ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d6cc01210h

Received 26th February 2026,
Accepted 20th May 2026

DOI: 10.1039/d6cc01210h

rsc.li/chemcomm

Light-responsive aggregation of vesicles using host–guest interaction of β-cyclodextrin and diazocine

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Reversible aggregation of vesicles in water is triggered by UV light and suppressed with green light. Aggregation is based on light-responsive host–guest interaction of cyclodextrins at the vesicle surface and tripodal diazocine as a supramolecular crosslinker, activated by its conversion to the *E*-isomer under UV irradiation.

Light is among the most attractive stimuli for responsive materials, as it provides important advantages such as spatial-temporal control and a wide range of wavelengths and intensities that can be used to trigger different responses within the same sample. Molecular photoswitches are a special class of compounds that enable the reversible manipulation of materials and systems by light. Upon photoisomerization with a specific wavelength, molecular photoswitches reversibly change their properties, such as shape and dipole moment. The most commonly used photoswitches are azobenzenes, azoheteroarenes (such as arylazopyrazole, AAP), spiropyranes, and diarylethenes.[1–4]

Diazocine has emerged as a rather special class of azobenzene photoswitches. Diazocine is different from azobenzene and related photoswitches as it has a thermodynamically stable *Z*-isomer, which upon irradiation with UV light (390 nm) transforms to the metastable *E*-isomer. This is exactly opposite to the majority of azobenzenes that have a thermodynamically stable *E*-isomer, which upon irradiation with UV light (365 nm) converts to the metastable *Z*-isomer.[1] To date, diazocine has primarily been used to create photoswitchable coordination cages, photopharmacological compounds, and self-assembled monolayers.[5–10] Recently, also the photoresponsive host–guest interaction of diazocines and cucurbiturils was reported.[11]

A key feature associated with hydrophobic azobenzenes is their host–guest chemistry in aqueous solution. A versatile host for azobenzene is cyclodextrin (CD), with the less polar *E*-azobenzene binding strongly to α-cyclodextrin as well as β-cyclodextrin, and the more polar *Z*-azobenzene binding only weakly.[12–15] Many strategies have been employed to create dynamic supramolecular materials that feature the reversible aggregation of nanoparticles and polymers, including techniques based on the photoresponsive host–guest interaction of CDs and azobenzenes.[13,16–24] The combination of photoswitches and CD has been used extensively by our group in the past to develop light-responsive reversible aggregation of nanoparticles and vesicles.[25–29] We utilized an azobenzene-based divalent ligand that exhibited reversible aggregation of CD vesicles (CDV) upon irradiation with 350 nm and 455 nm light due to the formation and rupture of non-covalent crosslinks.[25] Next, we showed the reversible aggregation of CDV using an AAP-based divalent ligand. Here, since AAP was used instead of azobenzene, the wavelengths of light that can be used for reversible aggregation of vesicles shifted to 365 nm and 520 nm.[28] In both these cases, azobenzene- or AAP-based ligands were used to act as a supramolecular glue, and the CDV aggregated immediately upon addition of the ligand to the system. Spontaneous aggregation occurs because both azobenzene and AAP have a thermodynamically stable *E*-isomer that preferentially binds to the cavity of β-CD compared to the metastable *Z*-isomer.

In the current report, we circumvent spontaneous aggregation by implementing diazocine as a photoswitch with a thermodynamically stable *Z*-isomer. Due to this modification, spontaneous aggregation of CDV will not occur upon the addition of diazocine-based ligand. Instead, it occurs only when the sample is irradiated with UV light (390 nm), providing complete photocontrol over the supramolecular aggregation. As a consequence, an inverse trend is observed with respect to previously used azobenzene and AAP ligands. Upon irradiation with UV light, the vesicles aggregate, and upon irradiation with green light (515 nm), they disperse, which is exactly opposite to previous supramolecular systems that featured aggregation upon irradiation with blue or green light and dispersion upon irradiation with UV light.[25,28] To the best of our knowledge, this is the first report where the reverse trend of assembly and

