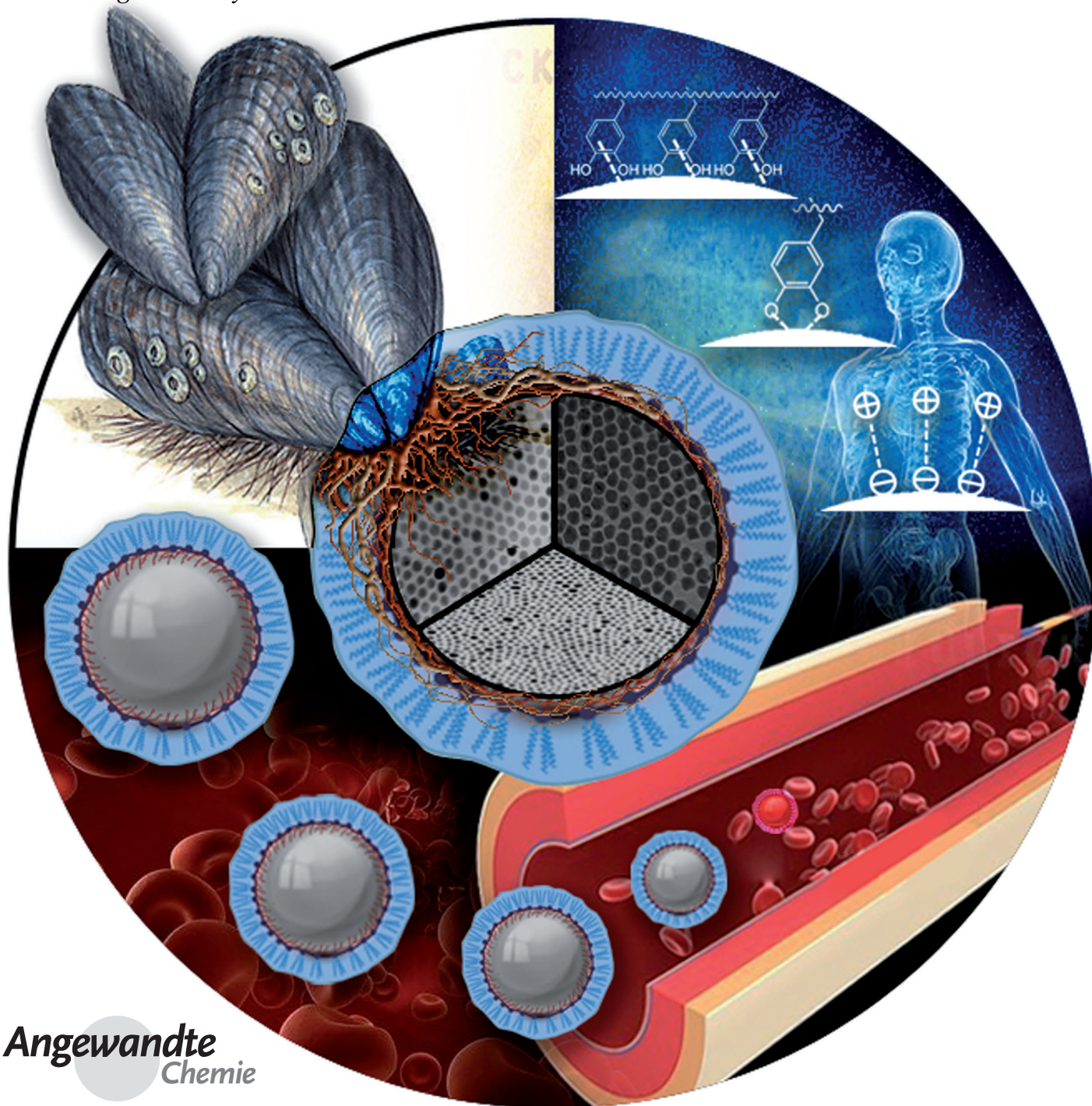


Multiple-Interaction Ligands Inspired by Mussel Adhesive Protein: Synthesis of Highly Stable and Biocompatible Nanoparticles**

