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Photoresponsive Supramolecular Gels based on Amphiphiles with Azobenzene and Maltose or Polyethyleneglycol polar head

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In the context of exploring new materials based on low molecular weight amphiphiles, we prepared a new series of photoresponsive gelators with azobenzene as photosensitive unit, D-maltose or poly(ethylene glycol) (PEG) as polar head, and L-phenylalanine as linker. The gelation properties of the final amphiphiles and the intermediate molecules have been studied in different solvents. Organogels are obtained for all of them, except for compound with PEG16 polar head. Gelation in polar solvents, as DMSO, was achieved. The morphology of supramolecular structures was characterized by electronic microscopy. The chiro-optical properties of gels, due to the supramolecular chirality imposed by molecular chirality, were also studied. The modifications under irradiation have been monitored by UV-visible spectroscopy and electronic circular dicroism (ECD). Two of the obtained materials showed a gel-sol transition by irradiation with UV light and further thermal cis-trans isomerization to gel state at room temperature.

Introduction

Supramolecular gels based on low molecular weight molecules are sensitive to external stimuli due to the reversibility of the supramolecular interactions that support the gel structure. Compared with reversible gels based on polymers with non-covalent cross-linking, they are expected to be more sensitive, and dynamic. In addition they give rise to a variety of supramolecular aggregates (fibers, helices, tapes, tubes...). The formation, shape and polymorphism of these aggregates may be controlled by application of different stimuli or fields (such as light, temperature, shear, electric or magnetic field). As a consequence, when a photoresponsive group is inserted in the gel structure, the supramolecular assembly can be modulated by light.1,2 If a photochromic unit is included in the molecular structure of the gelator, the supramolecular arrangement of the gel can be controlled as a consequence of the ability of the photochromic unit to alternate between two different chemical forms with light. Azobenzene hydrophobic groups are used in supramolecular assemblies to trigger reversible environmental changes, due to the reversible trans-cis photochemical isomerization experienced by azo-dyes.3-4 Several examples of trans-isomer supramolecular gels giving rise to a photostationary state of trans-cis mixtures that provide a sol state have been described.5-6 Most of them are organogels, for example based on cholesterol derivatives,7-14 on lipid,15 and aminoacids.16-17 derivatives, uree or hydrazine-amide-containing compounds.18 In water, most often, precipitation, full solubilisation or simple micellisation occur or even the formation of anisotropic fibrillary aggregates which however do not support a macroscopical gel. Thus, introducing the right balance of hydrophilic, hydrophobic parts, and interaction which enables the long-distance stacking to get hydrogels, can be hard to reach. However some examples of azobenzene hydrogels have been described, by appending hydrophilic blocks and blocks prone to develop strong hydrogen bonding, such as peptides,9-10 or saccharidic blocks11-12 or PEG.13

With the aim of finding new low molecular weight hydrogelators based on carbohydrates, we previously developed a series of hydrogelators based on the following bricks: maltose, cellulbiose, lactose as the polar head- and triazole as the linker.14-23 On the basis of the hydrogels obtained, we further introduced an azobenzene as photochromic group.21 These structures gave rise to stable gels in water or in a mixture of water and DMSO, however the gel-sol transition under UV-irradiation failed. In this work, gelators based on phenylalanine as the linker have also been developed. Phenylalanine is quite often introduced in gelator structure, since it provides a flexible side aromatic group involved in π-π stacking and amide groups which enable directional hydrogel bonding.24-27 Azobenzene has been introduced also in this case as a photoresponsive group. We selected both maltose and PEG chain with two different molecular weights as polar heads, with the objective to enable gelation in polar solvents. PEG has been described in a variety of supramolecular assemblies, including low molecular weight gelators,29-33 to provide hydrophilicity and stealth in biological applications.34-35 Moreover, it was previously used in our labs to synthesize amphiphilic block copolymers having the ability of self-assembling into different photoresponsive nano-objects in aqueous solutions.36-37 The influence of the polar head on the supramolecular assembly and the photoresponse of the gels was
Results and discussion

Synthesis of Materials. The synthesis of the amphiphiles was approached according to the synthetic pathway described in Scheme 1 and Scheme 2. The azobenzene carboxylic acid HOOC-Azo-C\textsubscript{18} was prepared by the azo coupling of sodium phenoxido and ethyl p-aminobenzoate to obtain compound 1. The carboxylic aliphatic chain was introduced by means of a Williamson reaction and subsequent hydrolysis of compound 2 gave rise to the desired acid compound HOOC-Azo-C\textsubscript{18}. This acid was used as precursor of Phe-Azo-C\textsubscript{18} which was obtained by previous activation of HOOC-Azo-C\textsubscript{18} with N-hydroxysuccinimide to obtain compound 3, and further reaction with L-phenylalanine. This reaction was made in a mixture of water/THF to enhance the solubility of both compounds. In the subsequent synthetic step Phe-Azo-C\textsubscript{18} was coupled with the corresponding amine-terminated PEG to obtain PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} (n=8 or 16) or with maltosylamine to obtain Malt-Phe-Azo-C\textsubscript{18} (Scheme 1 and Scheme 2, respectively). PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} (n=8 or 16) were synthesized using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC), hydroxybenzotriazole and THF as solvent. Commercial PEGs were used for the synthesis of PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} (monodisperse amino-PEG with a molecular mass of 383.48) and for PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} (amino-PEG with an average molecular mass of 750 and an average degree of polymerization of 16).

