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Programmed disassembly of supramolecular nanoparticles stabilized by heteroternary CB[8] host-guest interactions

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ABSTRACT

Controlled release is an important determinant of the *in-vivo* performance of drug delivering nanoparticles (NPs). Therefore the control over and understanding of the release mechanism, *e.g.* by disassembly or degradation of the carrier, is essential for the optimization of NP formulations. This paper presents a supramolecular toolbox approach for the formation and UV-induced disassembly of supramolecular nanoparticles (SNPs) which are either exclusively stabilized by cucurbit[8]uril (CB[8])/methyl viologen (MV)/azobenzene (Azo) interactions or CB[8]/MV/naphthol (Np) interactions, or by a combination of both. Photoisomerization of the Azo units enables UV-triggered disassembly of the CB[8]/MV/Azo host-guest complex. Depending on the valency of the electron-rich guest moieties (Np or Azo), either SNPs with a UV-responsive shell or a UV-responsive core were formed by assembling SNPs using a mixture of Azo and Np bearing guest molecules. In contrast, non-responsive SNPs or SNPs which disintegrate at both the core and the shell were formed by using exclusively CB[8]/MV/Np or CB[8]/MV/Azo interactions, respectively.

1. Introduction

Inorganic and organic nanoparticles (NPs) of different compositions are versatile platforms for biomedical applications, because they are able to carry small molecules or act as diagnostic tools [1–7]. Above all, selectively triggered nanoparticle (NP) disassembly is of substantial interest as encapsulated drugs or imaging agents can be released upon NP degradation [8–10]. In particular in drug delivery applications, control over the rate of degradation is of high importance to attain a constant and prolonged drug dose in the blood flow. When NP degradation occurs too fast, this can lead to a peak in drug concentration followed by a fast drop-off until re-administration, which effect is known to minimize the therapeutic performance of drug delivery vectors. Therefore, biodegradable polymer NPs and mesoporous silica nanoparticles have been developed to achieve prolonged drug release [11,12].

In oncology, most imaging and drug delivery NPs take advantage of the enhanced permeability and retention (EPR) effect, *i.e.* a preferential uptake of the NPs by the tumor caused by the higher permeability and porosity of tumor tissue in comparison to normal tissue [13]. This passive targeting enables NPs with sizes below 100 nm to penetrate and release the active compounds in the desired tissue. Nevertheless, Larsen et al. have shown that especially small NPs can re-enter the bloodstream after penetration [14]. Accumulation of NPs by aggregation is an alternative method to avoid out-diffusion of NPs from the carcinogenic tissue. Different strategies to induce NP aggregation have been reported, mostly restricted to inorganic NPs [15–18]. Examples of triggered NP disassembly or degradation employ external stimuli such as pH [19,20], temperature [21], chemical reduction [22], light [23] or combinations thereof [24,25]. Despite the interest in finding ways to control the degradation of NPs or to trigger the release of small molecules from the NPs, only few studies elucidate the underlying decomposition mechanism in more detail [26,27].

Supramolecular nanoparticles (SNPs) established by multiple host–guest interactions form a specific category of responsive NPs [28–30]. Their intrinsically stable yet reversible character and their chemical flexibility have been used to encapsulate DNA [31,32], drugs [33–35], and imaging agents [36,37] for the formation of biomedically relevant nanovectors. In previous publications reported by our group [23,38], SNP formation was achieved by employing multivalent heteroternary host–guest interactions between cucurbit[8]uril (CB[8]), methyl viologen (MV) and either naphthol (Np) or trans-azobenzene (Azo) as the second, electron-rich guest molecule. Hereto, MV was grafted onto poly(ethylene imine) (PEI) while the multivalent poly(amido amine) (PAMAM) dendrimer and monovalent poly(ethylene glycol) (PEG) were both functionalized with Np or Azo (see Fig. 1a, routes A and B).

