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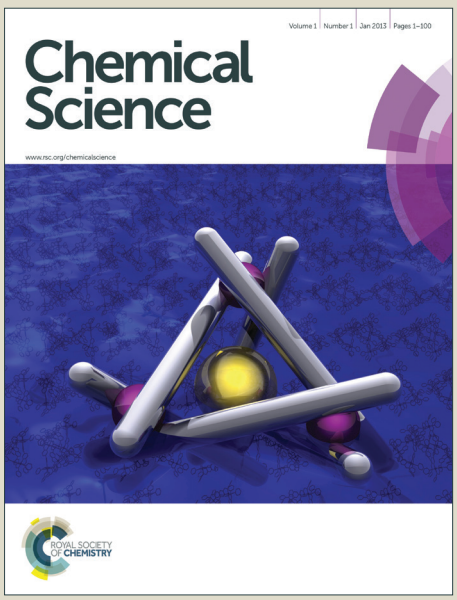

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Reversible photocontrolled disintegration of a dimeric tetraurea-calix[4]pyrrole capsule with *all-trans* appended azobenzene units

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Laura Osorio-Planes,[a] Mónica Espelt,[a] Miquel A. Pericàs[a,b]* and Pablo Ballester[a,c]*

A tetraurea aryl extended calix[4]pyrrole with four appended azobenzene groups dimerizes by encapsulating a bis-*N*-oxide acting as template. The assembly can be detected by ^{1}H NMR spectroscopy only when all eight azobenzene units are in their *trans* forms. The light-induced *trans*-to-*cis*-isomerization of a single azobenzene within the assembly triggers capsular disintegration, probably through a disassembly process. The reassembly of the encapsulation complex is achieved by *cis*-to-*trans* relaxation of the azobenzene photoswitches in the dark.

Introduction

Azobenzene units have been incorporated in many hosts structures such as crown ethers,[1] cyclodextrins,[2,3,4,5] dendrimers,[6,7] and polymers.[8,9] Properly positioned azobenzenes control the host's binding affinities by changing the geometry and inner space through photo isomerization.[10] An alternative approach to photocontrolled binding consists on the use of guests that are themselves equipped with an azobenzene unit. In this case, the host-guest binding affinity is modulated by the *trans-cis* photoisomerization of the azo-unit of the guest. In particular, using switchable 4-4'-dialkylazobenzene guests Rebek et al.[11,12,] demonstrated the photochemical control of both the encapsulation state (guest exchange) and the nature of the capsular assembly of hydrogen-bonded capsules.[13] The switching of azo-units installed in the interior of a coordination cage has also been used to modulate the receptor's binding affinity for a given guest.[14] However, to our knowledge, the light-controlled disassembly of supramolecular capsular aggregates not relying on switchable guests is unprecedented. We rationalized that the covalent attachment of azobenzene photoswitches to known molecular components of hydrogen-bonded capsules could provide an efficient way of integrating the *trans*-to-*cis* photoisomerization of the former with the disassembly of the latter.

Recently, we described the self-assembly of dimeric capsules based on tetraurea aryl-extended calix[4]pyrrole components i.e. **1a** (Figure 1).[15] The dimerization process of **1a** is templated by the encapsulation of 4,4'-bipyridine-***N***-oxide **2**. The capsular assembly **2⊂1a•1a** is primarily stabilized by a circular belt of eight unidirectionally oriented, hydrogen-bonded urea groups (16 hydrogen bonds). In addition, 8 hydrogen bonds are also formed between the two oxygen atoms of encapsulated **2** and the NHs of the two calix[4]pyrrole units located at the ends of the capsule.[16,17,18] We synthesized the closely related α,α,α,α-arylextended calix[4]pyrrole[19] **1b** that incorporates four photoswichable azobenzene units in the urea groups. The dimerization of *all-trans*-**1b** was induced by encapsulation of **2**. We demonstrate here that the photoisomerization of the azobenzene units in the **2⊂*all-trans*-1b•*all-trans*-1b** capsule is coupled to the disintegration of the aggregate. The subsequent *cis*-to-*trans* relaxation of the photoswitches in the dark results in the quantitative recovery of the capsular complex.