Malt-Phe-Azo-C\textsubscript{18} was synthesized from peracetylated maltosylamine, azobenzene moiety of the acetylated maltosylamine was made with a chloride derivative of Phe-Azo-C\textsubscript{18} (compound 6) in a DMF/THF mixture yielding the peracetylated compound OAc-Malt-Phe-Azo-C\textsubscript{18}. This compound was deprotected using MeONa in a mixture of MeOH and THF to obtain the aimed Malt-Phe-Azo-C\textsubscript{18}. All the compounds were adequately characterized by \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, IR and mass spectrometry, see experimental section. MALDI-TOF mass spectrometry experiments of PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} and PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} (see Figure SI1 in Supporting Information) showed that in the case of PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} the sample is monodisperse, however PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} displays a pattern of peaks separated about 44 (-[O-CH\textsubscript{2}-CH\textsubscript{2}]) due to the dispersity of the starting and commercial amine-ended PEG used in the synthesis.

\textsuperscript{1}H NMR spectra of PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18}, OAc-Malt-Phe-Azo-C\textsubscript{18} and Malt-Phe-Azo-C\textsubscript{18} are shown in Figure SI2 in Supporting Information. Spectra of PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} and PEG\textsubscript{n}-Phe-Azo-C\textsubscript{18} are in accordance with expected chemical structure. Moreover, OAc-Malt-Phe-Azo-C\textsubscript{18} and Malt-Phe-Azo-C\textsubscript{18} compounds were characterized by additional two-dimensional NMR experiments. The total deprotection of the acetylated groups was confirmed by \textsuperscript{1}H NMR when spectra of OAc-Malt-Phe-Azo-C\textsubscript{18} and Malt-Phe-Azo-C\textsubscript{18} are compared, Figure SI2 in the Supporting Information. As example, a two-dimensional TOCSY experiment of OAc-Malt-Phe-Azo-C\textsubscript{18} is shown in Figure SI3 in the Supporting Information.
Scheme 1 Synthesis of HOOC-Azo-C_{18}, Phe-Azo-C_{18} and PEG_{n}-Phe-Azo-C_{18} (n=8 or 16).

Scheme 2 Synthesis of Malt-Phe-Azo-C_{18}. 
Table 1 Thermogravimetric analysis and thermal transitions of the synthesized amphiphiles.

<table>
<thead>
<tr>
<th>Compound</th>
<th>T_{5%} lost °C</th>
<th>Tonset, °C</th>
<th>Thermal transition, °C [ΔH, kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phe-Azo-C_{18}</td>
<td>250</td>
<td>245</td>
<td>Cr 137 [5.6] Cr’ 153 [28.3] I</td>
</tr>
<tr>
<td>PEG_{8}-Phe-Azo-C_{18}</td>
<td>305</td>
<td>325</td>
<td>Cr 87 [1.0] Cr’ 97 [2.7] Cr” 116 [32.6] I</td>
</tr>
<tr>
<td>PEG_{18}-Phe-Azo-C_{18}</td>
<td>315</td>
<td>320</td>
<td>Cr 27 [53.4] Cr' 84 [4.2] Cr” 106 [33.5] I</td>
</tr>
<tr>
<td>Malt-Phe-Azo-C_{18}</td>
<td>220</td>
<td>235</td>
<td>Cr 112 [22.8] Cr’ 175 Dec</td>
</tr>
</tbody>
</table>

*T_{5\%}*, temperature at which 5\% of the initial mass is lost; *Tonset*, onset of the thermal decomposition process. Cr, crystalline; S, smectic mesophase; I, isotropic liquid phase.

Table 2 Solubility and gelation properties of synthesized compounds in different solvents.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>HOOC-Azo-C_{18}</th>
<th>Phe-Azo-C_{18}</th>
<th>PEG_{8}-Phe-Azo-C_{18}</th>
<th>PEG_{18}-Phe-Azo-C_{18}</th>
<th>Malt-Phe-Azo-C_{18}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Toluene</td>
<td>P</td>
<td>Gel (5)</td>
<td>S</td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>DCM</td>
<td>I</td>
<td>S(heat)</td>
<td>S</td>
<td>S</td>
<td>Gel (1.3)</td>
</tr>
<tr>
<td>Acetone</td>
<td>P</td>
<td>Gel (8)</td>
<td>S</td>
<td>I</td>
<td>Gel (0.5)</td>
</tr>
<tr>
<td>DMF</td>
<td>Gel (2)</td>
<td>S(heat)</td>
<td>S</td>
<td>S</td>
<td>S(heat)</td>
</tr>
<tr>
<td>DMSO</td>
<td>Gel (6)</td>
<td>Gel (10)</td>
<td>Gel (5)</td>
<td>S</td>
<td>P</td>
</tr>
<tr>
<td>Methanol</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Water</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

*I*, insoluble at rt; *P*, insoluble at rt and soluble on heating; *S*(heat), soluble at rt after heating; *S*, soluble at rt; Gel (minimum gel concentration, wt%).

Thermal properties. The thermal properties of the synthesized amphiphilic azocompounds were studied by thermogravimetric analysis (TGA), polarized light microscopy provided with a thermal stage and differential scanning calorimetry (DSC). Weight losses were observed in TGA at temperatures ranging from 200 to 325 °C as it has been summarized in Table 1. Acid compound HOOC-Azo-C_{18} has a high stability while introduction of L-phenylalanine makes that the temperature at which 5 % of the initial mass is lost decreases from 325°C to 250°C (first decomposition process of that compound). However, linking a PEG moiety produces an increase of the thermal stability. Temperatures for 5 % weight losses for PEG_{8}-Phe-Azo-C_{18} and PEG_{18}-Phe-Azo-C_{18} are around 310°C.

In the case of Malt-Phe-Azo-C_{18} thermal stability is lower than the PEG-analogs and it can be expected from the introduction of a sugar polar head.