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Angewandte
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Water-dispersible and biocompatible nanoparticles have attracted much interest for their various biomedical applications, which include biological sensing, labeling, imaging, cell separation, and disease treatment.^[1] For example, superparamagnetic iron oxide (SPIO) nanoparticles have already been used in clinical applications for magnetic resonance imaging (MRI).^[2] The prerequisite for the successful biomedical use of nanoparticles is their colloidal stability in harsh biological environments. One main approach to render nanoparticles water-dispersible is replacing the hydrophobic capping ligands with hydrophilic ones that harbor anchoring groups such as carboxylic acids, thiols, phosphines, and amines;^[3] in this case, the coordinating ability of ligands is most important for stable dispersion in water. Ligands that harbor multiple anchoring groups would provide notably improved colloidal stability.^[3j-m,4] Another approach employs hydrophobic interactions, through which amphiphilic polymers encapsulate the nanoparticles in a micelle form.^[5] Furthermore, the two approaches mentioned above can be combined to significantly enhance the stability of the resulting nanoparticles under very harsh biological conditions.^[6] Mussels have an adhesive protein that is rich in catechol and amine groups, and has interesting properties as it can attach to almost all kinds of surface.^[7] Inspired by mussels, catechol-derived dopamine-based ligands have also been utilized as high-affinity anchors for nanoparticle stabilization.^[3e-i,n] However, most of these ligands, which have single catechol binding units, impart poor stabilities to nanoparticles because of dopamine degradation and metal-ion leaching.^[3n,8] Herein, we report the design and

synthesis of a poly(L-3,4-dihydroxyphenylalanine) (poly-DOPA) based versatile multiple-interaction ligand (MIL) for ultrastable and biocompatible nanoparticles. To the best of our knowledge, this is the first report on the polyDOPA-based ligand for water-dispersible nanoparticles. Scheme 1 shows the design of MIL, which consists of methoxy poly(ethylene glycol) (mPEG) grafted cationic hyperbranched polyethylenimine (bPEI) and the multi-initiated peptide domain of polyDOPA. This mussel adhesive protein (MAP) mimicking structure has several binding modes. Firstly, MIL, which contains the polyDOPA domain and primary amine end groups, enables simultaneous multiple catechol binding and amine binding^[9] onto the surface of hydrophobic nanoparticles. Secondly, the amphiphilic hyperbranched block copolymer structure with both hydrophobic polyDOPA groups and hydrophilic PEG groups generates micelles encapsulated with nanoparticles. Finally, the positively charged bPEI moiety can interact electrostatically with negatively charged nanoparticles of many metals and metal oxides.^[3m,10] All these binding modes can work cooperatively to generate highly stable nanoparticles in harsh biological environments.

MIL was synthesized by the ring-opening polymerization reaction of di-*O,O'*-acetyl-L-DOPA-*N*-carboxylanhydride (DOPA-NCA), initiated from a macroinitiator of mPEG-grafted bPEI (Scheme 1b; synthesis and characterization of MIL are shown in detail in Scheme S1 and Figure S1 in the Supporting Information). The overall synthetic procedure is easy to scale up, and 5 g of the ligand can be produced by using a 1 L reactor. We varied the DOPA content of MIL and to result in MIL0, MIL1, and MIL2 (Table S1). To demonstrate the versatility of MIL for the stabilization of various nanoparticles, oleic acid capped nanoparticles of Fe₃O₄ and MnO, and 1-dodecanthiol capped Au nanoparticles were ligand-exchanged with MIL2 in chloroform at room temperature. After the chloroform was removed by evaporation, the resulting hydrophilic nanoparticles were highly dispersible in water, even at extremely high concentrations, with a water transfer yield of nearly 100% and without any noticeable aggregation. The excess ligands were removed by ultracentrifugation or washing 3–5 times through a spin filter. This procedure resulted in nanoparticles that were well-dispersed in water, as confirmed by transmission electron microscopy (TEM; Figure 1). Dynamic light scattering (DLS) measurements showed that the approximate hydrodynamic diameters (HD) of these nanoparticles are 31 nm for the MIL2-functionalized Fe₃O₄ nanoparticles (core diameter of 11 nm), 34 nm for the MIL2-functionalized MnO nanoparticles (core diameter of 13 nm), and 25 nm for the MIL2-functionalized gold nanoparticles (core diameter of 5 nm). Although MIL has a high molecular weight ($M_w \approx 40$ kDa), the MIL shell thickness d_{eff} is smaller than free linear PEG with $M_w = 40$ kDa, which is calculated to be 14 nm in aqueous solution [calculated from Eq. (1)^[12]]. On the other hand, the HD of MIL should be larger than that of free PEG with $M_w = 5$ kDa [4.47 nm from Eq. (1)]. Consequently, the MIL shell thickness of between 4.47 nm and 14 nm is reasonable. This small shell thickness of MIL seems to be derived from the

