JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Reversible Light-Controlled Cargo Release in Hydrogen-Bonded Dimeric Capsules

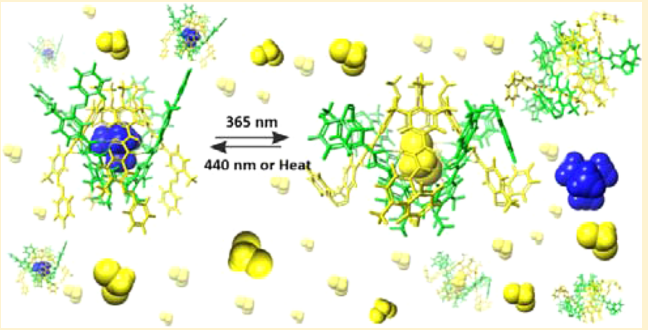
Frank A. Arroyave[†] and Pablo Ballester*[,†,‡]

[†]Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Avgda. Països Catalans 16, 43007 Tarragona, Spain

[‡]Catalan Institution for Research and Advanced Studies (ICREA), Passeig Lluís Companys, 23, 08010 Barcelona, Spain

Supporting Information

ABSTRACT: We describe the synthesis of three tetraureacalix[4]arenes having four appended terminal azobenzene groups. In CD_2Cl_2 solution and at millimolar concentration, the thermally equilibrated *all-trans*-tetraureas dimerize quantitatively, encapsulating one Me_4P^+ cation. The light-induced isomerization of the *all-trans* encapsulation complexes produced a plethora of isomeric *cis*-enriched counterparts displaying a reduction in cavity size. *cis*-enriched dimers not suitable for the encapsulation of the cation or a solvent molecule are also produced, leading to partial release of the cargo (Me_4P^+) to the bulk solution. The substitution of the terminal phenyl in the azobenzene groups plays a key role in controlling the amount of released cargo in quantities up to 70%. The switching between the two states (*all-trans* and *cis*-enriched capsules) proceeds with no detectable photodegradation, even when it is repeated multiple times.



INTRODUCTION

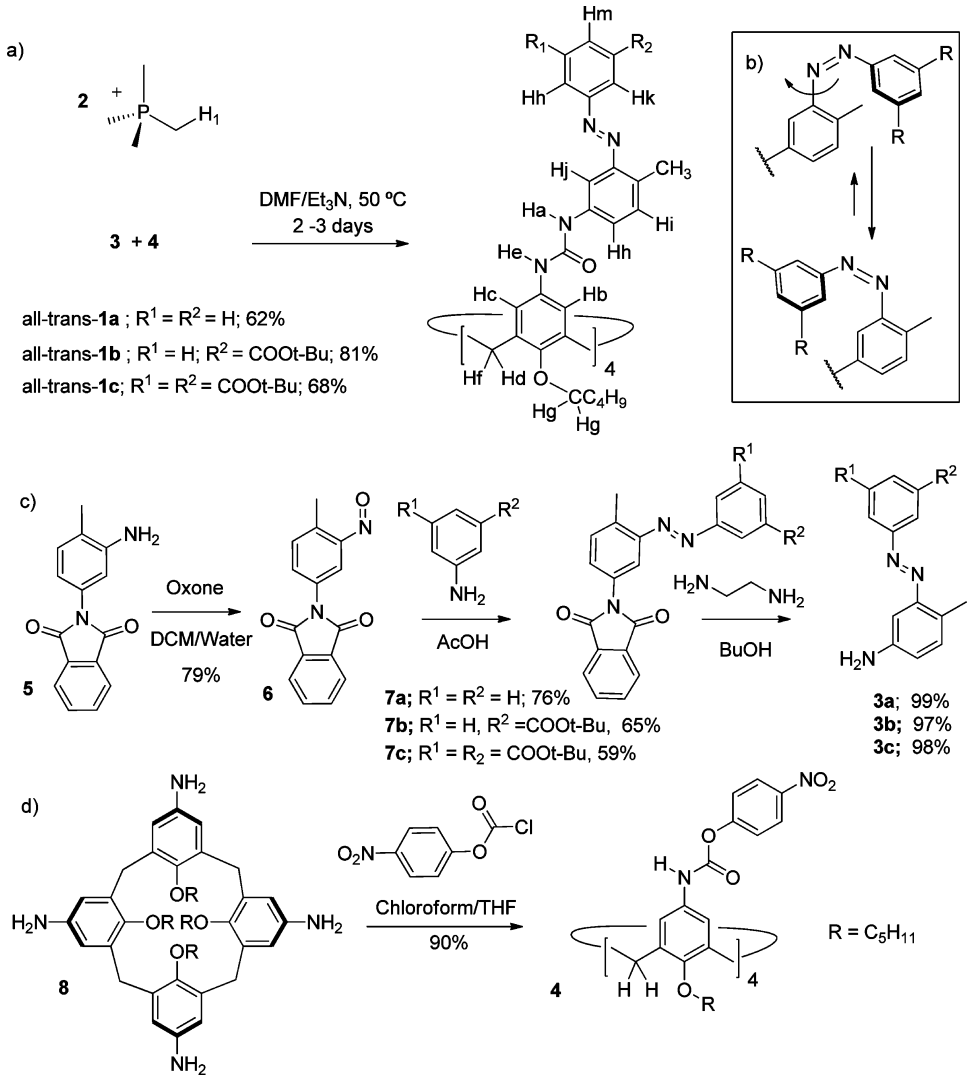
Light irradiation reversibly moves photochromic groups between two isomeric states having different absorption spectra. Certain classes of photochromic groups, aka molecular switches, experience a significant change in shape upon light isomerization: i.e., *trans* and *cis* forms of azobenzenes[1] or open and closed forms of dithienylethenes.[2] Examples of coupling photoisomerization (shape-changing) processes with supramolecular function abound in the literature.[3−7] For example, the incorporation of azobenzenes[8,9] and dithienylethene[10] photoswitchable units in the structure of metal-mediated molecular cages allowed the coupling of the isomerization processes with the modulation of their binding affinities. The UV irradiation interconverted the assemblies between different forms that retained a cagelike structure. In the same vein, the *trans*−*cis* isomerization of an azo unit present in the scaffold of an encapsulated guest was combined not only with the release of the *cis* form to the bulk[11,12] but also with the switching of the assembly between different capsular aggregates.[13] In this arena, a remaining challenge to be solved is the direct control of the assembly−disassembly processes of discrete and structurally well-defined supramolecular capsules by light.[14] Ideally, the assembly−disassembly processes of the capsule are concomitant with the encapsulation−release of intact cargo beyond simple solvent molecules.[15,16] Properly functionalized liposomal[17] and polymeric[18] nanostructured carrier systems featuring visible light-induced release of intact entrapped drugs have been reported. However, these molecular containers are colloidal and polydispersed aggregates. In addition, their release mechanism relies on permeabilization changes of their layers or shells rather than on disassembly. Recently, we demonstrated the use of light to control the disappearance from solution of a hydrogen-bonded molecular capsule with a polar interior on the basis of the dimerization of a tetraureacalix[4]pyrrole.[19] Unfortunately, the light irradiation of the solution containing the capsule induced the appearance of a solid precipitate. The ^{1}H NMR spectrum of the remaining solution showed ill-defined broad signals, which did not provide convincing evidence of a direct coupling among light irradiation, capsule disassembly, and concomitant guest release.

Here we introduce a series of tetraureacalix[4]arenes equipped with terminal diphenylazo groups **1** (Scheme 1). We show that in CD_2Cl_2 solution under thermal equilibration the tetraureacalix[4]arenes **1** self-assemble quantitatively into *all-trans* dimeric capsules $\mathbf{1}_2$. The dimerization process is preferentially induced by encapsulation of one molecule of the tetramethylphosphonium species **2** (Me_4P^+). We demonstrate that irradiation of the solutions containing the *all-trans* dimeric capsules $\mathbf{2}\subset\mathbf{1}_2$ produces both the appearance of *cis*-enriched capsular aggregates and the release, at different levels, of **2** to the bulk solution. We were able to achieve high levels of release (>70%) of the encapsulated guest **2** by carefully tuning the extent of the substitution of the terminal phenyl of the azobenzene groups in **1**. Thermal equilibration in the dark restores the system to the initial equilibrium state: that is, exclusive observation of the

Received: August 28, 2015
Published: October 12, 2015

DOI: 10.1021/acs.joc.5b02008
J. Org. Chem. 2015, 80, 10866−10873

Scheme 1. Synthetic Schemes for the Preparation of (a) Tetraureacalix[4]arenes 1 Equipped with Terminal Diphenylazo Groups and (c, d) Their Precursors and (b) Equilibrium between Two Conformers of the *cis* Form of an Azodiphenyl Group Highlighting the Effect of the *p*-Methyl Substituent[a]



[a]The line-drawing structure of the tetramethylphosphonium cation **2** used in the light-controlled encapsulation experiments is also shown in panel (a).

