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Countercation Transport Modeled by Porous Spherical Molybdenum Oxide Based Nanocapsules

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Dedicated to Prof. Dr. Wolfgang A. Herrmann

Abstract: Porous nanosized polyoxomolybdate capsule anions of composition $[\{Mo^{VI}(Mo^{VI}_5O_{21})(H_2O)_6\}_{12}(linker)_{30}]^{n-}$, where $(linker)_{30}$ is $\{Mo^{V}_2O_4(SO_4)\}_{30}$ ($n=72$) (**1a**) or $\{Mo^{V}_2O_4(SO_4)\}_{24}\{Mo^{V}_2O_4(CH_3COO)\}_6$ ($n=64$) (**2a**), model the (competitive) cellular transmembrane transport of Li^+, Na^+, K^+, and Ca^{2+} ions along ion channels. According to X-ray crystallography and ^7Li and ^{23}Na NMR spectroscopy, Li^+ and Na^+, the counterions for **1a** and **2a**, respectively, occupy internal sites of the capsule. This study of the counterion transport phenomenon shows that, while Li^+ ions can be replaced to a large extent by Na^+ and K^+ ions and completely by Ca^{2+} ions added to a solution of **1a**, external Li^+ ions do not replace the incorporated Na^+ ions of **2a** in an analogous experiment. In this context, related properties of the capsules and especially of their flexible channels, in connection with the complex pathways of cation uptake, are discussed briefly. The relevance of these investigations for lithium-based therapies is also addressed.

Keywords: ion channels · ion transport · molybdenum · nanocapsules · NMR spectroscopy · polyoxometalates

Introduction

Controlled transport of ions across biological membranes is at the heart of a number of key cellular processes, such as the generation of action potentials in neurons.[1a,b] The corresponding impulses allow communication between cells, for example, instructing muscle cells to contract. We are interested in modeling this type of process by employing soluble anionic spherical metal-oxide-based capsules with well-defined pores/channels; that is, we are considering the transport of (biologically relevant) cations from bulk solution through pores and channels into the cavities of capsules that act as artificial cells.[1c] Herein, we address polyoxomolybdate capsules, which are stable in solution, especially in organic solvents under exclusion of air.[1d] Due to confined conditions, the process can only be treated approximately with the classical equations of physical chemistry that are valid for larger/macroscopic systems, and we refer to them in this sense.

Consider a membrane bilayer that provides a barrier that slows down the transfer of ions A into or out of the cell. The thermodynamic tendency to transport A through the bilayer channels is determined by a concentration gradient across the membrane, which results in a difference in molar Gibbs energies between the inside and the outside of the cell [Eq. (1)]. This equation implies that transport of either neutral or charged species into the cell is thermodynamically favored if $[A]_{in}<[A]_{out}$. As A is an ion, there is a second component of ΔG_m that arises from differences in Coulomb repulsions on either side of the membrane and results in a membrane potential difference $\Delta\phi=\phi_{in}-\phi_{out}$. The final expression for ΔG is then given by [Eq. (2)], in which z is the charge of the ion and F is the Faraday constant.[2] [Eq. (2)] implies that there is a tendency for a species to move down concentration and membrane-potential gradients (i.e. electrochemical gradients) under the above conditions, a process which is called passive ion transport. In our situation, the

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chemical potential inside the capsule is strongly influenced by receptors for the cations, that is, sulfates in the present case.