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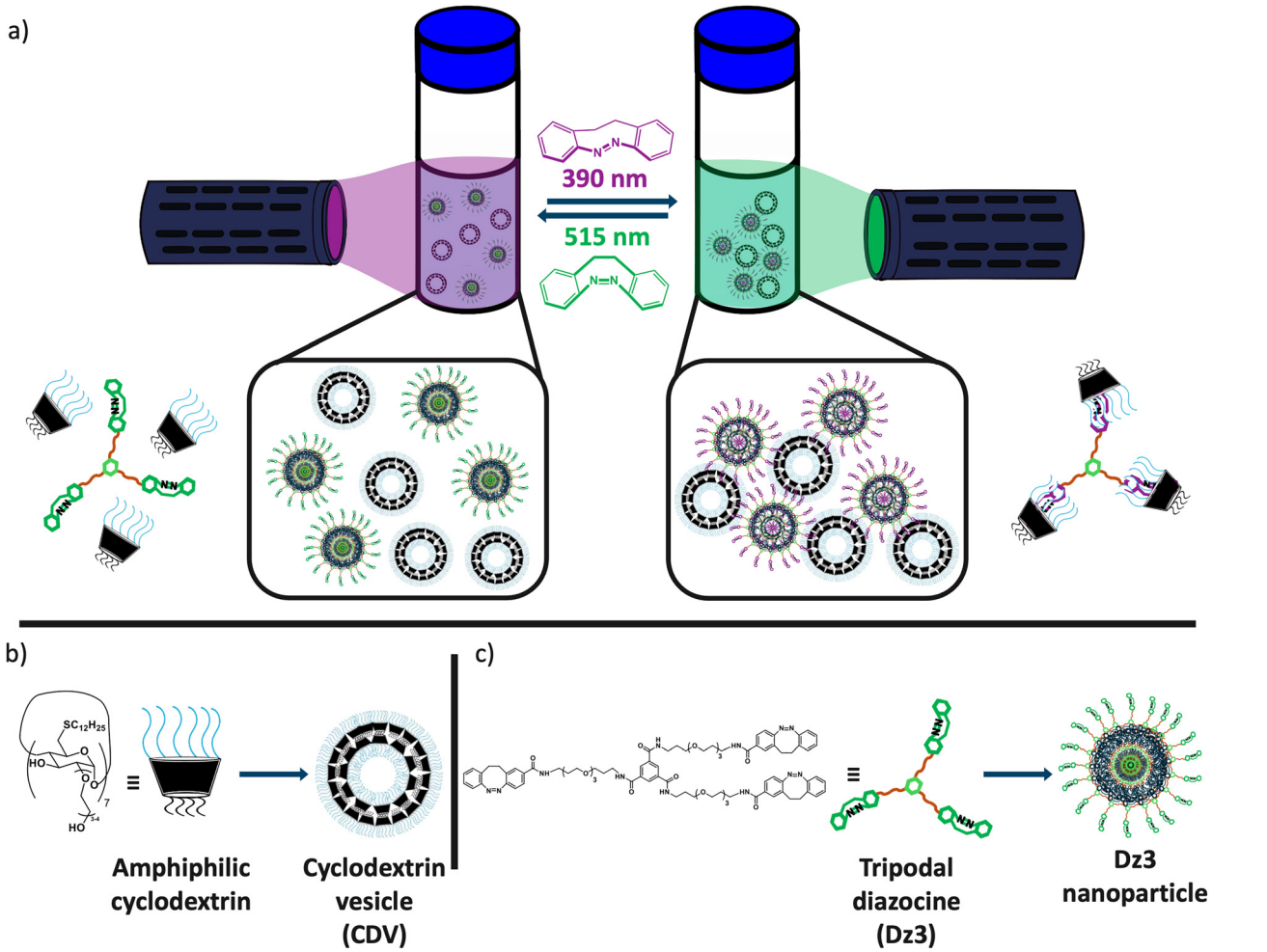

Fig. 1 Schematic representation of light-responsive aggregation of cyclodextrin vesicles (CDV) using tripodal diazocine (Dz3) crosslinkers. (a) Light-responsive aggregation of CDV and Dz3 *via* host–guest complex formation upon irradiation with UV light (390 nm) and green light (515 nm). (b) Amphiphilic cyclodextrins form CDV in water. (c) Amphiphilic Dz3 forms supramolecular nanoparticles in water.

disassembly is observed in photoresponsive supramolecular colloids and dormant supramolecular interactions are activated (rather than inactivated) with UV light. A schematic overview of light-responsive vesicle aggregation is shown in Fig. 1.

