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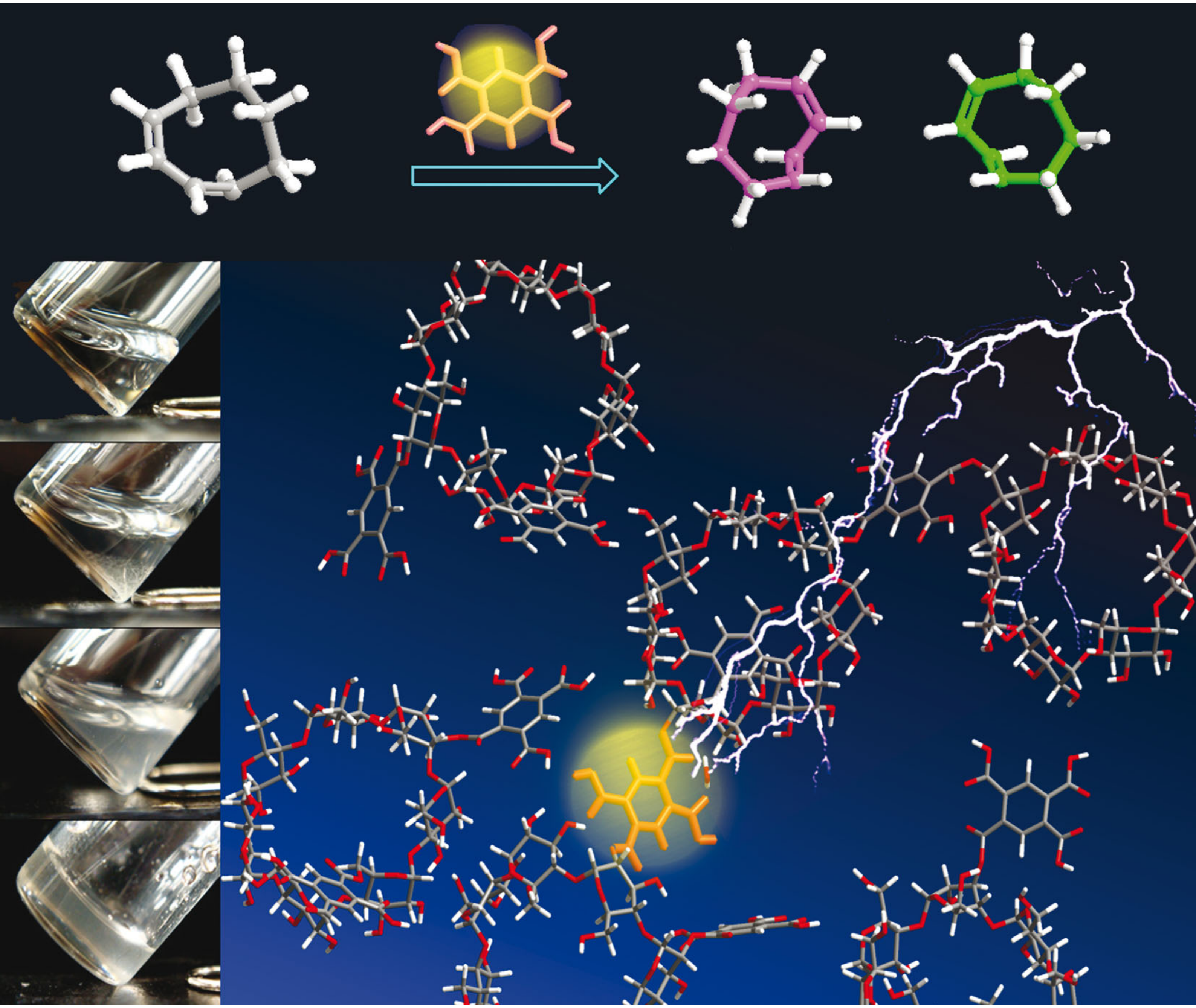

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Phase-controlled supramolecular photochirogenesis in cyclodextrin nanosponges†

