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Mimicking Biological Cation-Transport Based on Sphere-Surface Supramolecular Chemistry: Simultaneous Interaction of Porous Capsules with Molecular Plugs and Passing Cations

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Dedicated to Prof. Dieter Fenske on the occasion of his 65th birthday

Abstract: Spherical capsules of the type $[\{(Mo)Mo_5\}_{12}\{Mo_2(ligand)\}_{30}]^{n-}$ exhibiting 20 $\{Mo_9O_9\}$ pores with crown ether functions allowed us to perform a sophisticated study of the title phenomenon based on synthetic work as well as NMR spectroscopy. The pores of the host system interact in solution specifically with guests that can be noncovalently bonded, such as formamidinium and acetamidinium cations, while having different affinities to the pores. The exchange between the guest species present in solution and in the pores was investigated, including, besides the extreme scenarios of complete pore closing and complete opening, that of stepwise pore plugging. Because of this option it was possible to model for the first time passive transmembrane cation transport based on gated pores/channels. These have the appropriate dimensions and can even adopt different structure flexibilities in response to different cations. The present investigation is based on related syntheses as well as on numerous detailed ^7Li NMR studies of Li^+ transport/exchange equilibria in dependence of the pore environment/guest situations. One compound containing capsules with sulfate ligands (**2**) could be obtained in which all the pores are plugged with formamidinium cations and another corresponding one was obtained with additionally encapsulated Ca^{2+} ions (**3**); these were taken up after temporary release of some of the formamidinium plugs/guests upon short heating of the related solution.

Keywords: ion transport · nanocapsules · NMR spectroscopy · polyoxometalates · supramolecular chemistry

Introduction

Compounds with three-dimensional networks like zeolites exhibiting (nanoscale) holes and channels can serve as filters and traps/hosts for molecular guests[1a] and are correspondingly treated in a book series about supramolecular chemistry.[1b] They play an important role in many regards as they can be used for separation, storage, and transportation. On the other hand, structurally well-defined, *discrete* nanosized species with such properties/options are only few, one being the porous spherical molybdenum oxide based nanocapsules of the type $[\{(Mo)Mo_5O_{21}(H_2O)_6\}_{12}\{Mo_2O_4(ligand)\}_{30}]^{n-}$[2]—called "Keplerates" in the literature—that can also be considered as artificial cells, as they allow the modeling of passive ion transport through membranes[3] as well as cell response to stimuli.[4] This means they are able to interact specifically with their environment. Ion transport through membrane channels plays a key role in basic life processes,[5a–c] in the therapy of bipolar disorders,[5d] and in toxicology;[5e] for instance dendrotoxin, from the venom of the black mamba snake interferes with the voltage-gated K^+ channel, and the active component of curare (tubocurarine)—the arrow poison used by the natives in the Amazon region—blocks the acetylcholin receptor or prevents opening of its ion channel.[5e] The anionic porous nanocapsules with the

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above-mentioned model character can be obtained (most of these in facile syntheses[2h,i]) with differently charged incorporated ligands;[2] that is, correspondingly with different overall charges as well as (cavity) interiors,[2] the former property leading to different affinities for cations and the latter to different coordination options for cations entering into the capsules.[4d,f] Most importantly, in particular for the present investigation, the 20 $\{Mo_9O_9\}$-type pores have crown ether like functions and can therefore be closed noncovalently by plugging them with cationic guests in a supramolecular fashion.[6] In the present paper we systematically investigate for the first time the varying affinities of different (organic) guest species to the $\{Mo_9O_9\}$ pores of the host systems/capsules as well as their stepwise closing according to the equilibrium shown in Equation (1).

$$\{20\text{ guests} \subset 20\text{ capsule pores}\} \rightleftharpoons n\text{ guests} + \{(20-n)\text{guests} \subset 20\text{ capsule pores}\} \quad (1)$$

This scenario can be considered in the context of Lehn's statement that "supramolecular chemistry is a dynamic science",[7a] as we can refer to the temperature dependence of the equilibria in Equation (1) (see Conclusions section). As the present types of supramolecular chemistry studies based on porous capsules[7b] are performed in the presence of "additional" small cations being able to enter into the capsule cavity if the pores are—due to a release of some of the guests/corks—at least temporarily open, the scenario allows to refer not only to "sphere-surface supramolecular chemistry", but also to modeling passive cation transport by biological membranes with the option of channel/pore gating.

Results and Discussion

The reaction of an aqueous solution of compound **1**,[2k] containing the capsules **1a** that have 20 pores, with formamidinium cations results in the formation of **2a**, with all pores closed, and finally in the precipitation of crystalline **2**. Exposure of an aqueous solution of **2** to Ca^{2+} ions leads, under appropriate conditions, that is, only(!) at higher temperatures, to the formation of **3a**, in which Ca^{2+} ions are taken up and are integrated into the capsule cavity. The crystalline compounds **2** and **3** were characterized by elemental analyses, thermogravimetry (to determine the number of crystal water molecules), redox titration (to determine the number of Mo^V centers), spectroscopic methods (IR, Raman), and single-crystal X-ray structure analyses including bond valence sum (BVS) calculations.[8,9]

$(NH_4)_{72-n}[\{(H_2O)_{81-n}+(NH_4)_n\}\subset\{(Mo)Mo_5O_{21}(H_2O)_6\}_{12}\text{-}\{Mo_2O_4(SO_4)\}_{30}]\cdot\approx 200\ H_2O \equiv (NH_4)_{72-n}\cdot\mathbf{1a}\cdot\approx 200\ H_2O$ **(1)**[2k]

$(HC(NH_2)_2)_{42}(NH_4)_{10-n}[\{(HC(NH_2)_2)_{20}+(H_2O)_{81-n}+(NH_4)_n\}\subset\{(Mo)Mo_5O_{21}(H_2O)_6\}_{12}\{Mo_2O_4(SO_4)\}_{30}]\cdot\approx 120\,H_2O \equiv (HC(NH_2)_2)_{42}(NH_4)_{10-n}\cdot\mathbf{2a}\cdot\approx 120\,H_2O$ **(2)**[10,11a]