2⊂(*all-trans*-**1**)$_2$ capsules. The switching between the thermal equilibrium state and the photostationary state (PSS) proceeds with no detectable photodegradation even when it is repeated multiple times. The encapsulation complex **2**⊂(*all-trans*-**1**)$_2$ can be converted to a mixture of *cis*-enriched dimeric assemblies with the concomitant release of the encapsulated **2**.

RESULTS AND DISCUSSION

Synthesis. The series of three tetraureacalix[4]arenes **1** was prepared by heating at 50 °C for 2−3 days a DMF solution of the corresponding diphenylazoamine **3** and tetraurethanecalix[4]-arene **4** in the presence of Et_3N (Scheme 1).[20] The synthetic route started with monoprotection of 2,4-diaminotoluene to form the phthalimide derivative **5**, followed by the oxidation of the unprotected amino group to the respective nitroso compound **6**, which when subjected to Mills reactions afforded the diazo-protected derivatives **7a−c**. To avoid the reduction of the diazo group by hydrazine, the deprotection of compounds **7a−c** yielding the amines **3a−c** was carried out using ethylenediamine. In order to minimize the number of synthetic steps, we decided to use as a common synthetic intermediate the calix[4]arenetetracarbamate **4** that was obtained by reaction of tetraamine **8**[21] with *p*-nitrophenyl chloroformate. Condensation of (diazophenyl)amino compounds (**3a−c**) with **4** yielded the tetrakis(diazolylphenyl)calix[4]arenes **1a−c** in acceptable to high yields.Tetraureas **1** were isolated as solids in good yields (62−81%) after column chromatographic purification. Owing to the substitution of the calix[4]arene scaffold with four azo groups, tetraureas **1** can exist as six different stereoisomers: *tttt*, *cttt*, *cctt*, *ctct*, *ccct*, and *cccc*. In fact, tetraureas **1** were obtained as mixtures of *cis*−*trans* stereoisomers enriched in the *all-trans* isomer. However, DMSO-d_6 solutions of the isolated tetraureas **1** thermally isomerized in the dark (12 h, 70 °C) afforded ^{1}H NMR spectra consistent with the exclusive presence of the *all-trans* isomer *tttt*-**1**, displaying C_{4v} symmetry (see the Supporting Information). The three tetraureacalix[4]arenes **1a−c** were characterized by a full set of high-resolution spectra.

DOI: 10.1021/acs.joc.5b02008
J. Org. Chem. 2015, 80, 10866−10873

The incorporation of the *p*-methyl substituent, with respect to the urea function, in the azodiphenyl groups of **1** was intended to reduce the number of potential conformers in both *cis* and *trans* forms of the azo groups (Scheme 1b). We were particularly interested in avoiding *cis* conformers having the terminal phenyl group oriented away from the urea functions. The rationale was that steric clashes between the urea functions and the terminal phenyls of the azo groups in the *cis* form would disrupt the belt of hydrogen bonds and induce the disassembly of the capsular structure.

Study of the Self-Assembly of Hydrogen-Bonded Dimeric Capsules and the Ability To Switch Their Diphenylazo Groups by Light Irradiation. The solubility of the tetraureacalix[4]arenes **1** in chlorinated solvents was good, and thermal equilibration of $CDCl_3$ solutions provided ^{1}H NMR spectra displaying a single set of sharp and well-resolved proton signals (Figure S15 in the Supporting Information). These were diagnostic of the exclusive formation of dimeric capsular assemblies $CDCl_3\subset(\textit{all-trans}\text{-}\mathbf{1})_2$ with S_8 symmetry.[22]

We first investigated the switching ability of the azo groups in these dimeric capsules at 50 μM concentration, since closely related structures are known to dimerize quantitatively in $CHCl_3$ solution at this and even lower concentrations.[23] The obtained results (see Figures S2–S4 in the Supporting Information) indicated that (1) the photochromic azo units in the dimeric assembly $(\textit{all-trans}\text{-}\mathbf{1a})_2$ are responsive to the light stimuli, (2) light irradiation of the solution with wavelengths in the range of 300–380 nm induced the formation of *cis*-enriched tetraureas, (3) the photoisomerization process can be partially reversed by irradiating at 440 nm, yielding *trans*-enriched tetraureas, and (4) the reset of all azo switches to the *trans* form required thermal equilibration in the dark. The UV–vis experiments did not demonstrate that the *trans* to *cis* photoisomerization process was indeed coupled with the disruption of the dimers or the disassembly of their capsular structures. For this reason, we studied the photoisomerization process with ^{1}H NMR spectroscopy, using the complexes $\mathbf{2}\subset\mathbf{1}_2$, in which the encapsulated tetramethylphosphonium (Me_4P^+) cation **2** possesses two NMR active nuclei (Figure S14 in the Supporting Information).

We and others have reported that some tetraureacalix[4]arenes structurally related to **1** do not form dimeric capsules in CD_2Cl_2 solution; apparently, this solvent is not a good fit for the cavities.[24,25] Surprisingly, the ^{1}H NMR spectra of the tetraureas **1a** (Figure 1a) and **1b** (see the Supporting Information) in CD_2Cl_2 solution showed sharp proton signals that were indicative of the formation of capsular dimeric aggregates. We attribute this unexpected result to stabilization factors induced by the diphenylazo groups: i.e., changes in the acidity of the urea NHs and/or additional energetically favorable intermolecular CH–π contacts.

The addition of 0.25 equiv of $Me_4P^+\cdot PF_6^-$ ($\mathbf{2}\cdot PF_6^-$) to a CD_2Cl_2 solution of **1** produced the appearance of two sets of separated protons signals for **1** (Figure 1b). When 0.5 equiv of **2** was added, we observed only the sharp signals of the tetraurea **1** in a new aggregate that were diagnostic of the dimer assembly $\mathbf{1}_2$ with S_8 symmetry (Figure 1c). We detected a doublet resonating highly upfield, at δ −0.80 ppm ($\Delta\delta$ −2.74 ppm). This was assigned to the methyl protons of the encapsulated Me_4P^+ cation in a strongly shielding environment of the eight nearest aromatic panels of the capsules. The addition of more than 0.5 equiv of Me_4P^+ gave a new doublet at δ 1.94 ppm corresponding to the free Me_4P^+ cation but did not change any of the signals for encapsulated TMP (Figure 1d).

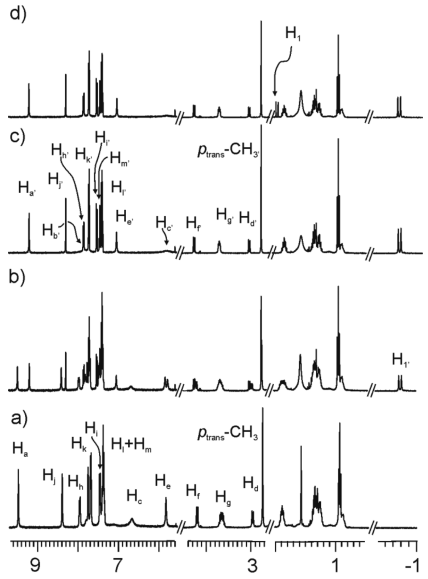


Figure 1. Selected regions of the ^{1}H NMR spectra acquired during the incremental addition of (a) 0 equiv, (b) 0.25 equiv, (c) 0.5 equiv, and (d) 1 equiv of Me_4P^+ to a CD_2Cl_2 solution with [**1a**] = 1.5 mM. The maximum solubility of TMP·PF_6 in CD_2Cl_2 is close to 0.4 mM. Hence, the addition of more than 1 equiv of TMP did not produce an increase in the intensity of the doublet resonating at δ 1.94 ppm that corresponds to the methyl protons of free Me_4P^+ in solution. See Scheme 1 for proton assignment. The intensities of the peaks in the aromatic region of the panels were doubled for clarity. Primed numbers indicate the protons in the encapsulation complex.