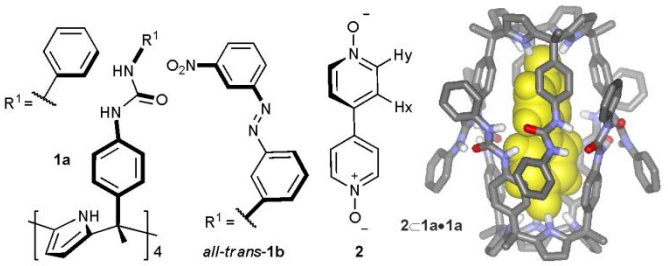

Figure 1. Left) Line drawing structures of arylextended tetraurea calix[4]pyrroles **1a** and **1b**, bis-pyridine-*N*-oxide **2**. Right) Energy minimized structure of the capsular assembly **2⊂1a•1a**.

Results and discussion

The tetraurea azocalix[4]pyrrole **1b** was isolated in 65% yield, as mixture of *cis-trans* stereoisomers (6 isomers are possible). It resulted from reaction of the *p*-nitrophenyl carbamate of the corresponding tetraamino aryl extended calix[4]pyrrole[15] **S1** with (*E*)-3-((3-nitrophenyl)diazenyl)aniline **S2** (see SI). Tetraazo tetraurea-calix[4]pyrrole **1b** was characterized using ^{1}H NMR spectroscopy and high resolution mass spectrometry (see SI). In the design of the photoswitchable azobenzene units

of **1b** we considered beneficial the introduction of a nitro group in the *meta* position of the terminal phenyl substituent. We hypothesized that any steric disruption caused to the capsular assembly by the *trans*-to-*cis* photoisomerization of its azobenzene units could possibly benefit from the formation of intramolecular hydrogen bonds between the nitro substituent and adjacent urea groups (Figure 2).†

The solubility of **1b** in non-polar chlorinated solvents is low but it improves significantly in polar solvents like THF-d_8 or DMSO-d_6. Most likely, this is due to the known tendency of calix[4]pyrrole tetraurea derivatives to oligomerize in non-polar solvents.[15] This behavior is eliminated in polar solvents that compete for hydrogen bonding. Thus, the ^{1}H NMR spectrum of **1b** in THF-d_8 solution displays sharp and well-resolved signals corresponding to a monomeric species (see SI). The more intense signals are consistent with the C_4 symmetry expected for the *all-trans*-**1b** stereoisomer. However, several sets of minor signals are also evident in the ^{1}H NMR spectrum. We conclude that the THF-d_8 solution of **1b** contains a mixture of *cis-trans* stereoisomers that is enriched in the *all-trans*-**1b** isomer. Irradiation of this solution with 380 nm light, while the tube is inserted in the NMR probe, resulted in photoisomerization and afforded a mixture of stereoisomers enriched in *cis*-**1b**. The process is evidenced by the significant increase of the minor signals, observed in the ^{1}H NMR spectrum of the original *trans*-**1b,** at the expenses of the major ones. After irradiation for 2 hours (SI) the photostationary state (PSS) was reached. The original equilibrium mixture was reestablished by keeping the solution in the dark for one week at room temperature.

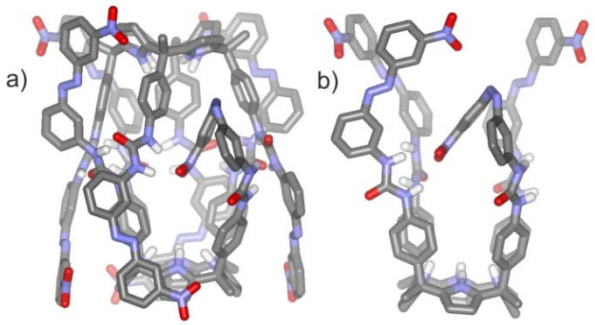

Figure 2. Energy minimized structures showing: a) how *trans*-to-*cis* isomerization of a single azobenzene group is expected to cause a steric disruption of the **1b•1b** assembly; b) formation of intramolecular hydrogen-bonding interactions between nitro and urea groups to assist capsule disassembly. Non-polar hydrogen atoms are omitted for clarity.

