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Photoresponsive Materials | *Hot Paper*

Light-Triggered Transformation of Molecular Baskets into Organic Nanoparticles

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Abstract: Discovering novel and functional photoresponsive materials is of interest for improving controlled release of molecules and scavenging toxic compounds for cleaning our environment or designing chemosensors. In this study, we report on the photoinduced decarboxylation of basket $\mathbf{1}^{6-}$, containing three glutamic acids at its rim. This concave compound is, in an aqueous environment (30 mM phosphate buffer at pH 7.0), monomeric (^{1}H NMR DOSY, DLS) with glutamic acid residues randomly oriented about its rim (^{1}H NMR and MM-OPLS3). The irradiation (300 nm) of $\mathbf{1}^{6-}$ leads to the exclusive removal of its α-carboxylates to give amphiphilic $\mathbf{2}^{3-}$ possessing γ-carboxylates. The photochemical transformation is a consecutive reaction with mono- and bis-decarboxylated products observed with ^{1}H NMR spectroscopy and ESI mass spectrometry. Amphiphilic $\mathbf{2}^{3-}$ is a preorganized molecule (MM-OPLS3) that, in water, aggregates into organic nanoparticles (ca. 50–200 nm in diameter; DLS, TEM and cryo-TEM) having a critical aggregation concentration of 12 μM (UV/Vis). As the transition of monomeric $\mathbf{1}^{6-}$ into nanoparticulate $\mathbf{2}^{3-}$ is triggered with light, we reasoned that stimuli-responsive formation of the soft material lends itself to nanotechnology applications such as controlled release or scavenging of targeted compounds.

Introduction

The assembly of small molecules or functional polymers into nanostructured materials[1] constitutes a powerful methodology for bottom-up construction of nanotubes, gels, vesicles, micelles, nanofibers and other hierarchical structures.[1b,2] In particular, the responsive characteristics[3] of such soft matter have been of a considerable interest for application in the areas of tissue engineering,[4] drug delivery,[5] systems chemistry[6] and sensing.[7] Accordingly, one could use light, ultrasound, chemical, magnetic or redox input to trigger a conformational change or rupture of weak bonds within the material's building blocks to switch its packing and therefore physical and chemical characteristics.[3b,8] The photochemical stimulus[9] provides precise spatial and temporal control over the switching process,[10] which is of particular value for the smart delivery of drugs.[8a,11] That is to say, one can reduce undesired side effects, improve selectivity and therefore optimize drug's potency by exposing affected areas to the stimulus and concurrently tune the pharmacokinetics via modulation of the exposure time/intensity.[12] So far, isomerization of azobenzenes, dithienylethene and spyropirans as well as degradation of *o*-nitrobenzyl derivatives constitutes prevalent photochemical strategies[13] for manipulating chemical/physical characteristics of soft matter with light.[14] It follows that developing novel photo-responsive[15] or photo-caging[16] methods could be beneficial for: (a) improving compatibility, stability and performance of materials in aqueous environments and (b) permitting utilization of parallel input signals for activation of "orthogonal" switches and building multifunctional structures. In this vein, we recently discovered[17] that molecular baskets with α-amino acids at their rim, and nerve-agent simulants residing in their cavity, undergo photo-induced decarboxylation[18] and precipitation, amounting to a method for the removal of toxic warfare agents from water. Will the irradiation of deeper-cavity $\mathbf{1}^{6-}$ (Figure 1), containing three glutamic acids at its rim, elicit the elimination of α- and/or γ-carboxylates to give fully or partly decarboxylated baskets in addition to other cyclic[19] and radical-mediated products?[20]

In this study, we found that C_3 symmetric and hexaanionic $\mathbf{1}^{6-}$ stays monomeric in water at pH 7 (Figure 1). When prompted with light stimulus, however, $\mathbf{1}^{6-}$ undergoes a consecutive loss of three α-carboxylates to give $\mathbf{2}^{3-}$ (Scheme 1).[17] Following, preorganized and amphiphilic $\mathbf{2}^{3-}$ (comprising a hydrophobic cage and three aliphatic chains conjugated to polar carboxylates) assembles into spherical nanoparticles as, we posit, concave hosts populate the space of such nanosized objects.[2f] With light stimulus triggering the formation of unique

