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Polyhedral oligomeric silsesquioxane (POSS) bearing glyoxylic aldehyde as clickable platform towards multivalent conjugates.

Nasreddine Kanfar,^[a] Ahmad Mehdi,^[b] Pascal Dumy,^[a] Sébastien Ulrich*^[a] and Jean-Yves Winum*^[a]

Abstract: The straightforward access to octafunctional “cubic” silsesquioxane platform grafter with pendant glyoxylic aldehydes is described. This clickable hybrid platform readily reacts with oxyamine or hydrazide compounds to provide, respectively, oxime and acylhydrazone conjugates, thereby offering a new and effective access from which one can elaborate multivalent systems for the targeting of biomolecules of interest.

Remarkable advances through the development of “chimie douce”^[1] has afforded innovative organic-inorganic hybrid nanostructures.^[2] In particular, polyhedral oligomeric silsesquioxanes (POSS) are of increasing interest as a platform that can be post-synthetically functionalized in order to introduce the desired chemical moieties for the application pursued. POSS have become very popular in material sciences for various applications, for instance as porous materials,^[3] ionic liquids,^[4] catalysts,^[5] nano-reactor,^[6] nanocomposites,^[2a] and supramolecular self-assemblies.^[7] One of the most prevalent and studied nanosized POSS is the well-defined and symmetrical T₈ structure (hexahedral octasilsesquioxane (RSiO_{1.5})₈) – abbreviated as COSS for Cubic Octameric Silsesquioxane – which possesses a compact and rigid three-dimensional cage-like structure made of an inorganic silica-like core flanked with eight functionalizable organic groups at the corners.^[2,8] COSS are monodisperse hybrid systems of nanometric size with a precise number of functional groups which, thanks to their biocompatibility and low toxicity,^[9] are currently finding increasing applications in biological sciences,^[10] for instance in drug delivery,^[11] anti-cancer drug,^[12] and biomedical imaging.^[13] This versatile class of organosilica compounds are indeed of great value as platforms for accessing multivalent conjugates for biomolecular recognition^[14] or enzyme inhibition,^[15] providing effective synthetic methods afford their complete functionalization.^[8]

COSS derivatives bearing reactive functional groups such as amine, azide, vinyl, cyano, halogen have been reported

in literature.^[2,8] The availability of 3-aminopropyl-functionalized COSS^[16] has prompted its functionalization through coupling with carboxylic acids, anhydrides and acyl chlorides.^[17] However, these coupling methods have a limited scope due to the lack of chemoselectivity. Therefore, click-type reactions have been recently implemented for the post-synthetic functionalization of COSS.^[8, 18] The azido and vinyl derivatives have thus attracted strong interest since ligands can be effectively attached through, respectively, copper-catalyzed azide-alkyne Huisgen cycloaddition and photo-initiated thiol-ene reaction.^[19] Hydrazone and oxime ligations have also gained strong interest due to their effectiveness (quantitative yields), chemoselectivity with respect to a variety of functional groups, mild reaction conditions that do not require additional catalysts that may be toxic and difficult to discard, and lack of by-products.^[20] COSS bearing aminoxy groups have been recently reported for oxime ligation.^[21] However, having pendant amino groups can be detrimental to the stability of the COSS core,^[22] thereby reviving interest in the alternative strategy of using COSS appended with aldehyde groups. Up to now, only two examples of COSS bearing aldehyde groups has been reported.^[23] However, these COSS derivatives are difficult to isolate and feature aromatic aldehydes which impede water solubility and are not optimal for the stability of hydrazone and oxime conjugates. Herein, we report the effective and straightforward synthesis of a COSS bearing glyoxylic aldehydes – which are known to lead to more stable conjugates^[24] – and demonstrate the formation of multivalent conjugates through hydrazone and oxime conjugation (Figure 1).

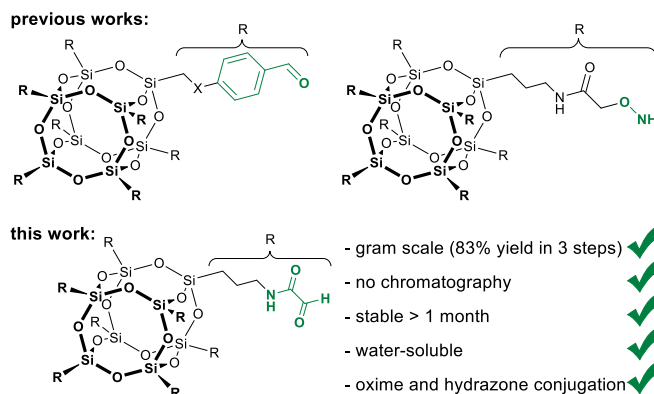


Figure 1. Summary of previously prepared COSS platform prepared for conducting oxime/hydrazone conjugates, and presentation of the platform presented here and its comparative advantages.

