These results indicate the severe limitation of the atypically small total pressure interval of ca. 5 MPa used in this study versus pressure intervals of ca. 100 MPa used in traditional reaction volume studies.[30]

The intrinsic reaction kinetics were too rapid to be captured with the present experimental setup. Indeed, characteristic times for gas–liquid mass transfer as well as liquid-phase mixing were on the order of a few minutes. Therefore, transport-controlled rather than intrinsic kinetics were observed.

Nevertheless, an informed assumption about the mechanism(s) can be proposed. After each perturbation, hydrogen activation on [$Rh_2(CO)_8$] (or equilibrated and unsaturated [$Rh_2(CO)_7$]) probably occurs very rapidly. After depletion of the dinuclear carbonyl species, the fragmentation of [$Rh_4(CO)_{12}$] (or possibly the equilibrated, open polyhedron structure [$Rh_4(CO)_{14}$])[31] is likely to be the rate-limiting step. Hence, the kinetics can be anticipated to involved contributions from a number of parallel pathways.

Finally, the BTEM analysis of data from previous and ongoing hydroformylation studies was performed. In these catalytic studies involving [$Rh_4(CO)_{14}$] as catalyst precursor in *n*-hexane with less reactive alkene substrates (i.e., cyclooctene and α-methylstyrene) it was possible to recover again the pure-component spectrum of [$HRh(CO)_4$]. The assignment of the fundamental vibrations at 2002.8 (w), 2041.6 (vs), 2071.8 (m) and 2123.6 (w) cm^{-1} is entirely reproducible. In some of these reconstructions, the rhodium–hydrogen vibration at 2002.8 cm^{-1} is better resolved or more pronounced.

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Spontaneous Deposition of Water-Soluble Substances into Microcapsules: Phenomenon, Mechanism, and Application**

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Novel hollow microcapsules with sizes ranging from 60 nm to 10 μm have recently been produced by the layer-by-layer (LBL) assembly of oppositely charged polyelectrolytes onto colloidal templates, followed by removal of the template cores.[1] Great progress has been made towards optimizing the fabrication conditions for capsules templated onto melamine formaldehyde (MF) particles, with an integrity of 90 % having

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been achieved.[2] The physicochemical properties of the capsule wall can be customized by introducing functional components such as nanoparticles, biomacromolecules, lipids, photosensitive dyes, inorganic crystals, and multivalent ions. Polyelectrolyte capsules with versatile properties have been fabricated and characterized with respect to their surface morphology, film thickness, elasticity, stability, pH sensitivity, capacitance, conductance and photosensitivity.[3]

Many efforts have been devoted to altering the properties of the interior of the capsule, in particular through the nanoscale encapsulation of polymers, drugs, minerals, dyes, proteins, enzymes, and genes. By modifying the solubility of a compound by solvent or pH variation, the hollow polyelectrolyte capsules have been filled with lipid micelles, and low-molecular-weight dyes such as 6-carboxyfluorescein (6-CF) and rhodamine 6G (Rd6G).[4] Macromolecules, such as poly(styrene sulfonate) (PSS), have also been incorporated into the capsules either by the extraction of multivalent ions, which constitute the inner layers of the capsule, with oppositely charged polymers that are then released into the capsule interior, or by in situ polymerization of monomers inside the capsules by a "ship-in-bottle" synthesis.[5] By changing the permeability of the capsule wall at different pH values, biomacromolecules such as dextran can be temporarily loaded inside the capsules.[6]

However, precipitation or polymerization inevitably occurs both in the capsule interior and in the bulk simultaneously, leading to difficulties with purification and low encapsulation efficiency. Since the loading amount is limited by the bulk concentration, a large degree of encapsulation, especially for water-soluble substances, is impossible. The harsh conditions may also destroy the microstructure and the integrity of the capsules. On loading PSS into the capsules, a size increase resulting from the osmotic pressure has been observed,[7] whilst a temperature increase may cause either capsule shrinkage or swelling depending on the composition of the capsule.[8]