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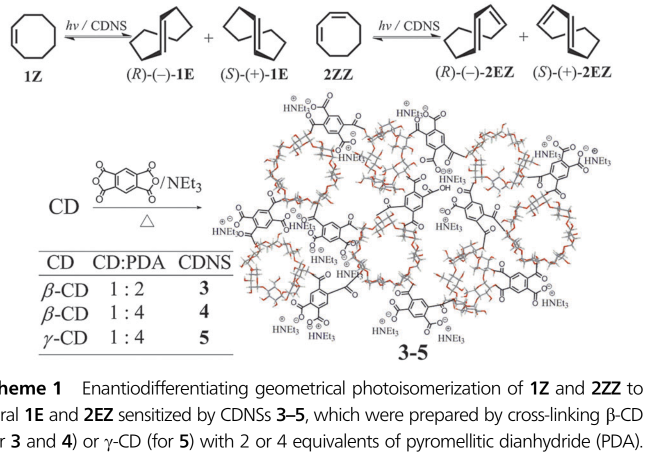
Pyromellitate-bridged cyclodextrin nanosponges (CDNSs) evolved from sol into gel state upon gradual increase of the concentration from 0.2 to 2000 mg mL^{-1} in water. The enantiodifferentiating geometrical photoisomerizations of (*Z*)-cyclooctene and (*Z*,*Z*)-1,3-cyclooctadiene sensitized by CDNS at various concentrations were critically affected by the phase transition of CDNS to afford the corresponding (*E*)- and (*E*,*Z*)-isomers in the highest enantiomeric excesses in the gel state.

Photochirogenesis is an intriguing, yet challenging, topic in current photochemistry,[1] requiring precise stereochemical control in weakly interacting, short-lived exited state. Indeed, the optical yields obtained in chiral photoreactions have long been rather modest. Of several strategies developed so far for achieving critical control of photochirogenic processes, the supramolecular approach[2] is the most attractive and promising, securing longer and more intimate chiral interactions in both ground and excited states. Thus, the foregoing studies on supramolecular photochirogenesis have focused primarily on the use of structurally well-defined, conformationally less flexible hosts, while supramolecular aggregates, such as micelles, vesicles, gels,[3a,b] liquid crystals[3c,d] and Langmuir–Blodgett films, have yet to be further explored as media for photochirogenesis. As a logical extension of our work on molecular[1a] and supramolecular[2a,b,d,4] control of chiral photochemistry to structurally less-defined hosts, we have recently become interested in the use of chiral supramolecular aggregates as more flexible, tunable and potentially more versatile photochirogenic media,[5] which led us to the present study on the enantiodifferentiating supramolecular photoisomerization of (*Z*)-cyclooctene (**1Z**) and (*Z*,*Z*)-1,3-cyclooctadiene (**2ZZ**) to chiral (*E*)-isomers **1E** and **2EZ** sensitized by pyromellitate-bridged β- and γ-cyclodextrin (CD)-based polymers, *i.e.* "cyclodextrin nanosponges (CDNSs)" **3–5** (Scheme 1).

A CDNS, prepared by crosslinking CDs with areneoligocarboxylic anhydride,[6] originally attracted us as a water-swellable photosensitizing supramolecular host with inherently chiral cavity and aromatic linker.[5b] Thus, the supramolecular photosensitizations of **1Z** and **2ZZ** with dilute CDNSs **3–5** (0.2 mg mL^{-1}) were examined in water to afford **1E** in up to 10% enantiomeric excess (ee) and **2EZ** in up to 7% ee.[5b] Interestingly, these CDNSs turned out to gradually aggregate to form gels at higher concentrations in water and exhibit phase-dependent photochirogenic behavior. In the present study, CDNSs were employed as supramolecular chiral photosensitizers for the enantiodifferentiating photoisomerization of **1Z** and **2ZZ** to elucidate the effects of the phase transition from sol to gel state on the stereochemical outcomes of these representative photochirogenic systems.[7]

CDNSs **3–5** were synthesized as triethylammonium salts by reacting β- or γ-CD with 2 or 4 equivalents of pyromellitic



CD	CD:PDA	CDNS
β-CD	1 : 2	3
β-CD	1 : 4	4
γ-CD	1 : 4	5

Scheme 1 Enantiodifferentiating geometrical photoisomerization of **1Z** and **2ZZ** to chiral **1E** and **2EZ** sensitized by CDNSs **3–5**, which were prepared by cross-linking β-CD (for **3** and **4**) or γ-CD (for **5**) with 2 or 4 equivalents of pyromellitic dianhydride (PDA).