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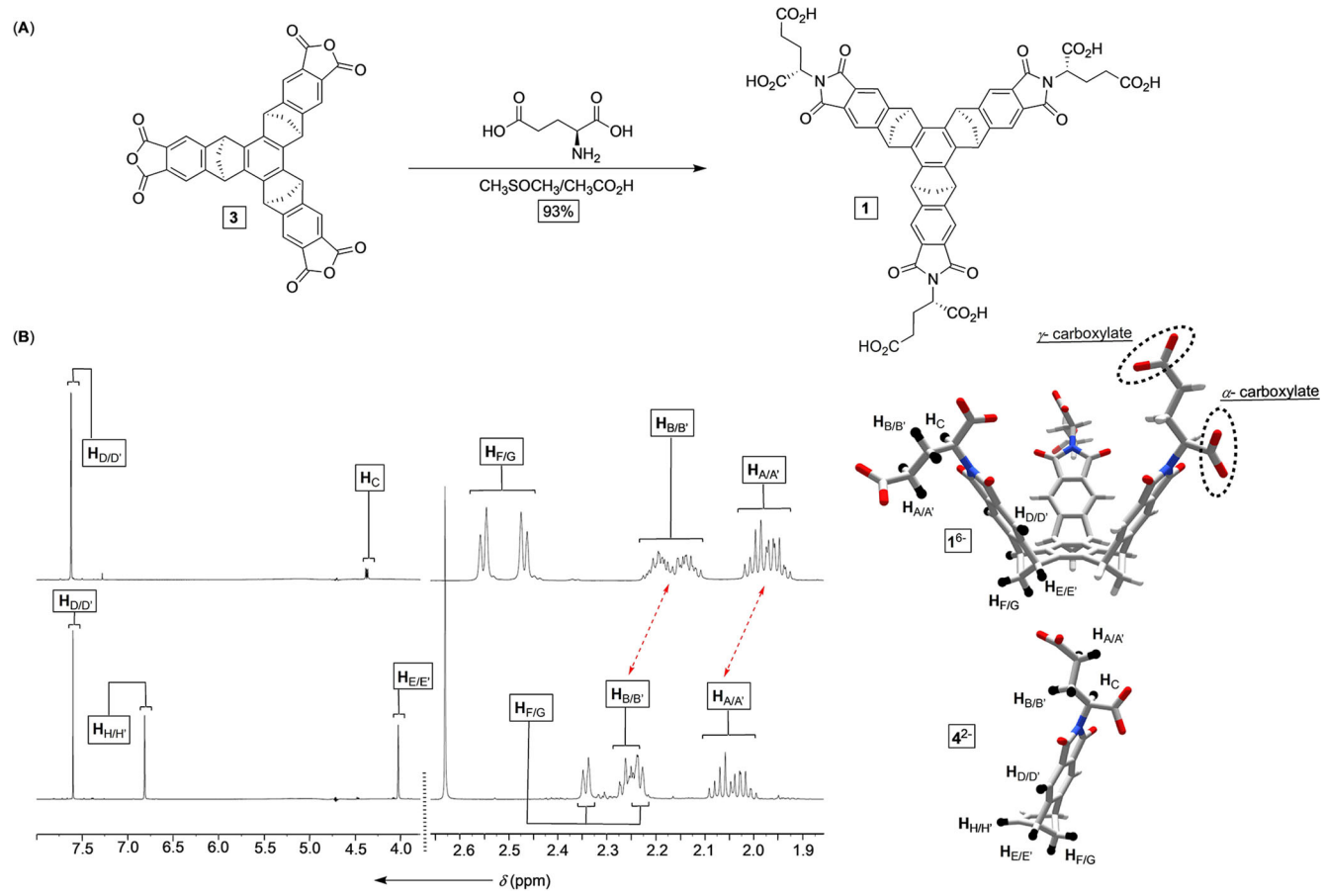
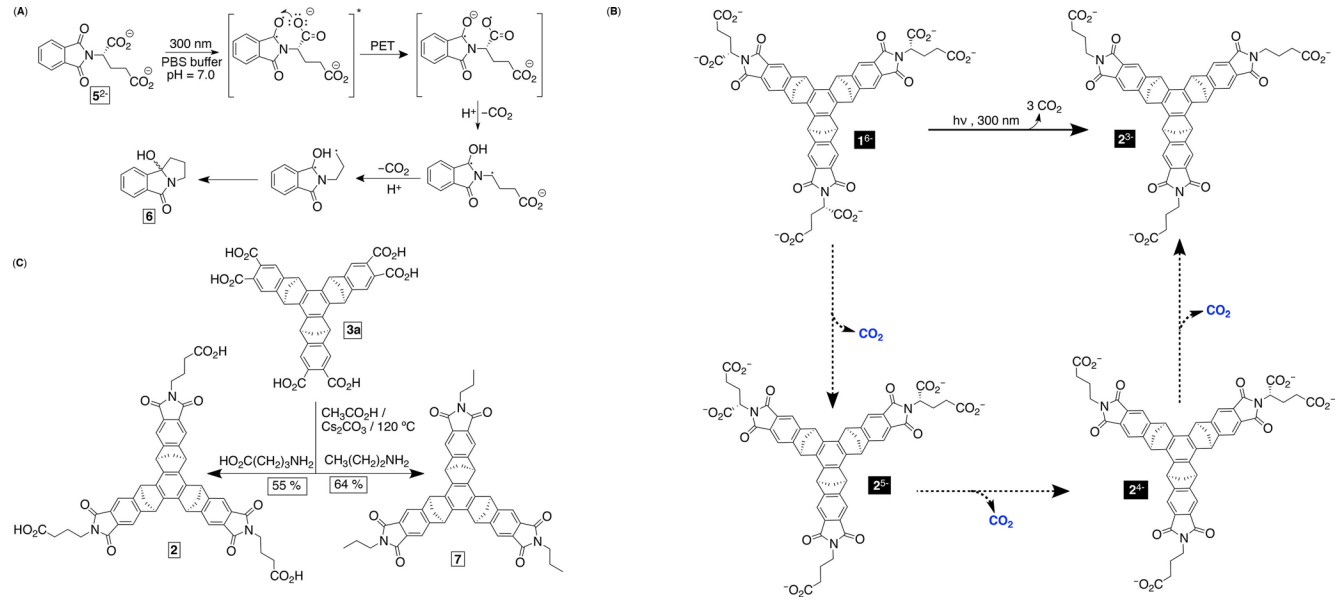