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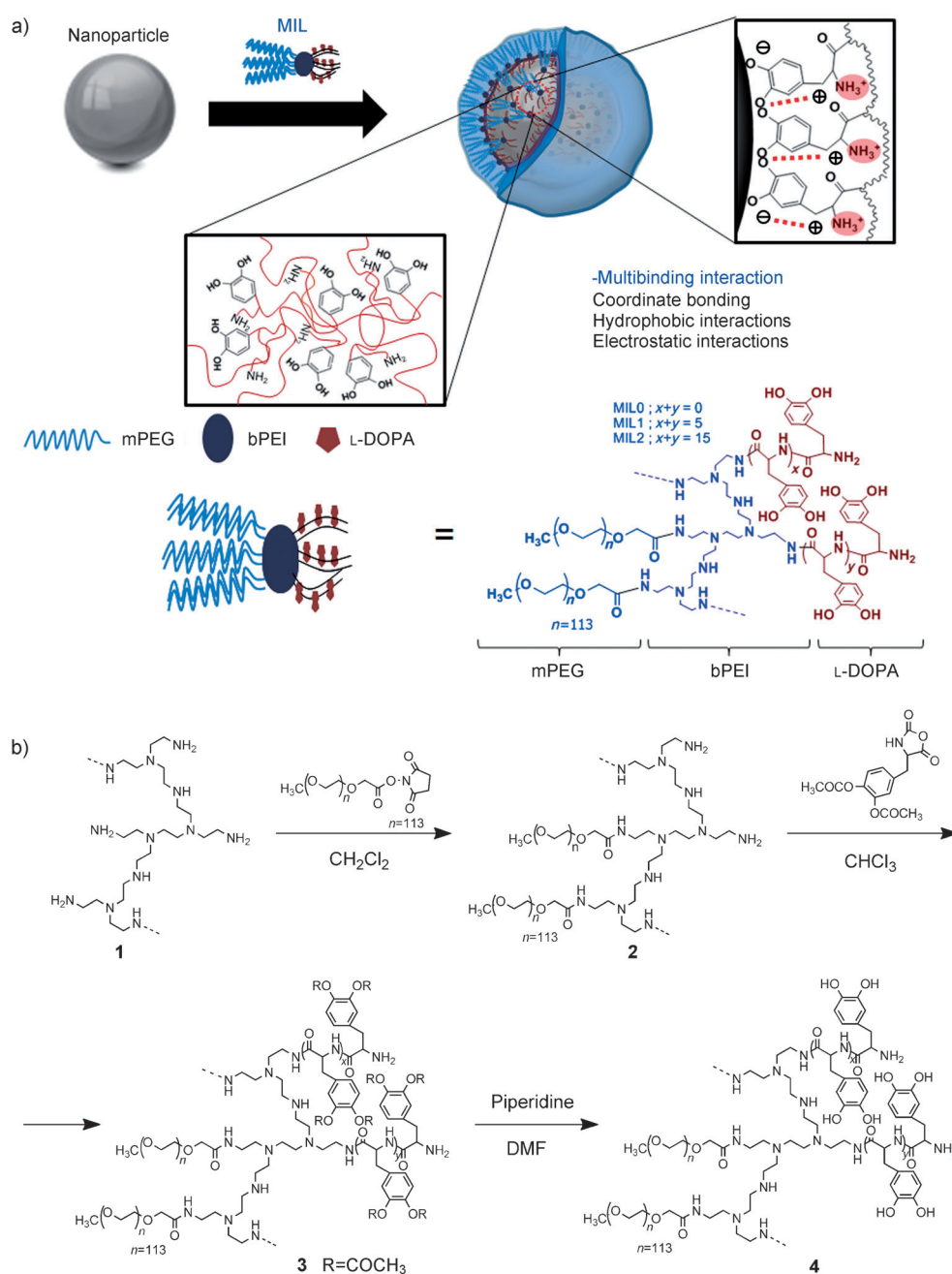
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Scheme 1. a) Formation of water-dispersible nanoparticles through multiple-interaction ligand (MIL) stabilization. b) Synthetic route to MIL.

