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Research Article

Silane-Functionalized Metal−Organic Frameworks for Stimuli-Responsive Drug Delivery Systems: A New Universal Strategy

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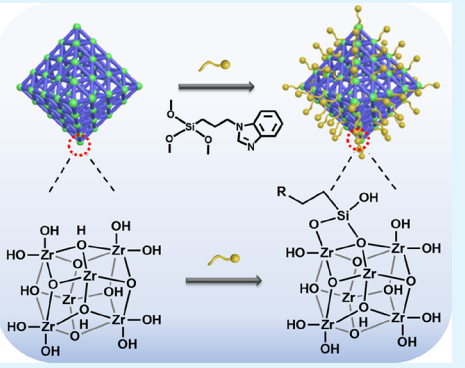
ABSTRACT: A new universal strategy for silane functionalization of metal−organic frameworks (MOFs) was developed. It was demonstrated that silanes were coupled both with terminal hydroxyl (OH) groups and with bridging OH groups of metal-oxo clusters of MOFs through condensation reactions between the silanols of hydrolyzed silanes and the terminal/bridging OH groups to form metal−O−Si bonds. A wide variety of functionalization of MOFs with conventional silanes can be realized by combining synthesis reactions in the solution phase and chemical modifications on the surface. Multivalent supramolecular nanovalves based on the host−guest chemistry of cyclodextrin polymer (CDP) and benzimidazole stalks silanized on the nanoscale MOF (NMOF) surface were successfully constructed. The CDP-valved NMOFs showed the excellent performance of low pH- and α-amylase-responsive controlled drug release. In vitro and in vivo results demonstrated that the CDP-valved NMOFs had a significant inhibitory effect on tumor growth and almost no damage/toxicity to normal tissues. The silanization strategy is universal and opens up a new way for the functionalization of MOFs, which are endowed with a wide variety of applications spanning gas storage, chemical sensing, adsorption and separation, heterogeneous catalysis, and drug delivery.



KEYWORDS: *chemotherapy, controlled drug release, metal−organic framework, silane functionalization, supramolecular nanovalve*

INTRODUCTION

Metal−organic frameworks (MOFs) are a class of porous crystalline materials consisting of metal ions/metal clusters cross-linked by various types of organic ligands via coordination interactions.[1,2] To be precise, "metal-oxo clusters" containing M−O−M bonds should be used to describe MOFs rather than "metal clusters", which are typically considered to contain M−M bonds. MOFs have been extensively studied in gas storage,[3] chemical sensing,[4] adsorption and separation,[5] heterogeneous catalysis,[6] and drug delivery[7−11] because the pore sizes and functionalities of these materials can be fine-tuned through the choice of organic ligands and metal-containing units. By selecting appropriate MOFs with large microporous or mesoporous sizes with good biocompatibility and high thermal, mechanical, and chemical durabilities,[12] tailor-made nanoscale MOFs (NMOFs) allow for entrapment of drugs within the large micropores or mesopores and subsequent capping of gatekeepers for the stimuli-responsive controlled release of drugs from gated NMOFs.

In general, the surface functionalization of NMOFs is a prerequisite for introducing responsive groups or smart materials on the NMOF surface to achieve the stimuli-responsive controlled drug release, and the surface functionalization of NMOFs is also in demand for use in various applications in other fields. However, compared with various kinds of MOF materials, surface modification methods are few and lack universality. In addition to polymer-coated NMOFs via electrostatic interactions and other non-covalent interactions,[13−15] which are affected by the ionic strength of the solution and lead to the instability of coated NMOFs, there are mainly two post-synthesis modification approaches for surface functionalization of NMOFs with modifiers to construct gated NMOFs reported to date.[11] The surfaces of NMOFs are modified or functionalized by means of the active groups of bridging ligands (such as amino groups for amidation linkage)[16] or the active groups pre-introduced to bridging ligands (such as azide groups for azide−alkyne "click chemistry" coupling).[17,18] However, this kind of functionalization approach is typically limited to special bridging ligands. Additionally, terminal amino-containing polymers were also covalently linked through the carboxylic acid groups at the external surface of MIL-100(Fe^{III}) using the amidation strategy;[19] however, the loaded drug molecules containing carboxylic acid groups might be amidated. Mirkin and co-

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