Herein we describe a novel encapsulation method based on a recently discovered property of the capsules: the spontaneous deposition of water-soluble substances under ordinary conditions (room temperature, pH 7.0, in pure water). The self-accumulation of water-soluble substances such as rhodamine, poly(allylamine hydrochloride) (PAH), and dextran leads to a higher concentration of such species in the interior of the capsule, rather than in the bulk; the encapsulation proceeds easily. Clarification that the mechanism was distinct from those methods described above was achieved when water-soluble biomolecules, such as albumin and peroxidase, were successfully deposited into the interior of the capsule. Under the optimal fabrication conditions for capsules templated on MF particles, $(PSS/PAH)_5$ capsules (negatively charged PSS is the first layer and positively charged PAH is the last layer, with five double layers in total) were successfully produced with higher than 90% integrity (Figure 1 a), and negatively charged 6-CF was used to label the capsules. After being aged at room temperature for one month, however, more intense fluorescence was observed from the capsule interior rather than from the bulk (Figure 1 b) when a suspension of the capsules was mixed with a solution of Rd6G under normal conditions. This phenomenon is spontaneous and has a lifetime of seconds, depending on aging and molecular weight. The ball-like morphology of the capsules when observed out of solution (Figure 1 b, inset) further confirmed the self-accumulation of rhodamine. This compares with the control experiment (Figure 1 a, inset) where the typical folds and creases for normal capsules can be discerned.

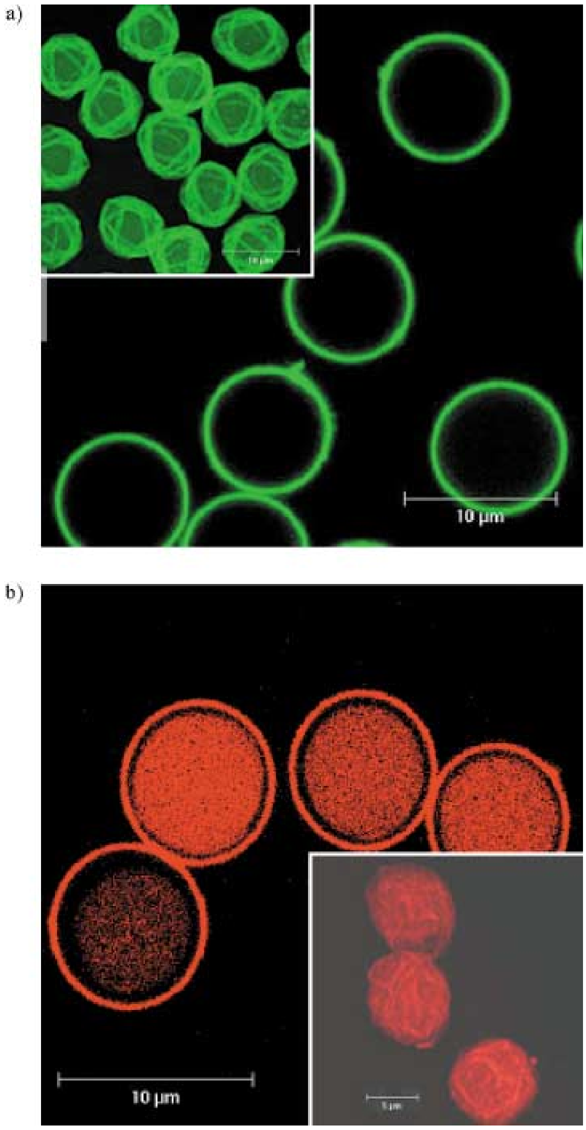

Figure 1. Confocal laser scanning microscopy (CLSM) images of control polyelectrolyte capsules composed of $(PSS/PAH)_5$ with a diameter of 8.7 µm both in (a) and out of solution (inset). After the capsules were incubated in Rd6G ($2\,mg\,mL^{-1}$) solution, spontaneous deposition occurred (b). The out-of-solution morphology revealed further that the capsules were filled with rhodamine (b, inset).

