Peptide Nanoparticles

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Nanoparticles and Peptides: A Fruitful Liaison for Biomimetic Catalysis**

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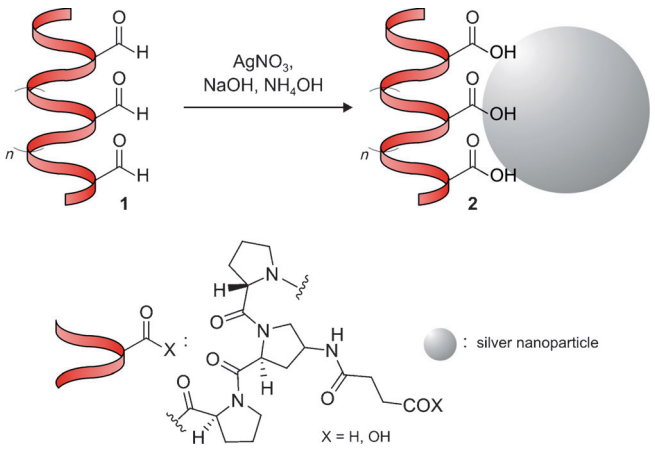
Within the course of evolution a multitude of biosynthetic pathways have emerged utilizing enzymes that can catalyze myriad organic reactions with unrivaled efficiency and selectivity under mild conditions. Nature's concepts of catalytic transformations have inspired chemists and have fueled intensive research focused on imitating the structural features and the mechanisms of enzymes in order to develop catalysts that ideally possess high turnover rates, specificity, and robustness, and are easy to prepare and apply.[1] Among the countless examples arising from these efforts, the reactions catalyzed by the single amino acid proline are particularly impressive and have significantly contributed to the dawn of a new era in modern chemistry—organocatalysis.[2] In the early 1980s, the biomimetic catalyst toolbox was further broadened by peptide-based catalysts. Thus the repertoire of reactions catalyzed by single amino acids was expanded, while the advantages of small-molecule catalysts were retained. Today, these minimalistic versions of enzymes[3a] can be found in various types of transformations, such as aldol additions, group-transfer reactions, oxidations, and Morita–Baylis–Hillman reactions.[3] Owing to the structural diversity and the relatively low cost of amino acids along with the inherent modularity of peptides, which makes it possible to readily adjust the reactivity and selectivity of a certain reaction, peptides are a very attractive and versatile catalyst platform especially in asymmetric transformations.

Despite the tremendous progress in catalyst development, the overall performance of artificial catalytic systems, however, can often not keep up with that of their natural analogues. One explanation of this phenomenon may be linked to the lower structural complexity of small-molecule catalysts compared to the elaborate architecture of enzymes. In such biocatalysts, many different sites, including residues remote from the actual catalytic center, play a decisive, often multifunctional role within the peptide framework and thus account for their outstanding efficiency. This fine-tuned relationship between structure and function is one of the hallmarks of enzymes. Macromolecular complexes, which are currently accessible in the size of small enzymes thanks to recent progress in supramolecular coordination chemistry, are able to mimic single characteristics intrinsic to enzymes, such as their cagelike structure, their unsymmetric construction, and their allosteric effects,[1b] but still fail to combine these features in one molecular scaffold.

A solution to this problem may be offered by the rapidly growing field of nanotechnology, from which especially nanoparticles (NPs) have emerged as a lively field of research. Because of their size- and shape-dependent properties, high chemical stability, and the simple functionalization of their surfaces, NPs have become important for a broad range of applications in, for example, electronic devices, sensing probes, and noninvasive diagnostics, and as drug carriers and catalysts.[4] The investigation of the interactions between metal nanoparticles (MNPs) and peptides is still in its infancy, but this area has attracted tremendous attention in the scientific community in the past few years. By offering not only a promising perspective in most diverse areas of technology, industry, and medicine, the preparation of such nanometer sized particles can also be achieved by the help of peptides.[5] Recently, the Wennemers group[6] showed that besides nucleation even the size of silver NPs can be programmed very efficiently by the use of conformationally stable, symmetric helices as additives. The rigid oligoproline scaffold **1**, which bears an aldehyde function on every third repeat unit, acts like a "molecular ruler"[6] with the aldehyde groups functioning as reducing agents (forming elemental silver from Ag^+) and as growth regulators of NPs at the same



Scheme 1. Size-controlled formation of Ag NPs by peptides.