Figure 1. (A) The condensation of (*S*)-Glu and *tris*-anhydride **3** gives basket **1** in 93% yield. (B) ^{1}H-NMR spectra (700 MHz, 298 K) of basket $\mathbf{1}^{6-}$ (top, 3.0 mM) and model compound $\mathbf{4}^{2-}$ (bottom, 3.0 mM) in 30 mM phosphate buffer at pH 7.0.



Scheme 1. (A) The irradiation (300 nm, Rayonet) of 3.0 mM solution of $\mathbf{5}^{2-}$ (10 mM phosphate buffer, pH 7.0) was monitored with ^{1}H NMR spectroscopy (Figure S24) to reveal the exclusive formation of **6**. A speculative and electron-pushing mechanism of the photoinduced cyclization is shown.[19] (B) The photochemical conversion of $\mathbf{1}^{6-}$ into $\mathbf{2}^{3-}$ occurs in a stepwise fashion via partly decarboxylated $\mathbf{2}^{5-}$ ad $\mathbf{2}^{4-}$. (C) The condensation of **3a** and γ-aminobutyric acid gives basket **2** in 55% yield. Similarly, the condensation of **3a** and propyl amine gives **7** in 64% yield.

nanosized structures,[21] composed of concave hosts, there exists an opportunity for creating novel and useful stimuli-responsive materials.[22]

Results and Discussion

Basket **1** was obtained by the condensation of *tris*-anhydride **3** and (*S*)-glutamic acid in dimethyl sulfoxide (Figure 1 A). ^{1}H NMR spectrum (700 MHz, 298 K) of $\mathbf{1}^{6-}$ showed a set of signals corresponding to a C_3 symmetric compound (Figure 1 B). We used ^{1}H–^{1}H COSY and NOESY along with ^{1}H–^{13}C HSQC spectroscopic correlations (Figures S1–S7) to assign all of the basket's resonances. Notably, diastereotopic $\mathbf{H}_{A/A'}$ and $\mathbf{H}_{B/B'}$ protons from $\mathbf{1}^{6-}$ exhibit a greater magnetic shielding than the corresponding nuclei in model compound $\mathbf{4}^{2-}$ (Figure 1 B).[23] As $\mathbf{H}_{A/A'}$ and $\mathbf{H}_{B/B'}$ could reside on top of the host's cavity (Figure 2 A), we surmised that the unique microenvironment of this concave region of space[24] could have an effect on the magnetic characteristics of these spins. On the contrary, two sides about the flat phthalimide $\mathbf{4}^{2-}$ (Figure 1 B) are, for $\mathbf{H}_{A/A'}$ and $\mathbf{H}_{B/B'}$ almost equivalent and similar to the outer side of $\mathbf{1}^{6-}$. To examine the above hypothesis and gain further insight into the conformational characteristics of $\mathbf{1}^{6-}$, we completed the Monte-Carlo conformational search of this molecule (Maestro, OPLS3)[25] in implicit water solvent. First, (α)C–H groups are for the thirty most stable conformers of $\mathbf{1}^{6-}$ (within 2.93 kcal mol^{-1} of their relative steric energies, Figure 2 A) eclipsed with the adjacent N–C(=O) bonds[23] (Figure 2 B) so that α-carboxylates become situated on the inner or the outer side of the basket. In particular, one α-carboxylate group in $\mathbf{1}^{6-}$ prefers the inner basket's side (Figure 2 A) with neighboring γ-carboxylate residing in bulk solvent. Another glutamic acid, however, positions its γ-carboxylate on the inner side of the host (Figure 2 A) with $\mathbf{H}_{A/A'}$ and $\mathbf{H}_{B/B'}$ methylene nuclei on top of the basket's cavity: the magnetic shielding of these protons is likely contributing to the observed and upfield NMR chemical shifts (Figure 2 B) thereby providing support to our hypothesis.