The thermal transitions were characterized by DSC and gathered in Table 1. The melting transition of PEG_{Azo-Phe-C_{18}} and PEG_{Azo-Phe-C_{18}} is detected at temperature around 110 °C and both exhibit polymorphic transitions before melting. In the case of the sugar derivative, Malt-Phe-Azo-C_{18}, the sample was previously dried and immediately analyzed. When this compound was studied by optical microscopy, the sample becomes brown above 170-175 °C due to decomposition of the sugar units. On a DSC experiment performed until 200°C, decomposition was detected at around 175°C as a decrease of the baseline.

Gelation properties. The solubility and gelation ability of the amphiphiles and the precursors HOOC-Azo-C_{18} and Phe-Azo-C_{18} were examined in different solvents by placing 5 mg of compound in the corresponding amount of solvent in a septum-capped test tube. If the compound was not soluble at rt, mixtures were first heated and then cooled down to rt. A solution, precipitate or a gel was then observed depending on the solvent. The formation of a gel was registered if the tube was turned upside down and no flow was observed.

All the compounds are not soluble in water even upon heating. However, they are able to form organogels in different solvents (at different minimum concentrations) except PEG_{18}-Phe-Azo-C_{18} that exhibit a good solubility in most of tested solvents, except hexane and 1-dodecanol. HOOC-Azo-C_{18}, Phe-Azo-C_{18}, PEG_{8}-Phe-Azo-C_{18} and Malt-Phe-Azo-C_{18} are able to form gels in 1-dodecanol at different concentrations. The lowest minimum gel concentration was reached in 1-dodecanol at 0.5 wt% for Malt-Tz-Azo-C_{18} compound. HOOC-Azo-C_{18}, Phe-Azo-C_{18} and PEG_{8}-Phe-Azo-C_{18} were also able to form gels in DMSO. Gelation in DMSO is not often described. DMSO displays a low toxicity and it has a low vapor pressure. These facts open its interest to many applications. Otherwise, to our knowledge, gels of HOOC-Azo-C_{18} have never been described yet. This compound is mostly known for its use in liquid crystals and Langmuir-Blodgett films.
The gelation ability for the synthetized molecules is different according to the molecular structure. The addition of phenylalanine block to \textit{HOOC-Azo-C}_{18} enables to switch from an insoluble compound in toluene and \textit{CH}_2\textit{Cl}_2 to gelation in these same solvents. \textit{Phe-Azo-C}_{18} is also able to gelate in DMSO and 1-dodecanol. The introduction of the PEG chain enables the gelation in methanol and acetone. Increasing the PEG chain up to 16 units tends to make soluble the molecule in nearly all the organic solvents tested. Otherwise, both PEG\textsubscript{8} and PEG\textsubscript{16} ensure a very broad enlargement of solubility in both polar and apolar solvents compared with \textit{HOOC-Azo-C}_{18} and \textit{Phe-Azo-C}_{18}. Introducing the maltose unit suppresses the gelation in DMSO, but it adds the gelation in THF. All gels are orange in color due to the azobenzene group, as can be seen for the examples selected in Figure 1, an opaque gel of \textit{Phe-Azo-C}_{18} in dichloromethane at 5 wt % and a transparent gel of \textit{Malt-Phe-Azo-C}_{18} in THF at 1.3 wt %.

**Figure 1** Opaque gel of \textit{Phe-Azo-C}_{18} in dichloromethane at 5 wt% (left), and transparent gel of \textit{Malt-Phe-Azo-C}_{18} in THF at 1.3 wt% (right).

**Morphological study.** In order to investigate the supramolecular organization of the gels derived from the synthesized amphiphiles, xerogels, formed by the removal of swelling agents, were first obtained from these compounds and studied by microscopic techniques.

Xerogels obtained from gels in 1-dodecanol of \textit{HOOC-Azo-C}_{18}, \textit{Phe-Azo-C}_{18}, PEG\textsubscript{8}-\textit{Phe-Azo-C}_{18} and \textit{Malt-Phe-Azo-C}_{18} (at their minimum gel concentration) were first investigated by scanning electronic microscopy (SEM). For \textit{HOOC-Azo-C}_{18} sample, non-well defined structures are observed (Figure 2a). Ribbons, having lengths and widths of around several micrometers are detected for PEG\textsubscript{8}-\textit{Phe-Azo-C}_{18} (Figure 2c). However, for \textit{Phe-Azo-C}_{18} and \textit{Malt-Phe-Azo-C}_{18} widths of the ribbons are at the nanometer scale, ranging from 50 to 200 nm for \textit{Phe-Azo-C}_{18} (Figure 2b) and from 90 to 160 nm in the case of \textit{Malt-Phe-Azo-C}_{18} (Figure 2d). Xerogels derived from gels in DMSO were also studied for the different compounds as can be seen in the Supporting Information, Figure SI4. Differences on the morphology or in the size of the fibrillar structure were observed depending on the solvent.

The self-assembly of the gelators, was also studied in diluted and negative stained samples of the amphiphiles by transmission electronic microscopy (TEM), using first in 1-dodecanol as solvent. Samples obtained from solutions 10 times more diluted than the minimum gel concentration were studied (see Figure 3 for \textit{Phe-Azo-C}_{18} sample and Figure SI5 in Supporting Information for \textit{HOOC-Azo-C}_{18}, PEG\textsubscript{8}-\textit{Phe-Azo-C}_{18} and \textit{Malt-Phe-Azo-C}_{18} samples). For \textit{Phe-Azo-C}_{18} sample, twisted ribbons are observed having widths of approx. 20-30 nm (Figure 3) with a torsion pitch around 50 nm, see close up in Figure 3. Microphotographs of the rest of amphiphiles also showed ribbons of different widths: approx. 0.5 mm for \textit{HOOC-Azo-C}_{18}, around 100 to 300 nm for PEG\textsubscript{8}-\textit{Phe-Azo-C}_{18} and 50 to 150 nm for \textit{Malt-Phe-Azo-C}_{18} (see SI).