Accordingly, capsular assemblies $\mathbf{2}\subset\mathbf{1}_2$ were quantitatively formed in solution by addition of 0.5 equiv of Me_4P^+; chemical exchange between free and encapsulated Me_4P^+ was slow on the NMR time scale, and the binding affinity of Me_4P^+ for the cavities of $\mathbf{1}_2$ was larger than 10^4 M^{-1}.[26] The formation of $\mathbf{2}\subset(\textit{all-trans}\text{-}\mathbf{1b})_2$ was also evidenced by a DOSY-NMR experiment that assigned the same diffusion constant ($(7.5\pm0.2)\times10^{-10}$ m^2 s^{-1}) to its two molecular components (see the Supporting Information). Using the Stokes–Einstein equation, we calculated a hydrodynamic diameter of 1.5 nm for the $\mathbf{2}\subset(\textit{all-trans}\text{-}\mathbf{1b})_2$ assembly. This value is in good agreement with the MM3 minimized structure depicted in Figure 2. We also calculated an optimum packing coefficient value[27] of 55% for the $\mathbf{2}\subset(\textit{all-trans}\text{-}\mathbf{1b})_2$ assembly that served to partially explain its high thermodynamic stability. Most likely, the excellent fit in size and shape that existed between the encapsulated Me_4P^+ cation and the capsule's cavity was complemented by attractive host–guest noncovalent forces. These include (a) cation–π interactions with the electron-rich internal π surfaces of the calix[4]arene units and (b) cation–dipole interactions with the urea groups forming the hydrogen-bonding belt.[28]

Studies of Light-Induced Cargo Release using the Prepared Self-Assembled Hydrogen-Bonded Dimeric Capsules. Irradiation of separated NMR tubes containing CD_2Cl_2 solutions of the capsular aggregates $\mathbf{2}\subset(\textit{all-trans}\text{-}\mathbf{1})_2$ (~0.75 mM) with 365 nm light,[29] using a UV lamp usually employed for inspecting TLC plates, resulted in the photoisomerization of some of the azo groups of the *all-trans*-**1** components and the simultaneous advent of *cis*-enriched isomers of **1** (Figures S7–S12 in the Supporting Information). ^{1}H NMR spectroscopy evidenced the photoisomerization process by the gradual disappearance of the signals assigned to $\mathbf{2}\subset(\textit{all-trans}\text{-}\mathbf{1})_2$

DOI: 10.1021/acs.joc.5b02008
J. Org. Chem. 2015, 80, 10866–10873

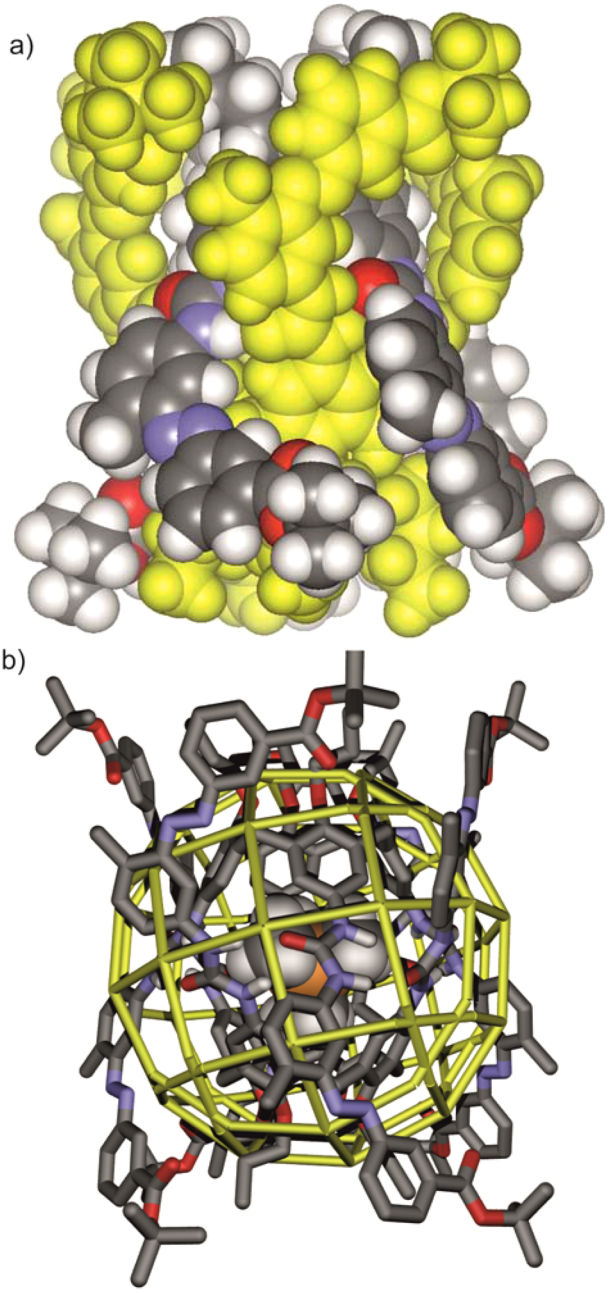


Figure 2. (a) MM3 energy minimized structure of **2**⊂(*all-trans*-**1b**)$_2$. The two tetraureas *all-trans*-**1b** are shown as CPK models, one using the atom color code and the other with all atoms in yellow. (b) Hydrodynamic diameter obtained from DOSY-NMR experiment depicted as a sphere defined by yellow sticks and centered in the geometrical center of the capsule. The encapsulated Me_4P^+ cation **2** is shown as a CPK model. The *all-trans*-**1b** tetraurea is represented as a stick model. For clarity, only polar hydrogen atoms are shown and the *O*-pentyl groups have been pruned to ethyl.

and the emergence of multiple and complex new sets of signals corresponding to the protons of several *cis*-enriched tetraureas **1**. Selected regions of the NMR spectra (^{1}H and ^{31}P) for the photoisomerization process experienced by the encapsulation complex **2**⊂(*all-trans*-**1b**)$_2$ are depicted in Figure 3.

Owing to the large concentrations of **1** used in the NMR experiments, reaching the PSS demanded irradiation times longer (15 min) than those observed in the UV−vis experiments (5 min). The stereoisomers of *cis*-enriched tetraureas **1** produced

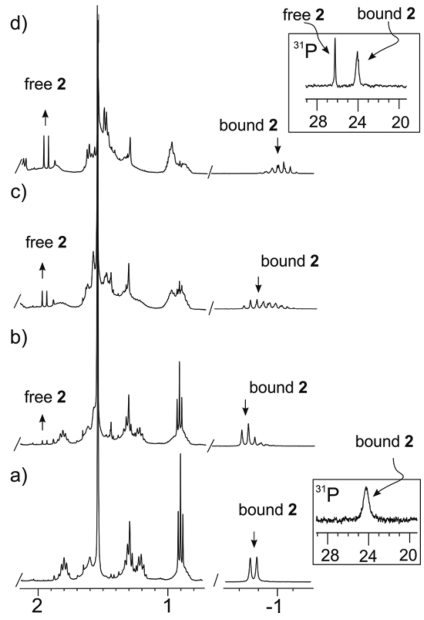


Figure 3. Selected upfield regions of the ^{1}H NMR spectra acquired after irradiating at 365 nm a CD_2Cl_2 solution of [**2**⊂(*all-trans*-**1b**)$_2$] = 0.75 mM for (a) 0 min, (b) 1 min, (c) 5 min, and (d) 15 min. The signals for released (δ 1.94 ppm) and encapsulated (δ −0.8 ppm) Me_4P^+ cations are indicated with arrows. The corresponding ^{31}P NMR spectra showing the signals for the free and encapsulated **2** at the beginning and at the end of the irradiation time are also displayed in panels (a) and (d).