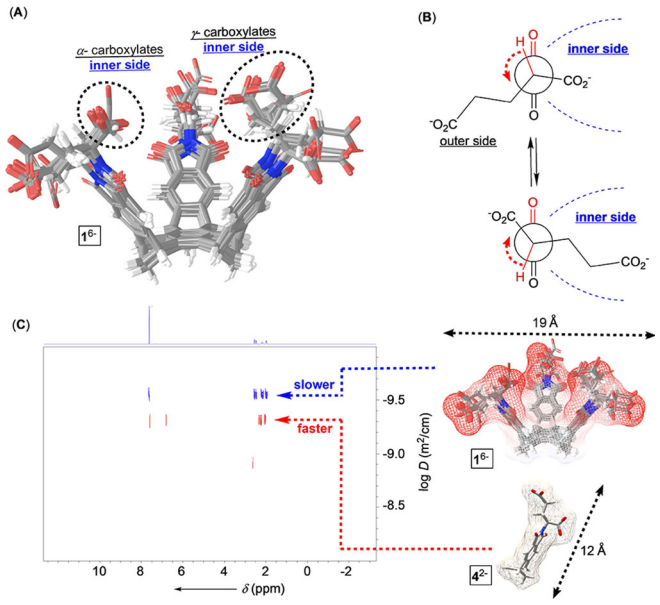


Figure 2. (A) Thirty conformers of $\mathbf{1}^{6-}$, with relative steric energy within 2.93 kcal mol^{-1}, were obtained from the Monte-Carlo conformational search (OPLS3, Maestro; Schrodinger) in implicit water. (B) The Newman projections of one glutamic acid moiety from $\mathbf{1}^{6-}$ with its stereogenic carbon at front. (C) DOSY NMR (600 MHz, 298 K) of 1.0 mM of $\mathbf{1}^{6-}$ and 1.0 mM $\mathbf{4}^{2-}$ in 30 mM phosphate buffer at pH 7.0; note that two DOSY experiments were run separately. (Right) van der Waals surface of $\mathbf{1}^{6-}$ and $\mathbf{4}^{2-}$, each with their diameter estimated using Spartan Software.

A hundred-fold dilution of an aqueous solution of $\mathbf{1}^{6-}$ (5.1 mM, Figure S8) had no effect on the line shape of its narrow ^{1}H NMR resonances. Moreover, the experimentally measured hydrodynamic radius $r_H = 8.3$ Å of $\mathbf{1}^{6-}$ ($D = 2.9 \times 10^{-10}$ m^2 s^{-1}; Figure S9) was consistent with the computed 11 Å (Figure 2 C) of a single molecule of $\mathbf{1}^{6-}$. Additionally, model compound $\mathbf{4}^{2-}$ was found to undergo translational diffusion at a faster rate ($D = 4.9 \times 10^{-10}$ m^2 s^{-1}, Figure S10) than $\mathbf{1}^{6-}$, corresponding to $r_H = 4.9$ Å and close to its estimated radius of 6.0 Å (Figure 2 C). DOSY NMR of $\mathbf{1}^{6-}$ and $\mathbf{4}^{2-}$ revealed two sets of signals with each compound moving as predominantly free species (Figure 2 C); the results of dynamic light scattering (DLS, Figure S11) and electrospray ionization mass spectrometry analyses (ESI-MS, Figure S12) of $\mathbf{1}^{6-}$ were in line with the host being monomeric in water. The solution behavior of $\mathbf{1}^{6-}$ is thus similar to baskets conjugated to hydrophobic amino acids[23] in spite of its nonpolar cage being bordered with six, instead of three,[23] negatively charged carboxylates. We presume that the conformational dynamics of glutamic acid moieties along with their different orientations about the rim of $\mathbf{1}^{6-}$ (as computed with molecular mechanics, Figure 2 A) is contributing to the poor preorganization of this host to frustrate its aggregation in water.[26]

After the absorption of 300 nm light, the phthalimide fragment of *N*-phthaloyl-α-amino acids[27] turns into transient but strong oxidizing agents capable of "pulling" an electron from α-carboxylate to instigate decarboxylation (Scheme 1).[19] In the case of baskets functionalized with hydrophobic α-amino acids,[17] we found that the photo-induced loss of CO_2 would render these hosts insoluble in water to prompt their precipitation. With six carboxylates within $\mathbf{1}^{6-}$, however, we wondered if a light stimulus would trigger their removal[20a] to give baskets possessing distinct recognition characteristics and/or solubility (Scheme 1 B). In fact, when *N*-phthaloyl-glutamic acid $\mathbf{5}^{2-}$ (10 mM phosphate buffer, pH 7.0) was exposed to 300 nm light (Scheme 1 A) there followed the exclusive formation of cyclized product **6** (Figure S13).[20a] On the basis of the literature,[19] we speculate that the formation of long-lived $^3\pi\pi^*$ triplet state of the phthalimide chromophore from $\mathbf{5}^{2-}$ triggers the removal of α and γ carboxylates to give diradical intermediate which then cyclizes into racemic **6** (the Norrish–Yang reaction).