Figure 2 shows that tetramethylrhodamine isothiocyanate-labeled PAH (TRITC-PAH) and TRITC-dextran could also self-deposit into the interior of capsules composed of either $(PSS/PAH)_5$ or $(PSS/PDADMAC)_5$ (PDADMAC = polydiallyldimethylammonium chloride), yielding a higher concentration than in the bulk material. Further studies revealed that this spontaneous deposition was observed as a general phenomenon for polyelectrolyte capsules templated on MF particles, rather than being an occasional result, regardless of

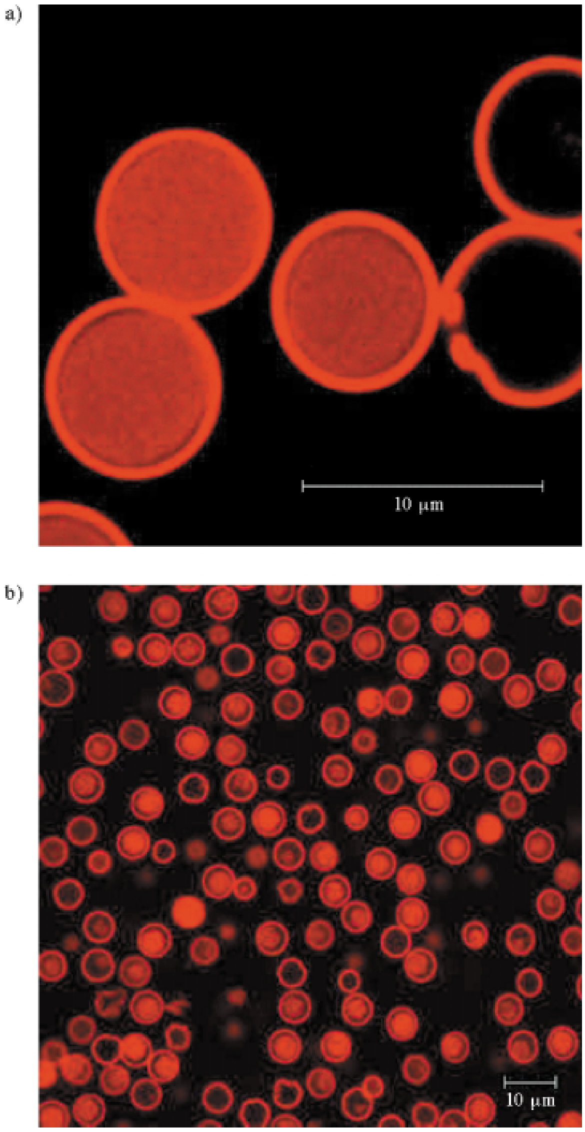

Figure 2. CLSM images illustrating that spontaneous deposition of water-soluble substances occurs within capsules templated on MF particles, regardless of the capsule size, diameter, and wall composition. a) TRITC-PAH self deposited into (PSS/PAH)$_5$ capsules with a diameter of 8.7 µm. b) TRITC-dextran ($M_w = 65$ kD) spontaneously incorporated into (PSS/PDADMAC)$_5$ capsules with a diameter of 5.5 µm.

the capsule size, layer thickness, and wall composition. Many water-soluble substances could be spontaneously encapsulated, but positively charged species displayed a more prominent tendency for self-deposition. In contrast, no self-deposition was observed for capsules derived from other templates such as CdCO$_3$, fluorescein diacetate, or red blood cells with the same nominal capsule composition, regardless of the charge of the water-soluble substances being encapsulated.

These results revealed the surprising fact that a substance can spontaneously diffuse from a low-concentration region to a high-concentration region of the capsule suspension system, without any means of assistance. There must, therefore, exist a force that drives the water-soluble substances from low- to high- concentration regions. A reasonable explanation for this phenomenon must be attributed exclusively to the special structure of the polyelectrolyte capsules templated on the MF particles. We postulate that the additional driving force emanates from the charged species already existing within the interior of the intact capsules. This would most likely constitute a complex formed from PSS, the negatively charged inner wall material, and the degradation product of MF, the positively charged core template (Figure 3). Upon subjecting the polyelectrolyte-coated MF particle (a) to lower pH conditions (0.1 M HCl) the core material, a slightly cross-linked MF resin, is degraded into small particles that penetrate through the capsule wall simultaneously, while the capsule increases its size because of the osmotic difference (b). While this process occurs, the first layer (PSS) is partially dissociated from the wall and released into the interior because of the removal of the supported MF core. Hence, a complex is formed by the negatively charged PSS and some of the positively charged MF degradation product, which is too large to penetrate through the intact capsule wall (c). The PSS/MF complex is negatively charged, as has been proved by zeta-potential measurements (see below). The existence of the PSS/MF complex provides an additional driving force that induces water-soluble substances, especially positively charged species, to penetrate through the capsule wall and deposit around the complex (d, e), thus promoting self-deposition (f). It should be noted that the deposited substance must be in an aggregated or complexed form, rather than in its free state, so that the concentration of the substance within the interior of the capsule is always lower than in the bulk.