We also investigated the photoisomerization process of **1b** using UV-vis spectroscopy in CH_2Cl_2. The absorption spectrum shows the bands expected for a *trans*-azo benzene, a very weak n-π* transition centered at 440 nm and a strong π-π* transition at 320 nm.[20] Both bands overlap with the shoulder of a large UV absorption typical for tetraurea aryl extended calix[4]pyrroles.[16] At 12 μM concentration in CH_2Cl_2 **1b** probably exists mainly as a monomeric species, but as a mixture of *cis-trans* azo stereoisomers of its four arms that is highly enriched in the *all-trans*-**1b** isomer (*vide supra* THF experiments). The spectroscopic earmarks of the stereoisomers of **1b** containing *cis*-azo groups cannot be identified in this starting mixture owing to the substantial overlap of absorption spectra of the *cis* and *trans*-isomers. Upon irradiation of the mixture of isomers of **1b** with 380 nm light, we observed a gradual decrease of intensity in the band at 320 nm and a concomitant increase for the band at 440 nm (Figure 3 top, left). It is known that compared to the *trans* isomer, the π-π* absorption band of the *cis*-azobenzene is shifted to shorter wavelengths (< 320 nm). This absorption decreases in intensity while the n-π* transition becomes allowed and increases in intensity.[20] The photostationary state (PSS) was reached within 3 minutes. Subsequent irradiation of the same solution at 480 nm for 5 minutes resulted in the recovery of the *cis-trans* equilibrium to a state close to the initial one, as shown by the regeneration of the original relative intensities of the absorption bands (Figure 3 top, right).

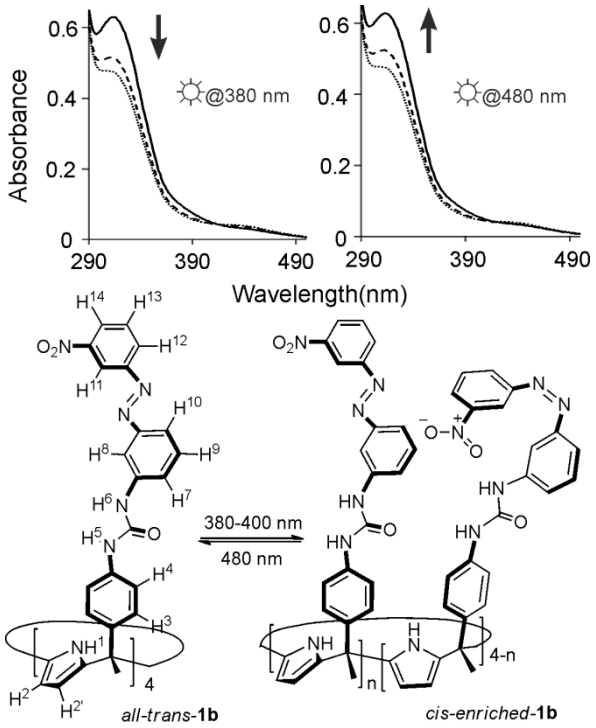

Figure 3. Top) Spectral changes of the absorption spectra of CH_2Cl_2 solution **1b** upon irradiation at 380 nm (solid line initial spectrum, dashed line 1 min irradiation and dotted line 3 min irradiation) and subsequent irradiation at 480 nm (dotted line initial spectrum, dashed line 1 min irradiation and solid line 5 min irradiation, [**1b**] = 12 μM. Bottom) Equilibrium in the photoisomerization process of **1b**.

The results obtained in the UV-vis and ^{1}H NMR irradiation experiments established the reversibility of the photoisomerization process of **1b** as a monomeric species. They also demonstrated that after irradiation the reversion of the mixture to a state enriched in *all-trans*-**1b** required different timescales depending on the method applied (standing in the dark for NMR experiments or irradiation at longer wave lengths for UV experiments). Unmodified *cis*-azobenzenes are known to undergo thermal relaxation on a timescale of days at room

temperature.[21] On the other hand, irradiation at ~440 nm produces a PSS enriched in the *trans*-isomer in shorter time. However, because the absorption spectra of the *cis* and *trans* isomers overlap substantially, when irradiated at 480 nm a PSS with maximum of ~65% *trans* can be expected for a molecule like **1b** with four azo-groups.§[21] Thus, thermal-dark equilibrations are preferred to reset all switches to the *trans* state and achieving larger changes in the *cis*-folded state.