by the photoisomerization process are involved in the assembly of dimeric aggregates having capsular and, possibly, not capsular structures (vide infra). The decrease in the integral values of the sharp singlet (δ 2.8 ppm, Figure S8, Supporting Information) for the *p*-methyl protons in the nonterminal azophenyl ring of *all-trans*-**1** allowed the calculation of an average 80:20 ratio of *cis* to *trans* forms in the PSS. This value was similar to that measured for a model system of the azo groups in **1** (Figure S5 in the Supporting Information), indicating that each azo group in **1** experienced an independent light-driven isomerization process.[30]

The photoinduced release of **2** to the bulk solution was demonstrated by the observation of a growing doublet of the free Me_4P^+ at δ 1.94 ppm (Figure 3b−d). Until the PSS was reached, the intensity of the doublet for the free Me_4P^+ increased at the expense of multiple upfield-shifted signals that appeared during the photoisomerization process and corresponded to methyl protons of encapsulated Me_4P^+ cations. The observation of new doublets that experienced an upfield shift testified that *cis*-enriched isomers of tetraurea **1** were involved in the assembly of a variety of isomeric **2**⊂**1**$_2$ capsules. The encapsulated Me_4P^+ cation experienced a different magnetic shielding in each encapsulation complex. Not surprisingly, the number and relative intensity of the doublets changed until the PSS was reached.

The signals of the encapsulated Me_4P^+ cations moved further upfield in response to the gradual *cis* enrichment of the capsules' components: tetraurea **1**. This latter observation suggested the presence of more constrictive cavities in *cis*-enriched capsules in comparison to the *all-trans* counterparts. The cavity size modulation exerted by the photoisomerization process of the azo groups in the tetraurea components of the capsules **1**$_2$ must be responsible for the release of Me_4P^+ to the bulk. Most likely, dimeric aggregates based on tetraurea components having experienced high levels of *cis* enrichment display reduced cavity

DOI: 10.1021/acs.joc.5b02008
J. Org. Chem. 2015, 80, 10866−10873

volumes that are more suitable for the encapsulation of CD_2Cl_2 instead of Me_4P^+. Alternatively, highly enriched *cis*-tetraureas might dimerize, forming noncapsular assemblies (Figure 5b).

A DOSY experiment performed on the solution mixture obtained at the PSS for the **2**⊂(*all-trans*-**1b**)$_2$ supported both the encapsulation of Me_4P^+ in multiple isomeric dimeric capsules and the presence in solution of dimers of *cis*-enriched **1b** tetraureas not encapsulating Me_4P^+ (Figure 4).[31] We did not

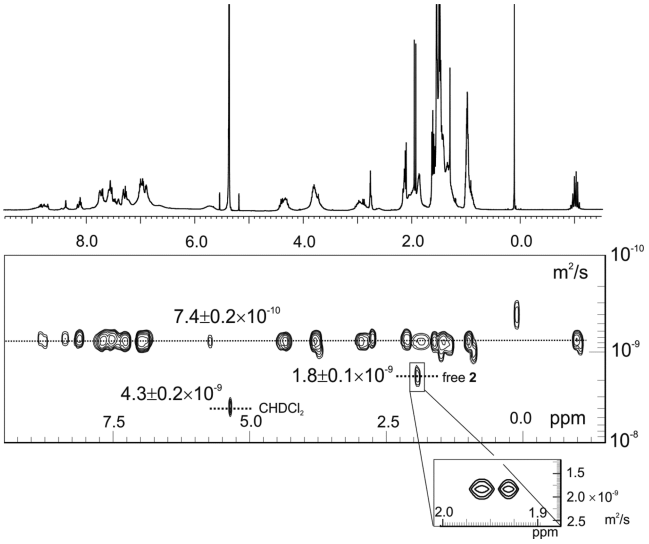


Figure 4. ^{1}H pseudo-2D DOSY plot of the mixture obtained after 15 min irradiation of a CD_2Cl_2 solution of [**2**⊂(*all-trans*-**1b**)$_2$] = 0.75 mM with 365 nm light.

observe the presence of larger oligomeric aggregates of *cis*-enriched **1b** that would be characterized by diffusion constant values smaller than that determined for the *all-trans* dimer.[32]

The kinetic data obtained for the photo induced Me_4P^+ release of the three *all-trans*-capsules **2**⊂(**1a-c**)$_2$ were fit to a reversible first order reaction model (Figures S20−S22 in the Supporting Information). We obtained a good fit of the experimental data to the theoretical model for the three cases. By extrapolating the fit, we calculated the percentages of Me_4P^+ encapsulated and Me_4P^+ free at the PSS, which is the equilibrium composition. Starting from the **2**⊂(*all-trans*-**1a**)$_2$ assembly, only 12% of the encapsulated Me_4P^+ cation was released to the solvent when the PSS was reached. The percentage of released Me_4P^+ increased to 33% as a result of the photoinduced isomerization of **2**⊂(*all-trans*-**1b**)$_2$ featuring one *tert*-butoxycarbonyl substituent in the terminal phenyl of the diphenylazo group. Finally, the capsular assembly **2**⊂(*all-trans*-**1c**)$_2$ with two *meta*-substituted *tert*-butoxycarboyl groups in the terminal azophenyl ring released to the bulk solution 70% of its cargo following light irradiation.

At first sight, the constant and high levels of photoinduced *trans*−*cis* isomerization (20:80) observed for the azo groups along the series of tetraurea dimeric capsules **2**⊂(**1a**−**c**)$_2$ are difficult to reconcile with the variable and in some cases low values observed for the guest release. Indeed, the *cis*−*trans* isomerization level was not directly coupled to the cargo release function demonstrated by the supramolecular capsules **2**⊂(*all-trans*-**1**)$_2$. Conversely, the substitution level of the terminal phenylazo group was a key factor in modulating their levels of guest release. We observed, however, that the steric clashes occurring among the photoisomerized *cis*-azo groups in the belt of hydrogen-bonded ureas, the aromatic walls, and other *cis*-azo groups were not enough to induce a substantial dimer disaggregation. We concluded that, given the same number of *cis*-isomerized azo groups in a **1**$_2$ dimer, the increase of substitution at the terminal azophenyl group was linked to a larger reduction or modification of the aromatic cavity owing to the intensification of steric clashes. An alternative, although closely related, explanation would be that *cis*-enriched tetraureas such as **1b**,**c** featuring bulky substituents in their terminal azo groups produced dimeric assemblies (capsular and not capsular) that are less suitable for the encapsulation of Me_4P^+ than **1a** (Figure 5).

■ CONCLUSIONS

In conclusion, we report the synthesis of three tetraureacalix[4]arene derivatives **1a**−**c** equipped with light-responsive azobenzene groups. The thermally equilibrated *all-trans*-**1**

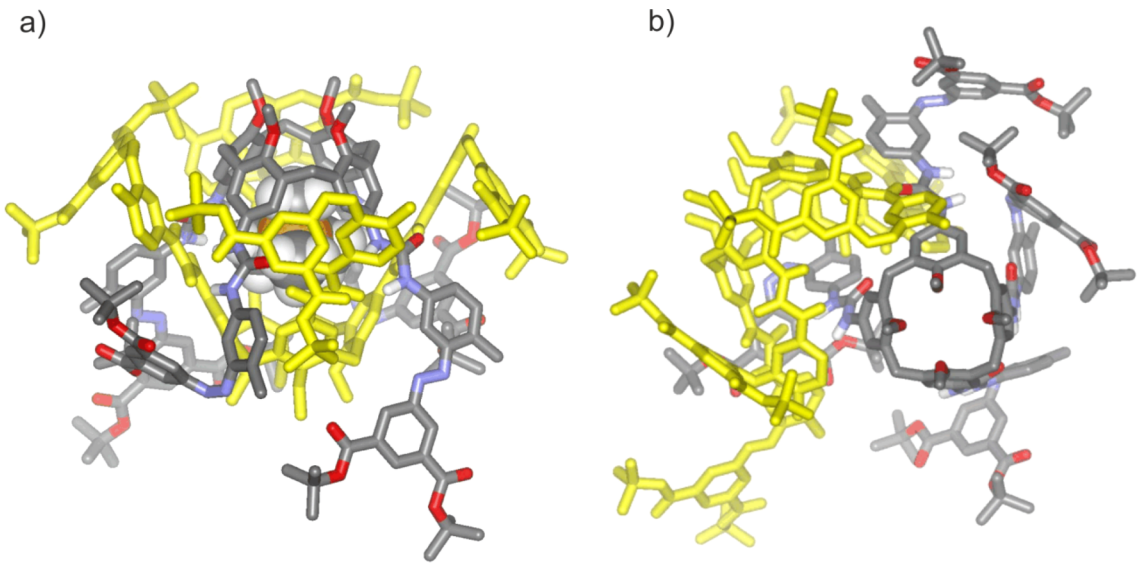


Figure 5. Energy minimized structures of (a) capsular assembly **2**⊂(**1c**)$_2$ and (b) a putative noncapsular (**1c**)$_2$ dimer. Both assemblies contain six azo groups in *cis* form and two in *trans* form.