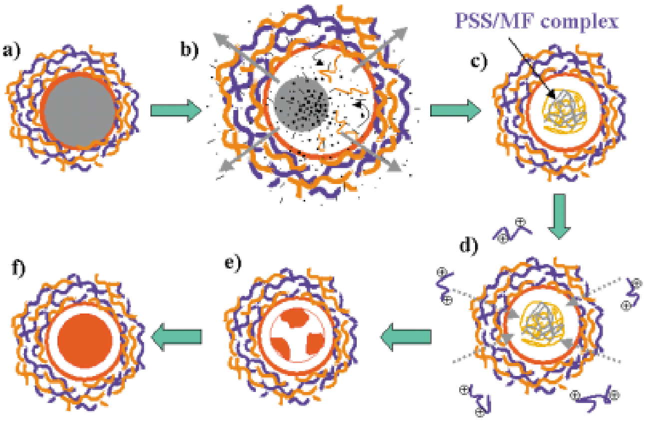

Figure 3. Schematic illustration of the spontaneous deposition mechanism, based on the formation of the PSS/MF complex during the core decomposition process.

To verify this postulation, a model complex of PSS/MF was prepared from PSS and the MF-core degradation product. The zeta potential of this complex is -30.4 ± 0.9 mV, demonstrating that it is negatively charged. Confocal laser scanning microscopy (CLSM) proves that the positively charged rhodamine or TRITC-dextran (zeta potential 10.8 ± 1.0 mV) is selectively adsorbed onto the negatively charged PSS/MF complex, while no adsorption is found when negatively charged 6-CF is employed. The particle size of the PSS/MF complex observed under CLSM ranges from several hundred nanometers to several micrometers. This is large enough so that the complex cannot penetrate through the intact capsule wall, whereas it can be released from the broken capsule interior through the large holes shown in Figures 2a and 2b. Spontaneous deposition was not observed for capsules with apparently broken shells under any conditions. This again proves that the existence of the complex is necessary and indispensable for the spontaneous deposition effect.