$(HC(NH_2)_2)_9(NH_4)_{19-n}Ca_6[\{(HC(NH_2)_2)_{20}+Ca_6+(H_2O)_{60-n}+(NH_4)_n\}\subset\{(Mo)Mo_5O_{21}(H_2O)_6\}_{12}\{Mo_2O_4(SO_4)\}_{30}]\cdot\approx 190\,H_2O \equiv (HC(NH_2)_2)_9(NH_4)_{19-n}Ca_6\cdot\mathbf{3a}\cdot\approx 190\,H_2O$ **(3)**[10]

According to a single-crystal X-ray structure analysis, the capsule **2a** shows the characteristic/basic spherical skeleton $\{(Mo)Mo_5\}_{12}(Mo_2)_{30}$,[2] while the 20 $\{Mo_9O_9\}$ pores are all closed by formamidinium cations acting as plugs (Figure 1). Furthermore, **2a** contains a $\{NH_4^+/H_2O\}$ assembly/aggregate within its cavity.[11a] The six calcium cations present in the

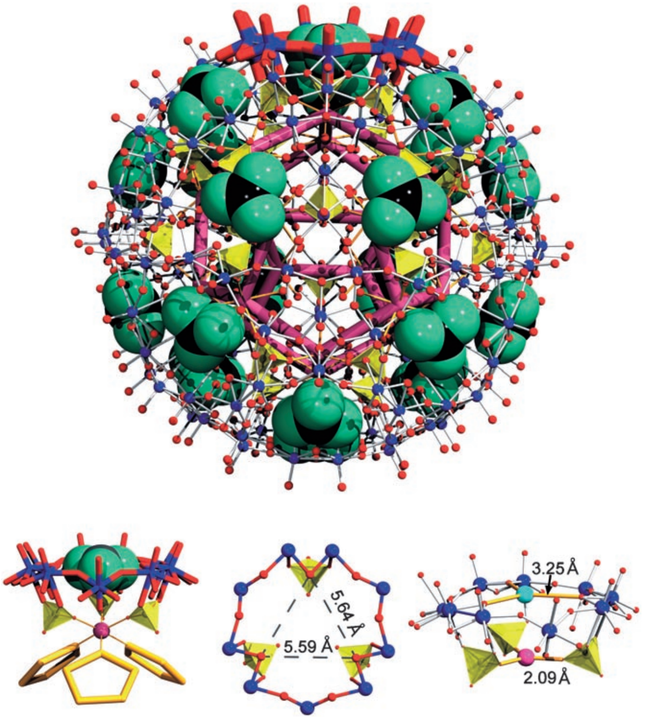

Figure 1. Top: Structure of the capsule **3a** with the molybdenum oxide skeleton in ball and stick representation (Mo blue, O red), sulfate ligands as yellow tetrahedra, formamidinium plugs in space filling representation (disordered in agreement with the C_3 axes passing through the pores; C black, N green), while (all possible) equivalent (underoccupied) sites for the encapsulated Ca^{2+} ions span the shown dodecahedron (magenta). One of the 20 host sites—a "$\{Mo_9O_9\}$ ring/pore"—is highlighted at the top of the figure in wireframe representation. Bottom left: The corresponding (extended) segment is shown with the coordination sphere/environment of one Ca^{2+} ion spanned by three O atoms of three sulfate ligands and three O atoms of three $(H_2O)_5$ pentagons of the encapsulated $\{H_2O\}_{60}\equiv\{(H_2O)_5\}_{12}$ water cluster (yellow). Bottom middle: Additionally shown is one of the $\{Mo_9O_9\}$ pores/rings with related distances together with three attached sulfate ligands, which limit to some extent the passage for entering cations (see below and reference [3c]). (We refer here approximately to a "tiny channel" formed by the $\{Mo_9O_9\}$ together with three sulfate ligands.) Bottom right: Shown are the distances (Å) which are, not considering the flexibility of the sulfate ligands, relevant for ion transport, that is, the distances between the channel-pore O atoms (red) and the center of the outside $\{Mo_9O_9\}$ pore (turquoise) on the one hand, and the center (lilac) of the related narrowest channel area—formed by three sulfate groups—on the other. The ligand flexibility reflects the important local interaction with entering cations, which formally leads to an adaption of the "channel"/ligands in response to the different cations; this allows cation passage through the channels, for example K^+, in spite of their size (i.e., from a geometrical point of view too large).[11b]

cavity of the corresponding capsule **3a** are found to be disordered over 20 equivalent positions forming a dodecahedron, while being located below the $\{Mo_9O_9\}$ pores, that is, on the C_3 axes at the end of the "channels" (Figure 1, bottom left). Each Ca^{2+} ion is octahedrally coordinated by three oxygen atoms of three sulfate ligands and three oxygen atoms belonging to the encapsulated $\{H_2O\}_{60} \equiv \{(H_2O)_5\}_{12}$ water shell/assembly (Figure 1, bottom left; for details about encapsulated water clusters see reference [4e]).