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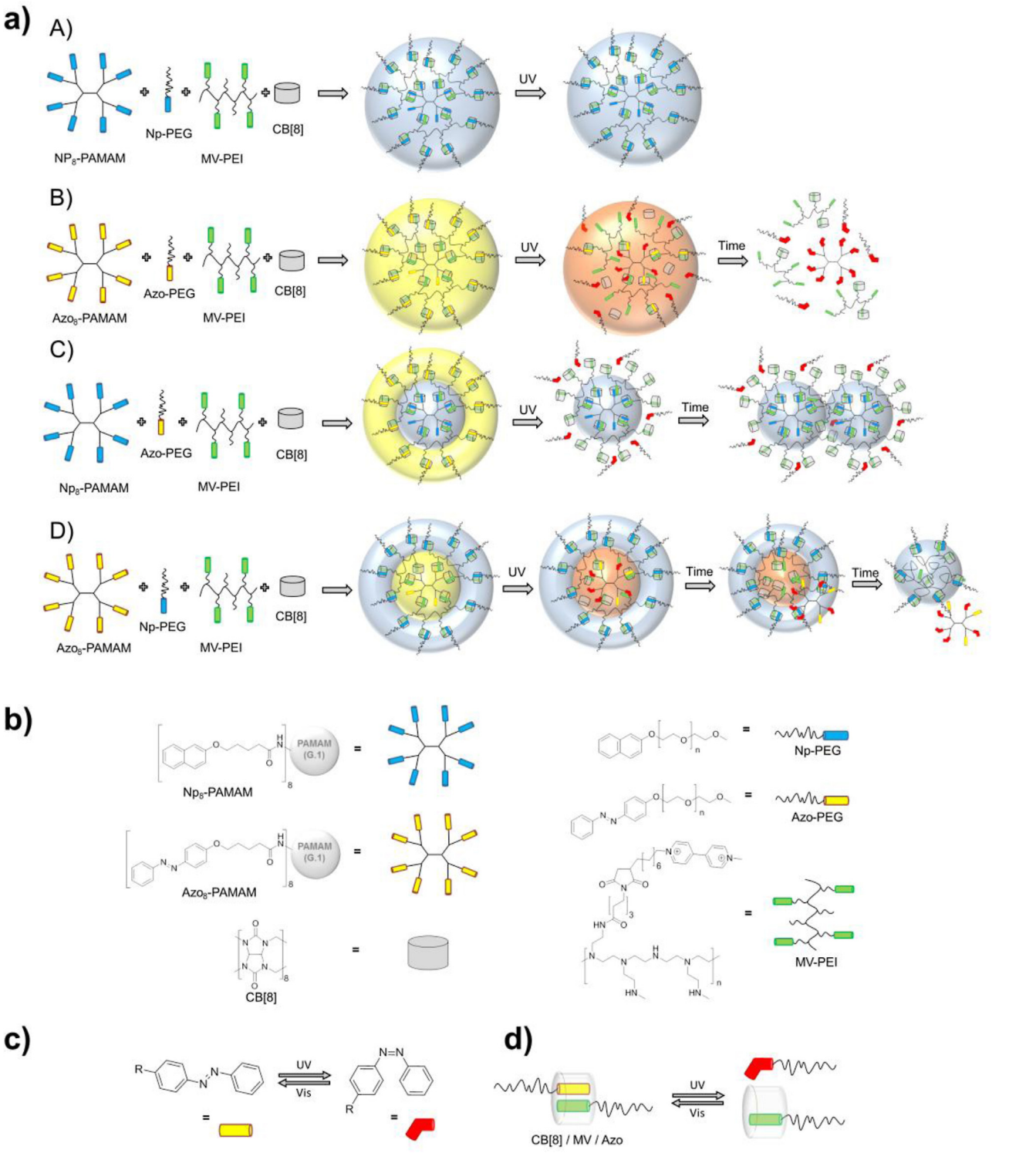

Fig. 1. (a) Schematic representation of the assembly of supramolecular nanoparticles (SNPs) mediated by the heteroternary complexes between cucurbit[8]uril (CB[8]), methyl viologen (MV), and naphthol (Np) and/or azobenzene (Azo), and the UV light-induced disassembly mechanisms of the different SNPs. (b) Molecules and abbreviations used here, (c) photoisomerization of azobenzenes, (d) schematic representation of the light-responsive ternary complex consisting of CB[8], azobenzene (Azo) and methylviologen (MV).

Regardless whether Np or Azo-terminated building blocks are used for SNP preparation, the SNP structures are stabilized by multiple charge transfer (CT) complexes employed by the electron donating MV and the electron accepting Np or Azo groups which are stabilized in the hydrophobic cavity of CB[8] (Fig. 1d). Furthermore the electron-donating and accepting molecules are connected within the CB[8] cavity in a head-to-tail fashion which is mainly attributed to steric hindrance of both molecules at the CB[8] portal [39,40]. These CB[8]-included CT complexes function as connectors between the multivalent dendrimer, the monovalent stopper units and the MV polymer. Irrespective of the stabilizing heteroternary complex, the electron-rich guest-bearing PAMAM dendrimers

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