DOI: 10.1021/acs.joc.5b02008
J. Org. Chem. 2015, 80, 10866−10873

isomers quantitatively dimerize in CD_2Cl_2 solution by encapsulating one molecule of the tetramethylphosphonium cation (Me_4P^+, **2**). The *trans*−*cis* photoisomerization of the azo groups in the **2**⊂(*all-trans*-**1**)$_2$ complexes prompted the release of the Me_4P^+ cation to the bulk solution and the appearance of *cis*-enriched capsular assemblies. The amount of Me_4P^+ released to the solution (12−70%) was proportional to the number of *tert*-butoxy carboxyl substituents present in the terminal phenyl azo group but not to the levels of the *trans*−*cis* isomerization, which remained constant for the whole series. The remote substitution of the terminal azophenyls in *all-trans* capsules is transmitted in an increase of the steric clashes in the *cis*-enriched counterparts. To minimize these steric clashes, the *cis*-enriched tetraureas dimerize in capsules featuring a reduced cavity size or in noncapsular dimers. In addition, the CD_2Cl_2 solvent molecules, having a volume smaller than that of the Me_4P^+ cation, became competitive encapsulation guests of the *cis*-enriched capsules. We have shown unprecedented and significant examples of light-controlled cargo release using hydrogen-bonded dimeric capsules. The release mechanism is connected to cavity size modulation and capsular structure destabilization but not to dimerization disruption. We are currently working on increasing the bulkiness of the substituents in the terminal phenylazo groups with the goal of inducing a complete release of the cargo and the dimers' disaggregation following the *trans*−*cis* photoisomerization.

EXPERIMENTAL SECTION

Methods and Materials. All reagents and starting materials were purchased from commercial sources and used without further purification, unless otherwise noted. All reactions were carried out under an argon atmosphere unless otherwise mentioned. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were collected on 400 and 500 MHz spectrometers. Chemical shifts for the deuterated solvents are given in ppm and were referenced relative to the solvent residual peak (δ_H 7.26 ppm and δ_C 77.16 ppm for $CDCl_3$; δ_H 2.50 ppm and δ_C 39.52 ppm for DMSO-d_6; δ_H 3.58 and δ_C 67.57 for THF-d_8, and δ_H 5.35 ppm and δ_C 54.00 ppm for DCM-d_2). All NMR *J* values are given in Hz. UV−vis measurements were carried out using quartz cells (1 mm path). High-resolution mass spectra were obtained using ESI ionization and a TOF mass analyzer. Light irradiation of the samples for the NMR experiments was carried out using a 4 W UV lamp having a light intensity of 6.9 mW at 365 nm. Light irradiation of the samples for the UV−vis experiments was carried out using a monochromator device equipped with a xenon light source.

2-(3-amino-4-methylphenyl)isoindoline-1,3-dione (5). 4-Methylbenzene-1,3-diamine (5 g, 40.9 mmol, 1 equiv) was dissolved in 15 mL of acetic acid and the solution stirred at 120 °C for 30 min. The mixture was cooled to room temperature, and a yellow solid precipitated. The solid was filtered, washed with acetic acid, air-dried, redissolved in DCM, and extracted with ∼4% aqueous HCl (4×, 70 mL each). The acidic aqueous washings were washed with DCM (1×, 20 mL), and solid sodium carbonate was added slowly until the mixture turned basic. A yellow solid precipitated, which was collected by filtration, washed with water, air-dried, and placed under high vacuum overnight: 1.895 g (18% yield). The other amine isomer and diprotected product can be recovered from the remaining acetic acid and DCM solution, respectively. ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.93 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.16 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.76−6.66 (m, 2H), 3.72 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 145.4, 134.4, 132.0, 131.0, 130.4, 123.8, 122.7, 116.8, 113.1, 17.3. Gradient 1-D NOE NMR, goesy, (500 MHz, Chloroform-*d*): δ 7.19 (d, *J* = 6.5 Hz, negative phase, 1H), 3.75 (s, negative phase, 1H), 2.22 (s, positive phase, 126H). HR-MS (ESI-TOF): *m*/*z* calcd for $C_{15}H_{12}N_2O_2$ ([M + H]$^+$) 253.0972, found 253.0983.

2-(4-Methyl-3-nitrosophenyl)isoindoline-1,3-dione (6). Monoprotected diaminotoluene **5** (0.6 g, 2.378 mmol, 1 equiv) was dissolved in 25 mL of CH_2Cl_2. To this solution was added Oxone, previously dissolved in 100 mL of water (2.92 g, 4.76 mmol, 2 equiv). The mixture was stirred vigorously at room temperature until monitoring by TLC (silica, EtOAc/Hx/DCM 1/2/0.2) indicated complete consumption of the starting material (∼24 h). The DCM layer was washed with water (2 × 25 mL), [0.5 N] HCl (1 × 25 mL), aqueous saturated sodium bicarbonate (1 × 25 mL), and water (1 × 25 mL) and then dried over Na_2SO_4. The solution was evaporated under reduced pressure. The compound was obtained as a pale green solid: 0.503 g (79% yield). ^{1}H NMR (500 MHz, chloroform-*d*): δ 7.95 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73−7.70 (m, 2H), 6.39 (d, *J* = 1.9 Hz, 1H), 3.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.9, 164.0, 142.2, 134.8, 133.9, 133.2, 131.7, 130.1, 124.1, 105.6, 17.2. HR-MS (ESI-TOF): *m*/*z* calcd for $C_{15}H_{10}N_2O_3$ ([M + Na]$^+$) 289.0584, found 289.0581.

2-(4-Methyl-3-(phenyldiazenyl)phenyl)isoindoline-1,3-dione (7a). Aniline (0.068 mL, 0.751 mmol, 2 equiv), nitroso compound **6** (0.1 g, 0.376 mmol, 1 equiv), and 8 mL of acetic acid were placed in a 25 mL round-bottomed flask. The mixture was stirred at 65 °C for 3 h. The reaction mixture was cooled to room temperature, and 2 mL of water was added. The solid was filtered, washed (first with acetic acid and then with MeOH), air-dried, and placed under high vacuum for 30 min. An orange solid was obtained: 0.097 g (76% yield). The product can be used without further purification, but it can also be purified by column chromatography (silica, DCM/Hx/ethyl ether 100/100/1). Additionally, this compound was also made using compound **5** and nitrosobenzene under similar conditions in 75% yield. ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.01−7.88 (m, 4H), 7.83−7.74 (m, 3H), 7.55−7.42 (m, 5H), 2.79 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.3, 152.9, 150.9, 138.5, 134.6, 132.0, 131.9, 131.2, 130.2, 129.2, 128.7, 123.9, 123.3, 114.1, 17.5. HR-MS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{15}N_3O_2$ ([M + Na]$^+$) 364.1056, found 364.1063.