branched structure of MIL, rather than the linear polymeric structure.^[11]

$$d_{\text{eff,PEG}} = 2r_h = 0.03824 M_w^{0.559}$$

(r_h = hydrodynamic radius,

M_w = molecular weight of PEG)^[12]

The absorption spectra of the Au nanoparticles before and after ligand exchange with MIL2 were nearly identical (Figure S2). The MIL2-functionalized Fe₃O₄ nanoparticles with a core diameter of 11 nm showed a specific relaxivity

value (r_2) of 151.55 mm⁻¹s⁻¹ (Figure S3), while the MIL2-functionalized MnO nanoparticles with a core diameter of 13 nm showed a specific relaxivity value (r_1) of 1.80 mm⁻¹s⁻¹ at 3 T (Figure S4). These results indicate that MIL promoted water dispersion without affecting the integrity or properties of the nanoparticles. Analysis of the FTIR spectra (Figure S5) showed that the absorption band at 1710 cm⁻¹ in the oleic acid capped Fe₃O₄ nanoparticles^[4] disappeared after the ligand exchange with MIL2, and that a new band related to the amide group appeared around 1660 cm⁻¹, thus indicating that oleic acid ligand was substituted with MIL2. Thermogravimetric analysis was performed to quantify the amount of MIL2 bound to the nanoparticles. The weight loss curve showed that the oleic acid capped Fe₃O₄ nanoparticles contained approximately 18% hydrophobic surfactant layer, whereas MIL2-functionalized Fe₃O₄ nanoparticles contained approximately 37% by weight of this layer (Figure S6). This dense polymer shell is necessary to provide high colloidal stability and presumably to extend the blood circulation time. The capacity of facile and successful ligand exchange with all these nanoparticles should arise from the multiple-interac-

tion properties of the MILs. All the above MIL2-functionalized nanoparticles are stable for more than 1 month at room temperature or more than 3 h in boiling water without any noticeable HD change (Figure S7). This excellent stability of the MIL2-functionalized metal oxide (Fe₃O₄ and MnO) nanoparticles seems to be predominantly because of the 1,2-benzenediol functional groups on MIL2, while the comparable stability of the MIL2-functionalized noble metal (Au) nanoparticles seems to result from a synergistic kinetic capping effect of the primary amine end groups in MIL.^[13]

To further explore the binding effect of the polyDOPA domain, we studied the stability of the resulting Fe₃O₄

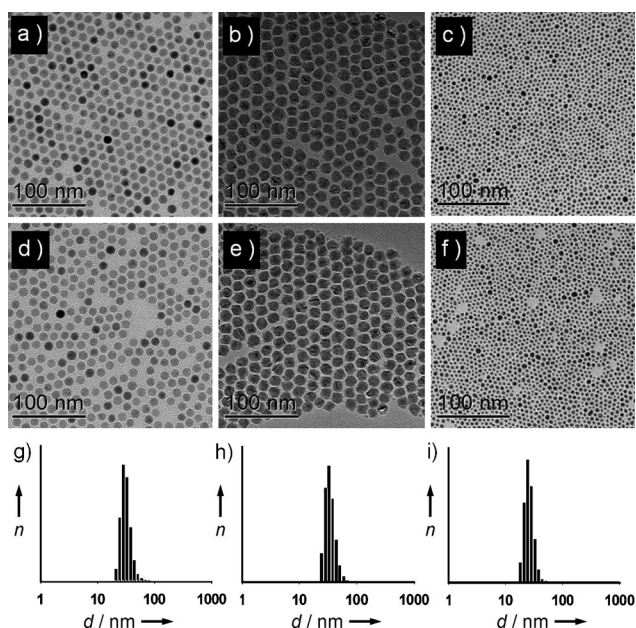


Figure 1. TEM images of hydrophobic nanoparticles (upper panels) and hydrophilic counterparts that are functionalized with MIL2 (center panels): a, d) 11 nm Fe₃O₄, b, e) 13 nm MnO, and c, f) 5 nm Au nanoparticles. DLS data for the MIL2-functionalized nanoparticles (lower panels): g) Fe₃O₄, h) MnO, and i) Au nanoparticles.