Next, we investigated the photoswitching ability of the azo-groups when the tetraurea **1b** was incorporated in the **1b•1b** capsular assembly. The low solubility of **1b** in CD_2Cl_2 solution hampered the observation of any proton signals when a suspension of the tetraurea **1b** in CD_2Cl_2 was analyzed using ^{1}H NMR (Figure 4a). The addition of 0.5 equivalent of the bis-*N*-oxide **2** led to partial dissolution of the suspension, which was analyzed using ^{1}H NMR. The spectrum revealed sharp and well-resolved proton signals corresponding to a discrete-species having the earmarks expected for the **2⊂1b•1b** capsule with S_8 symmetry (Figure 4b).[15] The pyrrole NHs, H^1, resonate as a unique singlet in the downfield region of the spectrum at δ = 9.3 ppm. The urea NHs, H^6 and H^5, appear as singlets at δ = 9 ppm and δ = 7.4 ppm, respectively. The furthest downfield signal corresponds to the urea NH proton attached to the azobenzene substituent. The β-pyrrolic protons resonate as diastereotopic signals, H^2 and $H^{2'}$, at δ = 5.7 ppm and δ = 5.3 ppm. The second signal is partially hidden by the residual signal of the partially non-deuterated solvent peak. The source of this asymmetry originates from the unidirectional orientation of the urea groups. They interconvert between the two possible senses of direction, at a rate that is slow on the ^{1}H NMR timescale.[15,16] The aromatic protons alpha to the urea group in the *meso*-phenyl substituent, H^4 and $H^{4'}$, are also diastereotopic but appear as a broad signal centered at δ = 6.65 ppm. This is due to the fast rotation of the C_{meso}-phenyl bond that counteracts the asymmetry provided by the belt of urea groups. The in/out exchange of the *N*-oxide **2** is slow and separate signals for the protons of free and bound **2** (80:20) are observed. The signals of the protons of the encapsulated *N*-oxide shifted upfield, δ = 5.9 and 4.8 ppm (x' and y', Δδ = 1.6 and 3.5 ppm, respectively), in response to the shielding provided by the four aromatic panels of each hemisphere. The assembly of the **2⊂1b•1b** capsule was also confirmed in solution by diffusion ordered spectroscopy (DOSY, DC = 5.28 × 10^{-10} m^2s^{-1}) and in the gas phase by ESI-MS spectrometry (see SI). The determined value for the diffusion coefficient of the **2⊂1b•1b** capsule is in complete agreement with the ones previously determined for closely related analogues.[15,16] The observation of a single set of proton signals for the assembly **2⊂1b•1b** together with a ROESY experiment showing intense cross peaks between the β-pyrrole protons and the protons of the terminal phenyl group of the azobenzene (Figure 5 and SI) confirm that the tetraurea component of the capsule is exclusively the *all-trans*-**1b** stereoisomer. In short, only the *all-trans*-**1b** stereoisomer is able to dimerize effectively by encapsulation of **2** yielding the assembly **2⊂***all-trans*-**1b•***all-trans*-**1b**. The other stereoisomers of **1b** do not assemble into CD_2Cl_2 soluble aggregates in the presence of **2**. This result also explains the partial dissolution of **1b** suspended in CD_2Cl_2 upon addition of **2** and the significant presence of free **2** in the ^{1}H NMR spectrum of the resulting solution, even when only 0.5 equiv. are added.