***tert*-Butyl 3-((5-(1,3-Dioxoisoindolin-2-yl)-2-methylphenyl)-diazenyl)benzoate (7b).** *tert*-Butyl 3-aminobenzoate (0.207 g, 1.07 mmol, 1 equiv), nitroso compound **6** (0.285 g, 1.070 mmol, 1 equiv), and 15 mL of acetic acid were placed in a 50 mL round-bottomed flask. The mixture was stirred at 70 °C for 3 h. The solvent was removed by rotary evaporation, and the resulting solid was washed with MeOH and filtered. Purification by column chromatography (silica, DCM/Hx 3/1) produced a bright orange solid: 0.309 g (65% yield). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.51 (t, *J* = 1.8 Hz, 1H), 8.15−8.02 (m, 2H), 7.96 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.87−7.73 (m, 3H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.53−7.44 (m, 2H), 2.80 (s, 3H), 1.63 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 165.3, 152.8, 150.7, 138.8, 134.6, 133.3, 132.1, 131.9, 131.8, 130.3, 129.1, 129.1, 126.4, 124.7, 123.9, 114.0, 81.7, 28.3, 17.5. HR-MS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{23}N_3O_4$ ([M + Na]$^+$) 464.1581, found 464.1569.

Di-*tert*-butyl 5-((5-(1,3-Dioxoisoindolin-2-yl)-2-methyl-phenyl)diazenyl)isophthalate (7c). Di-*tert*-butyl 5-aminoisophthalate (0.1 g, 0.341 mmol, 1 equiv), nitroso compound **6** (0.091 g, 0.341 mmol, 1 equiv), and 15 mL of acetic acid were placed in a 100 mL round-bottomed flask. The mixture was stirred at 65 °C for 60 h. The solvent was removed by rotary evaporation, and the resulting solid was washed with MeOH and filtered. Purification by column chromatography (silica, DCM/Hx/Et_2O 3/1/1) produced an orange solid: 0.109 g (59% yield). ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.68 (t, *J* = 1.6 Hz, 1H), 8.64 (d, *J* = 1.6 Hz, 2H), 7.97 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dt, *J* = 5.5, 2.6 Hz, 3H), 7.54−7.47 (m, 2H), 2.82 (s, 3H), 1.64 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 167.3, 164.7, 152.8, 150.6, 139.2, 134.6, 133.5, 132.3, 132.2, 131.9, 130.3, 129.4, 127.6, 124.0, 114.0, 82.2, 28.3, 17.5. HR-MS (ESI-TOF): *m*/*z* calcd for $C_{31}H_{31}N_3O_6$ ([M + Na]$^+$) 564.2105, found 564.2077.

4-Methyl-3-(phenyldiazenyl)aniline (3a). Diazo compound **7a** (0.360 g, 1.055 mmol, 1 equiv) was suspended in 20 mL of *n*-butanol, then ethylenediamine (0.7 mL, 10.55 mmol, 10 equiv) was added, and the mixture was stirred and warmed to 90 °C. The reaction was monitored by TLC (silica, EtOAc/Hx 1/1) until no starting material was seen (35 min). The solvent was removed by rotary evaporation, and

DOI: 10.1021/acs.joc.5b02008
J. Org. Chem. 2015, 80, 10866−10873

the crude product was purified by column chromatography (silica, EtOAc/Hx 1/1): 220 mg of a red solid was recovered (99% yield). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.97−7.84 (m, 2H), 7.59−7.40 (m, 3H), 7.13 (d, J = 8.1 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 6.76 (dd, J = 8.1, 2.5 Hz, 1H), 3.65 (s, 2H), 2.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.0, 151.1, 144.8, 131.9, 130.6, 129.0, 128.9, 122.9, 118.7, 101.3, 16.6. HR-MS (ESI-TOF): m/z calcd for $C_{13}H_{13}N_3$ ([M + H]$^+$) 212.1182, found 212.1185.

***tert*-Butyl 3-((5-Amino-2-methylphenyl)diazenyl)benzoate (3b).** Diazo compound **7b** (0.285 g, 1.00 mmol, 1 equiv) was suspended in 10 mL of *n*-butanol, and then ethylenediamine (0.43 mL, 6.5 mmol, 10 equiv) was added. The mixture was stirred at 70 °C. The reaction was monitored by TLC (silica, EtOAc/Hx 1/1) until no starting material was seen (30 min). The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography (silica, EtOAc/Hx 1/1): 220 mg of a a dense oil was obtained (97% yield). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.50 (t, J = 1.9 Hz, 1H), 8.16−7.95 (m, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.02 (d, J = 2.5 Hz, 1H), 6.78 (dd, J = 8.1, 2.5 Hz, 1H), 3.67 (s, 2H), 2.63 (s, 3H), 1.63 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4, 153.0, 151.1, 145.0, 133.3, 132.1, 131.4, 129.5, 129.1, 126.0, 124.7, 119.2, 101.4, 81.6, 28.4, 16.7. HR-MS (ESI-TOF): m/z calcd for $C_{23}H_{29}N_3O_4$ ([M + H]$^+$) 412.2231, found 412.2215.

Di-*tert*-butyl 5-((5-Amino-2-methylphenyl)diazenyl)-isophthalate (3c). Diazo compound **7c** (0.098 g, 0.181 mmol, 1 equiv) was suspended in 10 mL of *n*-butanol, and then ethylenediamine (0.121 mL, 1.809 mmol, 10 equiv) was added. The mixture was stirred at 65 °C. The reaction was monitored by TLC (silica, DCM/Hx/ether 2/1/1) until no starting material was seen (25 min). The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography (silica, DCM/Hx/ether 2/1/1). A bright orange solid was obtained: 0.073 mg (98% yield). ^{1}H NMR (500 MHz, chloroform-*d*): δ 8.66 (t, J = 1.6 Hz, 1H), 8.62 (d, J = 1.6 Hz, 2H), 7.15 (d, J = 8.1 Hz, 1H), 7.04 (d, J = 2.6 Hz, 1H), 6.79 (dd, J = 8.1, 2.5 Hz, 1H), 3.68 (s, 2H), 2.64 (s, 3H), 1.64 (s, 18H) . ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.7, 153.0, 150.9, 145.0, 133.4, 132.2, 131.9, 129.9, 127.4, 119.6, 101.3, 82.1, 28.3, 16.7. HR-MS (ESI-TOF): m/z calcd for $C_{18}H_{21}N_3O_2$ ([M + H]$^+$) 312.1707, found 312.1717.

Tetrakis(4-nitrophenyl) Calix[4]arenetetracarbamate (4). The tetraaminocalix[4]arene **8**[21] (75 mg, 0.098 mmol, 1 equiv) was dissolved in a 3/2 $CHCl_3$/THF mixture. The system was degassed by bubbling argon for 4 min, and then 4-nitrophenyl chloroformate (99 mg, 0.490 mmol, 5 equiv) was added in one portion. The reaction mixture was refluxed under Ar (temperature 82−85 °C) overnight. A silicone oil bubbler was connected to the top of the condenser to allow the release of HCl. The solvent was removed in vacuo at room temperature, and the resulting solid was sonicated in ethyl ether, filtered, washed with ethyl ether, and dried under high vacuum. A yellow solid was obtained: 106 mg (76% yield). ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.21 (d, J = 8.5 Hz, 8H), 7.30 (d, J = 8.9 Hz, 10H), 6.76 (s, 12H), 4.47 (d, J = 13.3 Hz, 4H), 3.88 (s, 8H), 3.15 (d, J = 13.4 Hz, 4H), 1.90 (q, J = 7.9 Hz, 8H), 1.39 (d, J = 9.1 Hz, 16H), 0.95 (dt, J = 7.2, 4.1 Hz, 12H). ^{1}H NMR (500 MHz, THF-d_8): δ 9.20 (s, 4H), 8.20 (d, J = 8.7 Hz, 8H), 7.37 (d, J = 8.6 Hz, 8H), 6.91 (s, 8H), 4.51 (d, J = 13.2 Hz, 4H), 4.17−3.71 (m, 8H), 3.15 (d, J = 13.3 Hz, 4H), 1.96 (t, J = 7.3 Hz, 8H), 1.45 (dq, J = 8.0, 5.0 Hz, 16H), 1.13−0.80 (m, 12H). ^{13}C NMR (126 MHz, THF): δ 157.3, 153.9, 151.2, 145.8, 136.3, 133.6, 125.7, 123.1, 119.6, 76.2, 32.4, 31.0, 29.6, 23.9, 14.7. HR-MS (ESI-TOF): m/z calcd for $C_{76}H_{80}N_8O_{20}$ ([M + Na]$^+$) 1447.5381, found 1447.5451.