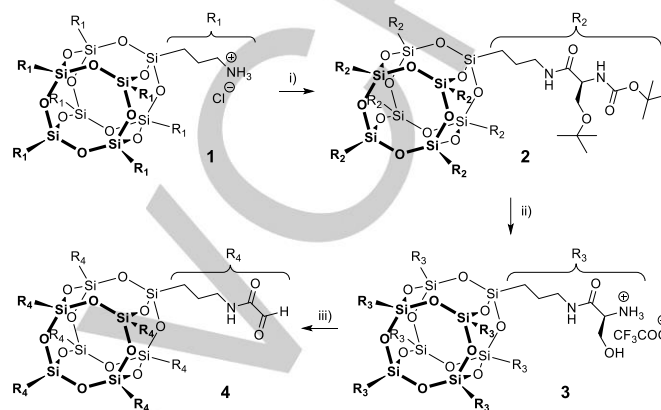
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The clickable T₈-silsesquioxane platform functionalized with eight glyoxylic aldehydes **4** was prepared as depicted in scheme 1, starting from the commercially available hydrochloric salt of the 3-aminopropyl substituted silsesquioxane T₈(CH₂CH₂CH₂NH₃⁺Cl⁻)₈ **1**.^[16] The peptide coupling with the protected serine Boc-L-Ser(O*t*-Bu)OH, mediated by HBTU as coupling reagent in the presence of diisopropylethylamine (DIEA) as a base, successfully afforded compound **2** in 92% yield after recrystallization. ¹H and ¹³C NMR analysis confirms the octa-functionalization of the platform (Figure S1 and S2), which is further supported by MALDI-ToF mass spectrometry (Figure S4) and elemental analysis. ²⁹Si NMR showed only one type of silicon nuclei at -66.90 ppm (Figure S3). This chemical shift is characteristic for T substructure^[8] and expected for a T₈-POSS unit and therefore indicates that the structure of the platform remains intact. The single peak at -66.90 ppm (T³ substructure) indicates that there is no cleavage of Si-O-Si bonds (absence of signals at -42 ppm (T¹ substructure) and -56 ppm (T² substructure)). In addition, the absence of resonance near -100 ppm corresponding to Q substructures denotes clearly that Si-C bonds remain intact during this chemical coupling. The subsequent deprotection of Boc and *t*-Bu groups was carried out in trifluoroacetic acid (TFA)/triisopropyl silane (TIS)/water 95/2.5/2.5, giving after trituration in diethylether compound **3** in 96% yield. The complete deprotection was proved by ¹H and ¹³C NMR (Figure S5, S6), MALDI-ToF mass spectrometry (Figure S8) and elemental analysis. ²⁹Si NMR analysis showed a single and sharp peak at -66,33 ppm (Figure S7), which again confirms that no cage opening or rearrangement take place during this step. Finally, the oxidative cleavage of the amino alcohol **3** was carried out in water using a slight excess of NaIO₄ (8.8 eq.) Unfortunately, purification by reverse phase HPLC and size exclusion chromatography did not yield the pure compound. Dialysis was found as an easier technique to isolate the desired T₈-glyoxylic aldehyde **4** which was obtained in 94% yield (see Supporting Informations). ¹H and ¹³C NMR showed characteristic signals indicating that compound **4** is present exclusively in its hydrated form, respectively at 5.31 ppm (-CH(OH)₂) and 86.81 ppm (-CH(OH)₂) (Figure S9-S10). ²⁹Si NMR confirmed the integrity of the T₈-POSS core with a single singlet signal observed at -65.41 ppm (Figure S11). For all compounds, Thermogravimetric analysis (TGA) were conducted from 25 °C to 850 °C under air (Figure S21, S22, S23). The progressive weight losses assigned to the decomposition of the organic groups are around 82% for the POSS-(Boc-L-Ser(O*t*-Bu))₈ **2**, 80% for the POSS-(L-Ser.TFA)₈ **3** and 75% for the POSS-(C(OH)₂)₈ **4**. These values are very close to the theoretical values of, respectively, 83%, 81% and 76%, which correspond to the loss of the organic side-chains. The difference of curve profile for compound **4** versus compounds **2** and **3** can be explained by the initial progressive dehydration of its hydrated form. IR analysis

also showed characteristic absorption band of silsesquioxane cages, in particular the narrow and intense Si-O-Si vibrations which appear at 1111, 1103 and 1088 cm⁻¹, and the Si-C vibrations which appear at 777, 721 and 748 cm⁻¹, respectively for **2**, **3**, and **4** (Figure S24, S25, S26).