The primary step required for the synthesis of diazocine-based ligand (Dz3) was the synthesis of diazocine acid 1, which was prepared according to the reported procedure.[30,31] Details of the synthesis and analysis are provided in the supplementary information (see SI Fig. S8). Intermediate 2 was also synthesized from the reported procedure from commercially available 3,3′-oxybis(propan-1-amine).[32] Next, 1 and 2 were coupled *via* amide bond formation between the primary amine of 2, and the carboxylic acid from 1, to obtain Boc-protected diazocine amide (Dz1-Boc, 3) in good yields. Then, 3 was deprotected *via* trifluoroacetic acid (TFA) to yield diazocine amide (Dz1), which was then coupled again *via* amide bond formation with benzene-1,3,5-tricarbonyl trichloride to obtain Dz3 in decent yield.[32]

UV-vis measurements confirmed the photoisomerization of Dz3 in water (Fig. 2). It was observed that Dz3 is photoswitchable similar to other diazocines: upon irradiation with 390 nm

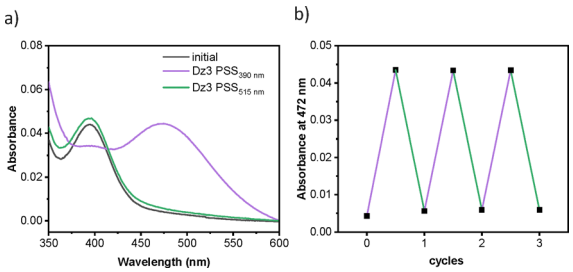

Fig. 2 Photoisomerization of Dz3. (a) Absorbance spectrum of Dz3 in Milli-Q after irradiation with UV light (390 nm, 3 W) and green light (515 nm, 3 W), each for 30 min. (b) Absorbance maxima at 472 nm after irradiation with UV light and green light. Concentration of Dz3: 50 μM in Milli-Q.

light, the characteristic absorption band at 395 nm that signifies the n → π* transition of the *Z*-isomer decreases, and a new band appears at 472 nm that signifies the n → π* transition of the *E*-isomer. Photoisomerization is repeatable at least up to 3 cycles. These absorbance experiments conclude that Dz3 acts

as a reversible photoswitch. The thermal half-life of the *E*-isomer in water was found to be 138 min (see SI Fig. S1). The photostationary state (PSS), as measured by NMR in dichloromethane, was found to be 76% for the *Z* to *E* transition with UV light and more than 95% for the *E* to *Z* transition with green light (see SI Fig. S14 and S15).

Furthermore, we investigated whether Dz3 can act as a guest for the host molecule β-cyclodextrin (β-CD). Binding studies were performed using isothermal calorimetry (ITC) with a titration of host β-CD to guest Dz3 (see SI Fig. S6). Dz3 was irradiated with 390 nm light for 30 min to convert to the *E*-isomer, and then a titration with β-CD was performed. It was observed that the *E*-isomer of Dz3 forms a 1 : 1 host–guest complex with a binding constant $K = 2.22 \times 10^3\ M^{-1}$. This shows significant binding between the *E*-isomer of Dz3 and β-CD. Also, the *Z*-isomer of Dz3 was studied for binding with the β-CD. After irradiating the solution for 30 min with 515 nm light, the *Z*-isomer shows a binding constant $K = 1.95 \times 10^3\ M^{-1}$ with β-CD.

Although the ITC data indicate a rather small difference in binding constants, we note that the binding constant determined for the *E*-isomer is likely underestimated due to the modest PSS of the *Z* to *E* photoisomerization as well as the time taken to complete the ITC measurement, which is comparable to the half-life of the *E*-isomer. Nevertheless, the values of d*H* and d*S* are very different for both isomers. In the case of the *Z*-isomer, the d*H* value is higher, and the d*S* value is slightly negative, indicating an enthalpy-driven process. In the case of the *E*-isomer, the process is more entropy-driven, with d*S* clearly positive and d*H* value lower. In any case, it can be concluded that the *E*-isomer of Dz3 binds to β-CD with a greater affinity than the *Z*-isomer. This finding is consistent with simulation studies by Herges and co-workers showing that *E*-diazocine binds strongly inside the cavity of β-CD, while *Z*-diazocine can only bind one phenyl ring and the azo part remains exposed to the solvent.[8]