(*E*)-5,11,17,23-Tetrakis(3-(4-methyl-3-(phenyldiazenyl)-phenyl)ureido)-25,26,27,28-tetrapentyloxycalix[4]arene (1a). Diazotolylamine **3a** (89 mg, 0.421 mmol, 6 equiv) was dissolved in dry DMF (4 mL), then 0.06 mL of Et_3N (0.058 mL, 0.421 mmol, 6 equiv) was added, and calix[4]arenetetracarbamate **4** (100 mg, 0.070 mmol, 1 equiv) was added afterward. The reaction mixture was covered with aluminum foil and stirred at 60 °C for 48 h. The reaction mixture was poured into aqueous K_2CO_3 (saturated), filtered, washed with K_2CO_3 (saturated) and water, and air-dried. The solid was purified by column chromatography (silica, gradient DCM/ether 10/0.1 then DCM/ether/MeOH 10/0.1/0.1). A red solid was obtained: 75 mg (62% yield). The compound was mostly obtained as an *all-trans* system. However, in order to get a single isomer for characterization, the compound was placed at 60 °C for 12 h in $CDCl_3$ or 30 min at 110 °C protected from light in DMSO-d_6. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.49 (s, 4H), 8.12−8.15 (s, 4H), 7.85−7.73 (m, 8H), 7.63 (d, J = 2.3 Hz, 4H), 7.59−7.44 (m, 12H), 7.34 (dd, J = 8.3, 2.3 Hz, 4H), 7.19 (d, J = 8.4 Hz, 4H), 6.80 (s, 8H), 4.34 (d, J = 12.9 Hz, 4H), 3.82 (t, J = 7.4 Hz, 8H), 3.13 (d, J = 13.1 Hz, 4H), 2.51 (s, 12H), 1.89 (d, J = 10.2 Hz, 8H), 1.40 (dt, J = 7.4, 3.9 Hz, 16H), 1.01−0.85 (m, 12H). ^{13}C NMR (126 MHz, DMSO): δ 152.3, 152.25, 151.2, 149.7, 138.5, 134.5, 133.3, 131.3, 131.1, 131.0, 129.3, 122.5, 121.2, 118.1, 103.9, 79.2, 74.7, 54.9, 30.7, 29.4, 28.0, 22.3, 16.4, 14.0. IR (neat) ν (cm^{-1}): 511 (m), 685 (s), 711 (m), 766 (m), 868 (w), 966 (m), 1209 (s), 1310 (m), 1466 (s), 1466 (s), 1542 (s), 1596 (m), 1656 (m), 2926 (w, br), 3330 (w, br). HR-MS (ESI-TOF): m/z calcd for $C_{104}H_{112}N_{16}O_8$ ([M + 2Na]$^+$) 879.4317, found 879.4329.

(*E*)-5,11,17,23-Tetrakis(3-(3-((3-(*tert*-butoxycarbonyl)-phenyl)diazenyl)-4-methylphenyl)ureido)-25,26,27,28-tetrapentyloxycalix[4]arene (1b). Diazoamine **3b** (59 mg, 0.189 mmol, 4.5 equiv) was dissolved in dry DMF (4 mL), then 0.035 mL of Et_3N (0.253 mmol, 6 equiv) was added, and calix[4]arenetetracarbamate **4** (60 mg, 0.042 mmol, 1 equiv) was added afterward. The reaction mixture was covered with aluminum foil and stirred at 50 °C protected from light for 72 h. The reaction mixture was poured into aqueous K_2CO_3 (saturated), filtered, washed with K_2CO_3 (saturated) and water, and air-dried. The solid was purified by column chromatography (silica, DCM/MeOH 100/2). A red solid was obtained: 72 mg, 81% yield. Mp: >230 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.53 (s, 4H), 8.24−8.07 (m, 8H), 7.97 (ddt, J = 17.1, 8.2, 1.4 Hz, 8H), 7.62 (t, J = 7.8 Hz, 4H), 7.54 (d, J = 2.3 Hz, 4H), 7.49 (dd, J = 8.3, 2.3 Hz, 4H), 7.19 (d, J = 8.4 Hz, 4H), 6.78 (s, 8H), 4.34 (d, J = 12.9 Hz, 4H), 3.82 (t, J = 7.3 Hz, 8H), 3.13 (d, J = 13.1 Hz, 4H), 2.48 (s, 12H), 1.88 (t, J = 7.3 Hz, 8H), 1.51 (s, 36H), 1.39 (d, J = 3.6 Hz, 16H), 1.08−0.70 (m, 12H). ^{13}C NMR (126 MHz, DMSO): δ 164.1, 152.4, 151.9, 151.3, 149.4, 138.6, 134.5, 133.3, 132.4, 131.44, 131.3, 131.2, 129.70, 126.30, 123.0, 121.6, 118.1, 103.8, 81.2, 74.7, 30.7, 29.4, 28.0, 27.6, 22.3, 16.2, 14.0. IR (neat) ν (cm^{-1}): 759 (m), 1146 (s), 1206 (s), 1297 (m), 1466 (m), 1538 (m), 1594 (w), 1714 (m), 2928 (w, br), 3343 (w, br). HR-MS (ESI-TOF): m/z calcd for $C_{124}H_{144}N_{16}O_{16}$ ([M + 2Na]$^+$) 1079.5365, found 1079.5369.

(*E*)-5,11,17,23-Tetrakis(3-(3-((3,5-bis(*tert*-butoxycarbonyl)-phenyl)diazenyl)-4-methylphenyl)ureido)-25,26,27,28-tetrapentyloxycalix[4]arene (1c). Diazotolylmine **3c** (60.6 mg, 0.147 mmol, 5 equiv) was dissolved in dry DMF (4 mL), then 0.025 mL of Et_3N (0.177 mmol, 6 equiv) was added, and calix[4]-arenetetracarbamate **4** (42 mg, 0.029 mmol, 1 equiv) was added afterward. The reaction mixture was covered with aluminum foil and stirred at 65 °C protected from light for 48 h. The reaction mixture was poured into aqueous K_2CO_3 (saturated), filtered, washed with K_2CO_3 (saturated) and water, and air-dried. The solid was purified by column chromatography first with DCM ether 10/0.1 as eluent (to remove diazotolylamine starting material and nitrophenol) and then DCM/ether/MeOH 10/0.2/0.1 (to obtain the product). An orange solid was obtained: 50 mg (68% yield). Mp: >230 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (s, 4H), 8.37−8.22 (m, 4H), 8.22−8.05 (m, 12H), 7.65 (dd, J = 8.5, 2.1 Hz, 4H), 7.43 (d, J = 2.6 Hz, 4H), 7.24 (d, J = 8.4 Hz, 4H), 6.79 (s, 8H), 4.34 (d, J = 12.9 Hz, 4H), 3.82 (t, J = 7.0 Hz, 8H), 3.13 (d, J = 13.1 Hz, 4H), 2.50 (s, ∼12H, same chemical shift as DMSO), 2.03−1.74 (m, 8H), 1.51 (s, 72H), 1.40 (dd, J = 6.8, 3.4 Hz, 16H), 1.09−0.75 (m, 12H). ^{13}C NMR (126 MHz, DMSO): δ 163.1, 152.44, 151.7, 151.3, 149.0, 138.7, 134.5, 133.3, 132.6, 131.9, 131.6, 130.8, 126.2, 122.3, 118.3, 103.7, 81.7, 74.7, 30.6, 29.4, 28.0, 27.5, 22.3, 16.1, 14.0. IR (neat) ν (cm^{-1}): 759 (m), 1154 (s), 1253 (m), 1470 (m), 1538 (m), 1718 (m), 2931 (w, br), 3555 (w, br). HR-MS (ESI-TOF): m/z calcd for $C_{144}H_{176}N_{16}O_{24}$ ([M + 2Na]$^+$) 1279.6414, found 1279.6425

Tetramethylphosphonium Hexafluorophosphate (2).[33] Tetramethylphosphonium chloride (80 mg, 0.632 mmol, 1 equiv) and silver(I) hexafluorophosphate (160 mg, 0.632 mmol, 1 equiv) were finely ground and added to 45 mL of an 8/1 DMC/acetonitrile mixture. The mixture was stirred for 30 min and then filtered through a 0.45 μm membrane. The solvent was removed by rotary evaporation, and the

DOI: 10.1021/acs.joc.5b02008
J. Org. Chem. 2015, 80, 10866−10873

resulting solid was stirred in water, filtered, and dried under vacuum. An off-white solid was obtained: 0.102 g (68.4% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.81 (d, J = 15.2 Hz, 12H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 8.92 (d, J = 55.3 Hz). ^{31}P NMR (162 MHz, DMSO-d_6): δ 28.32 (s), − 141.09 (hept, 711.9 Hz).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02008.