Irradiation (300 nm, Rayonet) of an aqueous solution of $\mathbf{1}^{6-}$ was, at 298 K, monitored with ^{1}H NMR spectroscopy (Figure 3 A). The signals corresponding to $\mathbf{1}^{6-}$ gradually disappeared over 180 minutes with the concomitant emergence of a set of poorly resolved and broadened resonances. Since there was no precipitate, to indicate the formation of water insoluble **7** (Scheme 1 B), we suspected that partial decarboxylation(s) of $\mathbf{1}^{6-}$ and/or other radical-mediated reactions[20b]

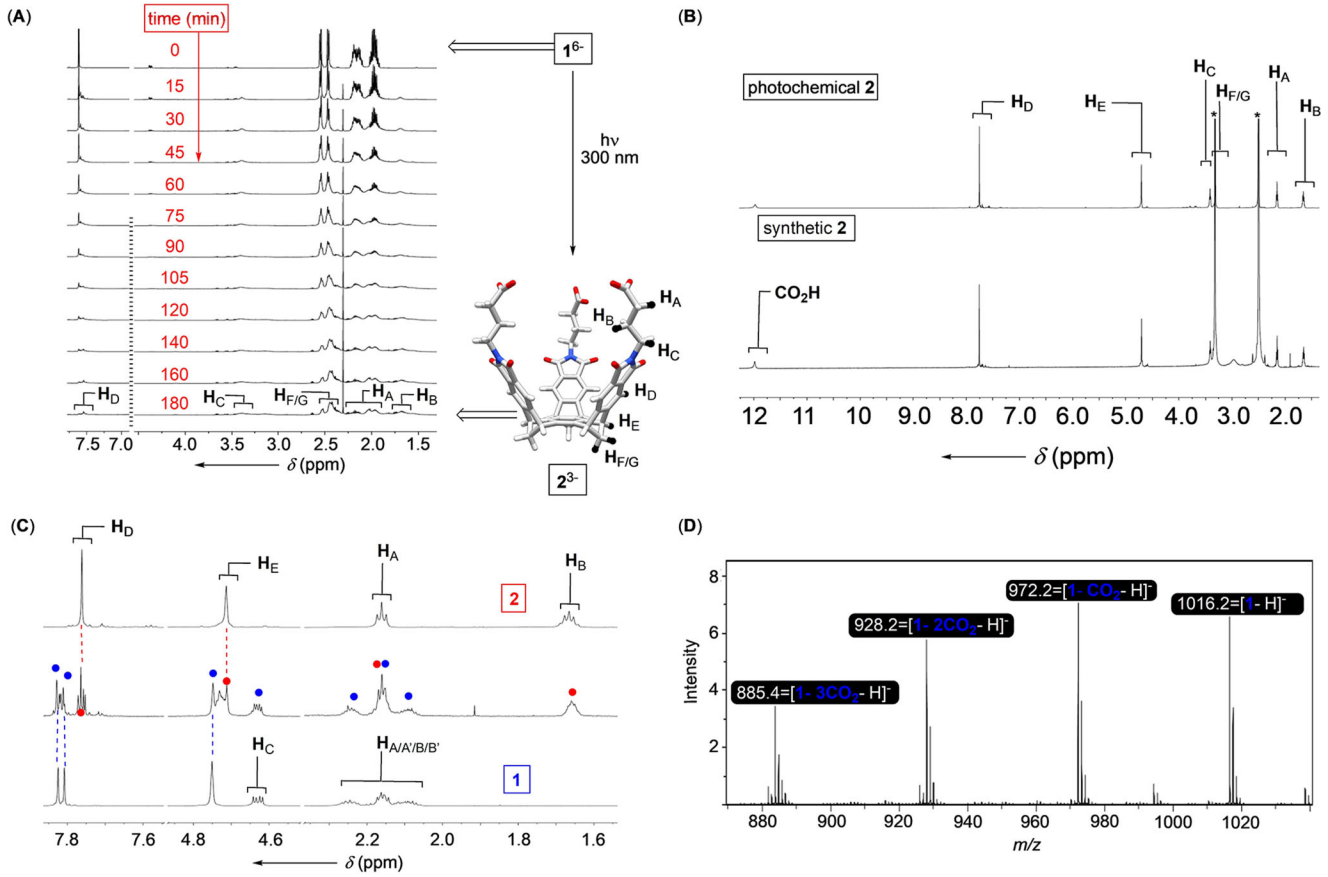


Figure 3. (A) Irradiation (300 nm, Rayonet) of basket $\mathbf{1}^{6-}$ (2.1 mM) dissolved in 30.0 mM phosphate buffer at pH 7.0 was monitored with ^{1}H NMR spectroscopy (600 MHz, 298 K); in the experiment, pH of the solution changed from 7.0 to 7.2. (B) ^{1}H NMR spectra (700 MHz, 298 K) of **2** in CD_3SOCD_3 with this molecule obtained from photochemical (top) and condensation (bottom) experiments. (C) ^{1}H NMR spectra (600 MHz, 298 K; CD_3SOCD_3) of **1** (blue, bottom) and **2** (red, top) along with the reaction mixture (middle) obtained after irradiation (300 nm, Rayonet) of $\mathbf{1}^{6-}$ (2.1 mM) in 30 mM phosphate buffer (20% D_2O) at pH 7.0 for 40 minutes. See Figure S19 for additional information. (D) ESI-MS of a sample obtained by Irradiation (300 nm, Rayonet) of $\mathbf{1}^{6-}$ (2.1 mM) in 30 mM phosphate buffer for 40 minutes followed by the addition of 2 M HCl with the resulting precipitate being dissolved in CH_2Cl_2/CH_3OH.

could have taken place. An ill-defined ^{1}H NMR spectrum obtained after 180 minutes of the light exposure (Figure 3A) could therefore denote: (a) a mixture of products and/or (b) one major product undergoing aggregation with/without a slow exchange of its conformers on the NMR time scale. To examine the matter more closely, we subjected $\mathbf{1}^{6-}$ to irradiation until its ^{1}H NMR signals disappeared (c.a. 180 min) and then precipitated all organics using 2 M HCl; ^{1}H NMR spectroscopy showed no presence of organics in the remaining aqueous layer (Figure S14). ^{1}H NMR spectrum of the solid dissolved in CD_3SOCD_3 (Figure 3B), however, showed a set of resonances