammonium/sulfate-based capsule with open pores;[4a] the X_{60} shell is geometrically similar to the known pure water assembly $\{H_2O\}_{60}$ shell such as that in **2a** (see also ref. [4b,c]). There is clear evidence that the NH_4^+ ions in **1a** are rather strongly fixed in the cavity, as shown by combined thermogravimetry, mass spectroscopy, and temperature-dependent elemental analyses studies up to 450 °C; remarkably, the release of the "last" NH_3 molecules out of the capsules upon heating occurs at rather high temperatures (A. Malecki, A. Bielanski, E. Diemann, A. Müller, unpublished results). On the other hand it is evident that a change of the positions of the NH_4^+ ions during the conversion of **1a** into **2a** occurs while a Ca^{2+}–NH_4^+ counter transport takes place which leads to very small values of n in **2** and is currently being investigated in detail by ^{15}N HSQC NMR spectroscopy (E. T. K. Haupt, A. Müller, unpublished results); b) A. Mix, H. Bögge, T. Mitra, D. Rehder, A. Müller, unpublished results; c) In an aqueous solution of **1** the ratio of open to closed pores is unknown. The complete pore closing observed in solid **2** is to some extent influenced by the fact that it lowers the capsule charge and leads to a lower solubility of **2**; d) A. Mix, H. Bögge, D. Rehder, T. Mitra, M. Schmidtmann, A. Müller, unpublished results.

[12] F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, *Advanced Inorganic Chemistry*, 6th ed., Wiley, New York, **1999**, page 59.

[13] a) D. T. Richens, *The Chemistry of Aqua Ions: Synthesis, Structure and Reactivity: A Tour Through the Periodic Table of the Elements*, Wiley, Chichester, **1997**; b) See also: H. Krüger, *Chem. Soc. Rev.* **1982**, *11*, 227 – 256; c) Regarding unprecedented coordination numbers it should be mentioned in this context that recently for the first time evidence for a fivefold coordination of a trivalent metal aqua ion, that is, of Al^{III} could be obtained

(T. W. Swaddle, J. Rosenqvist, P. Yu, E. Bylaska, B. L. Phillips, W. H. Casey, *Science* **2005**, *308*, 1450 – 1453).

[14] The exchange rate for water ligands in the Ca^{2+} complex is, for instance, too fast to be measured by dynamic NMR spectroscopy.[13]

[15] A. Müller, L. Toma, H. Bögge, M. Schmidtmann unpublished results; see also Ref. [4b].

[16] a) B. Hille, *Ion Channels of Excitable Membranes*, 3rd ed., Sinauer, Massachusetts, **2001**; b) D. E. Clapham, *Nature* **2003**, *426*, 517 – 524.

[17] The surface of the excitable cell type mentioned holds thousands of related channels that precisely control the timing and entry of Ca^{2+} ions. Furthermore, the inhibition of the Ca^{2+} ion entry through channels by antagonists/entry blockers is of tremendous importance for the treatment of hypertony and coronary heart diseases because an excess of Ca^{2+} ions in the cells has to be avoided, a situation which nature can normally remedy through an effective control by Ca^{2+} ion pumps (T. A. Scott, E. I. Mercer, *Concise Encyclopedia Biochemistry and Molecular Biology*, 3rd ed., de Gruyter, New York, **1997**; E. Mutschler, *Arzneimittelwirkungen*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, **1986**, p. 447).

