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COMMUNICATION

Supramolecular gels derived from nucleoside based bolaamphiphiles as a light-sensitive soft material

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Light-sensitive Low Molecular Weight Gelators (LMWGs) derived from glyconucleoside bolaamphiphiles containing a stilbene unit displayed gelation abilities in hydroalcoholic mixtures. These materials showed a gel-sol transition under UV irradiation thanks to *E* - *Z* isomerization of stilbene and could find potential applications as drug delivery systems.

Supramolecular gels resulting from the self-assembly of functional low molecular weight gelators (LMWGs) have gained an increasing interest in many fields ranging from tissue engineering to electronic devices.^{1–6} The dynamic nature of non-covalent interactions represents a powerful tool to modulate the physical behavior of LMWGs. Many changes or modifications, occurring at the molecular level (supramolecular structure, geometry) and / or at the macroscopic scale (gel - sol states, physico-chemical properties) have been reported.^{7,8} According to their hydrophilic to hydrophobic balance among other parameters, LMWGs can provide hydro-, organo- or oleogels. Falling between hydro- and organogels, hydroalcoholic gels are of particular interest for the formulation of various active pharmaceutical ingredients (APIs) as anti-inflammatory (including non-steroid molecules),^{9,10} anti-epileptic¹¹ or antifungal¹² drugs. However, these gels are mainly composed of mixtures of synthetic or natural polymers and penetration enhancers. In the last decade, responsive supramolecular gels sensitive to enzymes,^{13–16} magnetic/electric fields,^{17,18} or pH^{19,20} among other triggers have been extensively designed for diverse applications ranging from controlling cell behavior²¹ to drug release.²² Recently, light stimulation has attracted much attention as a minimally invasive stimulus allowing precise spatiotemporal

control and has successfully been applied in nanotechnology or biomedicine.^{23–25} Light-responsive gels generally rely on the presence of photochromic moieties that undergo ring-opening / -closing reactions (spiropyrans, diarylethenes) or *E* / *Z* isomerization (azobenzene, stilbene and derivatives).^{26–34} Stilbene has been particularly studied thanks to its well-known photoswitching behavior³⁵ to give light-sensitive gels based on cholesterol,³⁶ oxalyl amide,^{37,38} N,N'-dimethyldodecylamine³⁹ or amino acid⁴⁰ derivatives displaying gel-sol or sol-gel transitions under irradiation. To the best of our knowledge, hydroalcoholic supramolecular gels sensitive to an external stimulus such as light have not been reported so far. These materials could be used as models for drug delivery in the case of external use for example. However, the design of such stimuli-sensitive gels can profoundly impact the likelihood of successful gel responsiveness for a given application. The introduction of large hydrophobic photochromic units in a LMWG framework may disturb the self-assembly process and impeded effective photoisomerization in gel state due to steric hindrance. This behavior might be accentuated when photosensitive moieties are simultaneously tightly packed and strongly involved in the supramolecular assembly.^{41,42}

Bio-inspired amphiphilic substrates combining carbohydrate, nucleoside and lipid units have shown promising applications as LMWGs.^{43–46} Among them, bolaamphiphiles derivatives in which two glyconucleoside headgroups are linked covalently by a hydrophobic spacer have emerged as attractive scaffolds for biomedical applications.^{47–49} In this work, we present a series of light-sensitive supramolecular gels based on glyco-nucleoside-bolaamphiphile derivatives (GNBAs) featuring a thymidine, a glucose or a lactose and a stilbene, as photochromic moiety, within the hydrophobic part. The resulting responsive GNBAs led to the formation of thixotropic gels in hydroalcoholic solvents and a photoinduced gel-sol transition upon irradiation due to the stilbene photoisomerization.

A synthetic route was developed in 6 steps based on CuAAC chemistry / metathesis reactions, starting from commercial thymidine (Scheme 1A). The introduction of a propargyl unit at the N3 position under microwave conditions allowed the formation of N3-propargylthymidine **1**. The latter was then submitted to a CuAAC reaction with the desired peracetylated azidosugar to form

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the corresponding 1,2,3-triazole derivative, followed by the 5' position functionalization with an azide group. Intermediates **3** and **3'** were then involved in a second CuAAC reaction with the desired propargylic carbon chain **6a** or **6b** gathering a styrene ending group to form the corresponding glyconucleolipids. *E*-bolaamphiphile structures were then obtained *via* the stereoselective

homometathesis reaction using the Hoveyda-Grubbs II catalyst. Deprotection of the acetyl sugar groups under basic conditions allowed to reach the final general structure **9**. Using this strategy, three GNBA **9a**, **9'a**, **9'b**, displaying different hydrophobic chain lengths and sugar moieties, were synthesized (Scheme 1B).