corresponding to C_3 symmetric **2** lacking α- but still possessing γ-carboxylic groups! To confirm our structural assignment, we prepared **2** by condensation of *tris*-acid **3a** and γ-aminobutyric acid in acetic acid (Scheme 1B). Importantly, ^{1}H NMR spectra of "photochemical" and "synthetic" samples (Figure 3B) were identical to corroborate the sole formation of **2** with light; for complete characterization of **2** and **7**, see Figures S15–18. To sum up, we deduced that the ill-defined ^{1}H NMR spectrum in Figure 3A resulted from the aggregation of $\mathbf{2}^{3-}$.[26]

At this point, we were eager to examine the involvement of $\mathbf{2}^{4-}$ and $\mathbf{2}^{5-}$ intermediates in the photochemical conversion (Scheme 1).[17] In this regard, the available spectroscopic results from the photochemical transformation in Figure 3A were difficult to elucidate for identifying resonances from partly decarboxylated baskets. Accordingly, we terminated the reaction at approximately 50% conversion (Figure S19), precipitated all of the products with 2 M HCl and dissolved the precipitate in CD_3SOCD_3; note that in this experiment, no detectable organics remained in the water layer. ^{1}H NMR spectrum of the precipitate showed signals corresponding to **1** and **2** yet there were also additional resonances to, perhaps, suggest the presence of $\mathbf{2}^{4-}$ and $\mathbf{2}^{5-}$ intermediates (Figure 3C). Indeed, ESI-MS analysis of the sample verified the formation of singly- and doubly decarboxylated basket **1** (Figure 3D). The results are in support of a mechanistic scenario in which the light triggers a successive elimination of CO_2 molecules from $\mathbf{1}^{6-}$ to, via $\mathbf{2}^{5-}$ and $\mathbf{2}^{4-}$, give $\mathbf{2}^{3-}$ (Scheme 1). The rates by which these eliminations occur are likely different than in the case of hydrophobic α-amino acids conjugated to the basket's framework since these hosts did not give detectable quantities (NMR) of partly decarboxylated intermediates.[17]

As the light stimulus triggers decarboxylation of monomeric $\mathbf{1}^{6-}$ into $\mathbf{2}^{3-}$, we wondered: does the irradiation launch the for-

