Chemical Communication

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Towards Chemical Communication between Gated Nanoparticles**

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Abstract: *The design of comparatively simple and modularly configurable artificial systems able to communicate through the exchange of chemical messengers is, to the best of our knowledge, an unexplored field. As a proof-of-concept, we present here a family of nanoparticles that have been designed to communicate with one another in a hierarchical manner. The concept involves the use of capped mesoporous silica supports in which the messenger delivered by a first type of gated nanoparticle is used to open a second type of nanoparticle, which delivers another messenger that opens a third group of gated nanoobjects. We believe that the conceptual idea that nanodevices can be designed to communicate with one another may result in novel applications and will boost further advances towards cooperative systems with complex behavior as a result of the communication between simple abiotic individual components.*

Human beings primarily communicate through sound and sight. Voice, looks, and body language are the major means of active and direct communication. In today's rapidly accelerating age of information technology, digitized renditions of these primary tools of information sharing are becoming more and more popular. However, there is a more basic world of communication that largely escapes this progress—chemical communication. For the vast majority of creatures on earth, this way of communication is even the most important one.[1] It is presumably the oldest and most widespread form of communication.[2] Bacteria,[3] plankton,[4] insects,[5] vertebrates,[6] and plants use it[7] yet it also occurs between different forms of life such as bacteria and hosts in general[8] or certain plants and microbes in particular.[9]

Chemical communication—in the sense of the Latin *communicare* which means to share or exchange information—in manmade systems, on the other hand, is practically unknown. There are no relevant applications of anthropogenic origin in which chemical analogues to pheromones, kairomones, or other allelochemicals play a major role and connect the active states of two systems. In this context, the classic case of manmade systems responding to chemical stimuli is related to recognition. Such recognition itself can be further associated with a change of a physico-chemical property, resulting, for instance, in a signal that is subsequently transduced by a device as in a sensor[10] or in the delivery of compounds such as in drug-delivery systems.[11] In all of these cases, the receiver reacts on receiving the stimulus, but there is no sharing of information with other receivers in an information chain. Although several papers deal with chemical reaction networks and interacting synthetic molecules,[12] communication by an exchange of various chemicals as messengers between different systems such as, for instance, nanoscopic chemical objects has not been realized yet. The advantages of such systems, however, are immediately obvious; they constitute the basis of a dynamically interacting network eventually resulting in certain autonomy of the system. Consider an ensemble of different types of particles, each loaded with a certain chemical and containing a specific recognition element that controls the release of the payload. Consider further that some of the payload chemicals can serve as "keys" to control the release of the cargo of a third type of particle. Theoretically, an almost unlimited number of particle types can be envisioned that can indeed communicate with another in a designed fashion through their chemical messengers. Depending on the arrangement and device integration of the various particles, directional communication over longer distances, hierarchical communication within a larger population of such systems, and more complex cause-and-effect systems can be envisioned.

To rationalize the concept of "communicating nanoparticles", let our particles mimic the perhaps simplest living organisms that communicate with each other, cells. Cells are

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able to perceive and respond to their environment and to their peers through the exchange of chemical information which is basically accomplished by cellular receptors located on the cell's surface, often in close proximity to or in direct contact with transport structures in the cell membrane.[3,13,14] Cells can also communicate in a multicellular organism, a widely known prototype being neurons. Neurons share or process information and use neurotransmitters such as glutamate or GABA (γ-aminobutyric acid) to bridge the synaptic region and propagate information.[15] Coming back to our design, Figure 1 a summarizes how the idea of hierarchical information sharing between different species can be implemented with different types of specifically functionalized nanoparticles: the chemical messenger delivered by a first type of gated nanoparticle upon an external stimulus will open a second type of nanoparticle, which delivers another messenger that opens a third group of gated system, and so forth.