Our investigation shows that the 20 pores of the capsule **1a** can be easily completely closed by the cationic formamidinium guests, which leads to the formation of a spherical "multi-supramolecular species" **2a**.[6] Due to the approximately complementary shape/size, the present guests interact rather strongly with the $\{Mo_9O_9\}$ pores, that is, through hydrogen bonds between the pore O atoms and the H atoms of the two NH_2 groups (Figure 1; see also reference [4a]). (The guanidinium cations can react even more strongly by forming hydrogen bonds with the three NH_2 groups.[6]) A nice proof for the strong host–guest interaction is that the exposure of an *aqueous* solution of **2** to small cations, here to Ca^{2+} ions, leads to their uptake only upon heating, causing a release of at least some of the plugs. (The presence of Ca^{2+} within **3a** can easily be proven from IR spectroscopy by observing the shift of a specific sulfate band from 1032 cm^{-1} in **2** to 1053 cm^{-1} in **3**; for an explanation see reference [3a].) Clearly, "thermal activation" is required to shift the equilibrium depicted in Equation (1) towards the right, that is, to capsules having at least some open pores. To summarize, owing to the comparably high affinity of the formamidinium guests to the pores of **2a**, cations cannot enter into the cavity at room temperature as in that case the equilibrium in Equation (1) is shifted almost completely to the left[12] (see also Conclusions section).

Quite recently, Li^+ ion uptake/release processes have been investigated for the capsule **4a** by means of ^7Li NMR spectroscopy with DMSO as solvent.[3a,b] The total number of Li^+ ions in compound **4** corresponds to 28; some of these are integrated inside the capsule **4a** present in solution, while the number depends on the presence of other cations like formamidinium and on the water content in DMSO (for details see Figures 2–4 and 6 later).[3a,b] In this solvent, the velocity of the various exchange processes of Li^+ between the interior of the capsules and the bulk solution is slowed down to the extent that the different positions of the Li^+ ions,[3a] the timescale of exchanges, and the parameters influencing the exchanges can be studied successfully.[3,13] Now it will be shown that information about the strength of the host–guest interactions, that is, the affinity of formamidinium and acetamidinium cations to the 20 pores, can also be obtained from changes of the overall pattern of the ^7Li NMR spectra of solutions of **4a** under a variety of deliberately chosen conditions; this includes those in the presence of the formamidinium and acetamidinium cations/guests.

$[(CH_3)_2NH_2]_{44}Li_{28-n}[Li_n \subset \{(Mo)Mo_5O_{21}(H_2O)_6\}_{12}\{Mo_2O_4(SO_4)\}_{30}] \cdot \approx 250\,H_2O$ (**4**)[3a]

In a first experiment it could be shown that addition of increasing amounts of formamidinium hydrochloride to a solution of **4a** in DMSO evidently modulates the Li^+ ion equilibria earlier observed in the absence of the plugs[3a] (Figure 2). In the presence of an excess of formamidinium cations, these equilibria are essentially blocked. The corresponding spectrum is a very simple one (Figure 2 uppermost trace) with only two lines plus a very weak additional signal in between, the intensity of which depends on the water content in the sample and disappears in the absence of water (see below). The important result is that with increasing amounts of formamidinium cations—corresponding to an increasing number of closed pores—Li^+ exchange processes are increasingly (stepwise) suppressed and are finally blocked if the 20 pores are closed (see also text below).

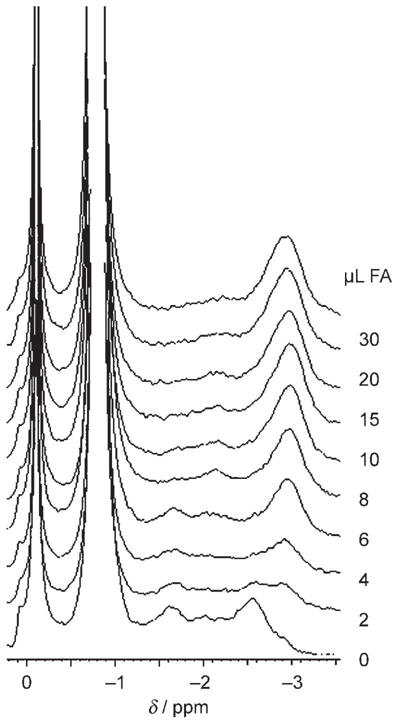

Figure 2. Stepwise pore closing leads to increasing suppression of the Li^+ exchange processes: ^7Li NMR spectra of a solution of **4** ($c(\mathbf{4a}) = 1$ mM in DMSO, $c(\text{pores}) = 20$ mM, $c(Li^+) = 28$ mM) measured after the addition of increasing amounts of formamidinium hydrochloride (FA) in DMSO solutions ranging from 2 µL to 30 µL equivalent to concentrations c(formamidinium hydrochloride) = 1.8 to 26.7 mM. The bottom trace corresponds to the "pure solution" of **4** ("standard spectrum" according to reference [3a]). The signal at ≈0 ppm represents an external standard, the signal at ≈−1 ppm is due to solvated Li cations. The uppermost spectrum was measured 24 h after the measurement of the spectrum marked with 30 µL. The ratio of Li^+ concentrations in solution and inside the capsule is about 5:1 obtained by the integration of the respective signals of the bottom trace while the total number of cations in **4** is 28 (see formula). Addition of formamidinium cations decreases the overall charge of **4a**, resulting in partial release of Li^+ as long as some pores are not yet blocked; that is, in the case that c(formamidinium) < 20 mM.

According to this result we can clearly argue that formamidinium cations act as appropriate plugs for the capsule