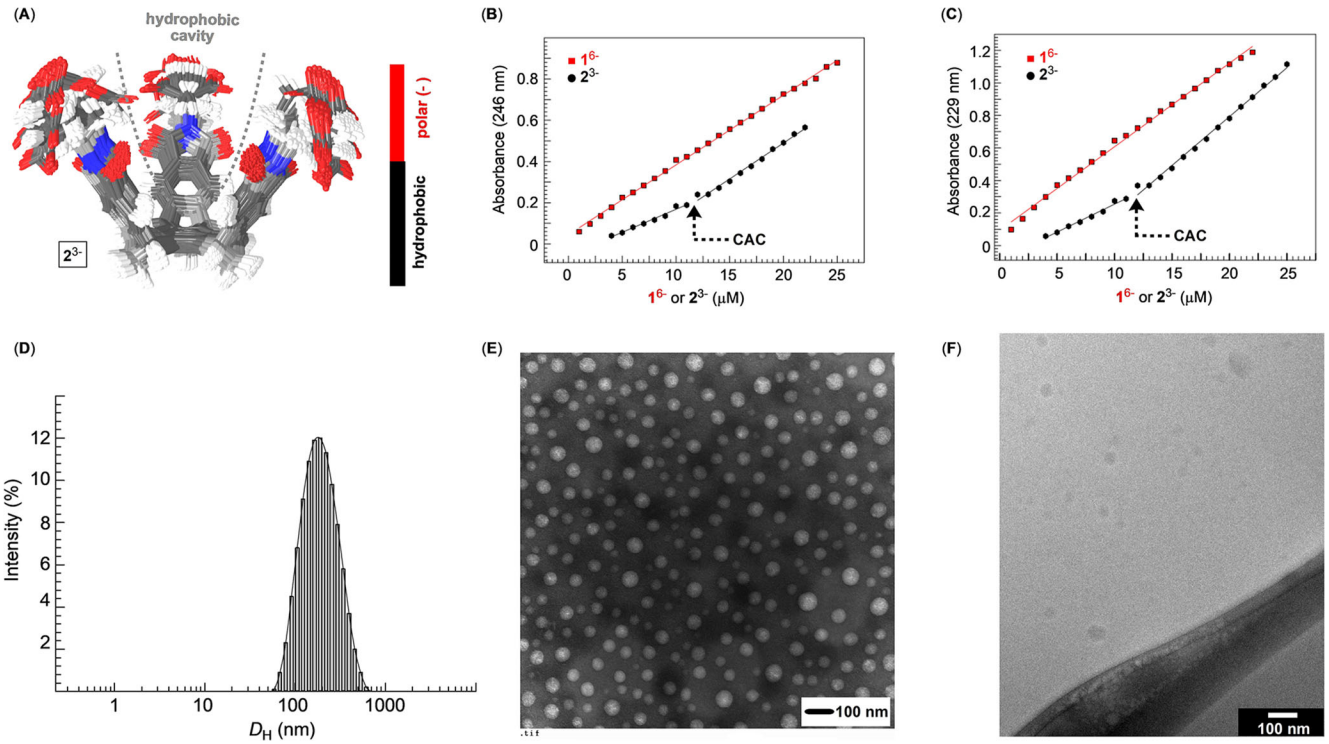


Figure 4. (A) Overlaid conformers of $\mathbf{2}^{3-}$ were generated with the Monte-Carlo conformational search (OPLS3, Maestro; Schrodinger). (B/C) Plots of absorbance (229 and 245 nm) as a function of concentration of standard solutions of $\mathbf{1}^{6-}$ and $\mathbf{2}^{3-}$ (30 mM phosphate buffer, pH 7.0). Each data set was subjected to a non-linear least square analysis and fit to a linear function using Sigma Plot ($R^2 > 0.98$). (D) Size distribution of 1.0 mM solution of $\mathbf{2}^{3-}$ (phosphate buffer, pH 7.0) examined with dynamic light scattering at 298.0 K. (E/F) Conventional TEM and cryo-TEM images of 1.0 mM $\mathbf{2}^{3-}$ (10 mM phosphate buffer, pH 7.0). For conventional TEM imaging, the sample was deposited on a copper grid and subsequently stained with uranyl acetate aqueous solution; for additional microscopy images, see Figures S23 and S24.

mation followed by assembly of amphiphilic $\mathbf{2}^{3-}$ into a distinct, perhaps, nanostructured material?[2e] After all, the observed regioselective removal of α- but not γ-carboxylates from $\mathbf{2}^{3-}$ could, in part, result from the reduced conformational dynamics of "aligned" hosts. That is to say, extended and confined GABA chains within assembled molecules $\mathbf{2}^{3-}$ are likely to impede γ-carboxylates from reaching the bottom portion of each basket thereby reducing the rate of intramolecular electron transfer preceding the removal of the appropriate CO_2 (Scheme 1 A).[19]

To study the conformational characteristics of $\mathbf{2}^{3-}$, we ran the Monte-Carlo conformational search (OPLS3) in implicit water solvent to find numerous conformers of which the most stable 154 (within 1.4 kcal mol^{-1} of steric energy) are shown in Figure 4 A.