$$\Delta G_m = G_{m,in} - G_{m,out} = RT\ln([A]_{in}/[A]_{out}) \quad (1)$$

$$\Delta G_m = RT\ln([A]_{in}/[A]_{out}) + zF\Delta\Phi \quad (2)$$

The artificial cells employed herein are represented by the anionic capsules of $[Me_2NH_2]_{44}Li_{28-n}$ $[Li_n\subset\{Mo^{VI}(Mo^{VI}{}_5O_{21})(H_2O)_6\}_{12}\{Mo^{V}{}_2O_4(SO_4)\}_{30}]\cdot\approx 250\,H_2O$ (**1**)[3a] and $[Me_2NH_2]_{52}Na_8[Na_6\subset\{Mo^{VI}(Mo^{VI}{}_5O_{21})(H_2O)_6\}_{12}\{Mo^{V}{}_2O_4(SO_4)\}_{24}\{Mo^{V}{}_2O_4(CH_3COO)\}_6]\cdot\approx 250\,H_2O$ (**2**).[4] The anions **1a** and **2a**, respectively, consist of 12 pentagonal building blocks $\{Mo^{VI}(Mo^{VI}{}_5O_{21})\}$ linked by 30 dinuclear $\{Mo^{V}{}_2O_4\}$ type linkers (Figure 1a). The capsule anions contain 20 pores/channels, which consist of crown ether like Mo_9O_9 rings with sulfates at the base (Figure 1a–c). The 28 Li^+ ions in **1** are associated with the bulk, the pores/channels, and the cavity of the capsules.[3,5] In the case of **2a**, six of the 14 Na^+ ions are, according to an X-ray crystallographic study, located inside the capsule.[4] Each of these six Na^+ ions is coordinated to three sulfate groups inside the cavity in the form of $[Na^+(\eta^1\text{-}SO_4)_3(H_2O)_3]$ units positioned on the C_3 axis (Figure 1a,b).[4] We used dimethyl sulfoxide (DMSO) as a solvent in order to approach the dielectric conditions pertinent to cellular fluids.

Figure 1d illustrates the size of the outer-surface Mo_9O_9 pore and of the narrowest channel aperture, which restricts the transport of cations to those that are sufficiently small and that contain a sufficiently labile solvent shell, where probably one of the H_2O molecules is not stripped off. The average distance between the center of the narrowest inside channel and the channel O atoms is 2.1 Å. Taking into account the van der Waals radius of the O atom (1.50 Å), the approximate radius of the inner aperture amounts to ≈0.6 Å. The cations investigated in this study (and their ionic radii in Å) are Li^+ (0.78), Na^+ (0.98), K^+ (1.33), and Ca^{2+} (1.06). (The radii indicated were calculated from the effective (close-packing) ion volumes.[6]) Thus, to allow passage of the larger cations such as Na^+ and especially K^+ through the channel, flexibility of the sulfate groups within a dynamic process has to be taken into account. These processes are initiated and powered by effective interaction of cations with the sulfate groups (see below). This finally leads to the formation of the rather stable segments $[Na^+(\eta^1\text{-}SO_4)_3(H_2O)_3]$. Na^+, K^+, and Ca^{2+} ions are, of course, physiologically important cations. Li^+ ions are of interest as they are used in lithium-based therapy of manic depression and other brain disorders,[7] as well as lithium–sodium counterion transport in the treatment of hypertension.[8] The