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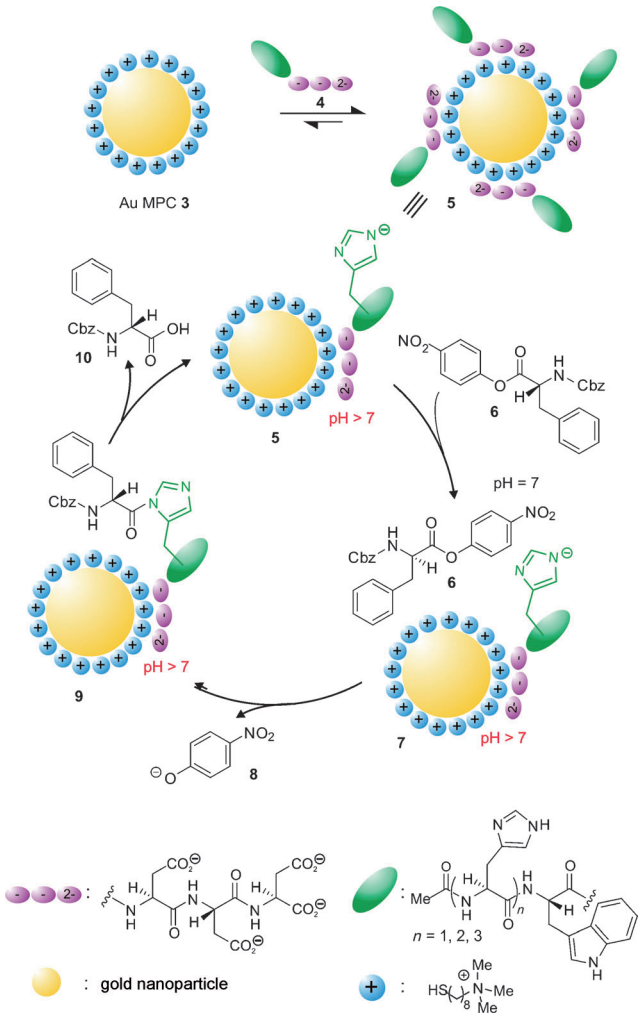
time (Scheme 1). As the length of the peptide is strictly linked to the NPs' diameter, these findings give the opportunity to conceive such size-defining additives by the transfer of the molecular proportions of a designed peptide to the nanoscopic dimensions of a NP.

Another aspect of peptide–NP research was added by the recent report of Scrimin, Prins, and Zaramella.[7] In their studies of metal-ion-based molecular systems, especially on functionalized gold nanoparticles and their application as enzyme models, they developed heterofunctionalized multivalent peptide–Au-NP complexes, which accelerate the hydrolysis of *p*-nitrophenyl ester **6** by at least two orders of magnitude (Scheme 2). These catalytically active peptide-



Scheme 2. Hydrolysis of ester **6** catalyzed by peptide-based NPs **5**.

derived NPs **5** are based on monolayer-protected Au clusters **3** (Au MPCs), in which the self-assembled monolayer (SAM) contains trimethylammonium head groups anchored to the metal core by a thiol moiety. The cationic surface of **3** was further modified by the attachment of anionic peptides **4**, which are composed of three deprotonated aspartates, one tryptophan, and a variable number of histidine residues, leading to heterofunctionalized multivalent scaffolds **5** showing increased structural complexity. These supramolecular structures **5** are readily prepared because the formation of the multivalent surface is based on self-assembly, thus avoiding the often tedious preparation of structurally complex macromolecules.