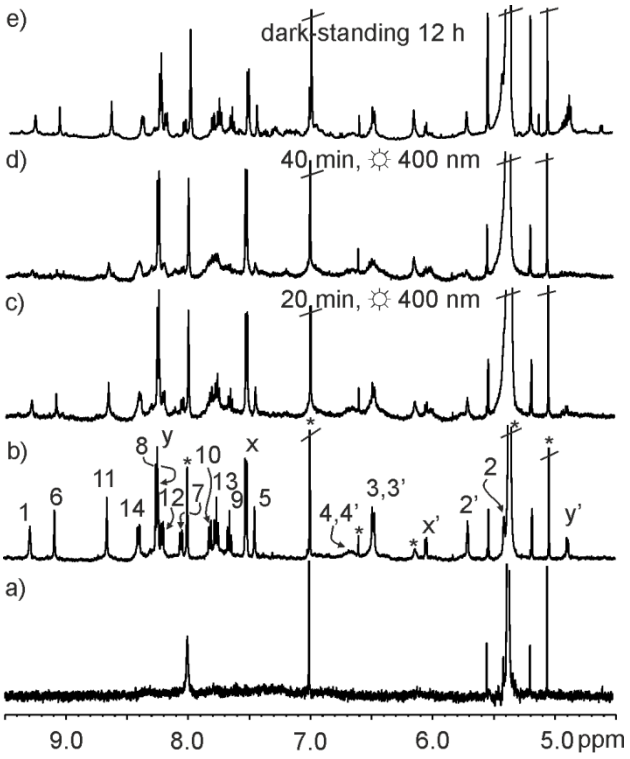

Figure 4. Downfield region of the ^{1}H NMR spectra of CD_2Cl_2 solutions of: a) **1b** (not soluble), b) **1b** + 0.5 equiv of **2**; c) solution b irradiated for 20 min with 400 nm light; d) solution b irradiated for 40 min with 400 nm light; e) solution d after dark standing for 48 h at r.t., CD_2Cl_2 was added due to solvent evaporation. ∗ = Solvent peaks and impurities. See Figures 1 and 3 for proton assignment.

The solution containing **2⊂***all-trans*-**1b•***all-trans*-**1b** and free **2** was irradiated at 380 nm during 2 h. However, no change occurred in the ^{1}H NMR spectrum of the mixture. Interestingly, the absorption spectrum of **2** in CH_2Cl_2 solution displayed a strong band centered at 347 nm (ε = 2 × 10^4 M cm^{-1}), tailing on the low energy side to approximately 400 nm (see SI). Owing to the reduced power (0.3 μW/cm^2) of the light source used for the irradiation experiments, we surmised that the excess of **2** remaining outside the capsule was absorbing most of the photons (acting as an inner filter) and the remaining flux of photons was not enough to induce the *trans*-to-*cis* isomerization of the azobenzene groups to a significant extent.$ When the irradiation of the solution containing the capsular assembly and free **2** was carried out at 400 nm, we observed a gradual reduction of the signal intensity of the protons assigned to the capsule (Figure 4c). After 40 min of irradiation, the proton signals of the *all-trans* capsular assembly had almost disappeared (Figure 4d). In contrast, the intensity of the proton signals for free **2** did not change during the irradiation and several broad and unresolved signals of low intensity appeared. Taken together, these observations indicate that light energy at

400 nm is not absorbed by free **2** and is, thus able, to provoke the *trans*-to-*cis* isomerization of the azo-groups in the capsule. Moreover, this isomerization process induces the conversion of the **2**⊂*all-trans*-**1b**•*all-trans*-**1b** capsule into other less soluble aggregates.

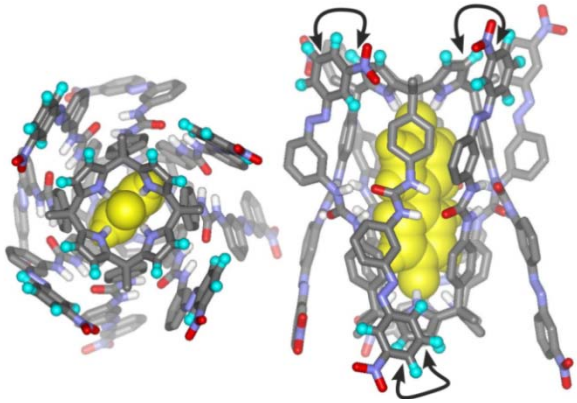

Figure 5. Top and side views of the energy minimized structure of the three particles assembly **2**⊂*all-trans*-**1b**•*all-trans*-**1b.** The β-pyrrole and terminal azo-phenyl protons showing intense cross peaks in the ROESY experiment are colored in turquoise and displayed in ball-and-stick. The urea-azobenzene arms of the *all-trans*-**1b** isomer are depicted as different rotational conformers. In all of them the β-pyrrole protons and the aromatic protons of the terminal phenyl groups are close in space (double headed arrow). Non-polar protons are omitted for clarity.