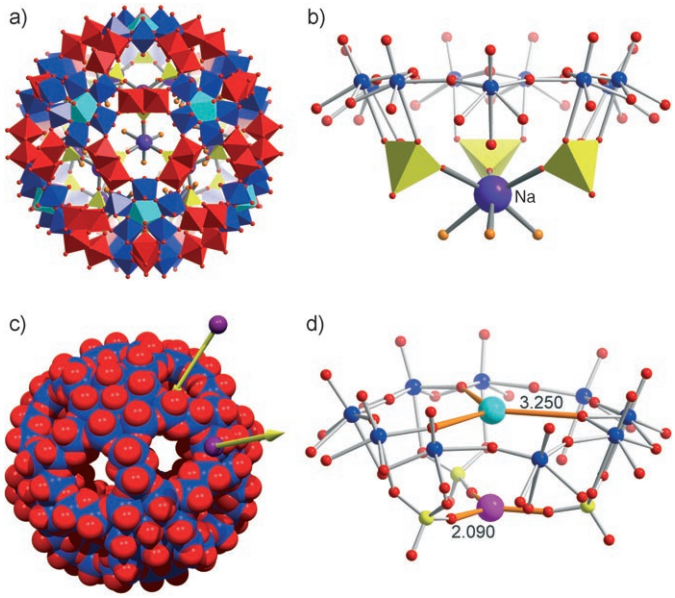

Figure 1. a) Structure of **2a** in polyhedral representation viewed along a C_3 symmetry axis (without the acetate-type linkers, which are not involved in the exchange process). The cluster surface is highlighted nicely, showing four of the 20 nanoscale pores and emphasizing the central one. Only one of the encapsulated Na^+ ions (violet), coordinated to three sulfate groups (S yellow, O red) and water oxygen atoms (orange) is shown.[4] b) Lateral view of the coordination of a Na^+ ion positioned on the C_3 axis to three sulfate groups at the inner interface (S yellow, O red (sulfate) and orange (water), Mo blue). c) Schematic space-filling representation of the uptake and release of cations (counterion transport) through the 20 pores of a highly charged anionic capsule (Mo blue, O red). d) The distances (Å) relevant to ion transport, that is, those between the channel-pore O atoms (red) and the center of the outside Mo_9O_9 pore on the one hand, and the center of the related narrowest channel area inside the channels (formed by three sulfate groups) on the other, are shown. The centers of the outside and inside apertures of the channel are in turquoise and lilac, respectively. In the case of **1a**, the Li^+ ions, which could only be localized indirectly by X-ray crystallography,[3a] are each coordinated to only one sulfate ligand.

Abstract in German:
Poröse, nano-skalige, anionische Polyoxomolybdat-Kapseln der Zusammensetzung $[\{Mo^{VI}(Mo^{VI}{}_5O_{21})(H_2O)_6\}_{12}(linker)_{30}]^{n-}$ – $(linker)_{30}$ entspricht $\{Mo^{V}{}_2O_4(SO_4)\}_{30}$ ($n=72$), **1a**, oder $\{Mo^{V}{}_2O_4(SO_4)\}_{24}\{Mo^{V}{}_2O_4(CH_3COO)\}_6$ ($n=64$), **2a** – modellieren den (kompetitiven) zellulären Transmembran-Transport von Li^+, Na^+, K^+ und Ca^{2+} über Ionenkanäle. Gemäß Röntgenstrukturanalyse und ^{7}Li- sowie ^{23}Na-NMR-spektroskopischen Untersuchungen besetzen die Gegenionen von **1a** und **2a**, Li^+ und Na^+, interne Positionen der Kapsel. Die hier vorliegende Studie zum Phänomen des Counter-Transportes der Ionen zeigt, dass bei externer Zugabe von Na^+ und K^+ zu Lösungen von **1a** das Li^+ weitgehend, bei Zugabe von Ca^{2+} vollständig ausgetauscht wird. Andererseits zeigt das komplementäre Experiment – die externe Zufuhr von Li^+ zu Lösungen von **2a** – dass inkorporiertes Na^+ nicht verdrängt wird. Eigenschaften der Kapseln (und insbesondere ihrer Kanäle) werden im Kontext des komplexen Mechanismus' der Aufnahme von Kationen kurz diskutiert. Die Relevanz dieser Untersuchungen für Therapien, die auf Lithium basieren, wird gleichfalls angesprochen.

function of lithium may be traced back to the interaction of Li^+ ions with the intracellular K^+/Na^+ balance, hence the neural response.

When considering counterion transport (as well as symport), one factor to be considered is the ion mobility u, which depends on the viscosity η of the (liquid) solvent and the hydrodynamic radius of the ion. The mobility is larger for larger cations (7.62 for K^+, 5.89 for Na^+, in the usual units).[2a] Several processes for the cation uptake/interaction may be relevant:[9] outer- or inner-sphere association between the cations and the outer interface of the capsule with Mo=O groups; fixation of the ion by the channels/pores; capture by functionalities (sulfate) at the cavity interior; complexation at the inner interface by Mo=O groups; and integration into the internal water shell structures as in case of $[NH_4]^+$ ions.[4,9]

The present study is an extension and sophistication of our previous investigations of the transport of Li^+ ions[3,5] as well as the counterion transport reported in reference [3c]. Based on ^7Li and ^{23}Na NMR spectroscopy,[10] we address herein the competing situations encountered when lithium, sodium, potassium, or calcium cations[11] are added to solutions of the porous polyoxomolybdate capsules **1a** and **2a**.