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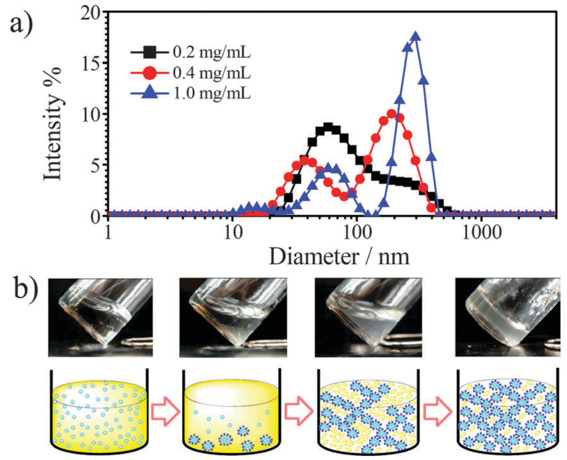

Fig. 1 (a) DLS intensity as a function of particle size measured for aqueous solutions of CDNS **3** at 0.2, 0.4 and 1.0 mg mL^{-1} concentrations. (b) Upper panel: photographs of aqueous solutions of **3** at 0.5, 10, 200 and 2000 mg mL^{-1} (from left to right). Lower panel: schematic drawings of the phase evolution of CDNS.

dianhydride (PDA) in the presence of triethylamine, as reported previously.[6] Thermogravimetric analyses (Fig. S4–S6, ESI†) revealed that these CDNSs contained 6–8% water in weight (Table S2, ESI†), which is comparable to those found in β- and γ-CD crystals.[8] All of the synthesized CDNSs were readily dispersible in water, probably due to the hydrophilic CD as well as the ammonium salt of the pyromellitate linker. The particle size distributions of CDNSs at various concentrations were evaluated by using the dynamic light scattering (DLS) technique (Fig. 1a and S7–S9, ESI†). As shown in Fig. 1a (squares), an aqueous solution of CDNS **3** at 0.2 mg mL^{-1} concentration already contained some aggregates of *ca.* 300 nm diameter, although the main peak at *ca.* 60 nm was still dominant. The mean diameter (zeta average size) of CDNS at 0.2 mg mL^{-1} was determined by DLS as 120 nm for **3**, 170 nm for **4** and 180 nm for **5**, indicating enhanced crosslinking with increasing PDA/CD ratio from 2 to 4 upon preparation. By increasing the concentration of **3** from 0.2 to 0.4 and then to 1.0 mg mL^{-1}, the aggregate peak at *ca.* 300 nm gradually grew to eventually surpass the dispersed CDNS peak at 40–60 nm (Fig. 1a, circles and triangles).

Further increasing the CDNS concentration led to sequential phase evolution for all of the three CDNSs. First, transparent precipitates were formed at 1.0 mg mL^{-1} concentration of CDNS **3** (Fig. 1b, second left). Optical microscopy examinations of the precipitates showed that the particle size gradually increases with increasing CDNS contents. At higher contents, the solution became a gel-like diphasic system containing both liquid and gel phases or "flowing gel" (Fig. 1b, second right), and eventually gave a rigid gel (Fig. 1b, far right) at critical gelation ratios (CGR) of 2.0 mg mL^{-1} for **3**, 0.6 mg mL^{-1} for **4** and 0.9 mg mL^{-1} for **5**.

Although the gelation mechanism is to be elucidated, the inter-particle complexation of pyromellitate linkers with CDs exposed at the surface of CDNS particles is likely to play crucial roles in the progressive sol-to-gel phase evolution. In line with this idea, CDNS **4**, being more crosslinked and hence possessing more pyromellitate moieties (Table S5, ESI†), gave a much lower CGR (0.6 mg mL^{-1}) than CDNS **3** (2.0 mg mL^{-1}). The relatively high CGRs for these CDNSs may reflect the weak hydrophobic driving force for aggregation.