Scheme 1. Synthetic route leading to light-sensitive bolaamphiphiles (A) and chemical structures of GNBA **9a**, **9'a** and **9'b** (B)

Reagents and conditions: **a** - NaH (60 % dispersion in oil, 1.15 equiv), propargylbromide (80 % wt. in toluene, 1.2 equiv), anhydrous DMF, 45 min, microwaves, 84 %; **b** - Peracetylated azidosugar (1 equiv), CuSO₄, 5H₂O (0.1 equiv), sodium ascorbate (0.2 equiv), ^tBuOH/H₂O (1:1), 15 h, 65 °C, 64-71 %; **c** - PPh₃ (1.2 equiv), NaN₃ (5 equiv), CBr₄ (1.2 equiv), anhydrous DMF, 24 h, RT, 61-71 %; **d** - KOH aqueous solution (1.5 M, 2.5 equiv), 4 h, 0 °C; **e** - alkyl alcohol (1.2 equiv), K₂CO₃ (1.2 equiv), anhydrous DMF, 48 h, RT; **f** - Propargylic chain (1.1 equiv), CuSO₄, 5H₂O (0.1 equiv), sodium ascorbate (0.2 equiv), ^tBuOH/H₂O (1:1), 15 h, 65 °C, 83-90 %; **g** - Hoveyda Grubbs II catalyst (0.05 equiv), anhydrous DCM, 16 h, 40 °C, 27-47 %; **h** - Sodium methoxide solution (1M in anhydrous MeOH), anhydrous DCM/MeOH, 1-2 h, RT, 51-70 %.

The *E*-configuration of the stilbene chromophore was assessed from ¹H NMR of the model structure (**11**). Chemical shifts associated to aromatic (δ = 6.85-6.91 and 7.38-7.45 ppm) and ethylenic protons (δ = 6.92 ppm) are in agreement with the sole formation of the *E*-isomer as reported in the literature.⁵⁰ Thus, no signal corresponding to the *Z*-stilbene configuration was detected (Figure S17). The photoresponse of **11** in MeOH and DMSO solutions was investigated using monochromatic UV irradiation at 336 nm (Figure 2 and S10). The spectral changes were monitored by UV-Vis and NMR spectroscopy to determine the temporal evolution of the absorbance and composition of the samples. During irradiation, the absorbance at long wavelength was found to decrease in agreement with photoinduced *E* - *Z* isomerization.

In the case of **11**, the composition of the photostationary state (PSS) was determined by ¹H NMR to be 0.15 and 0.28 (*E* : *Z*) in MeOH and DMSO respectively (Figure S14, Table S15). The greater proportion of *E*-isomer in DMSO reflects a greater efficiency for the $\Phi_{Z \rightarrow E}$ process in this solvent and some solvatochromism of the *Z*-isomer. However, the isomerization *E* - *Z* was moderately sensitive to solvent effects ($\Phi_{E \rightarrow Z}$ = 0.37 in MeOH and 0.39 in DMSO). Calculated quantum yields $\Phi_{E \rightarrow Z}$ of bolaamphiphiles **9a**, **9'a**, **9'b** were found to be 0.31, 0.30 and 0.36 respectively. These values are similar to $\Phi_{E \rightarrow Z}$ of **11** in DMSO, indicating a limited impact of the two glyconucleoside heads on the photoisomerization process (Table S15, Figures S11-S13). The photoisomerization was also

qualitatively observed in FT-IR experiments on the intermediate **12**. Characteristic bands of *E*-configuration at 965.2 cm⁻¹ and 940.1 cm⁻¹ (C-H bending vibration) decreased in intensity after irradiation combined with the appearance of a new band at 879.4 cm⁻¹ (C-H bending vibration), corroborating the *E* - *Z* transition (Figure S16).

Figure 2. Spectral changes in the electronic absorption spectrum of **11** (88.0 μM in DMSO) upon irradiation at 336 nm and the variation of the composition of the solution versus irradiation time.