After the photophysical characterization and host–guest binding studies, Dz3 was examined for self-aggregation. For this purpose, a 50 μM solution of Dz3 was prepared in water using a 0.5 mM stock (1 : 1, DMSO : water). The critical aggregation concentration as determined by absorbance was found to be 15 μM (see SI Fig. S2). The Dz3 solution was then examined by dynamic light scattering (DLS), which indicated the formation of aggregates with a size of 140 nm. Furthermore, it was investigated whether photoisomerization affects the size of the supramolecular nanoparticles of Dz3. To examine this, the Dz3 solution was exposed to three cycles of alternating 390 nm light (30 min) and 515 nm light (30 min). Although the size of the supramolecular nanoparticles fluctuated during irradiation, no pattern in the size change was observed with respect to the corresponding wavelength of light (see SI Fig. S4 and S5). The solution of Dz3 (50 μM) was then assessed *via* transmission electron microscopy (TEM). It was observed that spherical aggregates were formed with a size of 118 ± 29 nm, consistent with DLS. The sample of Dz3 (50 μM) was also analyzed by atomic force microscopy (AFM), and the size of the spherical aggregates was 71 ± 11 nm with a height of 3 ± 2 nm. We assume that the aggregation of Dz3 is the result of hydrophobic

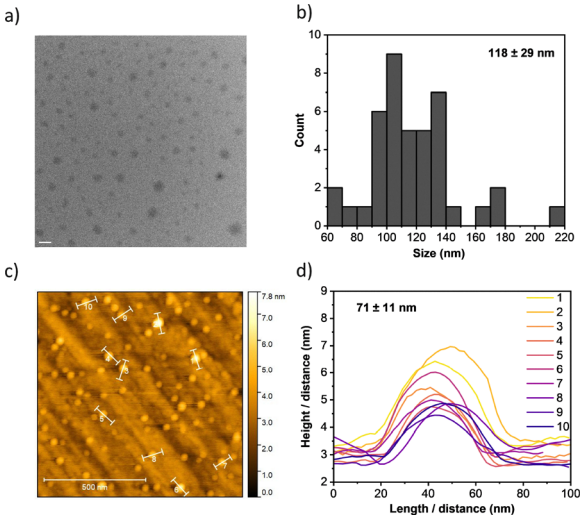

Fig. 3 Size and morphology of supramolecular nanoparticles formed by Dz3. (a) TEM. (b) Size distribution based on TEM. (c) AFM. (d) AFM height sections as shown in the AFM scan. For AFM, ten aggregates were randomly selected and marked 1–10 in (c), and their size and height are reported in (d). Scale bar for (a) 200 nm and for (b) 500 nm. Concentration of Dz3: 50 μM in Milli-Q.

interactions of the tripodal amphiphile, giving rise to soft supramolecular nanoparticles that flatten upon adsorption on the TEM and AFM substrates (Fig. 3). It should be noted that DLS, AFM and TEM each show limitations in the analysis of these supramolecular nanoparticles and drying effects for AFM and TEM as well as the hydration shell for DLS affect the observed size. However, the measured values are in good agreement and give a consistent estimate for the size.

To investigate the host–guest interaction of CDV with Dz3, CDV with an average size of 100 nm were prepared from amphiphilic β-CD as described.[33,34] In brief, amphiphilic β-CD was dissolved in $CHCl_3$ and then evaporated under argon to form a thin film. Upon addition of water, amphiphilic β-CD forms multilamellar vesicles that are extruded through a 100 nm filter to regulate the size. The dispersion of CDV was then mixed with Dz3 solution, which resulted in a 1 : 1 mixture of 50 μM CDV and 50 μM Dz3. The average size of the assemblies was *ca.* 100 nm as determined by DLS. Next, the mixture was irradiated with 390 nm for the duration of 30 min, which converts *Z*-diazocine to *E*-diazocine, and hence Dz3 could bind more strongly to the β-CD at the surface of the CDV, thus causing aggregation, and indeed the average assembly size increased to *ca.* 300 nm. Next, the sample was irradiated with 515 nm for 30 min, converting *E*-diazocine back to *Z*-diazocine, and thus diazocine escaped out of the cavity of β-CD, which caused the disaggregation of the CDV and the average assembly size changed back to *ca.* 100 nm. The aggregation and disaggregation cycles were repeatable at least 3 times, as observed *via* DLS. Overall, upon irradiation with UV light (390 nm), the average size of the assemblies increased to 313 ± 27 nm, and upon irradiation with green light (515 nm), the average size of the assemblies decreased to 97 ± 3 nm (Fig. 4a and b).