CDNSs **3–5** in aqueous solution consistently exhibited negative induced circular dichroism extrema in the ^1L_a (*ca.* 270 nm) and ^1L_b (*ca.* 300 nm) regions (Fig. S11–S13, ESI†) throughout the measurable concentration range (*i.e.*, from 6 × 10^{-5} to 2.0, 0.6 and 0.9 mg L^{-1} for **3–5**, respectively), suggesting lateral inclusion of the pyromellitate liner by CD cavity (according to the sector rule).[9]

Complexation behavior of **1Z** and **2ZZ** with CDNSs was examined spectroscopically. However, the addition of **1Z** or **2ZZ** to aqueous solutions of CDNSs did not induce any appreciable circular dichroism spectral changes. This result is considerably different from that observed for conventional sensitizer-modified monomeric CDs, where the originally self-included sensitizer moiety is driven out by competitive guest substrate to cause an inversion of the original circular dichroism signals,[4e,f,7b] and may indicate that the cyclooctene guest cannot compete with the intramolecular complexation of the linker.

Photoisomerizations of **1Z** and **2ZZ** sensitized by CDNSs were carried out at various CDNS/water ratios and temperatures. In isotropic solution phase, β- and γ-CDNSs **3–5** at 0.2 mg mL^{-1} concentration showed distinctly different photochirogenic performances. Upon photoisomerization of **1Z** at 0.5 °C, β-CDNSs **3** and **4** gave (+)-**1E** in 7.5% and 2.7% ee, respectively, while γ-CDNS **5** afforded antipodal (−)-**1E** in 4.7% ee; for a full list of the results, see Table S6 (ESI†). Similarly, the photoisomerization of **2ZZ** afforded (+)-**2EZ** in 4.7–4.9% ee upon sensitization by β-CDNSs **3** and **4** under the comparable conditions, while the use of γ-CDNS **5** led to the formation of the same enantiomer in 0.7% ee (Table S7, ESI†). The contrasting photochirogenic behavior exhibited by β- *versus* γ-CD-based NSs may originate from the different chiral environment provided by β- and γ-CD cavities for the enantiodifferentiating photoisomerizations of **1Z** and **2ZZ**.[5b,7b]

The enantioselectivity turned out to be a critical function of the CDNS concentration or the phase condition. For instance, upon photoisomerization of **2ZZ** sensitized by β-CDNS **3** (Fig. 2, top), the ee of **2EZ** decreased from 4.7% to zero by increasing the concentration of **3** from 0.2 to 0.5 mg L^{-1}, synchronized with the phase transition from sol to suspension. Although β-CDNS **4** behaved very similarly to show a decrease of ee from 4.9% to 1.8% (Fig. 2, middle), γ-CDNS **5** consistently gave almost racemic **2EZ** in both sol and suspension region (Fig. 2, bottom).

These ee patterns may be rationalized by the different degree of CDNS aggregation. At a 0.2 mg mL^{-1} concentration, CDNS particles are less aggregated and hence the CD cavities at the particle surface are available for the inclusion of the guest substrate, thus enabling the sensitized photoisomerization of **2ZZ** in the CD cavity to afford appreciable ee's. At higher concentrations, the CDNS particles start to aggregate and the CD cavities on the particle surface are occupied by pyromellitate linkers, driving out the guest substrates to the loose inter-particle voids. However, such voids are much less effective in inducing chirality and afford the racemic product upon photoirradiation in the suspension state.

Intriguingly, the enantioselectivity started to depart from the racemic line in the flowing gel region, and rapidly increased to give the maximum ee at the border of the flowing and rigid gel regions, but somewhat decreased in the rigid gel region. The highest ee's obtained with **3** and **4** were 6.1% and 11.1% at CDNS–H_2O = 2.5 and 1.0 g mL^{-1}, respectively. Notably, **5** in the