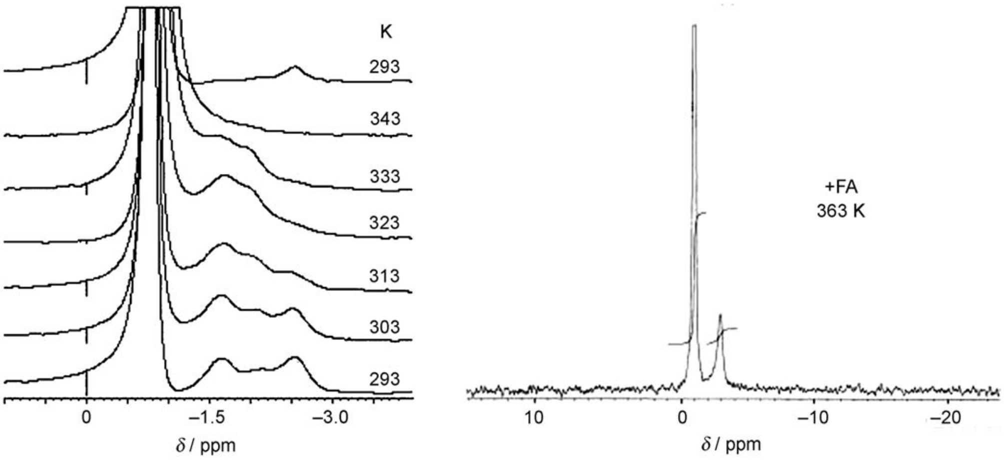

Figure 3. Left: ^{7}Li NMR spectra of the "pure solution" of **4** in DMSO ("standard spectrum" with the same Li^+ concentrations as given in Figure 2; see reference[3a]) upon heating, while fast exchange is observed at 343 K. The uppermost trace corresponds to the spectrum immediately obtained after cooling. Right: spectrum measured at 363 K of a solution of **4** ($c(\mathbf{4}) = 2.8$ mM, c(pores) = 56 mM, $c(Li^+) = 78$ mM) in DMSO after addition of formamidinium hydrochloride (FA) in excess (0.7 M). Here, no significant coalescence is observed up to that temperature. The ratio of Li^+ concentrations in solution and inside the capsule (ca. 10:1) corresponds to the shown integration of the peaks.

pores and can, if present in excess, prevent exchange processes between external solvated Li^+ and Li^+ in the cavity. For the closed capsule **4a** we find the largest yet observed upfield chemical shift of Li^+ in this capsule system, namely at −3 ppm (see also below), which appears to be the "real" chemical shift of completely fixed Li^+ ions coordinated to the sulfate ligands inside the (closed) capsule cavity.[3a] In other words, the signals that represent the various exchange equilibria earlier observed for solutions of the "pure Li^+ salt" **4** ("standard spectrum")[3] are shifted to lower field compared to that of fixed Li^+ ions. The signals, which correspond to equilibria between Li^+ positioned on different sites (mostly inside the open capsule), thus appear in the range in between the two extremes; that is, the signal for the solvated lithium cations on the one hand and that of the completely immobilized encapsulated Li^+ ions inside the capsule on the other (see Figure 2). A preliminary study (not shown here) supports this interpretation, as the upfield signal at −3 ppm for the internal Li^+ does not change after a lanthanide shift reagent has been added to the solution.

The most significant change of the mentioned Li^+ equilibria occurs on (stepwise) heating solutions of **4**, both in the presence and absence of formamidinium cations. Whereas, in a solution of **4** containing no formamidinium cations, several steps of coalescence are observed up to the final disappearance of all upfield peaks at 343 K (Figure 3, left), indicating a variety of fast exchange processes between Li^+ positioned on the different sites, the related spectra in presence of an excess of formamidinium ions, that is, corresponding to the pore closing scenario, do not change up to 363 K (Figure 3, right).

Detailed studies have shown that the processes investigated here strongly depend on the water content in the liquid reaction mixture. Water is normally introduced into the solvent as crystal water of **4** and by its presence in the solvent DMSO. (Note: A weathering process of crystalline **4** even at

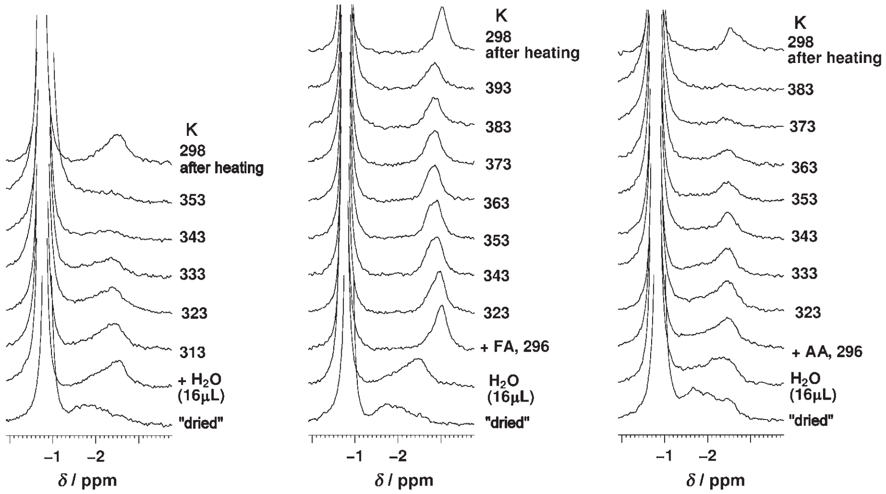

Figure 4. Temperature-dependent ^{7}Li NMR spectra. Left: spectra of a 1 mM solution of dried **4** in DMSO (see text) after addition of water (16 μL; c(water) = 1.3 M) at room temperature and upon heating ($c(\mathbf{4}) = 1$ mM, c(pores) = 20 mM, $c(Li^+) = 28$ mM). Fast exchange is observed at 353 K. The ratio of Li^+ concentrations in solution and inside the capsule (ca. 10:1) corresponds to the integration of the related peaks in the case of the second trace from the bottom. Middle: Same conditions, but after addition of formamidinium hydrochloride (FA, 23 mM) while no coalescence/fast exchange is observed up to 393 K. Right: Same conditions, but after addition of acetamidinium hydrochloride (AA, 20 mM) in DMSO resulting in fast exchange at 383 K.

room temperature leads slowly to partial removal of crystal water.) To ascertain reproducible conditions and especially to study the "water effect" systematically, **4** was dried over P_2O_5 and afterwards dissolved in DMSO which was constantly kept over 4 Å molecular sieves. To study the water influence on all types of equilibria, the spectra were measured under conditions in which well-defined amounts of water were added to the solution of dried **4** in DMSO (this still contains a defined small amount of water). In an appropriate experiment (for details see Figure 4, left), coalescence starts at around 323 K and is completed at 353 K, while for the case of an excess of formamidinium cations, the signals remain essentially constant up to 393 K (Figure 4, center). This is due to the fact that formamidinium cations plug the pores and therefore prevent exchange processes. An interesting related side-effect is that the spectrum obtained at rather high temperature proves that the stability of the spherical capsule is considerably increased upon pore closing.[13b] The reason is that the reactive oxygen functions of the $\{Mo_9O_9\}$ pores are protected against attack.