**Figure 2** SEM image of xerogel (1-dodecanol) obtained from: a) \textit{HOOC-Azo-C}_{18} at 5 wt %; b) \textit{Phe-Azo-C}_{18} at 10 wt %; c) PEG\textsubscript{8}-\textit{Phe-Azo-C}_{18} at 5 wt % and, d) \textit{Malt-Phe-Azo-C}_{18} at 0.5 wt %.

**Figure 3** TEM image of \textit{Phe-Azo-C}_{18} (sample obtained from a solution at 1 wt % in 1-dodecanol).

The amphiphilic structure of PEG\textsubscript{16}-\textit{Phe-Azo-C}_{18} should promote aggregation and self-assembly, although gelification was not observed in the tested solvents. Self-assembly of PEG\textsubscript{12}-\textit{Phe-Azo-C}_{18} compound was studied in DMSO solutions (0.5\%) by carefully addition of water. Turbidity was monitored as a means of detecting aggregation threshold.\textsuperscript{41} (see Figure SI6 in Supporting Information). The final dispersion was then dialyzed against water for 2 days to remove the organic solvent. The morphological analysis of the dialyzed aggregate solution was then performed by TEM on a sample stained with uranyl acetate. Fibrillar aggregates with a length around 100 nm were observed, see Figure 4a. PEG\textsubscript{8}-\textit{Phe-Azo-C}_{18} compound was also studied in DMSO, where this compound forms a gel in a concentration of 5 wt % and consequently should aggregate in this solvent even at a lower concentration. For the study of supramolecular aggregation, diluted sample at 0.1 wt % was prepared, heated to complete solubility and then cooled to obtain a clear solution. A drop of the solution was placed onto a copper grid and negative stained by uranyl acetate (Figure 4b). Fibrillar aggregates have a length of several microns in this case.
The hydrophobic/hydrophilic balance seems to play a crucial role in the self-assembly and the dimensions of the aggregates of these amphiphilic molecules. In case of PEG<sub>4</sub>-Phe-Azo-C<sub>18</sub>, having a higher hydrophobic content (60/40 molecular weight hydrophobic/hydrophilic part ratio) than PEG<sub>16</sub>-Phe-Azo-C<sub>18</sub>, the network is consistent enough to entrap the solvent. Meanwhile for PEG<sub>16</sub>-Phe-Azo-C<sub>18</sub> with a higher hydrophilic content (44/56 molecular weight hydrophobic/hydrophilic part ratio taking as reference n=16), the aggregates cannot form a consistent network to entrap the solvent.

Irradiation studies. Irradiation experiments in solution as well as in gel state were carried out. The modification of the supramolecular organization by light has been studied by UV-visible and ECD spectroscopy, and macroscopic observations. Solutions of PEG derivatives in DMSO were irradiated at 365 nm, around the maximum corresponding to the π−π* transition of the trans-isomer. As an example, Figure SI7 displays the corresponding spectra of PEG<sub>4</sub>-Phe-Azo-C<sub>18</sub> in DMSO at 10<sup>-4</sup> M. Evolution of the sample was monitored by UV-vis spectroscopy in order to check trans-cis isomerization. The band is approximately symmetrical and has a maximum at 365 nm corresponding to the π-π* transition of trans-isomer, which is in accordance with a relatively low aggregation. Under irradiation, PEG<sub>4</sub>-Phe-Azo-C<sub>18</sub> solution exhibits a decrease of the absorbance at λ<sub>max</sub> due to the decrease of the trans-isomer and the absorbance at 445 nm, corresponding to the n-π* transition, increases due to the appearance of the cis-isomer. Photostationary state was reached at around 6 min. Partial recovery of the initial UV-vis spectrum was achieved when samples were kept in the dark for 24 h.

Photoirradiation was also carried out in the gel state using a 5 wt % DMSO gel (the same solvent that solution studies) of PEG<sub>4</sub>-Phe-Azo-C<sub>18</sub> in DMSO. Malt-Phe-Azo-C<sub>18</sub> was studied at 0.5 wt% in 1-dodecanol, due to the very low minimum concentration of gelification in this solvent. UV-vis spectra of the studied gels were analyzed before and after irradiation to explore the changes caused by the trans-cis isomerization. In addition, studies by electronic circular dichroism (ECD) were performed in order to get more insight into the chiral supramolecular organization and modification by irradiation. The circular dichroism spectra were registered in a small amount of the gels and sandwich between two fused silica discs. We confirmed that the contribution of the linear dichroism to the ECD spectra was negligible by comparing several ECD spectra recorded at different angles around the incident light beam.

Before irradiation UV-vis absorption spectrum in gel state of PEG<sub>4</sub>-Phe-Azo-C<sub>18</sub> at 5 wt % in DMSO (Figure 5, top) shows a slightly broaden curve compared with solution and the λ<sub>max</sub> value appears at 362 nm (in solution 365 nm). The λ<sub>max</sub> value for a Malt-Phe-Azo-C<sub>18</sub> organogel at 0.5 wt % in 1-dodecanol (Figure 6, top) appears at around 339 nm. The broadness of the UV-vis bands and the blue-shifted maxima, in particular for Malt-Phe-Azo-C<sub>18</sub>, are a consequence of the aggregation of azobenzene chromophores in the gel structure. In the case of PEG<sub>4</sub>-Phe-Azo-C<sub>18</sub> gel at 5 wt % in DMSO, under UV irradiation (Figure 5, top) at 365 nm (using the same irradiation conditions as in solution) a decrease in the trans-azobenzene UV band was observed. After irradiation for 45 min, UV-vis spectrum is more similar to the one exhibited by the cis-isomer, however, the trans to cis isomerization was clearer appreciated when the sample was irradiated for 3h. As it is expected from the results and the evaluation of the degree and rate constant of isomerization (see in Supporting Information, Table SI1 and Figure SI8), the photoisomerization is more hindered in the case of gel than in solution, due to the self-assembly of the chromophores, which gives account of the slower conversion. For Malt-Phe-Azo-C<sub>18</sub> gel at 0.5 wt % in 1-dodecanol gel under irradiation at 365 nm is detected a less hindered trans-to-cis conversion with respect to PEG<sub>4</sub>-Phe-Azo-C<sub>18</sub> gel (Figure 6, top). Partial recovery of the initial UV-vis spectrum was achieved when gel samples were kept in the dark for 24 h at rt (see Figure 5, top and Figure 6, top).