The gelation abilities of bolaamphiphiles **9a**, **9'a** and **9'b** were evaluated in organic and aqueous solvents. All molecules were insoluble in organic solvents but different behavior were noticed in polar solvents (Table S17). While **9'b** did not form any

supramolecular assemblies, **9a** and **9'a** in water / ethanol mixtures led to gels of qualitatively different stabilities based on the qualitatively inversion test tube method. The viscoelastic moduli G' and G'' of **9a** and **9'a** based-gels at 5 % (w/v) and 2 % (w/v) respectively in $H_2O/EtOH$ (1:1) were measured by oscillatory rheology. Over the entire frequency range, G' exceeded more than five times G'' and values displayed a weak dependence, indicating a solid-like behavior ($G' = 64.4 \pm 5.7$ kPa for **9a** and 8.0 ± 0.9 kPa for **9'a** at 1 Hz; Figure 3). Interestingly, at the same molar concentration (13.25 mM; 2.4 % (w/v)), G' values of **9a** based-gel (30.0 ± 2.6 kPa at 1 Hz) remained higher than **9'a** indicating a stiffer material probably due to an increase of hydrogen bonding capabilities provided by the lactose moieties (Figure S19). Besides, both gels showed thixotropic properties. This behavior was first estimated using rheology by applying successive low (inside the LVR region) / high strain values (above the flow point, 50 %) to disrupt the 3D network until the flow and test its recovery ability when the high strain is stopped. A high strain led to an immediate collapse of gels as G'' became superior to G' but instantaneously after its removal, G' recovered nearly 70 % of its initial value and reached 100 % in 50 minutes (Figure 3). This behavior was then evaluated by gel extrusion through a syringe and the gel state was confirmed by a G' value superior to G'' (SI video, Figure S120). Finally, high transition temperatures from gel to sol were measured at 54 °C (**9a**) and 60 °C (**9'a**) (Figure S118).

Transmission electron microscopy performed on bolaamphiphiles **9a** and **9'a** based-gels at 5 % (w/v) and 2 % (w/v) respectively exhibited similar entangled network composed of helicoidal nanofibers of around 20 nm in diameter and 140 nm in pitch (Figures 4 and S122).

Figure 3. Frequency sweep experiments on **9a** and **9'a** based-gels at 5 % (w/v) and 2 % (w/v) respectively (constant strain: 0.05 % for **9a** and 0.02 % for **9'a**) and step-strain assay on **9'a** based-gel at 2 % (w/v) (constant frequency: 1 Hz, successive cycles: 1/ strain of 0.02 % for 5 minutes, 2/ strain of 50 % for 2 minutes, 3/ identical to 1/ for 60 minutes).

To investigate the potential of these systems as light-sensitive materials, gels were submitted to UV light. Irradiation at 336 nm allowed the destruction of supramolecular architectures to form liquid solutions caused by the expected photoisomerization of *E*-stilbene. However, the rigidity conferred by the interpenetrating network led to a slow process (5 to 6 hours). Irradiation with a more powerful lamp at 312 nm allowed to reduce the time of exposure to 2 hours even if the proportion of *Z*-isomer in the PSS was lower at this wavelength (PSS = 0.54 for **11** in solution in DMSO). Liquid states highlighted a network of smaller nanofibers in transmission electron microscopy, responsible thereby for the absence of gelation (Figure 4).

Figure 4. Transmission electron microscopy images of **9a** based-gel at 5 % (w/v) (A) and **9'a** based-gel at 2 % (w/v) (B) before and after UV irradiation at 312 nm. Scale bars: 2 μ m and 1 μ m.

As a gel-sol transition was observed in response to light-stimuli, we would expect the *E* - *Z* transition and a majority of *Z*-isomer in solution states. UV spectra of irradiated **9a** and **9'a** gels at 312 nm exhibited a *Z*-isomer pattern due to the $\pi \rightarrow \pi^*$ electronic transitions, indicating therefore the proper photoisomerization (Figure S123). Besides, the absorbance measured at the maximum of absorption of the *E*-isomer (332 nm) allowed to estimate the proportion of *E*- and *Z*-isomers after irradiation. A high proportion of *Z*-isomer, estimated at 75 %, was highlighted in both case. This result suggested that the complete destruction of the supramolecular architecture into sol states required a similar proportion of *Z*-isomer calculated in the PSS in solution.

In this study, we have synthesized GNBA featuring a photo switchable stilbene moiety as light-sensitive LMWGs. The self-assembly of **9a** and **9'a** in water / ethanol mixture at low concentrations ($\leq 5\%$ w/v) revealed the formation of fibrillar networks. Besides, these physical gels featured high elastic moduli (higher than 60 kPa in the case of **9a**), thixotropic properties and

gel-sol transitions compatible with biomedical applications. By using photosensitive GNBAAs, in which the stilbene moiety changed its configuration from *E* to *Z* under irradiation, the self-assembly could be controlled by UV light leading to macroscopic changes i.e. gel-sol transition. These new supramolecular responsive hydroalcoholic materials could be an alternative to the existing polymer based-drug delivery systems for external use as the UV light stimulation may provide a faster drug release when needed.

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Conflicts of interest

There are no conflicts to declare.

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