One can refer to a well-defined water concentration (see legend to Figure 4) for which not only the plug function of the formamidinium cations is optimal, but also the option to observe by NMR spectroscopy the related Li^+ exchange processes, as shown in Figure 4, left. Whereas at (much) lower water concentrations, there is evidently a lack of transport medium and the Li^+ exchange processes are reduced to a minimum or even do not take place at all, much higher concentrations of water cause faster exchange processes, and in particular do not allow complete locking of all the pores (important: water can pass through the pores in contrast to DMSO[3b]). In such cases, the coalescence/fast exchange temperature is lowered (not shown here) compared to the case discussed above (i.e. corresponding to Figure 4, center). Also, the "standard solution",[3a] that is, the solution of undried **4**, evidently contains too much water to allow complete locking of the pores, at least with formamidinium cations; this is indicated in Figure 2 at the two uppermost traces by the residual signal in the area between the flanking signals. As the residual signal disappears in the case of complete pore closing (cf. Figures 2 versus 4, center) it may serve as indicator for the completeness of the locking process.

To understand the conditions of the plugging process better, we also looked at the influence of acetamidinium cations on the Li^+ equilibria; that is, that of cationic guests which fit less well into the pores than formamidinium ions because of the related steric hindrance by the methyl group. Correspondingly, fast exchange is observed at a lower temperature than with formamidinium cations (see Figure 4, right).

The described results based on the action of formamidinium cations could be confirmed by a room-temperature EXSY-spectrum. The measurements were done with a solution of **4** in presence of an excess of formamidinium cations; the solution was first heated to 363 K and then cooled to room temperature. As the spectrum does not show any cross-peaks (Figure 5, bottom), that is, in contrast to that of the "pure standard solution" spectrum of **4** (Figure 5, top),[3b] it is evident that even at higher temperatures the pores are effectively closed, thus preventing an exchange of the Li^+ ions.

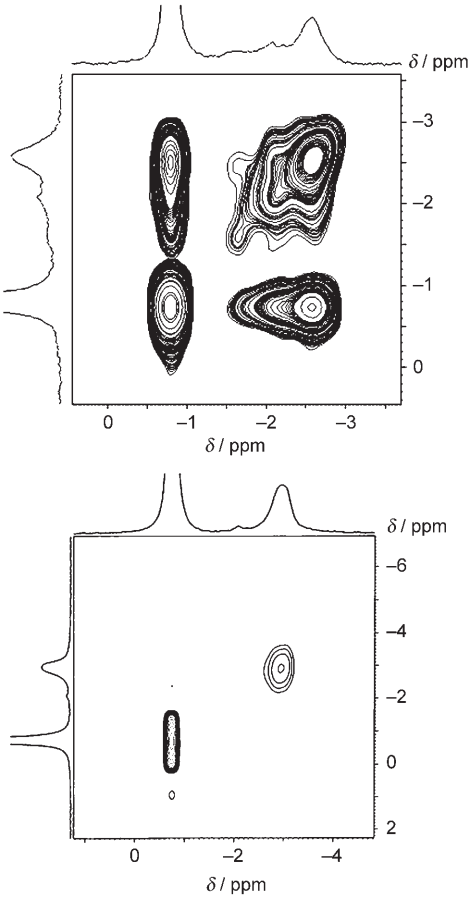

Figure 5. ^{7}Li-EXSY NMR spectra of solutions of **4** in DMSO, which after heating to 363 K were cooled back to room temperature. Top: Spectrum of the 1 mM "standard solution" of **4**; although the signals are not well resolved, the off-diagonal patterns indicate clearly that various slow-exchange type equilibria between Li^+ ions positioned at different sites exist. Bottom: The spectrum of a solution of **4** (2.8 mM) after addition of formamidinium hydrochloride in excess (0.7 M); within the detection limit, no off-diagonal peaks are observed (see text).

Referring to our earlier studies on counter transport processes,[3c] for example, regarding the option to exchange encapsulated Li^+ in **4a** against added Na^+ to the corresponding solution, it was expected that this process should be suppressed in the presence of formamidinium cations. This is indeed the case (Figure 6).

Conclusions

Here we refer to structurally well-defined, spherical, porous, anionic, molybdenum oxide based nanocapsules/artificial

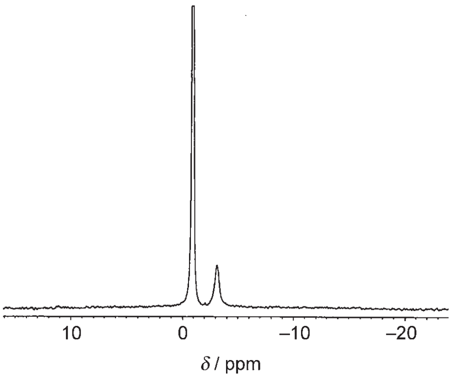

Figure 6. ^{7}Li NMR spectrum of a solution of **4** in DMSO ($c(\mathbf{4}) = 2.8$ mM, c(pores) = 56 mM, $c(\mathrm{Li}^+) = 78.4$ mM) measured according to the following conditions/steps: addition of formamidinium hydrochloride (0.7 M), heating up to 363 K, cooling down to room temperature, addition of a 5×10^2 mM solution of NaBr dissolved in DMSO (50 μL; final c(NaBr) = 35.7 mM). Result: No replacement of Li^+ by Na^+ is observed (the ratio of the Li^+ concentrations inside and outside the capsule is the same as in Figure 3 right).