Both organogel PEG<sub>4</sub>-Phe-Azo-C<sub>18</sub> at 5 wt% in DMSO (Figure 5, bottom) and Malt-Phe-Azo-C<sub>18</sub> gel at 0.5 wt% in 1-dodecanol (Figure 6, bottom), show a positive exciton couplet corresponding to the π-π* transition of the azobenzene units. These results indicate a chiral organization of the azobenzene moieties imposed by the molecular quirality of L-phenylalanine (and maltose in case of Malt-Phe-Azo-C<sub>18</sub>). As expected, the ellipticity values of non-irradiated samples are higher than the irradiated material as a consequence of the decrease of the chiral aggregation due to the increase of the cis-azobenzene moieties. Once irradiated, the gel samples partially recovered its original ECD spectra after 24h at darkness at rt (see Figure 5, bottom and Figure 6, bottom).
Irradiation of the PEG-Phe-Azo-C\textsubscript{18} gel (5 wt % in DMSO) and Malt-Phe-Azo-C\textsubscript{18} gel (0.5 wt % in 1-dodecanol) were carried out in a 1mm thickness cuvette, in order to check if a gel to sol transition is photoinduced. In fact, this transition was observed in both cases, by using irradiation conditions similar to UV-vis and ECD studies. For PEG-Phe-Azo-C\textsubscript{18} gel (5 wt % in DMSO), after 45 min of irradiation a partial dark red solution was observed at the bottom of the cuvette and after 3h almost all the gel became sol state (Figure 7a). Gel was reformed after 96 h and sol state was again obtained under irradiation at 365 nm. For Malt-Phe-Azo-C\textsubscript{18} gel (0.5 wt % in 1-dodecanol) a gel to sol transition was reached after 10 min of irradiation at 365 nm (Figure 7b). Gel was reformed after 6 h and the process was reversible by cycles of irradiation at 365 nm and subsequent thermal back cis-trans isomerization in darkness. Therefore, in both cases a gel-sol photoresponse was achieved under UV light, however this process is faster in the case of the maltose derivative.

Conclusions

Amphiphilic molecules, based on a photoresponsive azobenzene hydrophobic block and poly(ethylene glycol) or maltose as polar heads, which are connected by L-phenylalanine have been designed and synthesized. Precursors HOOC-Azo-C\textsubscript{18} and Phe-Azo-C\textsubscript{18}, and the amphiphiles PEG\textsubscript{8}-Phe-Azo-C\textsubscript{18} and Malt-Phe-Azo-C\textsubscript{18} form gels in different organic solvents, including polar solvents such as DMSO. The gelation ability can be moved toward more apolar solvents with phenylalanine while adding PEG units moved the gelation toward more polar solvents. The molecular weight of PEG is a key factor for balancing gel formation and full solubility. While PEG\textsubscript{8}-Phe-Azo-C\textsubscript{18} is able to
form organogels in polar solvents, PEG_{18}-Phe-Azo-C_{18} is soluble in main solvents. For this compound, gelation was not observed however when it is first dissolved in an organic solvent it forms fibrillar self-assembled structures in aqueous solution. The morphology of the gels depends on the gelator and the gel medium as it has been confirmed by different microscopic techniques. The photoisomerization of the azobenzenes units, has been studied in solution and gel state. Two gels, PEG_{2}-Phe-Azo-C_{18} gel at 5 wt % in DMSO and Malt-Phe-Azo-C_{18} gel at 0.5 wt % in 1-dodecanol were able to switch reversibly from the gel to the sol state, under irradiation at UV light. Malt-Phe-Azo-C_{18} gel (0.5 wt% in 1-dodecanol) shows a faster response to the irradiation than the PEG_{2}-Phe-Azo-C_{18} gel (5 wt% in DMSO). In the maltose derivative, despite the apparent slight modifications of UV-vis and ECD spectra, the gel-sol transition is photoinduced in a few minutes, and this fact evidences than slight changes into the supramolecular organization of amphiphiles may lead to significant changes at the macroscale. The gel-sol transition is reversible by thermal back cis-to-trans isomerization in both switchable organogels.

Experimental Section

Characterization data (elemental analysis, \(^1\)H and \(^{13}\)C NMR, FTIR and MS) for the intermediate compounds are collected in the Supporting Information. Only data corresponding to the final compounds are included in this section.

Syntheses

4-hydroxy-4’-(ethyloxycarbonyl)azobenzene (1)
Ethyl 4-aminobenzoate (9.26 g) was dissolved in 45 mL of water and cooled in a water-ice bath. 20 mL of HCl (37%) solution was added dropwise. The mixture was stirred for 24 h. The reaction was monitored by TLC using hexane/ethyl acetate 1:1 as eluent. A solution of HCl (37%) was added until pH 7-8. It was filtered and washed with water. The product was finally purified by flash chromatography using dichloromethane as eluent. A red solid was obtained (6.55 g, 45%). For characterization data, see Supporting Information.