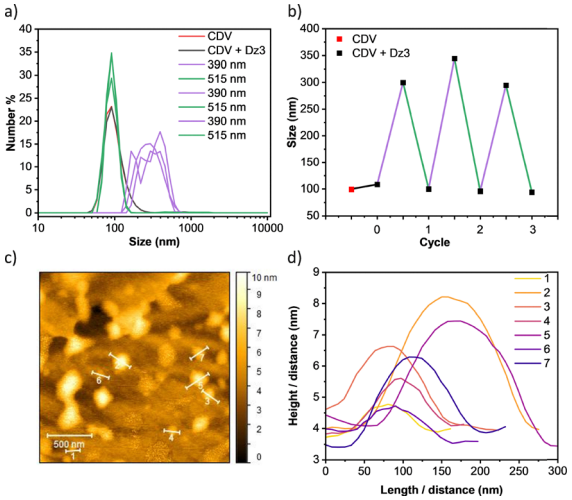

Fig. 4 Photoresponsive aggregation of CDV and Dz3 after irradiation with UV light (390 nm) and green light (515 nm) each for 30 min. (a) Size distribution by DLS. (b) Average size by DLS. (c) AFM scan after irradiation with UV light. (d) AFM height sections as shown in the AFM scan. For AFM, six aggregates were randomly selected and marked 1–6 in (c), and their size and height are reported in (d). Concentration of Dz3: 50 μM, concentration of CDV: 50 μM (in Milli-Q).

Although the analysis of the size change in the mixture of Dz3 and CDV could not be performed by TEM due to the aggregation of CDV during drying, the mixture of Dz3 and CDV (50 μM each) was analyzed by AFM. A height profile of 3 ± 2 nm was observed, and the size was similar to that of CDV from previously reported AFM.[28] Some smaller assemblies of 100 nm or less can also be observed, which might indicate the presence of individual CDV and Dz3 nanoparticles. However, aggregates of two or more vesicles forming a larger aggregate are also observed, corresponding to the larger assembly formation in DLS upon irradiation with UV light (Fig. 4c and d). Finally, to confirm the hypothesis that the photoresponsive change in size is due to host–guest interaction of cyclodextrin and diazocine, excess β-CD (10 mM) was added to the mixture of Dz3 and CDV (50 μM each) to act as competitive inhibitor.[35] Indeed, the size of assembly decreased from *ca.* 550 nm (observed upon irradiation with 390 nm light for 30 min) to *ca.* 200 nm upon addition of β-CD, indicating that Dz3 binds with the excess of free β-CD instead of the amphiphilic β-CD at the surface of the CDV (see SI Fig. S7).

In conclusion, a diazocine-based tripodal ligand (Dz3) was synthesized, characterized, and its binding with β-CD and CDV was investigated. It was observed that Dz3 forms supramolecular nanoparticles in water and acts as a supramolecular glue for CDV due to the photoresponsive multivalent host–guest interaction of Dz3 and β-CD on the surface of the vesicles. Indeed, we could induce the reversible aggregation of the assemblies upon photoirradiation with UV and green light, which is the inverse of comparable systems consisting of azobenzene- and AAP-based ligands. These findings are relevant to the development of supramolecular materials based on dormant components that are inactive in the dark and assemble only upon irradiation with light.

BJR and AK conceptualised the work. AM performed the synthesis and characterization of Dz3. AK performed the photophysical characterisation, binding studies, AFM studies, and reversible aggregation studies, and wrote the manuscript. DM performed the TEM measurements and reviewed the manuscript. BJR provided supervision, reviewed and edited the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: detailed experiments and details related to the synthesis and characterization of the diazocine-based ligand, including experiments such as DLS, TEM, and half-life measurements. See DOI: https://doi.org/10.1039/d6cc01210h.

Acknowledgements

AK and BJR are grateful to the CIM-IMPRS Graduate School at the University of Münster. This work was funded by the Deutsche Forschungsgemeinschaft (DFG CRC 1459 Intelligent Matter – Project ID 433682494).

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