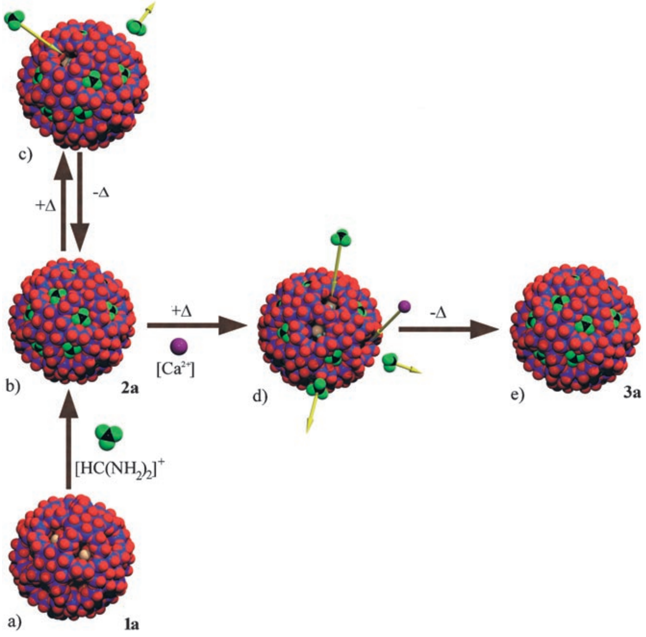

Figure 7. Sphere-surface supramoleular chemistry and modeling biological ion transport: Demonstration of exchange processes of small as well as larger cations (plugs/guests) present in aqueous solutions with those in the capsules' pores and/or their interior. This refers to **1a**, **2a**, and **3a**. The capsule **2a** is obtained when the formamidinium cations close the pores of **1a** (process a→b). As the temperature is raised (+Δ), the "organic plugs" of the (completely closed) capsule **2a** get partly released in aqueous solution (b⇄c), which leads to a situation in which pores remain open for a time interval sufficiently long to allow added "cations" like Ca^{2+} to pass through the pores into the cavity (b→d), while upon temperature decrease (−Δ) the pores again get completely closed by formamidinium cations (d→e). The basic process type a→b also occurs in DMSO proven by the present NMR studies, while processes of type b→c are not favoured in that solvent, even upon heating as for the case in water (color code: Mo blue, O red and light brown, C black, N green, H light turquoise and blue, Ca magenta; +Δ stands for increase of temperature, −Δ for its lowering).

cells of the type $\{\mathrm{Pentagon}\}_{12}\{\mathrm{Linker}\}_{30}{}^{n-}$,[2] which allow unprecedented nanochemistry and to follow new routes to different disciplines, like in materials science (e.g., construction of a nano-ion chromatograph,[4f] corresponding to the positioning/separation of cations on a nanoscale, like Ca^{2+} in the present case), physics (especially regarding studying encapsulated/confined matter,[4e] here evident regarding the encapsulated $\{\mathrm{H_2O/NH_4}\}$ assemblage), and discrete mathematics (concerning the tiling problem of spherical surfaces). Important in the context are the following facts: the size of the capsules and especially their pores/channels can be varied as well as opened and shut. Furthermore, the internal cavity's shell can be differently functionalised due to the presence of differently integrated ligands, which has an influence on the structure of the encapsulated complexes, especially that of encapsulated cations and water molecules as in the present case. Due to the presence of the twenty pores with crown ether function there is the option to perform multisphere-surface supramolecular chemistry, which is the "fundament" for the present studies. Based on the mentioned facts, one has the options for the following future studies:

- Performing sphere-surface supramolecular chemistry more systematically (see, for example, Figure 7) with the option to vary and even to tune the strength of the interaction between the pores and the cationic guests/plugs, that is, by changing the (negative) capsule charges. This is possible due to systematical and even step-by-step exchange of internal ligands with different charges (like acetate by sulfate), which allows to influence systematically the degree of pore-opening/closing events. For further studies, the choice of guests/plugs should not be restricted to those studied here. It would be very interesting to look at the protonated amino acid arginine with the guanidinium type function. In that sense the capsule can be considered as an arginine receptor.
- Modeling biological cation uptake/release processes for more complicated cases, for example, those with sets of different cations. Referring to the biological cation uptake, including counterion transport, we should realize that cells can be considered as busy areas exhibiting—through pores and transmitter channels—traffic in all directions, from the cell surface to the interior and back. With respect to this scenario we have a similar situation in the case of our artificial cells (Figures 1 and 7). Whereas we referred before to the $\mathrm{Li}^+/\mathrm{Na}^+$ counter transport in context with the option to model processes related to the treatment of bipolar disorders,[3c] this could be extended to studies of the competition between Li^+ and Mg^{2+}, an aspect which is considered in the title of a related paper as the "[…] underlying theme in the proposed mechanisms for the pharmacological action of lithium salts in bipolar disorder".[14] Important research could refer to situations in which the cations are not taken up

but are positioned "a little bit" below the pores like Cs^+ [4f] or at the capsule surfaces, which can occur due to their too large (intrinsic) sizes or as they are strongly fixed within a ligand environment, respectively. Important: this has an influence on the charge density on the capsule surface which influences the capsule's interaction with the environment. In this context we should refer to the fact that a condition for the biological cell activity is that specific pores/channels are opened, for example, due to a change in voltage across the membrane (voltage-gated channels),[5a,e] while voltage gating can be modeled by placing a larger number of cations on the capsule/artificial cell surface (see also reference [15]) as this decreases, according to a lowering of the negative charge, the pore affinity to the corks, and therefore promotes pore opening. Regarding gating we could also refer to the discussed temperature-dependent, reversible equilibria according to Equation (1). This includes situations in which upon heating the capsule pores, due to a release of the plugs, get opened for a time interval that is sufficiently long to allow smaller cations like Ca^{2+} to be taken up, and afterwards get closed again upon cooling (see for instance Figure 7). This scenario can be considered as a type of "temperature gating".