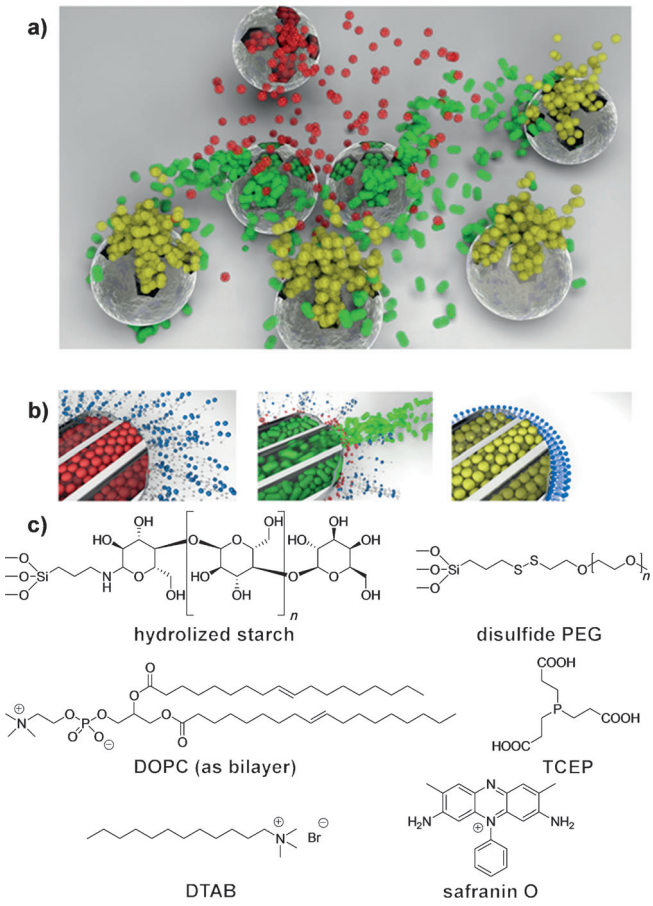

Figure 1. a) Illustration of global system design: red cargo released from the first type of particle opens the pores of a second type of particles, which release green cargo to open the pores of the third type of particle; for clarity only a limited number of particles are displayed and gating chemistries have been omitted. b) Enlargment to illustrate the design of single systems. Left: **S1** in capped mode with TCEP cargo (red) and starch capping layer; middle: **S2** in single-pore release mode with DTAB cargo (green) and PEG capping layer; right: **S3** in capped mode with safranin O cargo and DOCP capping bilayer. c) Structural formula of the functional groups involved in the gating chemistry in detail.

For concept realization, we relied on gated mesoporous hybrid nanoparticles. The architecture resembles particulate delivery systems in which a carrier or container particle is loaded with a large amount of cargo molecules. The container voids are then sealed by stoppers or caps which are attached to the particle's outer surface through a suitably chosen functional group, which is susceptible to a specific stimulus only (Figure 1 b,c).[16,17] Due to object size, pore size and morphology, ease of functionalization and handling as well as robustness, mesoporous silica nanoparticles (MSNs) are ideally suited and have received considerable attention in the field of drug delivery, the majority of the systems relying on chemical or biochemical gating.[18–30] However, in contrast to many delivery systems which should release their cargo at a certain dose over a longer period of time, faster releasing gated systems are important for our purposes here.[31] The crucial task for achieving such "chemical communication" is the careful selection of the gated hybrids and the messengers. The first gated solid (**S1**) in the communication chain is an enzyme-triggered MSN loaded with the first messenger **M1**, the reducing agent tris(2-carboxyethyl)phosphine (TCEP, red balls in Figure 1). The pores of **S1** are capped with a saccharide derivative (Glucidex). The second MSN (**S2**), which is capped with polyethylene glycol (PEG) chains attached through disulfide linkages to the silica surface, contains the second messenger dodecyltrimethylammonium bromide (DTAB, **M2**, green cylinders in Figure 1) as cargo. Finally, a third system (**S3**) hosts a capping lipid bilayer (prepared from 1,2-dioleoyl-*sn*-glycero-3-phosphocholine, DOPC) and is loaded with a dye (safranin O, yellow balls in Figure 1).

The communication sequence is as follows (cf. Figure 1 a). In the presence of a specific enzyme (pancreatin) in an aqueous suspension containing **S1**, **S2**, and **S3**, the hydrolysis of the grafted polysaccharide in **S1** is induced with the subsequent delivery of **M1**. In the second step, **M1** would trigger the delivery of **M2** from **S2** by rupture of the redox-labile disulfide bonds. Finally, **M2** molecules would disrupt the lipid bilayer around **S3**, leading to the delivery of the entrapped dye safranin O.

In order to obtain these gated nanodevices, silica mesoporous (MCM-41-type) nanoparticles (ca. 100 nm) were selected as the inorganic scaffold. For the preparation of the final capped nanoparticles the calcined MSNs were first loaded with a certain cargo and then capped with the corresponding molecular ensemble. All the prepared solids were fully characterized using standard procedures. For instance X-ray diffraction pattern of **S1**, **S2**, and **S3** (Figure 2) show the characteristic (100) diffraction peak for mesoporous systems, indicating that in all cases the loading process and capping with the corresponding gated ensemble have not modified the structure of the mesoporous scaffolding. The presence of the mesoporous structure in the calcined MCM-41 sample and the final functionalized solids was also confirmed by transmission electron microscopy (TEM) analysis. The typical hexagonal porosity and channels of the MCM-41 matrix as alternate black and white stripes are observed in all cases (Figure 2).