The host has a shape of truncated cone with distinct hydrophobic and hydrophilic zones: three butyric acid chains cluster their carboxylates at the northern and outer side of the basket to cast a deep hydrophobic pocket. Clearly, amphiphilic $\mathbf{2}^{3-}$ is preorganized and shaped[2e] to form nanostructured materials.[26,28]

To examine the mode of aggregation of $\mathbf{2}^{3-}$, we decided to begin with probing the potential phase transition of the material as distinguished with critical aggregation concentration (CAC).[29] In the aggregated form, molecules of $\mathbf{2}^{3-}$ should form close contacts that may perturb the electronic state of their phthalimide chromophores.[30] Additionally, the nanosized aggregates should scatter the incident light beam (Tyndall effect) and therefore alter its transmission intensity. To sum up, the onset of the aggregation of $\mathbf{2}^{3-}$ (CAC) may be possible to discern as a deflection in the linear behavior described with the Beer–Lambert law.[31] From UV/Vis spectra of standard solutions of $\mathbf{1}^{6-}$ and $\mathbf{2}^{3-}$ (Figures S20 and S21), we plotted a change in the absorbance as a function of the concentration (Figure 4 B/C); As expected, the Beer–Lambert law holds for $\mathbf{1}^{6-}$ in the entire range of the examined concentrations to corroborate its monomeric state (Figure 4 B). However, two linear curves were distinguished for $\mathbf{2}^{3-}$ converging at around 12 μM concentration to suggest a two-state phase transition;[29] note that ^{1}H NMR spectrum of $\mathbf{2}^{3-}$ would also sharpen at ≈10 μM concentrations (Figure S22). Accordingly, we conclude that CAC of $\mathbf{2}^{3-}$, at which the host effectively changes from its monomeric to aggregated state, is 12 μM. Dynamic light scattering (DLS) measurements of 1.0 mM solution of $\mathbf{2}^{3-}$ showed a single peak centered at 180 nm (Figure 4 D) to indicate the formation of particles having hydrodynamic diameter $D_H = 20(\pm 25)$ nm and a narrow distribution of sizes (PDI = 0.25). Transmission electronic micrographs of 0.1 mM solution of $\mathbf{2}^{3-}$ revealed the formation of circular objects with a dark boundary resulting from the negative stain (Figure 4 E).[32] The diameter of these structures is circa 90 nm and somewhat smaller than the size of particles detected with DLS. At last, cryo-TEM imaging of $\mathbf{2}^{3-}$ (Fig-

ure 4F) revealed the formation of spherical nanoparticles having a distribution of sizes, with large ones being 80 nm in diameter and without a distinct boundary to depict a vesicular double-layer.[33] The packing mode of $\mathbf{2}^{3-}$ within organic nanoparticles is, at this point, difficult to envision yet the formation of already described micelle-like aggregates (MLAs)[2f] from amphiphilic block-copolymers containing a hydrophobic interior and hydrophilic surface presents an intriguing hypothesis that remains to be elucidated.[34]

Conclusions

In conclusion, the photoinduced electron transfer (PET) decarboxylation[19] of baskets comprising three glutamic acids at the rim is a regioselective, consecutive and quantitative reaction that gives rise to an amphiphilic host. The host assembles into stable, spherical and organic nanoparticles.[35] Alongside the capacity of amino acid functionalized baskets to trap nerve agent simulants,[17,23] small hydrocarbons[36] or other complementary guests,[37] here described light-induced formation of organic nanoparticles[38] offers a potential[39] for creating soft materials capable of (a) spatial and temporal removal of targeted molecules by their encapsulation in the interior of nanoparticles, (b) release of molecules induced by the nanoparticle formation and finally (c) control of chemical reactivity in complex chemical environments. Indeed, the use of UV light as a stimulus can be damaging to biological tissues to, at present, limit a direct application of our system for in vivo drug delivery. Despite this limitation, these findings lend themselves to applications related to the selective removal of toxic substances from environment and/or controlling chemical non-orthogonal reactions in systems chemistry. Our plan is to continue with pursuing such objectives.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cavitands · molecular recognition · organic nanoparticles · photoresponsive system · self-assembly

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FULL PAPER

Photoresponsive Materials

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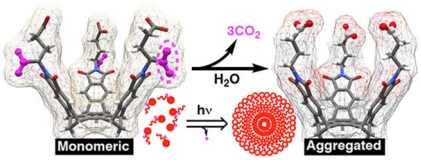
Light-Triggered Transformation of Molecular Baskets into Organic Nanoparticles



Filling the basket: Photoinduced decarboxylation of molecular baskets functionalized with glutamic acids was found to, in water, give amphiphilic cavitands. These cavitands assemble into organic nanoparticles that could be used for scavenging toxic molecules, promoting chemical reactions or delivering drugs.