- General aspects: The present investigations could also be extended by studying systematically a variety of solvents, especially mixtures of the type organic solvent/water with increasing concentrations of water, which causes an increase of each type of cation mobility; for example, the release of the plugs/guests as well as the extent of uptake/release processes of the small cations. (Important: The capsules behave like semipermeable inorganic membranes allowing water to pass through but not the organic solvents like DMSO.[3b,18]) In this context one could also compare in more detail the processes occurring in pure water as solvent with those in organic solvents (NMR studies). In the present synthetic study we could show that the molecular guests present in the pores are released in water at temperatures at which this does not occur in an organic solvent. Another important aspect regarding options for future studies should also be mentioned: the "tiny ion channels"—formed by the $\{Mo_9O_9\}$ rings and the internal ligands—are flexible and adaptable with regard to the passage of different cations. This is related to the fact that remarkable local interactions between the not strongly coordinated (that is, flexible) ligands, like sulfate (Figure 1 bottom), and the entering cations take place,[16] showing that for the uptake process not only geometrical features have to be taken into account.[3c] Formally it can be compared with a recent result published by MacKinnon and co-workers,[17] who conclude that in the case of their investigated potassium ion channel a relevant aspect of ion selectivity is the channel's ability to adapt its structure differently to K^+ and Na^+ ions.

Experimental Section

Synthesis of 2: Formamidinium hydrochloride (1.2 g, 14.90 mmol) was added under stirring to a solution of **1**[2k] (1 g, 0.04 mmol) in water (120 mL). After the pH value of the solution was adjusted to ≈2 with 2 M H_2SO_4, the solution was kept at 50 °C for 30 min and then after cooling at room temperature was left to stand for crystallization. Brown crystals of **2** appeared after 24 h. The crystals were filtered off after 48 h, followed by washing with a small amount of cold water and then with ethanol. Yield: 0.54 g; elemental analysis calcd (%): C 2.53, N 6.38; found: C 2.4, N 5.9; IR KBr pellet, selected bands for the range 1750–945 cm^{-1}): $\tilde{\nu} = 1720$ (s, $\delta(\mathrm{C}\overset{\cdots}{-}\mathrm{N})$), 1625 (s, $\delta(H_2O)$), 1400 (w, $\delta(NH_2)$), 1197 (w), 1137 (m), 1032 (w) (all $\nu_{as}(SO_4)$), 974 (s), 942 cm^{-1} (w) (both $\nu(\mathrm{Mo{=}O})$).

Synthesis of 3: $CaCl_2 \cdot 2H_2O$ (0.5 g, 3.4 mmol) was added under stirring to a solution of **2** (0.5 g, 0.016 mmol) in water (35 mL). After keeping the solution at 60 °C for 1 h, NH_4Cl (0.5 g, 9.34 mmol) was added. The resulting solution was stored at room temperature in an open 100 mL beaker. Crystals of **3** were collected after three weeks; they were then washed with a small amount of cold water and ethanol. Yield: 0.15 g; elemental analysis calcd (%): C 1.18, N 3.66, Ca 1.63; found: C 1.1, N 3.5 , Ca 1.5; IR (KBr pellet, selected bands for the range 1750–945 cm^{-1}): $\tilde{\nu} = 1718$ (m, $\delta(\mathrm{C}\overset{\cdots}{-}\mathrm{N})$), 1620 (m, $\delta(H_2O)$), 1400 (m, $\delta_{as}(NH_4)$), 1184 (m), 1143 (m), 1053 (w–m, $\nu_{as}(SO_4)$), 970 (s), 945 cm^{-1} (w) (both $\nu(\mathrm{Mo{=}O})$).

^7Li NMR spectra were recorded on a Bruker Avance 400 (Figures 2, 3 right, 4, and 5) or a Varian Gemini 2000 (Figures 3 left, and 6) spectrometer at 155.51 MHz and 77.72 MHz, respectively, usually in non-rotating 5 mm diameter vials with the following parameter settings: ^7Li NMR: relaxation delay = 2 s, acquisition time = 3.5 s, pulse width = 30°; all data are reported relative to the internal reference list of the spectrometer, corresponding to LiCl in D_2O.[19]

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[6] The first published related example referred to the integration of 20 $[C(NH_2)_3]^+$ ions/guests into the 20 $\{Mo_9O_9\}$ pores/rings. The O···H–N hydrogen bonding is comparable to that between a classical crown ether host and the guanidinium cation; for details see reference [4a] and literature cited therein. The interaction of the formamidinium guests/plugs with the capsule containing formate ligands instead of sulfate ligands was studied, too; but until now the reproducibility of the obtained compounds caused problems: A. Müller, S. K. Das, E. Krickemeyer, R. Tomsa, unpublished results.

[7] a) "Supramolecular chemistry is by nature a dynamic chemistry in view of the lability of the interactions connecting the molecular components of a supramolecular entity. The reversibility of the associations allows a continuous change in constitution, which may be either internal, by rearrangement of the components with modification of the connectivity between them, or external, by exchange, incorporation, or extrusion of components, therefore conferring constitutional plasticity to the system. Thus, supramolecular chemistry is a constitutional dynamic chemistry."; see: J.-M. Lehn, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4763–4768; b) The spherical type of capsules have, apart from the mentioned specific interactions with their environment, other interesting properties; for ecample, they show under appropriate conditions a new type of self-association in aqueous solution leading to giant supramolecular species, the size of which depends on the pH value (T. Liu, B. Imber, E. Diemann, G. Liu, K. Cokleski, H. Li, Z. Chen, A. Müller, *J. Am. Chem. Soc.* **2006**, *128*, 15914–15920); the $\{Mo_{132}\}$ type species show selfassociation in mixtures of water and organic solvents (M. L. Kistler, A. Bhatt, G. Liu, D. Casa, T. Liu, *J. Am. Chem. Soc.* **2007**, *129*, 6453–6460).