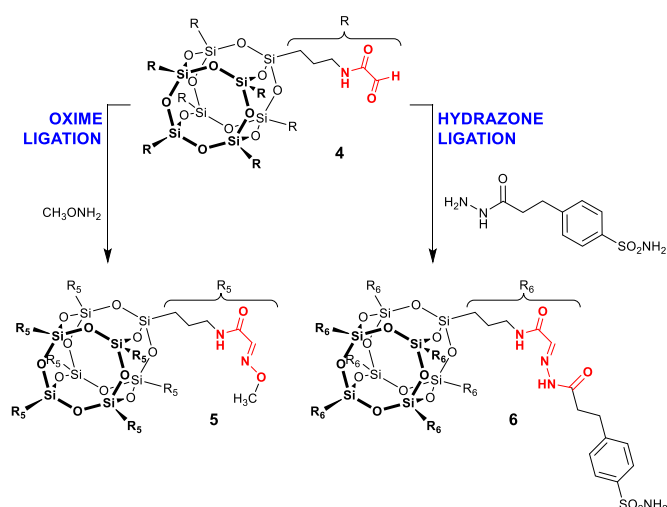


Scheme 1. Synthesis of COSS bearing glyoxylic aldehyde **4**. i) Boc-L-Ser(O*t*-Bu)OH, HBTU, DIEA, 92%; ii) TFA/TIS/H₂O 95/2.5/2.5, 96%; iii) NaIO₄, 94%.

Taken together, these results prove the structural integrity of the POSS platform throughout the synthesis, and show that this POSS platform **4** can be obtained in three straightforward synthetic steps, only involving recrystallization and dialysis and no column or HPLC chromatography, in an overall yield of 83% and up to the gram scale. It is also noteworthy to mention that we found compound **4** to be stable, as a solid and even in aqueous solution, for at least a month.

In order to demonstrate the utility of this platform for accessing multivalent conjugates, we carried out oxime and acylhydrazone ligation reactions (Scheme 2). The oxime ligation was carried out in acidic water (H₂O/TFA 99.9/0.1) using methoxyamine (16 eq.) as reactive partner. The acylhydrazone ligation was conducted in acidic buffer (100 mM sodium acetate, pH 5.0) as previously described,^[25] using a specific hydrazide (16 eq.) flanked with an aromatic sulphonamide that we recently prepared as carbonic anhydrase inhibitor.^[15a] MALDI-ToF mass spectrometry show, in both cases, the complete conjugation of the eight sites (Figures S16 and S20). ¹H NMR data show integrals ratio converging toward complete functionalization although slight differences with theoretical values probably indicate that there are still some intermediates as minor products (Figures S13-S17). Satisfyingly, ²⁹Si NMR confirmed the integrity of the T₈-POSS core with single singlets observed at -66.28 ppm for compounds **5** and **6** (Figures S15 and S19). Both multivalent conjugates **5** and **6** could be successfully isolated by precipitation in, respectively, 56% and 14%. Taking into account that eight ligation reactions

take place, this amounts to individual yields of, respectively, 93% and 78%.



Scheme 2. Preparation of multivalent conjugates through oxime and acylhydrazone ligation reactions onto the clickable platform **4**. Conditions for oxime ligation: H_2O with 0.1% TFA, for acylhydrazone ligation: acetate buffer (100 mM, pH 5.0).

In conclusion, we reported here the straightforward synthesis in three steps with simple purification that enables the effective preparation, with an overall yield of 83%, of a functionalized T_8 -POSS bearing eight reactive glyoxylic aldehyde groups. We demonstrated the structural integrity of the COSS platform throughout the synthesis. All the COSS-based nanostructures were extensively and unambiguously characterized via multinuclear magnetic resonance (^1H , ^{13}C and ^{29}Si NMR), as well as mass spectrometry. Finally, we have shown, as proof-of-principle, that oxime and acylhydrazone ligation reactions can be effectively conducted in order to generate multivalent bioconjugates. The ease of synthesis of this novel clickable platform, coupled with the wide variety and availability of functionalized aminoxy and hydrazide derivatives provide an easy entry to elaborate multivalent systems based on a biocompatible COSS core.

Acknowledgements

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Keywords: silsesquioxane • multivalent platform • oxyamine • hydrazone • ligations

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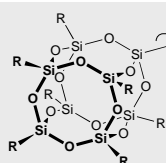
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Clickable “cubic” silsesquioxane platform with glyoxylic aldehydes offers effective access to new multivalent systems via chemoselective oxime or hydrazone conjugation.