Initial investigations on the role of **5** in catalysis unambiguously showed that the histidine portion in **4** is crucial for the nucleophilic catalysis. Nevertheless, neither intra- nor intermolecular cooperative interactions arising from multiple imidazole rings within one molecule or from different molecules contribute to the activity of **5**, as often observed in multivalent imidazole-containing catalysts.[8] The acceleration in the saponification of **6** is the result of a cooperative effect of the peptide **4** with the Au MPC **3**, which results in an increased pH of roughly 7.7 at the monolayer surface compared to pH 7.0 in the overall reaction mixture. The higher local pH leads to deprotonation of the histidine side chain in peptides bound to the Au MPC surface. This increases the nucleophilicity of the imidazole nitrogen and thus accelerates the transesterification. Henceforth, self-assembly of **5** constitutes a precondition for the catalytic process, as peptide **4** alone showed no enhanced hydrolysis rate and this allows the catalyst to be operated under turnover conditions. In addition, the highest catalytic activity of **5** was detected at peptide concentrations lower than the maximum surface saturation. This, together with the nonlinearity of the initial rate plotted versus ester concentration, clearly indicates that the protected phenylalanine **6** must also be linked temporarily to the Au MPCs (cf. **7**) which is accomplished by hydrophobic interactions between the apolar substrate **6** and lipophilic parts of the SAM. This self-assembly of the catalytic entity **5** and ester **6** generates an enhanced local stoichiometry of starting material and reactant by bringing the two components into close proximity. The multivalent surface therefore plays a dual role in influencing the catalytic reactivity by generating a unique chemical environment thus mimicking the concept of cooperativity usually attributed to enzymes. By changing the overall structure of the peptides employed, diverse reactivities of the catalytic unit might be triggered, opening this catalytic system for a multitude of possible applications at the frontier between homogeneous and heterogeneous catalysis.

The highlighted publications impressively illustrate that by the combination of two branches of organic chemistry, here small peptides and nanoparticles, new strategies can be unlocked, leading to new, inspiring solutions of often long-standing problems. On the basis of the presented novel concept of catalysis, further investigations are indeed essential to examine the potential of peptide-based NPs, also for other types of reactions, in order to advance them to broadly applicable promoters in organic chemistry. This new research area thus holds great promise for the development of an innovative generation of highly active and recyclable catalysts.

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[1] a) R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146–153; b) M. J. Wiester, P. A. Ulmann, C. Mirkin, *Angew. Chem.* **2011**, *123*, 118–142; *Angew. Chem. Int. Ed.* **2011**, *50*, 114–137.
[2] *Asymmetric Organocatalysis* (Eds: A. Berkessel, H. Gröger), Wiley-VCH, Weinheim **2005**.
[3] a) R. Breslow, *Chem. Biol.* **1998**, *5*, R27–R28; b) S. J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601–610; c) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812; d) H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036–12041.
[4] a) M.-C. Daniel, D. Astruc, *Chem. Rev.* **2004**, *104*, 293–346; b) D. Astruc, F. Lu, J. R. Ruiz Aranzaes, *Angew. Chem.* **2005**, *117*, 8062–8083; *Angew. Chem. Int. Ed.* **2005**, *44*, 7852–7872; c) N. L. Rosi, C. A. Mirkin, *Chem. Rev.* **2005**, *105*, 1547–1562; d) D. A. Giljohann, D. S. Seferos, W. L. Daniel, M. D. Massich, P. C. Patel, C. A. Mirkin, *Angew. Chem.* **2010**, *122*, 3352–3366; *Angew. Chem. Int. Ed.* **2010**, *49*, 3280–3294; e) A. A. Shemetov, I. Nabiev, A. Sukhanova, *ACS Nano* **2012**, *6*, 4585–4602, and references therein.
[5] M. B. Dickerson, K. H. Sandhage, R. R. Naik, *Chem. Rev.* **2008**, *108*, 4935–4978.
[6] G. Upert, F. Bouillère, H. Wennemers, *Angew. Chem.* **2012**, *124*, 4307–4310; *Angew. Chem. Int. Ed.* **2012**, *51*, 4231–4234.
[7] D. Zaramella, P. Scrimin, L. J. Prins, *J. Am. Chem. Soc.* **2012**, *134*, 8396–8399.
[8] a) L. Pasquato, F. Rancan, P. Scrimin, F. Mancin, C. Frigeri, *Chem. Commun.* **2000**, 2253–2254; b) E. Delort, T. Darbre, J. L. Reymond, *J. Am. Chem. Soc.* **2004**, *126*, 15642–15643; c) M. O. Guler, S. I. Stupp, *J. Am. Chem. Soc.* **2007**, *129*, 12082–12083.