4-(octadecyloxy)-4’-(ethyloxycarbonyl)azobenzene (2)
Compound 1 (1.84 g, 7.4 mmol) was dissolved in acetone (30 mL), under an argon atmosphere, KI (0.28 g, 1.85 mmol) and K_2CO_3 (1.89 g, 1.48 mmol) was added. Once the solvent is refluxing, the octadecyl bromide (2.72 g, 8.88 mmol) was added dropwise. The mixture was stirred for 24 h. The reaction was monitored by TLC (hexane/ethyl acetate, 7:3). The solvent was partially removed. Dichloromethane (60 mL) was added and washed three times with water, and dried with anhydrous MgSO4. The product was recrystallized in ethanol yielding an orange solid (2.08 g, 55%). For characterization data, see Supporting Information.

4-(octadecyloxy)-4’-(hydroxyxycarbonyl)azobenzene (HOOC-Azo-C_{18})
Compound 2 (2.08 g, 3.9 mmol) and KOH (1.58 g, 27.3 mmol) were dissolved in ethanol (50 mL) and stirred and heated under reflux for 24 h. The reaction is monitored by TLC with dichloromethane as eluent. 70 mL of water was added and the product finally precipitated upon addition of HCl (37%) until pH 2. It was filtered and washed with water. It was obtained as an orange powder which was recrystallized in acetic acid (1.55 g, 80%).

\(^1\)H NMR (400 MHz, DMSO, 90°C, δ ppm): 0.87 (t, 3H, J=7.2 Hz, CH_3-CH_2-), 1.47-1.27 (m, 30 H, -(CH_2)_15-), 1.80-1.76 (m,2H, (CH_2)_15-CH_2-CH_2-O-), 4.13 (t, 2H, J=6.4 Hz, CH_2-CH_2-O-), 7.13-7.11 (m, 2H, CHa), 7.91-7.86 (m, 4H, CHa), 8.12-8.10 (m, 2H, CHa).

\(^{13}\)C (100 MHz, DMSO, 90°C, δ ppm): 14.0, CHa, 22.3, 25.8, 28.9, 29.1, 29.3, 30.3, 31.6, CHb, 68.9 O-CHa, 115.7, 122.4, 125.2, 130.8, CHar, 132.9, 147.0, 155.3, 162.6, 167.7 Car, CO. ESI^+: 495.4 [M + H]^+.

IR (KBr, cm⁻¹): 2918, 2849, 1680, 1602, 1501, 1471, 1419, 1290, 1249, 1143, 837, 544.

Compound 3
HOOC-Azo-C_{18} (2.49 g, 5.04 mmol) was dissolved in 240 mL of anhydrous THF. This solution was heated until the benzoic acid derivative HOOC-Azo-C_{18} was dissolved and N-hydroxysuccinimide (0.81 g, 7.13 mmol) in 40 mL of THF solution was added. The mixture was cooled to room temperature and then placed in a water-ice bath. Dicyclohexylcarbodiimide (DCC) (6.60 g, 32 mmol) was dissolved in 35 mL of THF and added to the mixture and was stirred for 96 h at room temperature. The reaction mixture was filtered and the solvent was distilled off. The product was recrystallized from isopropanol to obtain a red solid (2.56 g, 86%). For characterization data, see Supporting Information.

Phe-Azo-C_{18}
L-Phenylalanine (0.66 g, 3.99 mmol) and diisopropylethylamine (1.40 mL, 8.12 mmol) were dissolved in 25 mL of water and 30 mL of THF. A solution of 3 (2.40 g, 4.06 mmol) in 100 mL of THF was added. The mixture was stirred at room temperature for 60 h. The reaction was monitored by TLC using hexane/ethyl acetate 1:1 as eluent. A solution of HCl (37%) was added until pH = 4. The solvent was partially removed and the resulting aqueous phase was extracted with dichloromethane (3 x 250 mL). The organic layer was dried with anhydrous MgSO4 and finally the solvent was evaporated. The product was purified by flash chromatography using dichloromethane and increasing the polarity with methanol. A red solid was obtained (1.502 g, 58%).

\(^1\)H (300 MHz, CDCl3, δ ppm): 0.88 (t, 3H, J=6.7 Hz, CH3-CH2-), 1.26-1.50 (m, 30H, -(CH2)15-), 1.78-1.87 (m, 2H, -O-CH2-CH2-), 3.24-3.46 (m, 2H, -CH2-CH2-), 4.05 (t, 2H, J=6.6 Hz, -O-CH2-CH2-), 5.07-5.17 (m, 1H, -CH2-CH2-), 6.59 (d, 1H, J=7.2 Hz, NH-CO-), 6.99-7.02 (m, 2H, Har-CO-CH2-), 7.22-7.33 (m, 6H, Har), 7.80-7.94 (m, 4H, Har).

\(^{13}\)C (75 MHz, CDCl3, δ ppm): 14.1 CH2=CH2, 22.7, 26.0, 29.2, 29.4, 29.5, 29.6, 29.7, 31.9, CH2=CH2, 37.2 -CH2-CH2-CH2-CH2-, 53.7 -CH2-CH2-, 68.5 O-CH2-CH2-, 114.8, 122.7, 125.2, 127.4, 128.0, 128.8, 129.4 CHar, 134.3, 135.5, 146.8, 155.8, 162.3 Car, 167.0 OH-CO, 174.3 COOH.


Anal. Calcd. for C_{14}H_{22}N_{2}O_{7}: C, 74.85; H, 8.64; N, 6.55. Found:
PEG₈-Phe-Azo-C₁₈ and PEG₁₆-Phe-Azo-C₁₈

40

MALDI-TOF (DCTB+NaTFA): 1029.8 [M (n=8) +Na]

13 H-J= 6.7Hz, 2H, -O-CH₂-CH₂-)

PEG₁₆-Phe-Azo-C₁₈

40

MALDI-TOF (DCTB+NaTFA): 1249.8 [M (n=13) +Na]

39.4 –O-CH

ar-CH-NH-CO, 1H, CH

For characterization data, see Supporting Information.