nanoparticles as a function of different DOPA ratio in various acidic, basic, and salt solutions. We found that MIL0 (0 DOPA unit) functionalized Fe₃O₄ nanoparticles are unstable in strong acidic, basic, or concentrated NaCl solutions (Figure 2), and even precipitated in distilled water within a few weeks, whereas the MIL1- and MIL2-functionalized Fe₃O₄ nanoparticles are very stable (Figure S8). The MIL1 (5 DOPA units) functionalized Fe₃O₄ nanoparticles were shown to be stable at pH 1–13 and at a high NaCl salt concentration (up to ca. 3 M), whereas the MIL2 (15 DOPA units) functionalized Fe₃O₄ nanoparticles exhibited an amazing stability in an almost-saturated NaCl solution of up to 5 M and a very broad pH range of 1–14 (Figure 2). The MIL2-functionalized Fe₃O₄ nanoparticles can maintain their shape and size under the extremely acidic conditions of pH 1 for up to one day before they slowly decompose through the etching process, according to TEM measurements (Figures S9 and S10). This effect may be attributable to the existence of a hydrophobic polyDOPA layer that prevents hydrophilic species such as H⁺ ions from reacting with the nanoparticles.^[14] Furthermore, the metal catecholate complex formed in the polyDOPA layer^[15] might inhibit metal-ion leaching and consequently maintain the stability of the whole matrix. The DOPA-content-related stability suggested that more DOPA units make more bonding points on nanoparticle surfaces, and consequently induce increased hydrophobic interaction with the nanoparticles. The increased hydrophobicity of MIL2 with increased DOPA content was confirmed by a critical micelle concentration (CMC) test (Figure S1–7).

The confocal laser scanning microscopy (CLSM) study (Figure S11) and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (Figure S12) showed

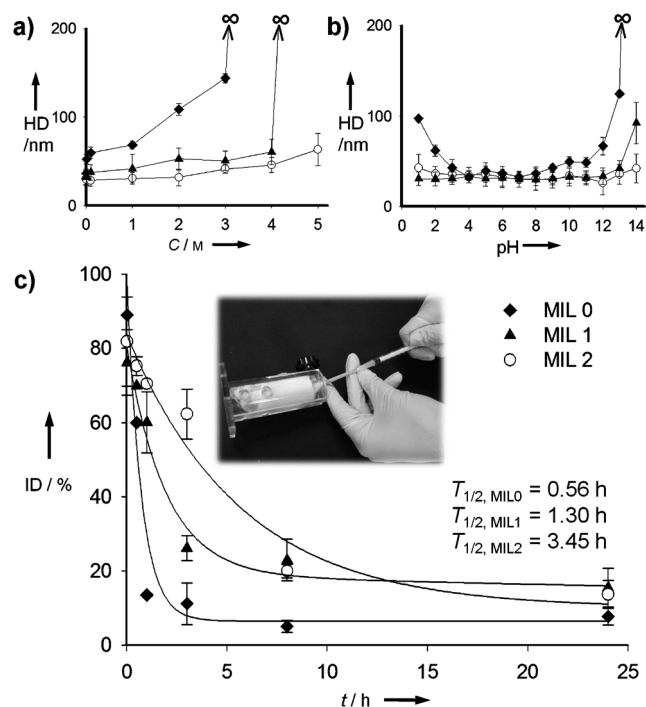


Figure 2. In vitro stability tests of MIL0 (◆), MIL1 (▲), and MIL2 (○) functionalized Fe₃O₄ nanoparticles as a function of a) NaCl concentration and b) pH. c) In vivo stability tests: blood circulation data (plasma iron concentration versus time relationships) of MIL0, MIL1, and MIL2-functionalized Fe₃O₄ nanoparticles injected into 8 weeks BALB/c mice (see inset; n = 3 for each group, 3 mg [Fe] per kg of mice body weight).