As indicated above, only the *all-trans*-**1b** isomer dimerizes and solubilizes to the necessary extent to be detected by ^{1}H NMR spectroscopy. The *trans*-to-*cis* isomerization of a single azo-group of the *all-trans* capsule causes its disappearance from solution and the formation of unknown and unidentifiable aggregates with reduced solubility. These aggregates are responsible for the broad proton signals that emerge during the irradiation experiment. We hypothesize that the isomerization process destabilizes the *all-trans* dimeric capsule resulting mainly in its disassembly. C*is*-enriched tetraurea calix[4]pyrrole-**1b** can still include one molecule of **2** forming 1:1 complexes. However, these complexes have reduced solubility and they tend to oligomerize while in solution. Remarkably, the initial ^{1}H NMR spectrum corresponding to the original capsule was completely restored simply by leaving the suspension in the dark for 12 h (Figure 4d). The reversibility of the disassembly-assembly process rules out the option of a disassembly process driven by substantial photodecomposition of the tetraurea **1b** or the bis-*N*-oxide **2**.

Conclusions

In conclusion, a tetraurea aryl extended calix[4]pyrrole **1b** decorated with four azobenzene groups at the upper rim was synthesized. It self-assembles into a hydrogen bonded dimeric capsule **2**⊂**1b•1b** in the presence of 4,4'-bipyridine bis-*N*,*N*'-oxide **2.** Only the *all-trans*-**1b** stereoisomer appears to dimerize effectively and provide sharp protons signals in the ^{1}H NMR spectrum. The *all-trans* hydrogen-bonded capsule disappears from solution when irradiated with 400 nm light. We suggest that the *trans*-to-*cis* isomerization of a single azo-group is probably sufficient to provoke the disassembly of the capsule. This study represents a unique example of light controlled reversible disintegration/disassembly of a tetraurea-based capsule by photoswitches located on the container components.

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Notes and references

[a] Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans, 16, 43007, Tarragona, Spain.

[b] Departament de Química Orgànica, Universitat de Barcelona, 08028 Barcelona, Spain.

[c] Catalan Institution for Research and Advanced Studies (ICREA), Passeig Lluís Companys, 23, 08018 Barcelona, Spain.

† We are aware that intra-arm hydrogen bonding interactions between the nitro substituents in the *cis*-form of the azobenzene and the urea group are geometrically plausible only in high energy conformers. However, related inter-arm interactions are geometrically reasonable. These interactions represent a direct competition to the hydrogen-bonding urea belt that stabilizes the capsule.

The ratio of the *all-trans*-**1b** with respect to *cis*-enriched-**1b** forms was estimated to be close to 65% by dividing the integral of the signal corresponding to H^{11} in *all-trans*-**1b** by the sum of the integrals of the signals assigned to same proton in all the stereoisomers.

§ In a tetra-azobenzene system like **1b**, irradiation at 400 nm is expected to produce a PSS containing the *all-trans*-**1b** isomer in a maximum of 65% (90×90×90×90). Likewise, irradiation at 380 nm is expected to produce a PSS enriched in *all-cis*-**1b** stereoisomer in a maximum of 52% (85×85×85×85). These estimations assume PSSs with maximum of ~90% and ~85% for the *trans* and *cis* azo-isomers, respectively, in each one of the four arms of the tetraurea.

$ The capsule **2**⊂*all-trans*-**1b**•*all-trans*-**1b** can be assembled without free **2** in solution by using the calix[4]pyrrole in large excess. The ^{1}H NMR spectrum of the mixture shows a bumpy baseline probably due to the production of ill-defined oligomeric aggregates in a larger extent under these conditions. Nevertheless, the irradiation of the resulting solution at 380 nm led to the disintegration of the capsule demonstrating that the presence of free **2** was indeed hampering the process.

Electronic Supplementary Information (ESI) available: Experimental procedures for the synthesis of the compounds and the self-assembly of the capsule, characterization data of the synthesized compound and their 1D ^{1}H and ^{13}C NMR spectra, 1D and 2D ^{1}H NMR spectra (DOSY, COSY, ROESY) of the capsular assembly **2**⊂**1b•1b**, ^{1}H NMR spectra of additional irradiation experiments discussed in the manuscript. See DOI: 10.1039/b000000x/

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