Malt-Phe-Azo-C₁₈

OAc-Malt-Phe-Azo-C₁₈ (131.1 mg, 0.10 mmol) were dissolved in 5 mL of anhydrous DMF. Sodium methoxide (50.0 mg, 0.92 mmol) was then added. The solution was stirred at room temperature until the reaction was complete (TLC, dichloromethane/ethyl acetate 1:1). Amberlyst IR 120 (H⁺ form) was added to exchange sodium ions until pH 7-6. The resin was filtered off and the solvent was evaporated in vacuum to give a red solid (58% yield).

H NMR (500 MHz, DMSO δ ppm): 0.85 (t, 3H, J = 6.7 Hz, -CH₃(2)), 1.71-1.49 (m, 30H, -CH₂(2)), 1.70-1.81 (m, 2H, -O-CH₂-CH₂-), 3.04-3.22 (m, 2H, -CH₂-CH₂-), 3.31 (s, 3H, -OCH₃), 3.32-3.70 (m, nH, -(O-CH₂-CH₂)ₙ-O-CH₂-CH₂-NH-), 3.98 (t, 2H, J = 6.5Hz, -CH₂-CH₂-), 4.73-4.84 (m, 1H, -CH₂-CH₂-), 6.60 (s, 1H, CH₃-CH₂-NH-CO-), 6.92-6.95 (m, 2H, Har-CO-CH₂-), 7.04 (d, 1H, J = 7.6 Hz, CH₃-CH₂-NH-CO-), 7.16-7.26 (m, 5H, Har), 7.82-8.77 (m, 6H, Har).

13 C NMR (125 MHz, DMSO δ ppm): 13.5 - (CH₂)₁₃C₁₇H₂₁, 52.5, 28.4, 28.7, 31.0 -CO-CH₂(CH₂)₁₃C₁₇H₂₁, 37.3 CH₂-CH₂-Car, 54.6, 54.7 CH₂-CH₂-Car, 68.1, -O-CH₂-CH₂, 61.0, 70.2, 71.7, 72.0, 72.2, 72.4, 73.3, 76.9, 77.1, 79.3, C2, C3, C4, C5, C6, C7, C8, C9, C10, 79.9-C11, 100.6 Cl, 115.0, 121.6, 124.6, 125.9, 127.8, 128.3, 129.0 Har, 135.6, 137.9, 138.0, 146.2, 153.6, 165.4, 171.6 Car, CH₃-CH₂-NH-CO-.


IR (KBr, cm⁻¹): 3300, 2920, 2850, 1636, 1531, 1251, 1144, 1107, 838.

Hepta-O-acetyl-β-maltosylazide (4) and hepta-O-acetyl-[β-maltosyl amine (5) have been previously described.¹⁸

Compound 6

Phe-Azo-C₁₈ (740 mg, 1.15 mmol) was dissolved in 25 mL of anhydrous THF. Oxaly chloride (0.30 mL, 2.81 mmol) and anhydrous DMF (0.3 mL) were added. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure. The product was used without further purification.

OAc-Malt-Phe-Azo-C₁₈

Compound 6 (0.9 mg) was dissolved in 10 mL of anhydrous DMF. Pyridine (0.1 mL, 1.24 mmol) was added and the solution was cooled to 0 °C. A solution of compound 7 (1.15 mmol) in 10 mL of anhydrous DMF and 15 mL of THF was added. 20 mL of THF were added to complete solubilization. The reaction mixture was stirred for 48 h at room temperature and poured into 150 mL of water. The aqueous phase was extracted with 3 × 150 mL of hexane/ethyl acetate 1:1. The organic phase was dried with anhydrous MgSO₄. The solution was filtered and the solvent was removed under reduced pressure. The resulting product was purified by flash chromatography using dichloromethane and increasing the polarity with methanol. A red solid was obtained (401 mg, 85% for PEG₈-Phe-Azo-C₁₈, 315 mg, 84% for PEG₁₆-Phe-Azo-C₁₈).

PEG₈-Phe-Azo-C₁₈

1H(500 MHz, CDCl₃ δ ppm): 0.87 (t, 3H, J= 6.7Hz, CH₂-CH₃), 1.16-1.53 (m, 30H, -(CH₂)₁₅H), 1.78-1.85 (m, 2H, -O-CH₂-CH₂)-, 3.10-3.29 (m, 2H, -CH₂-CH₂-), 3.36 (s, 3H, -O-CH₃), 3.32-3.73 (m, 32H, -(O-CH₂-CH₂)ₙ-O-CH₂-CH₂-NH-), 4.05 (t, 2H, J = 6.5Hz, -O-CH₂-CH₂-), 4.77-4.86 (m, 1H, -CH₂-CH₂-), 6.28 (s, 1H, CH₃-CH₂-NH-CO-), 6.97-7.07 (m, 3H, Har-C-O-CH₂-), 7.20-7.37 (m, 5H, Har), 7.85-7.99 (m, 6H, Har).