The unequivocal discrimination between the individual and collective behavior of **S1**, **S2**, and **S3** is only possible with

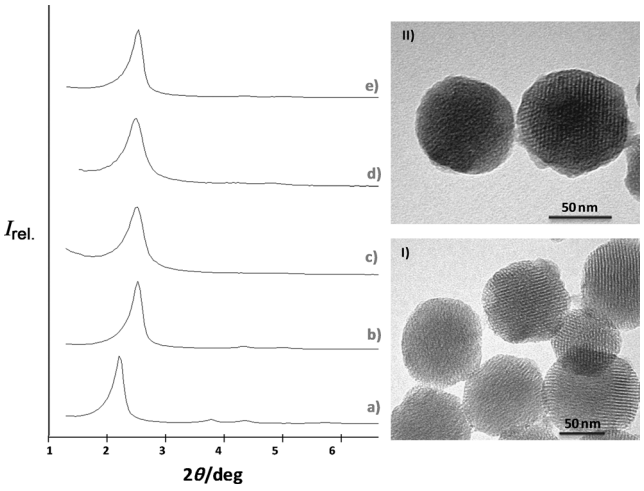

Figure 2. Left: powder X-ray patterns of the solids a) MCM-41 as synthesized, b) calcined MCM-41, c) solid **S1**, d) solid **S2**,and e) solid **S3**. Right: TEM images of calcined MCM-41 sample (I) and solid **S2** (II) showing the typical porosity of the MCM-41 mesoporous matrix.

Table 1: Content of cargo molecules and capping moieties for the prepared solids in $mg\,g^{-1}$ SiO_2.

	Glucidex	TCEP	RhB	PEG	DTAB	Safranin	DOPC
S1	58.8	56.7	–	–	–	–	–
$\mathbf{S1_{dye}}$	59.3	–	44.1	–	–	–	–
$\mathbf{S1_{blank}}$	57.9	–	–	–	–	–	–
S2	–	–	–	137.4	58.1	–	–
$\mathbf{S2_{dye}}$	–	–	–	257.5	–	53.3	–
$\mathbf{S2_{blank}}$	–	–	–	315.5	–	–	–
S3	–	–	–	–	–	27.1	170.8

appropriate reference systems. For this purpose, the gated hybrids $\mathbf{S1_{dye}}$, $\mathbf{S2_{dye}}$, $\mathbf{S1_{blank}}$, and $\mathbf{S2_{blank}}$ were also prepared and investigated. $\mathbf{S1_{dye}}$ and $\mathbf{S2_{dye}}$ are equipped with the same capping system as **S1** and **S2** yet contain a dye as cargo which facilitates the assessment of their capping/uncapping performance through conventional fluorometric techniques. In particular, $\mathbf{S1_{dye}}$ incorporates rhodamine B and $\mathbf{S2_{dye}}$ safranin O. Moreover, to demonstrate the crucial role played by the messengers in the chemical communication, $\mathbf{S1_{blank}}$ and $\mathbf{S2_{blank}}$ were synthesized, both containing the same functional groups on the outer surface as **S1** and **S2** yet lacking the cargo inside the pore voids.

The N_2 adsorption–desorption isotherms of the starting calcined MSN show an adsorption step with an intermediate P/P_0 value (0.1–0.3). From this curve, a pore volume of 0.81 $m^3\,g^{-1}$ was calculated by the BJH model on the adsorption branch of the isotherm. The application of the BET model resulted in a value of 1034 $m^2\,g^{-1}$ for the total specific surface area. Moreover, from the XRD, porosimetry, and TEM measurements, a pore diameter of 2.59 nm was determined. The N_2 adsorption–desorption isotherms for the capped materials are in general agreement with a mesoporous system possessing filled mesopores, and a significant decrease in the N_2 volume adsorbed and surface area was observed. The main structural features of the prepared solids, such as BET specific surface values, pore volumes, and pore sizes are listed in the Supporting Information. Moreover, cargo and capping contents were determined by elemental and thermogravimetric analyses and the results are listed in Table 1.

