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Synthesis and functionalization of nanoengineered materials using click chemistry

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ABSTRACT

The synthesis of nanoengineered materials with precise control over material composition, architecture and functionality is integral to advances in diverse fields, including biomedicine. Over the last 10 years, click chemistry has emerged as a prominent and versatile approach to engineer materials with specific properties. Herein, we highlight the application of click chemistry for the synthesis of nanoengineered materials, ranging from ultrathin films to delivery systems such as polymersomes, dendrimers and capsules. In addition, we discuss the use of click chemistry for functionalizing such materials, focusing on modifications aimed at biomedical applications.

Contents

Abbreviations: Ab, antibody; ATRP, atom transfer radical polymerization; Az, azide; BSA, bovine serum albumin; Cu, copper; CuAAC, copper-catalyzed alkyne-azide cycloaddition; CB(6), cucurbit[6]uril; CD, cyclodextrin; DA, Diels–Alder [4+2] cycloaddition; DNA, deoxyribose nucleic acid; DOX, doxorubicin; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide ene alkene; HYA, hyaluronan; LbL, layer-be-layer assembly; LCST, lower critical solution temperature; NAS, N-acroyloxysuccinimide; NCCM, noncovalently connected micelle; NHS, *N*-hydroxy succinimide; PAA, poly(acrylic acid); PBLG, poly(γ-benzyl-L-glutamate); PCL, poly(ε-caprolactone); PDPA, poly(2-diisopropylamino ethyl methacrylate); PEG, poly(ethylene glycol); PHEMA, poly(2-hydroxy ethyl methacrylate); PGA_{Alk}, alkyne-modified poly(L-glutamic acid); PGA, poly(L-glutamic acid); PMA, poly(methacrylic acid); PMMA, poly(methyl methacrylate); PNIPAM, poly(*N*-isopropylacrylamide); POEGMA–PDMA–PDEA, poly(oligo(ethylene glycol) monomethyl ether methacrylate)-b–poly(2-dimethylamino) ethyl methacylate-b–poly(2-diethylamino) ethyl methacylate); PPDSM, poly(pyridyl disulfide ethyl methacrylate); PS, poly(styrene); PSS, poly(styrene sulfonate); PtBA, poly(*tert*-butyl acrylate); PVPON, poly(*N*-vinyl pyrrolidone); Qβ, capsid of bacteriophage; rDA, retro-Diels–Alder; RGD, arginine–glycine–aspartic acid; ROP, ring opening polymerization; SAMs, self-assembled monolayers; SPAAC, strain-promoted cycloaddition of alkynes and azide; SPIO, superparamagnetic iron oxide.

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1. Introduction

The development of functional nanoengineered materials is fundamental for advances in diverse fields such as biomedicine, optics, and green energy production. The synthesis of such materials requires synthetic techniques that afford precise control over material properties. In the last decade, click chemistry has emerged as a promising technique to engineer the architecture and function of materials [1,2]. Typical click reactions display several important criteria, such as high efficiency under mild conditions, minimal byproducts, and limited side reactions. The most well-documented example is the copper (Cu) (I) catalyzed alkyne-azide cycloaddition to form 1,2,3 triazoles. However, recently a number of other reactions, including Cu-free click and Diels–Alder cycloaddition, have also generated significant interest.

Recently, the application of these click techniques has found widespread use in the synthesis of novel nanostructured polymers. There are a number of comprehensive reviews highlighting this area, detailing the complex and innovative polymer building blocks that can be designed [3,4]; hence this review will not discuss these studies. However, this enhanced versatility in polymer design has led to the development and functionalization of a range of new nanoengineered films, particles and scaffolds. In this trend article we highlight the recent developments for synthesizing materials using click reactions, focusing on materials with application in biomedicine. We also discuss the application of click techniques to functionalize both new and existing nanoengineered materials to optimize their interactions both *in vitro* and *in vivo*.

2. Fundamentals of click chemistry

Sharpless and co-workers introduced the concept of a click reaction in 2001 [5]. The reactions were identified by a stringent set of criteria, including simple reaction conditions, high efficiency, regio- and stereoselectivity, and amenable to reaction under mild conditions. Click reactions achieve these characteristics by having a high thermodynamic force, usually greater than 20 kCal mol^{-1}. Such reactions proceed rapidly to completion and tend to be highly selective. The latter characteristic is important for applications where there is a diverse range of functionality present, for example *in vivo*.

In 2002, both the Sharpless and Meldal laboratories reported a dramatic increase in reaction rate for the traditional Huisgen cycloaddition using a copper catalyst [6,7]. This new reaction, termed copper-catalyzed alkyne-azide cycloaddition (CuAAC), has since become the premier example of click chemistry. Since 2004, this reaction has been applied to the construction of numerous new materials from block copolymers through to complex dendrimer or self-assembled materials [8].

2.1. Copper-catalyzed alkyne-azide cycloaddition

The CuAAC reaction occurs between an organic azide and a terminal alkyne in the presence of Cu(I) to form a 1,4 disubstituted 1,2,3 triazole (Fig. 1a). This is in contrast to the noncatalyzed reaction, which proceeds under elevated temperatures to form a mixture of 1,4- and 1,5-triazole regioisomers [9]. The rate of the CuAAC reaction is over 10^7 times faster than the conventional reaction, which means it proceeds efficiently at room temperature. The CuAAC mechanism is complex and some aspects are still unclear, such as the form of the copper acetylide intermediate. However, it basically involves three key steps: firstly there is the initial formation of a 5-triazolyl copper intermediate. Secondly, this intermediate coordinates the organic azide and then the nucleophilic carbon on the copper(I) acetylide reacts with the electrophilic terminal nitrogen on the azide. Finally, this metallocycle undergoes ring contraction and subsequent dissociation of the product to regenerate the catalyst [9].

CuAAC proceeds in many protic and aprotic solvents, including water, and is unaffected by most inorganic and organic functional groups. Due to its tolerance for other functionality, a number of species can be added without affecting the CuAAC reaction, including inorganic azides in large excess. Cu(I) is required to catalyze the click reaction; however, it can either be added or produced *in situ*. One typical approach is to use a Cu(I) salt such as copper iodide, chloride or acetate. However, it can be challenging to keep the Cu active throughout the reaction. Among the common oxidation states of Cu (0, +1 and +2), the +1 state is the least thermodynamically favored. Therefore, cuprous ions can be readily oxidized to form Cu(II) or disproportionate to a mixture of Cu(II) and Cu(0) [10]. When present in significant amounts, Cu(II) can facilitate Glaser-type alkyne coupling processes while impairing triazole formation. Thus, when using Cu(I) directly, it is often necessary to perform the reaction under oxygen-free conditions.

A common alternative to the use of Cu(I), which removes the need for oxygen-free conditions, was developed by Hein and Fokin [10]. This process involves combining Cu(II) salts, such as copper(II) sulfate pentahydrate or copper(II) acetate, with a mild reductant such as sodium ascorbate. In addition to reducing the