^{1}H and ^{13}C NMR spectra of all new compounds, ^{1}H NMR spectra registered during the photoisomerization of model compound **7a**, ^{1}H and ^{31}P NMR spectra registered during the light-induced isomerization experiments of the series of encapsulation complexes **2**⊂(*all-trans*-)**1**$_2$, DOSY NMRs of $[Me_4P]^+[PF_6]^-$ in DCM-d_2 and DOSY NMR of **2**⊂(*all-trans*-**1b**)$_2$ before and after light irradiation, and fits of the kinetic data obtained in the NMR irradiation experiments (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for P.B.: pballester@iciq.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Gobierno de España MINECO (projects CTQ2014-56295-R and Severo Ochoa Excellence Accreditation 2014-2018 SEV-2013-0319), FEDER funds (Project CTQ2014-56295-R), and the ICIQ Foundation for funding. We also thank Dr. Gabriel González, Germán Gomez, and Israel Macho for the acquisition of DOSY NMRs.

■ REFERENCES

(1) Beharry, A. A.; Woolley, G. A. *Chem. Soc. Rev.* **2011**, *40*, 4422−4437.

(2) Tian, H.; Wang, S. *Chem. Commun.* **2007**, 781−792.

(3) Merino, E.; Ribagorda, M. *Beilstein J. Org. Chem.* **2012**, *8*, 1071−1090.

(4) Berryman, O. B.; Dube, H.; Rebek, J. *Isr. J. Chem.* **2011**, *51*, 700−709.

(5) Park, J.; Sun, L. B.; Chen, Y. P.; Perry, Z.; Zhou, H. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5842−5846.

(6) Russew, M. M.; Hecht, S. *Adv. Mater. (Weinheim, Ger.)* **2010**, *22*, 3348−3360.

(7) Berdnikova, D. V.; Aliyeu, T. M.; Paululat, T.; Fedorov, Y. V.; Fedorova, O. A.; Ihmels, H. *Chem. Commun.* **2015**, *51*, 4906−4909.

(8) Murase, T.; Sato, S.; Fujita, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5133−5136.

(9) Park, J.; Sun, L. B.; Chen, Y. P.; Perry, Z.; Zhou, H. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5842−5846.

(10) Han, M. X.; Michel, R.; He, B.; Chen, Y. S.; Stalke, D.; John, M.; Clever, G. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1319−1323.

(11) Dube, H.; Durola, F.; Ajami, D.; Rebek, J. *J. Chin. Chem. Soc. (Weinheim, Ger.)* **2010**, *57*, 595−603.

(12) Clever, G. H.; Tashiro, S.; Shionoya, M. *J. Am. Chem. Soc.* **2010**, *132*, 9973−9975.

(13) Dube, H.; Ajami, D.; Rebek, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3192−3195.

(14) Sakano, T.; Ohashi, T.; Yamanaka, M.; Kobayashi, K. *Org. Biomol. Chem.* **2015**, *13*, 8359−8364.

(15) Swaminathan Iyer, K.; Norret, M.; Dalgarno, S. J.; Atwood, J. L.; Raston, C. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6362−6366.

(16) For a recent example of photoreversible switching between assembly and disassembly of a supramolecular polymer, see: Ogoshi, T.; Yoshikoshi, K.; Aoki, T.; Yamagishi, T. *Chem. Commun.* **2013**, *49*, 8785−8787.

(17) Carter, K. A.; Shao, S.; Hoopes, M. I.; Luo, D.; Ahsan, B.; Grigoryants, V. M.; Song, W.; Huang, H.; Zhang, G.; Pandey, R. K.; Geng, J.; Pfeifer, B. A.; Scholes, C. P.; Ortega, J.; Karttunen, M.; Lovell, J. F. *Nat. Commun.* **2014**, *5*, 4546.

(18) Erokhina, S.; Benassi, L.; Bianchini, P.; Diaspro, A.; Erokhin, V.; Fontana, M. P. *J. Am. Chem. Soc.* **2009**, *131*, 9800−9804.

(19) Osorio-Planes, L.; Espelt, M.; Pericas, M. A.; Ballester, P. *Chem. Sci.* **2014**, *5*, 4260−4264.

(20) Vysotsky, M. O.; Bolte, M.; Thondorf, I.; Bohmer, V. *Chem. - Eur. J.* **2003**, *9*, 3375−3382.

(21) Jakobi, R. A.; Boehmer, V.; Gruettner, C.; Kraft, D.; Vogt, W. *New J. Chem.* **1996**, *20*, 493−501.

(22) Shimizu, K. D.; Rebek, J. *Proc. Natl. Acad. Sci. U. S. A.* **1995**, *92*, 12403−12407.

(23) Castellano, R. K.; Craig, S. L.; Nuckolls, C.; Rebek, J. *J. Am. Chem. Soc.* **2000**, *122*, 7876−7882.

(24) Mecozzi, S.; Rebek, J. *Chem. - Eur. J.* **1998**, *4*, 1016−1022.

(25) Chas, M.; Gil-Ramirez, G.; Ballester, P. *Org. Lett.* **2011**, *13*, 3402−3405.

(26) A similar encapsulation experiment performed in $CDCl_3$ solution produced a mixture of two capsules, $CDCl_3$⊂**1a**$_2$ and Me_4P^+⊂**1a**$_2$, in a 3/1 molar ratio. $CDCl_3$ is a competitive guest for the capsule's cavity owing to its volume and high concentration in comparison to that of Me_4P^+.

(27) Mecozzi, S.; Rebek, J. *Chem. - Eur. J.* **1998**, *4*, 1016−1022.

(28) Vysotsky, M. O.; Pop, A.; Broda, F.; Thondorf, I.; Bohmer, V. *Chem. - Eur. J.* **2001**, *7*, 4403−4410.

(29) The use of 365 nm light was convenient, since at this wavelength the absorption for the $\pi-\pi^*$ transition (*trans*−*cis*) is relatively strong and that of the n−π^* transition (*cis*−*trans*) is relatively low.

(30) The *trans*−*cis* photoisomerization process studied on a model system (Supporting Information) for the azo groups in **1** showed that the *p*-methyl substituent in the nonterminal azophenyl shifted from δ 2.8 ppm in the *trans* form to δ 2.3 ppm in the *cis* isomer and that the *cis*/*trans* ratio reached in the PSS was 90/10. In agreement with these results, during the photoisomerization process of **2**⊂(*all-trans*-**1a**)$_2$ the *p*-methyl substituent resonating as a sharp singlet at δ 2.74 ppm diminished in intensity. Simultaneously, several singlets corresponding to *p*-methyl substituents of the *cis*-azo groups pertaining to *cis*-enriched isomers of **1** appeared in the region of 2.3 ppm. Their intensity increased at the expense of that of the singlet at 2.7 ppm.

(31) On the basis of the integral value of the OCH_2 signals the concentration of the tetraureas did not change during the photoisomerization process. This result ruled out the formation, to a significant extent, of oligomeric species not detectable by ^{1}H NMR spectroscopy.

(32) We obtained a very good fit of the amplitude of the proton signals to a monoexponential decay, and the diffusion constant was in agreement with that determined for the dimer. This result supported the existence in solution of species that are not involved in chemical exchange processes: i.e. monomer, dimer, oligomer. In our hands, the resolution of the DOSY experiment was not enough to detect a size difference between *all-trans*-**1b**$_2$ and its *cis*-enriched stereoisomers.

(33) Blau, H.; Malisch, W.; Weickert, P. *Chem. Ber.* **1982**, *115*, 1488−1493.

DOI: 10.1021/acs.joc.5b02008
J. Org. Chem. 2015, 80, 10866−10873