Results and Discussion

The ^7Li NMR spectrum of **1** in DMSO (concentration of **1** = 1 mM, $[Li^+]$ = 28 mM, $[H_2O] \approx 0.3$ M; H_2O is intrinsically present in commercially available $[D_6]$DMSO and as water of crystallisation associated with **1**) shows a strong and narrow signal for solvated Li^+ ions at −0.8 ppm, which consist mainly of $[Li(dmso)_x]^+$ that accounts for about 80% (from this follows that n = 5–6 for **1**) of the overall intensity. There are also three broad (linewidths $W_{1/2}$ = 50–100 Hz) but distinct signals at −1.6, −2.2, and −2.6 ppm. These signals, indexed by a concentration- and solvent-dependent study,[5] correspond to lithium sites associated with the pores/channels and the interior of the capsule, with the most-internal site(s) tentatively assigned to the −1.6 ppm feature.[3,5] This situation is represented by the bottom trace in the series of ^7Li NMR spectra shown in Figure 2a. The broadening of the signals for capsule-associated Li^+ compared to that of $[Li(dmso)_x]^+$ is primarily a consequence of a lowering of the local symmetry at the quadrupolar ^7Li nucleus, thus giving rise to more efficient quadrupolar relaxation than in the case of, say, cubic symmetry.

The introduction of sodium bromide to solutions of **1** in increasing concentrations (10→30 mM) results in a gradual decrease in the integral intensities of the high-field signals and rearrangement of the overall pattern (Figure 2a, left). This clearly indicates that Li^+ ions "leave" the sites where they are associated with the cluster anion. The remaining signal (at −2.0 ppm; uppermost trace in Figure 2a, left), recorded after the introduction of Na^+ ions in amounts roughly equimolar to the overall $[Li^+]$, corresponds to only ≈3% (n = 1 in **1**) of the total amount of Li^+ ions present. No further change occurs as more Na^+ ions are added; that is, this residual Li^+ site is stable to exchange. There are two plausible explanations for the extrusion of the lithium ions: 1) sodium ions interact with the capsule superficially, that is, by forming outer-sphere complexes $Na^+{-}OH_2{\cdots}O{=}Mo$ and/or $Na^+{-}O{=}Mo$ or coordinating to the Mo_9O_9 pore, thus reducing ΔG_m [Eq. (2)]; 2) sodium ions enter the capsule, explicitly displacing lithium ions. In view of the adequate size of the Na^+ ions (considering some flexibility of the sulfate sites mentioned above) and the fact that Na^+ ions were shown by single-crystal XRD analysis to coordinate strongly to three sulfate ligands below the channel, that is, exposed to the cavity of the capsule (Figure 1b),[4,9,12] the latter explanation is the correct one. In fact, the uptake of Na^+ ions by the capsule is also proven by ^{23}Na NMR spectroscopy. As NaBr is added to a solution of **1** in DMSO, two ^{23}Na resonances are observed (Figure 2a, right), which corresponds to $[Na(dmso)_y]^+$ (−0.6 ppm, $W_{1/2}$ = 250 Hz) and $Na^+{\subset}$capsule (−13 ppm, $W_{1/2}$ = 850 Hz), with an intensity ratio of 2:1. The broad high-field signal corresponds to internalized Na^+ ions in the local C_{3v} environment of $[Na^+(\eta^1\text{-}SO_4)_3(H_2O)_3]$, as found by X-ray crystallography.[4,9] This is nicely illustrated by a comparison between the ^{23}Na NMR spectrum for the sodium cluster anion **2a** and that of the solution of the lithium cluster anion **1a** treated with NaBr (Figure 3).