that the RITC (rhodamine B isothiocyanate) labeled MIL2-functionalized Fe₃O₄ nanoparticles can be easily transfected to MDA-MB-231 cancer cells, but showed no appreciable cytotoxicity, thus indicating their excellent biocompatibility. The cytotoxicity of MIL2-functionalized Fe₃O₄ nanoparticles was further evaluated by MTT assay, trypan blue exclusion assay, and live and dead assay of Hela cells (Figures S12 and S13). The MTT assay showed that cell viability was not hindered following culture with a concentration of 600 µg Fe mL⁻¹ for both 24 h and 72 h after the incubation. Trypan blue exclusion assays also showed that cell proliferation was not reduced in the presence of the MIL2-functionalized Fe₃O₄ nanoparticles even after 72 h. Furthermore, for the live and dead assay, no toxicity was found by fluorescence microscopy in the cells treated with various concentrations of the MIL2-functionalized Fe₃O₄ nanoparticles. These results demonstrated that the MIL2-functionalized Fe₃O₄ nanoparticles are highly biocompatible. The in vivo mice pharmacokinetic studies showed that the MIL2-functionalized Fe₃O₄ nanoparticles (T_{1/2, MIL2} = 3.45 h) had a longer blood circulation time than that of MIL1- and MIL0-functionalized Fe₃O₄ nanoparticles (T_{1/2, MIL1} = 1.30 h, T_{1/2, MIL0} = 0.56 h). We attribute this variation to the different DOPA content of MIL. The blood half-lives of both the MIL1- and MIL2-functionalized Fe₃O₄ nanoparticles are much longer than that of previously reported iron oxide based nanoparticles.^[16] Bio-distribution studies showed a relatively high accumulation of the MIL-functionalized Fe₃O₄ nanoparticles in the spleen and

liver (Figure S14), as has been commonly observed for nanoparticles in vivo.^[16] As a representative biomedical application, MRI was performed using the MIL2-functionalized Fe₃O₄ nanoparticles as a T₂ MRI contrast agent. The in vivo mouse MRI results (Figure 3 and Table S2) obtained

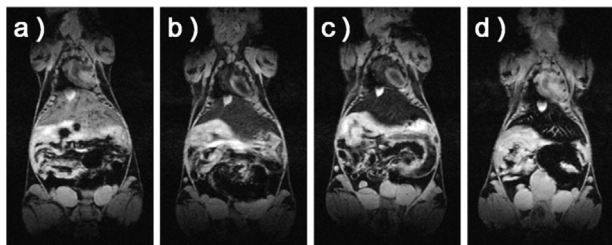


Figure 3. Time-dependent T₂-weighted MR images of a nude mouse a) before, b) immediately after, c) 2 h after, d) 24 h after intravenous administration of the MIL2-functionalized Fe₃O₄ nanoparticles (2.5 mg [Fe] per kg of mouse body weight).

by using the MIL2-functionalized Fe₃O₄ nanoparticles showed that the nanoparticles exhibited a long blood circulation time and accumulated in lymph nodes, as shown in the MR image obtained 24 h after injection (Figures S15 and S16).^[17] These data indicated that the MIL2-functionalized Fe₃O₄ nanoparticles are highly stable in blood stream presumably because PEG-grafted branched structure of MIL reduces undesirable interactions with proteins.^[18] These results clearly demonstrated that the MIL-functionalized nanoparticles are highly stable in various harsh biological media for diverse biomedical applications such as MRI and cell labeling.

In summary, a mussel-inspired multiple-interaction ligand (MIL) was developed by combining poly(ethylene glycol), polyethylenimine, and polyDOPA. The MIL can stabilize various nanoparticles of metals and metal oxides by various cooperative binding modes, including direct binding with catechol and amine groups, micelle formation, and electrostatic interaction between positively charged ligands and the negatively charged nanoparticle surface. The MIL2-stabilized nanoparticles of Fe₃O₄, MnO, and Au exhibited extremely high stability in various harsh aqueous environments, including highly acidic and basic media, highly concentrated NaCl solutions, and even boiling water. The synthetic procedure is easy to scale up, and the ligand-exchange process is very simple and short. The successful in vivo MRI application using the MIL2-functionalized Fe₃O₄ nanoparticles confirmed the suitability of these species for various biomedical applications.

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