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[9] Crystal data for **2**: $H_{896}C_{62}Mo_{132}N_{134}O_{765}S_{30}$, $M_r = 29391.01\ g\,mol^{-1}$, space group $R\bar{3}$, $a = 32.8327(13)$, $c = 74.376(4)$ Å, $V = 69434(5)$ Å^3, $Z = 3$, $\rho = 2.109\ g\,cm^{-3}$, $\mu = 1.904\ mm^{-1}$, $F(000) = 43050$, crystal size = $0.3 \times 0.2 \times 0.1$ mm. A total of 138032 reflections ($1.53 < \Theta < 26.99°$) were collected of which 33524 reflections were unique ($R(\text{int}) = 0.0893$). An empirical absorption correction using equivalent reflections was performed with the program SADABS 2.03. The structure was solved with the program SHELXS-97 and refined using SHELXL-97 to $R = 0.0596$ for 21335 reflections with $I > 2\sigma(I)$, $R = 0.1146$ for all reflections; max/min residual electron density 1.632/−1.709 e Å^{-3}. Crystal data for **3**: $H_{865}C_{29}Ca_{12}\ Mo_{132}\ N_{77}\ O_{814}\ S_{30}$, $M = 29429.82\ g\,mol^{-1}$, space group $R\bar{3}$, $a = 32.859(2)$, $c = 73.940(7)$ Å, $V = 69141(9)$ Å^3, $Z = 3$, $\rho = 2.12\ g/cm^3$, $\mu = 1.98\ mm^{-1}$, $F(000) = 43062$, crystal size = $0.4 \times 0.34 \times 0.3$ mm. A total of 132281 reflections ($1.49 < \Theta < 27.01°$) were collected of which 33383 reflections were unique ($R(\text{int}) = 0.0691$). An empirical absorption correction using equivalent reflections was performed with the program SADABS 2.03. The structure was solved with the program SHELXS-97 and refined using SHELXL-97 to $R = 0.0655$ for 24206 reflections with $I > 2\sigma(I)$, $R = 0.1019$ for all reflections; max/min residual electron density 2.121/−2.005 e Å^{-3}. Crystals of **2** and **3** 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 cm). (SHELXS/L, SADABS from G. M. Sheldrick, University of Göttingen **1997/2001**; structure graphics with DIAMOND 2.1 from K. Brandenburg, Crystal Impact GbR, 2001). CCDC-631298 (**2**) and CCDC-631299 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] The number of crystal water molecules mentioned in the formula is in agreement with that of the unit cell volume assuming all related positions are occupied. Analyses were done quickly after the isolation of the compounds because of the weathering process leading to a release of crystal water.

[11] a) The shell system of the encapsulate present in the cavity of **2a** and spanned by $n\mathrm{NH_4}^+/m\mathrm{H_2O} = \mathrm{X}$ centers ($m \gg n$) shows a strongly distorted rhombicosidodecahedron X_{60} (practically $\{H_2O\}_{60}$), an X_{20} dodecahedron and an X group in the center; the two-shell system is, for example, also found in the ammonium/sulfate-based capsules **1a** with open pores.[4c] b) Indications for flexibility are: K^+ ions enter into the capsule cavity, which is, according to their size, only possible if the ligand/sulfate flexibility within a dynamic process is taken into account. (However, Cs^+ ions which are much larger and also have a lower positive charge density leading to weaker ligand interactions do not pass through the channel.[4f]) A direct cation influence on the ligands/channels was - based on the results of an X-ray crystallographic study—found in case of the Li^+ scenario.[3a]

[12] If an aqueous solution of capsules that contains 20 protonated urea $H^+OC(NH_2)_2$ species in the pores instead of formamidinium cations, like in case of **2a**, is exposed at room temperature to Ca^{2+} ions, the Ca^{2+} ions penetrate the inorganic membrane of the artificial cell and get positioned below the pores.[4g] As the stability of the deprotonated (compared to the protonated) guest species is very high there is an easy release of neutral urea as this has practically no affinity to the pores. In order to isolate/precipitate the compound analogue to **3** containing integrated Ca^{2+} and with all pores closed, it was necessary to get rid of most of the solvent water as this leads to a reasonable concentration of protonated urea that can get integrated into the pores of the capsule thereby lowering the solubility of the resulting compound due to the decrease of negative capsule charge.[4g] (The high solubility of the sulfate-based capsules, which without counting the integrated cations have a formal negative charge of 72−, generally causes problems regarding precipitation.)

[13] a) The attempt to achieve a better resolution of the results by using ^6Li NMR was not successful. The expected decrease in line width is

negligible evidently due to the dominating broadening induced by slow exchange; b) the conditions for stability of the capsules—regarding solvent, pH, and temperature dependence—have been systematically studied by Raman spectroscopy (A. Müller, S. Roy, unpublished results).

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[16] This interaction leads for instance in case of **3a** to the formation of $[Ca^{2+}(\eta^1\text{-}SO_4)_3(H_2O)_3]$ groups below the 20 pores (Figure 1, bottom left); see also reference [3c].

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[18] In this context, osmosis on a molecular level can be tentatively studied. There is also the option to consider these types of spherical capsules like the polyelectrolyte species $\{Mo_{72}Fe_{30}\}$[7b] in the context of studying related Donnan equilibria. (The Donnan equilibrium determines the distributions of ions between two solutions, one of which contains a polyelectrolyte, in contact through semipermeable membrane: P. Atkins, J. de Paula, *Atkins' Physical Chemistry*, 7th ed., Oxford University Press, Oxford **2002**, p. 180.)

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