Before investigating the chemical interplay between the particles, we confirmed the designated capping/uncapping behavior of the single ensembles with the aid of the dye-loaded nanoparticles $\mathbf{S1_{dye}}$, $\mathbf{S2_{dye}}$, and **S3** and fluorescence spectroscopy. In all cases, the delivery studies demonstrated that virtually no ("zero") delivery is observed in neutral aqueous solution. The payload was released only in the presence of the appropriate stimulus, that is, the fluorescent cargo of $\mathbf{S1_{dye}}$ was liberated only after addition of pancreatin as a consequence of the enzyme-induced hydrolysis of the glycosidic bonds anchoring the starch fragments to the outer surface of the particles. Delivery studies with $\mathbf{S2_{dye}}$ revealed a similar behavior in the absence and the presence of the stimulus TCEP, the latter reducing the disulfide groups and cleaving the PEG caps. Finally, **S3** remained also capped and displayed no dye release in pure water, whereas the presence of the surfactant DTAB induced the opening of the pores due to the surfactant-induced rupture of the DOCP lipid bilayer. The details of the single-particle behavior including kinetic delivery profiles are shown in the Supporing Information. Additional controls were then performed to verify that no delivery from the particles occurs when the "wrong" trigger was used. Indeed, $\mathbf{S1_{dye}}$ remained closed in the presence of TCEP and DTAB, $\mathbf{S2_{dye}}$ in the presence of pancreatin and DTAB, and the same robustness was found for **S3** when pancreatin and TCEP were added to its aqueous suspension.

Having established the cargo delivery/retention performance of the individual nanoparticles with regard to stimulus selectivity, we next addressed actual chemical communication between particles. In this complex scenario, the final release of the dye from **S3** is expected to be related to the information that three different nanoparticles (**S1**, **S2**, and **S3**) have previously shared via two different chemical messengers (**M1** and **M2**). In a typical experiment, 1.0 mg each of **S1**, **S2**, and **S3** was suspended in 6 mL of water at pH 7. After division of the suspension into two aliquots, pancreatin was added to one aliquot while the other was used as a control. Fractions of both suspensions (0.3 mL) were then centrifuged and the dye release was monitored by sampling at certain time intervals and measuring the fluorescence emission of safranine O at 585 nm ($\lambda_{exc} = 520$ nm). Typical delivery profiles of safranin O from **S3** in the presence and absence of pancreatin are displayed in Figure 3.

Whereas in the absence of the enzyme, negligible safranin O release from **S3** was observed, a remarkable delivery of the fluorophore occurred in the presence of pancreatin, resulting in the liberation of 80% of the entrapped guest after 1 h. If one recalls the control experiments mentioned above in which no dye delivery was found for **S3** alone in the presence of pancreatin, the high fluorescence generated from the community of the three different types of nanoparticles must have its origin in chemical interparticle communication in the fashion illustrated in Figure 1, involving enzyme-triggered uncapping of

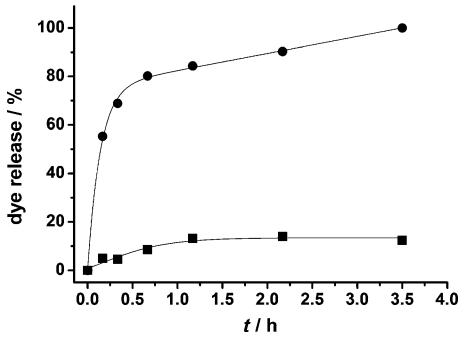

Figure 3. Release of safranin O from solid **S3** in aqueous mixture containing **S1**, **S2** and **S3** in the absence (■) and in the presence (●) of pancreatin enzyme.

S1, delivery of **M1**, **M1**-induced opening of **S2**, delivery of **M2**, and **M2**-induced opening of **S3**. The opening of the pores of **S3** thus occurs remotely through the information chain through the stimulus selective only for the gating chemistry of **S1**.

In a hierarchical, cascade-like system like that presented here, direct and sequential communication between the different particles is crucial and unintended cross-talk or "Chinese whispers" must be avoided. This means that the specific interplay of gating chemistries and messenger molecules is essential. To better understand our communicating particle ensemble, additional studies were performed with $\mathbf{S1}_{blank}$ and $\mathbf{S2}_{blank}$—the gated hybrids lacking the cargo—in the place of **S1** and **S2**. If the community **S1**/**S2**/**S3** shown above "talks" properly with one another, the communities $\mathbf{S1}_{blank}$/**S2**/**S3**, **S1**/$\mathbf{S2}_{blank}$/**S3** and $\mathbf{S1}_{blank}$/$\mathbf{S2}_{blank}$/**S3** should not be able to do so; their communication should either be disturbed or break down entirely, resulting in the absence of dye release from **S3**. The experiments were again carried out in water at pH 7 and pancreatin was introduced as the sole stimulus. As can be deduced from the release profiles shown in Figure 4, in the three "frustrated" communities the final message (safranin O delivered from **S3**) was not disclosed, impressively stressing the essential role of the messengers in interparticle communication. Simplified into Boolean logics, Table 2 collects how the observed output (delivery of safranin O from **S3**) depends on the nanoparticles being endowed with suitable messengers (**S1** and **S2** vs. $\mathbf{S1}_{blank}$ and $\mathbf{S2}_{blank}$) and the presence of the primary stimulus pancreatin. The last row in Table 2 shows that a highly selective final response was found only for an intact community of gated MSNs.