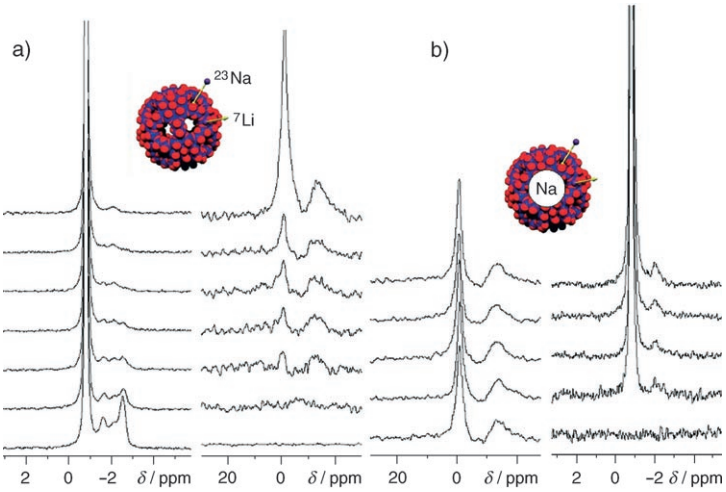

Figure 2. a) ^7Li (left) and ^{23}Na (right) NMR spectra of a solution of **1** in DMSO ($[Li^+]$ = 28 mM) treated with increasing amounts of NaBr; $[Na^+]$ (from bottom to top) = 0, 10, 13, 17, 20, 23, 30 mM. b) ^{23}Na (left) and ^7Li (right) NMR spectra of a solution of **2** in DMSO ($[Na^+]$ = 14 mM) treated with increasing amounts of LiBr; $[Li^+]$ (from bottom to top) = 0, 10, 17, 23, 30 mM.

The situation analogous to the system **1**+NaBr, that is, introduction of LiBr to a solution of **2**, is represented by the ^{23}Na and ^7Li NMR spectra in Figure 2b. While the ^{23}Na NMR spectrum remains unchanged as increasing amounts of LiBr are added (10→30 mM, that is, up to twice the concentration of Na^+), the signal at δ = −2.0 ppm of the ^7Li spectrum grows, which implies that the internal lithium site is occupied step by step. (As not all Na^+ sites are occupied, some channels are open, that is, ready for uptake.) Im-

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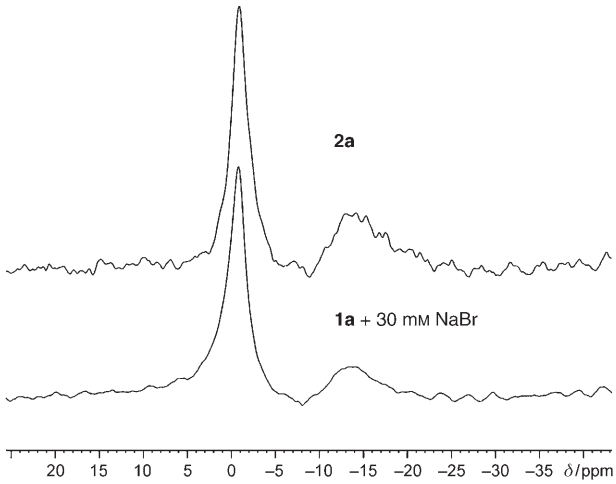

Figure 3. ^{23}Na NMR spectra of **1a** (concentration of **1a** = 1 mM) + 30 mM NaBr and **2a** (concentration of **2a** = 1 mM, $[Na^+]$ = 14 mM). The solvent is DMSO. The comparatively sharp low-field signal corresponds to solvated sodium ions ($[Na(dmso)_y]^+$), whereas the broad high-field signal corresponds to internal sodium ions ($Na^+\subset$capsule).

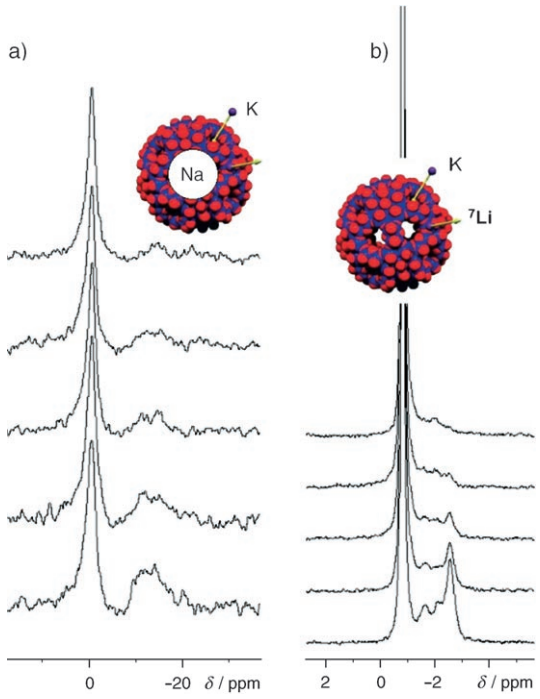

Figure 4. a) ^{23}Na NMR spectra of a solution of **2** in DMSO ($[Na^+]$ = 14 mM) treated with different amounts of KBr; $[K^+]$ (from bottom to top) = 0, 10, 17, 23, 30 mM. b) ^{7}Li NMR spectra of a solution of **1** in DMSO ($[Li^+]$ = 28 mM) treated with KBr; $[K^+]$ (from bottom to top) = 0, 10, 17, 23, 30 mM.