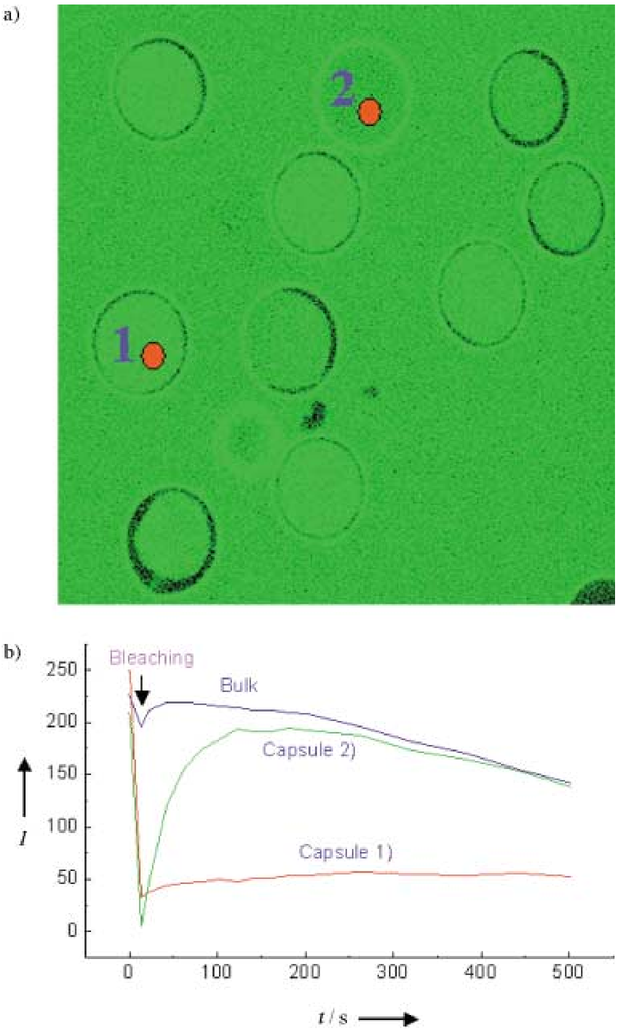

Figure 4. Fluorescence recovery after photobleaching (FRAP) analysis demonstrates that water-soluble substances only self-deposit in an aggregated or complexed form, rather than in their free state. FITC-dextran ($M_w = 77$ kD) was employed as a detecting probe. Two capsules were bleached simultaneously at the marked spots in (a). Capsule 1 exhibits the spontaneous deposition effect, while capsule 2 does not. After bleaching, the fluorescence intensity profiles (b) were obtained.

It has previously been shown by single-particle light scattering (SPLS) measurements that as much as 4% of the total mass of the capsule is formed from residual core material. Energy transfer studies, performed using a rhodamine labeled core and a fluorescein isothiocyanate (FITC) labeled wall, have further confirmed the existence of core residues within the interior of the capsule.[2] A possible explanation that self-deposition only occurs in aged capsules is that the PSS/MF complex may contain an excess of the MF component. The smaller MF particles would only gradually be released from the complex and diffuse to the bulk solution, leaving net charges in the PSS/MF complex.

The fluorescence recovery after photobleaching (FRAP) technique has been employed to demonstrate that water-soluble substances are deposited in an aggregated or complexed form (Figure 4); FITC-dextran ($M_w = 77$ kD) was used as a detecting probe. Two capsules were selected: capsule 1 exhibited spontaneous deposition, whereas capsule 2 did not. After photobleaching the spots shown in Figure 4a, the interior of capsule 2 became dark, which proved that the fluorescein was completely destroyed. In contrast, only the bleached spot in capsule 1 became dark, which suggests that there had been no mass exchange within the interior. The fluorescence recovery profiles (Figure 4b) clearly demonstrate that no recovery occurs for capsule 1, whereas recovery is apparent for capsule 2, which indicates that mass exchange had occurred. These results prove that deposited materials should be in an aggregated or complexed form, and that capsule 2 has large holes in its walls.

Spontaneous deposition provides a route for the encapsulation of many water-soluble substances, especially biomolecules such as proteins, enzymes, and genes. At pH 7.0 albumin is negatively charged (Figure 5a; the zeta potential of FITC-albumin is -15.4 ± 3.6 mV) and, therefore, spontaneous deposition of FITC-albumin was not observed. After decreasing the pH value to 2.5, below the isoelectric point of albumin (4.2), the charge of FITC-albumin was reversed (zeta potential $+44.6 \pm 1.1$ mV), and was then found to spontaneously accumulate within the interior of the capsule (Figure 5b). The scanning force microscopy (SFM) image, obtained in tapping mode and out of solution, clearly displays

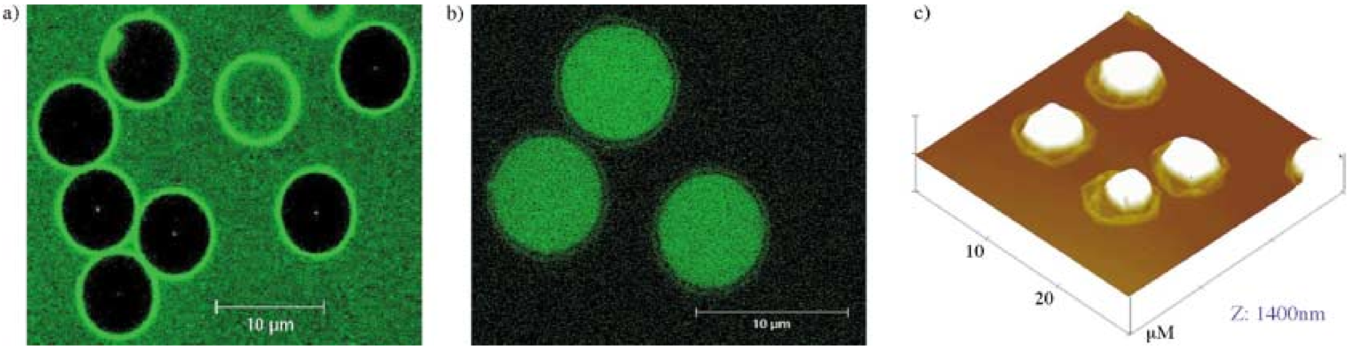

Figure 5. Spontaneous encapsulation of albumin utilizing the self-deposition effect. a) At pH 7.0 albumin is negatively charged hence no encapsulation occurs. b) After decreasing the pH value to 2.5 the charge was reversed and, hence, albumin was spontaneously encapsulated. c) Out-of-solution scanning force microscopy (SFM) clearly displays the large quantity of deposited albumin.

that a large accumulation of albumin had taken place (Figure 5c). Peroxidase and vitamin B2 have also been successfully encapsulated by employing this method.