¹¹(125 MHz, CDCl₃ δ ppm): 14.1 CH₂-CH₃, 22.7, 26.0, 29.2, 29.4, 29.4, 29.5, 29.6, 29.7, 31.9 -CH₂-, 38.9 -CH₂-CH₂-, 39.4 -O-CH₂-CH₂-NH, 55.1 -CH₂-CH₂-, 59.0 -O-CH₃, 68.5 O-CH₂-CH₂-, 69.5, 70.3, 70.5, 70.5 -CH₂-, 68.5 O-CH₂-CH₂-, 69.5, 70.3, 70.5, 70.5 -CH₂-, 68.5 O-CH₂-CH₂-, 69.5, 70.3, 70.5, 70.5 -CH₂-, 68.5 O-CH₂-CH₂-, 69.5, 70.3, 70.5, 70.5 -CH₂-.
Techniques

$^1$H and $^{13}$C NMR spectra were recorded on BRUKER AV-300, AV-400 or AV-500 spectrometers. IR spectra were measured on Thermo NICOLET Avatar 360 FT-IR spectrophotometer using KBr pellets. Mass Spectrometry was performed using a MALDI$^+$/TOF Bruker Microflex system with a DIT + NaFTA matrix and MicroTOF Bruker equipment for exact mass measurements. Elemental analysis was performed using a Perkin Elmer CHN2400 microanalyzer.

The thermal and mesogenic behavior was studied by optical microscopy with an Olympus BH-2 polarizing microscope equipped with a Linkam THMS hot-stage central processor.

Differential scanning calorimetry (DSC) was performed using a DSC Q2000 from TA Instruments with samples sealed in aluminum pans and a scanning rate of 10 °C/min under a nitrogen atmosphere. Temperatures were read at the maximum of the transition peaks and. Thermogravimetric analysis (TGA) was performed using a TGA Q5000IR from TA Instruments at a rate of 10 °C/min under a nitrogen atmosphere. Circular dichroism was measured using a Jasco J-810 equipment. The ECD spectra of the samples were registered by rotating the sandwich every 60 degrees around the light beam axis. PEG$_2$-Phe-Azo-C$_{18}$ gel (5 wt % in DMSO) was placed onto between two fused silica slides at room temperature with a 25 µm spacer. The case of Malt-Phe-Azo-C$_{18}$ gel (0.5 wt % in 1-dodecanol) w a 100 µm spacer was used. Spacers were selected in order to reach absorption below 2.

SEM measurements were performed using a QUANTA FEG 250 and TEM measurements were performed using a TECNAI G$^2$ 20 (FEI COMPANY), 200 kV, both at the Laboratory of Advanced Microscopy (LMA) of the ‘Instituto de Nanociencia de Aragon’. For TEM sample preparation, a drop of the solution (gel diluted) was placed on a copper grid and left to dry for 15 min. The copper grid was then placed again over a drop of 1% uranyl acetate solution as a negative stain for 30 s and was then left to dry.

Irradiation with UV light was carried out using an Hg lamp (100 W, Oriel) with an infrared water filter and an absorption filter 365 nm ± 5 nm. (intensity was 3.4 ± 0.3 mW/cm$^2$).

Gelation test: The gelator and the solvent were placed in a septum-capped test tube. The resulting mixture was heated until a gelation test: The gelator and the solvent were placed in a septum-capped test tube. The resulting mixture was heated until a gel and solution did not flow, the formation of a gel was registered. Aggregation study of PEG$_2$-Phe-Azo-C$_{18}$. The sample was first dissolved in DMSO (0.5 wt %) and water was carefully added to the solution (20 µL of Milli-Q water to 1.0 mL of solution) with slight shaking. Turbidity (as a modification of the apparent optical density of the sample) of the solution was measured after every addition of water at a wavelength of 650 nm using a quartz cell (path length 1 cm) with a UV/vis spectrophotometer. The solution was left to equilibrate till the turbidity value remains constant. The cycle of water addition, equilibration and turbidity measurement was continued until the increase in turbidity upon water addition was very small. The solution was then dialyzed against water for 2 days to remove the organic solvent using a regenerated cellulose membrane with a molecular weight cutoff of 1000 a. m. u.

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Notes and references

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$^d$ Electronic Supplementary Information (ESI) available: [Characterization data of compounds 1-4 and OAc-Malt-Phe-Azo-C$_{18}$, MALDI-TOF MS of PEG$_2$-Phe-Azo-C$_{18}$, PEG$_2$-Phe-Azo-C$_{18}$, PEG$_{16}$-Phe-Azo-C$_{18}$, PEG$_{16}$-Phe-Azo-C$_{18}$, PEG$_{16}$-Phe-Azo-C$_{18}$]. NMR of PEG$_2$-Phe-Azo-C$_{18}$, PEG$_{16}$-Phe-Azo-C$_{18}$, OAc-Malt-Phe-Azo-C$_{18}$ and Malt-Phe-Azo-C$_{18}$. TOCSY spectrum of OAc-Malt-Phe-Azo-C$_{18}$. SEM images of HOOC-Azo-C$_{18}$ and Phe-Azo-C$_{18}$ in DMSO. TEM images of HOOC-Azo-C$_{18}$, PEG$_{16}$-Phe-Azo-C$_{18}$, Malt-Phe-Azo-C$_{18}$. Turbidity curve of PEG$_{16}$-Phe-Azo-C$_{18}$. Absorption spectra of a 10$^4$ M solution of PEG$_{16}$-Phe-Azo-C$_{18}$ in DMSO at different irradiation times at 365 nm. Degree of isomerization for azobenzene moieties for PEG$_2$-Phe-Azo-C$_{18}$ gel and solution and Malt-Phe-Azo-C$_{18}$ gel. The dependence of ln ([A$_{\infty}$-A]/[A$_{\infty}$-A$_0$]) on irradiation time for PEG$_2$-Phe-Azo-C$_{18}$ gel and solution and Malt-Phe-Azo-C$_{18}$ gel]. See DOI: 10.1039/b000000ax


Photoresponsive supramolecular gelators have been synthesized using PEG or D-maltose as polar head. Incorporation of azobenzene photoresponsive moieties allows controlling the supramolecular gel structure, including a reversible gel-sol transition using light as external stimulus.