portantly, no extrusion of Na^+ ions was observed within the limits of error. Both complementary series of experiments thus show that the affinity of Na^+ ions to internal cluster sites is much more pronounced than that of Li^+, although several Li^+ ions still interact along with Na^+ within the same capsule. This can be reasoned as follows: whereas each Na^+ ion is positioned on the C_3 axis and coordinated to three sulfate ligands,[4,9] the small Li^+ ion can only coordinate to one ligand[3a] and is therefore less strongly bound.

In contrast, introduction of KBr to solutions of **2** leads to (only) partial Na^+ ion leaching (Figure 4), thus reflecting the similar polarizing abilities and binding qualities of sodium and potassium ions.[9] This is in agreement with comparable affinities for the same positions on the C_3 axis defined by the oxygen atoms on the three sulfate ligands. As in the case of NaBr, introduction of KBr to **1** results in effective extrusion of Li^+ ions (Figure 4), again with a stabilization for residual $Li^+\subset$capsule characterized by the weak signal at $\delta = -2.0$ ppm. Interestingly, as is again demonstrated by single-crystal XRD analysis, K^+ ions enter the capsule and coordinate in the same way as Na^+ ions.[13] The displacement of Li^+ by K^+ ions is thus due to direct competition for internal cluster sites. The situation changes when rubidium ions are employed, as the radius of Rb^+ (1.49 Å) dramatically exceeds that of the channel aperture. Furthermore, even when the flexibility of the sulfates is taken into consideration, Rb^+ ions do not "react" with them as strongly as, for example, Na^+ and Ca^{2+} ions (see below) because of their smaller charge density. However, Rb^+ ions can interact with the capsule by complexation, for example, with the external surface; they are not found in the cavity, that is, below the channels.[14] The extrusion of Li^+ ions on the introduction of RbBr to a solution of **1** in DMSO (not shown) should thus be due to the decrease in the difference in Gibbs free energy ΔG_m caused by the second part of [Eq. (2)].[13]

According to an X-ray crystallographic study, as the ionic radius of Ca^{2+} is comparable to that of Na^+, both are found at approximately the same sites, that is, below the channels of the C_3 axis (Figure 1a and b).[4,9,15] As demonstrated in Figure 5, the lithium ions are completely removed from the capsule when equimolar amounts of $CaBr_2$ (relative to the overall concentration of Li^+) are added stepwise to solutions of **1**, thus suggesting that besides the effects discussed for Na^+ ions, the high charge density increases the affinity

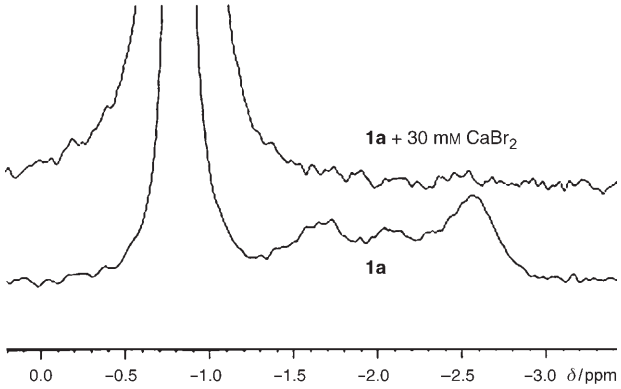

Figure 5. ^{7}Li NMR spectra of **1** dissolved in DMSO ($[Li^+]$ = 28 mM), and after introduction of $CaBr_2$ (30 mM).

of each Ca^{2+} ion to the three sulfate groups below the pores. Alternatively, depletion of internal Li^+ sites was achieved with cryptand C211.[5]

Conclusion

Many basic functions of cellular processes, including neural responses, are closely related to the proper functioning of the transport of essential cations (Na^+, K^+, Ca^{2+}) across the cell membrane. Thus, the maintenance of the correct osmotic conditions and chemical- as well as electric-potential gradients across the cell membrane is of central importance. Ca^{2+} ions, in particular, are an indispensable second messenger. Any disturbance of these parameters can lead to malfunction and even severe pathogenic dysfunction. Channels, which are usually voltage-, chemically (ligand), or mechanically gated, are responsible for passive ion transport. An exception exists for K^+ ions, for which open (leaky) channels also exist.[16] Certain dysfunctions, such as hypertension[8,17] and manic depression,[7] have been treated with lithium therapy. A possible explanation of the action of Li^+ ions is their competitive interactions with Na^+ and K^+ ions,[18] which we have investigated here.

