Amphipathic metal-containing macromolecules with photothermal properties†

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Metal-containing macromolecules with extraordinary properties have attracted a great deal of interest owing to their potential application in the development of functional materials. Here, we report the synthesis of novel amphipathic metal-containing macromolecules by the click reaction of methoxypolyethylene glycol azides with a unique metalla-aromatic complex containing a terminal alkynyl group. The resultant amphipathic macromolecules self-assembled into micellar nanoparticles with diameters of ca. 145 nm in water, which exhibited high stability, water-dispersibility, biocompatibility, and excellent photothermal behavior under 808 nm laser irradiation. Our study opens promising avenues for providing metal-containing macromolecules as photothermal materials.

Macromolecules that incorporate a metal as building blocks are interesting and valuable materials, because many of them can carry out the functions of both macromolecular and metal-containing units.1 Metal-containing macromolecules have been developed as functional materials2 on the basis of their electroactive,3 photoactive,3 bioactive,4 magnetic and other interesting properties.5 For example, polyferrocenylsilane and its copolymers exhibit excellent properties,6 including redox activity and an ability to grow into metallosupramolecular polymers.7 Ferrocene-functionalized polycetylenes and polyphenylenes have been used as precursors to prepare magnetic ceramics and nanoparticles.8 Macromolecules with other metal-containing units have also been reported as functional materials with unexpected or exceptional properties.9 However, to the best of our knowledge, metal-containing macromolecules that exhibit photothermal properties have not been reported.

Photothermal therapies for killing tumors using near-infrared (NIR) light with its superior tissue penetration ability10 have recently become a promising theranostic method.11 The reported photothermal materials mainly include NIR-absorbing organic molecules or polymers,12 gold nanomaterials,13 and inorganic and other materials.14

As a continuation of our efforts to synthesize new metalla-aromatic complexes,15 we recently prepared an interesting metalla-aromatic complex 2 from the reaction of complex 1 with phenylacetylene in air (Scheme 1).16 Complex 2 exhibits broad absorption in the UV–Vis–NIR regions and excellent photothermal behavior when exposed to an NIR laser with a wavelength of 808 nm. However, the metalla-aromatic complex 2 is water-in-
soluble and poorly biocompatible, thus hindering its application in vivo. When tentatively packed in an amphiphilic macromolecular micelle, complex 2 can be used as a biomaterial for the thermal ablation of cancer cells in vivo.16 However, the stability of the micelle is a potential obstacle to its biomedical applications. Therefore, in this work, we for the first time covalently linked metalla-aromatic complex 2 with water-soluble mPEG polymers to form a new class of amphiphilic macromolecules, with the aim of achieving micellization of the resultant macromolecules in water to afford novel photothermal materials with enhanced stability and biocompatibility (Fig. 1).

In order to synthesize the target amphiphatic macromolecule, it is necessary to introduce organic functional groups into the metalla-aromatic complex 2. To this end, we prepared complex 3, which contained a terminal alkynyl group, from the reaction of complex 1 with 1,4-diethynylbenzene in the presence of AgBF4 (Scheme 1). The structure of complex 3 was characterized by nuclear magnetic resonance (NMR), high-resolution mass spectrometry (HRMS) and elemental analysis (EA). The 31P{1H} NMR spectrum shows three signals at 9.71 (t, JPP = 6.5 Hz, CPPh3), −9.50 (dd, JPP = 253.5 Hz, JPh = 6.5 Hz, OsPPh3) and −18.55 (dd, JPP = 253.5 Hz, JPh = 6.5 Hz, OsPPh3) ppm, which are similar to those of complex 2.16 The 1H NMR spectrum shows a characteristic Os-CPh signal as a doublet at 13.24 ppm with a JPh coupling constant of 21.6 Hz. In the 13C{1H} NMR spectrum, the signals of C1, C4 and C7 are located at 207.9 (br, C1), 201.0 (dt, JPC = 253.5 Hz, JPh = 6.5 Hz, OsPPh3) and −18.55 (dd, JPP = 253.5 Hz, JPh = 6.5 Hz, OsPPh3) ppm, respectively. These results show that the structure of complex 3 is similar to that of complex 2. The molecular formula of complex 3 was also confirmed by HRMS (m/z = 1349.3782). Unfortunately, we failed to acquire high-quality single crystals of complex 3. To further confirm the structure of complex 3, we successfully grew single crystals of complex 4, prepared by an anion exchange reaction of complex 3 with NaBPh4 in methanol (Scheme 1); the obtained crystals were of sufficient quality for single-crystal X-ray diffraction analysis.