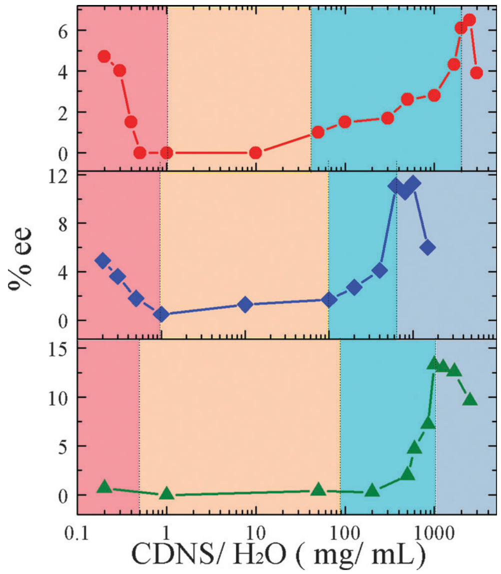

Fig. 2 The ee profile of **2EZ** as a function of the concentration of **3** (top), **4** (middle) and **5** (bottom) upon enantiodifferentiating photoisomerization of **2ZZ**. The pink, yellow, blue and violet regions represent the solution, suspension, flowing gel and rigid gel states, respectively.

gel state (1.0 g mL^{-1}) gave **2EZ** in 13.3% ee, which is the highest value ever reported for the supramolecular photosensitization of **2ZZ**.[5] This result suggests that the photochirogenic environment, which is more effective than the conventional CD cavity, is created in the CDNS gel. We deduce that the hydrophobic void surrounded by the outside walls of CD created in the gel becomes more compact at higher CDNS concentration to form a chiral sensitizing site suitable for the enantiodifferentiating photoisomerization of **1Z** and **2ZZ** (Fig. 3). This idea is supported by the high resolution magic angle spinning (HRMAS) NMR spectra of **2ZZ** dissolved in gel **5**. HRMAS and T2-filtered ^{1}H NMR spectra showed sharp peaks of **2ZZ** protons (Fig. S14 and S15, ESI†), indicating that the substrate is freely moving around on the NMR time-scale in the void spaces of the gel despite the high viscosity.

The product's ee was highly phase-dependent also in the photosensitization of **1Z**. As shown in Table S6 and Fig. S16 (ESI†), the photoisomerization of **1Z** sensitized by **3** gave (*S*)-**1E** in 7.5% ee in the sol state (0.2 mg mL^{-1}), which however rapidly faded out to almost zero by increasing the concentration to 1.5 mg mL^{-1} and stayed low throughout the suspension region (1.5–40 mg mL^{-1}), but revived at higher concentrations of **3** to give *antipodal* (*R*)-**1E** in 7.6% ee in the gel state (2 g mL^{-1}). A very similar chirality inversion by altering phase was observed for β-CDNS **4**, affording (*S*)-**1E** in 2.7% ee in the sol state (0.2 mg mL^{-1}) but antipodal (*R*)-**1E** in 9.5% ee in the gel state (0.625 mg mL^{-1}), while γ-CDNS **5** behaved differently to give racemic product throughout the suspension, flowing gel and rigid gel regions.

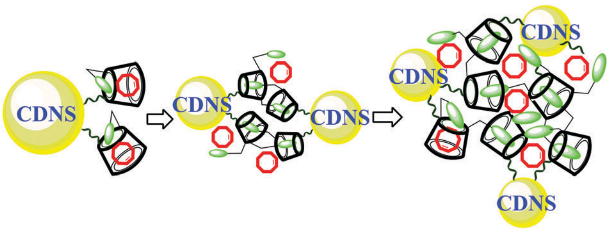

Fig. 3 Switching of the sensitizing site for the substrate (red) upon gradual aggregation of CDNS at higher concentrations.

Switching the chiral sense of the product in asymmetric synthesis may seem infeasible without using an antipodal chiral source, but has been demonstrated to occur in chiral photoreactions by manipulating the entropy-related environmental variants, such as temperature, pressure and solvent.[1a,2a,7] Similar switching behavior has rarely been reported for a supramolecular system, most probably due to the well ordered, but less dynamic nature of the framework. One of the available strategies to alter the chiral environment in a supramolecular system is the phase change associated with supramolecular aggregation, which was proven effective in this study. Without changing the chemical structure of the chiral source employed (*i.e.* CD), the chirality switching was achieved through the change in aggregation mode. This strategy is promising as a new tool for manipulating the stereochemical outcomes in supramolecular (photo)chirogenesis.

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