Our spherical polyoxomolybdates,[1c] that is, porous nanocapsules that contain a cavity (filled with well-structured water clusters together with cations, reminiscent of the situation encountered within cells) and channels connecting the cavity to an external medium, are well-suited to model cation transport, especially under the exclusion of oxygen; generally speaking, this means that it is possible to model exchange processes between external (extracellular) media and interior (intracellular) sites, in particular, the competitive behavior with respect to mobility/affinity of ions that exhibit different sizes and charge densities. We can thus consider our porous capsules as artificial cells. In the present study, we have (directly or indirectly) shown, based on ^7Li and ^{23}Na NMR spectroscopic studies, that the cations Li^+, Na^+, Ca^{2+}, and K^+, with ionic radii (for the naked ion) of 0.78–1.33 Å, all can enter the cavity of the artificial cells through the narrowest part of the funnel-shaped channels (shown explicitly in Figure 1 d). The most fascinating aspect is that the larger cations can only pass through that narrow area if they react/interact strongly with the sulfate groups and water molecules, thus resulting in the formation of the fragments $[M^{n+}(\eta^1\text{-}SO_4)_3(H_2O)_3]$ accompanied by a change in the orientation of the sulfates. For the Li^+ cluster **1a**, Na^+ and K^+ ions can replace most (but not all) of the internal Li^+ ions, whereas Li^+ ions, when added to a solution of the Na^+ cluster **2a**, do not replace the Na^+ ions, but still interact to some extent with the cluster, and are accommodated with it along with the Na^+ ions. The final and starting situations are independent of one another. The Ca^{2+} ion, the charge density of which differs significantly from that of all of the other cations investigated, fully removes Li^+ ions from the relevant cluster sites. As large rubidium ions do not enter the cavity but are found, for example, below the Mo_9O_9 rings, they act by decreasing the electric-field gradient across the cluster "membrane". More detailed investigations into this exciting phenomenon and the complex transport mechanism are in progress.[13]

Experimental Section

The two polyoxomolybdates employed in this investigation, **1**[3a] and **2**,[4] were prepared according to procedures in the literature. NaBr, KBr, LiBr, and $CaBr_2$, all of purissimum grade, were obtained from Sigma–Aldrich and kept under dry conditions. $[D_6]$DMSO (99.8% deuterated, Deutero GmbH), was used as the solvent throughout without drying.

NMR spectra were recorded with a Bruker Avance 400 spectrometer at 155.51 MHz (^7Li) and 105.84 MHz (^{23}Na), usually in nonrotating 5-mm diameter vials with the following settings: ^7Li NMR: relaxation delay = 2 s, acquisition time = 3.5 s, pulse width = 30°; ^{23}Na NMR: relaxation delay = 0.1 s, acquisition time = 1.3 s, pulse width = 90°. All data are reported relative to the internal reference list of the spectrometer.[19]

Acknowledgements

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[9] A. Müller, H. Bögge, M. Henry, *C. R. Chim.* **2005**, *8*, 47–56. Although all final cation positions subsequent to their uptake were correctly described here, it became evident that cations such as Na^+ (but even more so K^+, in contrast to Li^+) can only pass through the channels in the presence of flexible SO_4^{2-} ligands. An appropriate procedure is to look at experimentally found distances (rather than van der Waals radii), that is, from the center of the narrowest area in the channel to the channel O atoms ($\approx$2.1 Å; Figure 1d) as well as from the cation positions to the sulfate O atoms in the final structure (Figure 1a) with encapsulated cations such as Na^+ (Na–O $\approx$2.3 Å).[4] This clearly indicates that the narrowest channel area is too small for the passage without allowing flexibility of the SO_4^{2-} ligands.
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