The structure of complex 4 is shown in Fig. 2 (the anion is omitted), and contains a terminal alkynyl and an acetyl groups. The crystal unit cell (a = 13.8 Å, b = 18.0 Å, c = 18.3 Å) contained only one molecule of complex 4. The shape of complex 4 was like an ellipsoid with distances of ca. 11.7, 12.4, and 16.6 Å in three dimensions and was close to its unit cell. The osmium in complex 4 was surrounded by a conjugated 12-carbon chain (C1–C12). The metallacycle comprising Os1 and C1–C12 was approximately coplanar, as reflected by the small mean deviations from the least-squares plane (0.074 Å). The substructure of the metallacycle was similar to that of complex 2. Structurally, the ethynylbenzene group in complex 4 was attached at C9, which was the same position as that of the ethynylbenzene group in complex 3.

Click reactions have been demonstrated to be a powerful method for preparing functional ferrocene-containing metallo-polymers.17 As complex 3 contains a functional terminal alkynyl group, we therefore tried the reaction of complex 3 with the water soluble methoxypolyethylene glycol azide (mPEG-N3) to prepare the amphiphatic macromolecules. To determine whether the expected click reaction could occur effectively in our system, we first used a small organic azide, 1-azido-2-(2-methoxyethoxy)ethane, to test our idea. On the basis of the NMR data, we deduced the structure of complex 5. For example, the 31P{1H} NMR spectrum shows three signals at 9.61 (t, JPP = 6.5 Hz, CPPh3), −9.24 (dd, JPP = 253.5 Hz, JPh = 6.5 Hz, OsPPh3) and −18.54 (dd, JPP = 253.5 Hz, JPh = 6.5 Hz, OsPPh3) ppm, which are similar to the signals of complex 3, and confirm the presence of the organometallic unit. The 1H NMR spectrum of complex 5 shows six signals of protons on the metallacycle: 13.20 (d, JHH = 20.6 Hz, H11), 8.69 (s, H3), 7.91 (s, H10), 7.64 (s, H5), 7.57 (s, H6), and 6.58 (s, H12) ppm. The presence of the 1,2,3-triazole substructure was confirmed by the signal at 8.42 ppm as a singlet in the 1H NMR spectrum. In addition, the (CH3)2O(CH2)2OMe group was also confirmed by the signals at 4.70 (t), 4.02 (t), 4.48 (t), 3.70 (t), and 3.41 (s) ppm. These results show that the preparation of the title metal-containing macromolecule using a click reaction of complex 3 with mPEG-N3 is reliable.

Osmium-containing macromolecules 6–8 were then readily prepared using mPEG-N3 with higher molecular weights.
Precipitates were seen until concentrations of 1 mg mL$^{-1}$ dissolved/dispersion behaviors. When dissolved in water, enhanced permeability and retention (EPR) effects. Particles fall within the best range, from 50 to 200 nm, for NIR absorption band at 700 nm. Macromolecules containing metal-containing macromolecules was successful. Experimentally, macromolecules containing metal-containing macromolecules was successful. To verify their suitability as photothermal agents, 7 and 8 in solutions with concentrations ranging from 0.25 to 1.00 mg mL$^{-1}$ were exposed to 808 nm NIR laser irradiation at a power density of 1.0 W cm$^{-2}$. A concentration-dependent temperature increase in solutions 7 and 8 was observed. In particular, solutions containing 0.75 mg mL$^{-1}$ 7 and 1.00 mg mL$^{-1}$ 8 exhibited rapid temperature increases from 26 to 52 °C and 26 to 47 °C, respectively, within 5 min at a laser power density of 1.0 W cm$^{-2}$ (Fig. 4b and S34†), indicating excellent photothermal properties of 7 and 8.

To study the biocompatibility of 7 and 8, standard methyl thiazolyl tetrazolium (MTT) assay experiments were carried out to determine the cytotoxicity of macromolecules 7 and 8 through the measurement of the relative viabilities of HeLa cells. The cells were incubated with 7 and 8 at concentrations ranging from 0.25 to 0.75 mg mL$^{-1}$. It was observed the macromolecules with longer mPEG exhibited lower cytotoxicity. The viability of the HeLa cells was greater than 80% after they had been incubated with macromolecule 8 at a substantially high concentration (0.75 mg mL$^{-1}$), indicating that 8 has low cytotoxicity similar to some other reported photothermal therapy agents (Fig. 5).
In summary, we successfully prepared a new class of amphiphatic metal-containing macromolecules with excellent photothermal properties. Self-assembly of the amphiphatic macromolecules led to nanoparticles with very low cytotoxicity. These macromolecules have great potential for use as theranostic agents in photothermal therapy.

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Notes and references

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