In summary, we have presented here the first proof of concept of a hierarchically organized community of different nanoparticles that can communicate through chemical messengers. The cargo delivery from a certain type of nanoparticle (**S3**) can only be triggered by a stimulus that acts remotely on another type of nanoparticle (**S1**) if the intermediate communication chain is intact. In particular, we sequentially used an enzyme (pancreatin) as the primary stimulus, a redox-active compound (TCEP) and a surfactant (DTAB) as the first and second messengers, and a dye as the final reporter. For our proof-of-principle, we used three different types of nanoparticles, yet the design features make it apparent that the concept can be extended to a larger

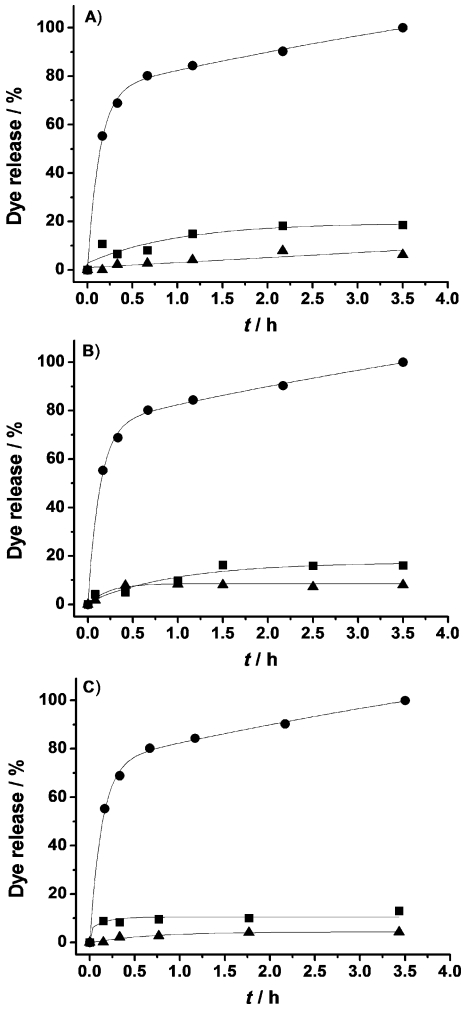

Figure 4. Safranin O released from A) $\mathbf{S1}_{blank}+\mathbf{S2}_{blank}+\mathbf{S3}$ in the absence (▲) or in the presence (■) of pancreatin; B) $\mathbf{S1}_{blank}+\mathbf{S2}+\mathbf{S3}$ in the absence (▲) or in the presence (■) of pancreatin; C) $\mathbf{S1}+\mathbf{S2}_{blank}+\mathbf{S3}$ in the absence (▲) or in the presence (■) of pancreatin. For the sake of comparison in all three graphics the release behavior of solids $\mathbf{S1}+\mathbf{S2}+\mathbf{S3}$ in the presence of pancreatin (●) is also plotted.

Table 2: Release of safranin O from **S3** in the cascade chemical communication system depending on the use of capped nanoparticles containing messengers 1 (**S1**) and 2 (**S2**) or empty nanoparticles ($\mathbf{S1}_{blank}$ and $\mathbf{S2}_{blank}$) and the presence or absence of pancreatin.

External trigger[a] (enzyme)	Presence of messenger **M1**[a] (TCEP)	Presence of messenger **M2**[a] (DTAB)	Response[b] (safranin O)
0	0	0	0
0	1	0	0
0	0	1	0
1	0	0	0
1	1	0	0
1	0	1	0
1	1	1	1

[a] The presence or absence of the trigger and messengers in the MSN is represented by "1" and "0", respectively. [b] Delivery or nodelivery of dye from **S3** is represented by 0 = no delivery, 1 = delivery. In particular "1" refers to a maximum dye release (100%) whereas "0" represents no release or poor release (typically less than 15%).

number of interconnected nanodevices. Although we are aware that the system we report herein is of limited practical use, we believe that the conceptual idea that nanodevices can be designed to communicate with each other harbors enormous prospects for the development and application of cooperative systems in which complex behavior can emerge as a result of a chemical interplay between individual simple abiotic components. Besides delivery,[16,17] sensing,[32] and catalysis,[33] our approach may open new, exciting, and fruitful directions in the field of functional biomimetic chemistry.[34]

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