It has been shown that many water-soluble substances such as rhodamine, PAH, and dextran can spontaneously accumulate in the interior of the aged polyelectrolyte capsules templated on MF particles, forming filled capsules under ordinary conditions. The driving force for this phenomenon is attributed to the existence of a negatively charged complex (PSS/MF) within the capsule interior. The deposited material is in an aggregated or complexed form, rather than existing in its free state, which constrains the system so that the real concentration of the deposited substance within the interior of the capsule remains lower than in the bulk. By utilizing this effect, biomolecules such as albumin have been successfully encapsulated in large quantity by simple alteration of the pH value. In conclusion, we have shown herein that spontaneous and quantitative encapsulation of a drug can occur by deposition within the interior of a macromolecule, which specifically binds to it and initiates its precipitation. This process might in turn be useful in controlling the sustained release of water-soluble agents.

Experimental Section

The sources of the chemicals employed in this study were as follows: PSS ($M_w = 70$ kD), PAH ($M_w = 15$ kD), and PDADMAC ($M_w = 200$–350 kD, 20% w/w in water, Aldrich; FITC-albumin (12:1 FITC:albumin molar ratio), FITC-Dextran ($M_w = 77$ kD), TRITC-dextran ($M_w = 65$ kD) and Rd6G, Sigma; MF particles, Microparticles GmbH, Berlin, Germany. All chemicals were used as received. TRITC-PAH was prepared by the literature route.[9] The water used in all experiments was prepared in a three-stage Millipore Milli-Q Plus 185 purification system and had a resistivity higher than 18.2 MΩ cm.

Membrane filtration was employed to consecutively adsorb PSS and PAH onto MF particles.[10] The adsorption of polyelectrolyte (1 mgmL^{-1}) was conducted in 0.5 M NaCl solution for 5 min followed by three washings in H_2O. After the desired number of oppositely charged layers had been adsorbed, the coated particles were added to 0.1 M HCl solution, in order to decompose the MF cores. The decomposition products and any excess HCl were then removed in H_2O by filtration with gentle agitation until pH neutrality was established. The model PSS/MF complex was prepared by dropping the core decomposition solution into a stirred 0.25 mgmL^{-1} PSS solution, followed by sufficient washing and filtration to remove the excess PSS or MF decomposition products.

Equal amounts of capsule suspension (aged for at least one month) and Rd6G, TRITC-PAH, TRITC-dextran, FITC-dextran, or FITC-albumin solution (2 mgmL^{-1}) were mixed together and stored for several minutes at room temperature to obtain the filled capsules. The solutions were then directly observed using CLSM.

CLSM images were taken with a Leica TCS NT inverted confocal system (Leica, Germany) equipped with a 100× oil immersion objective. The images of capsules in aqueous solution were acquired immediately, whereas images of species out of solution were taken after any residual water had evaporated. The marked spots in FITC-dextran filled capsules were bleached for 1 sec at maximum laser output at 488 nm. The recovery images were recorded and the relative fluorescence intensity was calculated automatically by using Leica TCS NT software.

SFM images were recorded in air at room temperature (20–25 °C) using a Nanoscope III Multimode SFM (Digital Instrument Inc., Santa Barbara, CA). The samples were prepared by applying a drop of the capsule solution onto freshly cleaved mica.

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Solid-State and Solution Studies of a Tetrameric Capsule and Its Guests**

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Synthetic capsules, assembled and even self-assembled from their many components, are host structures available in variety. Whether held together with hydrogen bonds or metal–ligand interactions, their reversible encapsulation of guests provides a modern vehicle for physical organic chemistry. Molecular recognition, stabilization of reactive

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