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Glycidyl alkoxysilane reactivities towards simple nucleophiles in organic media for improved molecular structure definition in hybrid materials†

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For hybrid materials, the relationship between the macroscopic properties and the molecular structures and dynamics at the microscopic between the organic and inorganic components level is crucial. The characterization of these components as well as their reactivity have to be emphasized in order to design and synthesize improved hybrids. We report herein the first comprehensive study of the reactivity in organic media of (3-glycidyloxypropyl)trialkoxysilanes, widely used as precursors in sol–gel hybrid synthesis, towards common nucleophiles. Thorough investigations of the reactions allowed us to draw clear conclusions about the reactivities of both epoxide and alkoxysilane functions. Furthermore, the nucleophile properties and the method of activations have a great influence on the reaction outcomes, and unexpected results were found in some cases. The importance of the nature of the alkoxy residues (methoxy, ethoxy…) was also investigated highlighting chemoselective reactions on glycidyl silane derivatives (GPTMS, GPTES and PECS) and opening a new library of original sol–gel precursors.

Introduction

Hybrid organic–inorganic materials have been the source of a number of studies in which smart and tailor-made materials combine the best properties of organic and inorganic moieties. These hybrid materials, with their unique and improved characteristics, have led to major innovations in fields ranging from coatings,[1] sensors,[2] catalysis,[3] tissue engineering,[4] chromatography,[5] and many others.[6] In the course of our longstanding studies on tissue engineering, we focused on hybrid materials obtained by sol–gel chemistry in order to allow micro-invasive surgery.[7–10] In this context, we investigated more specifically hybrid materials obtained by siloxane functionalisation of biopolymers by means of glycidylalkoxysilane.

Hybrid materials have been divided into two classes according to the nature of their interactions at the molecular level between the organic and inorganic components.[11,12] In class I hybrids, the two moieties are embedded and the links between them are due exclusively to weak forces such as van der Waals or hydrogen interactions, or ionic bonds. In contrast, class II hybrids are materials in which the two moieties are partly linked through strong covalent or iono-covalent bonds. A wide range of class II hybrids are based on sol–gel reactions of silicon, tin and transition metal alkoxides.[13] Specifically, the siloxane network based on functional organosilanes is particularly widespread due to the strong Si–C_{sp^3} bond (E = 451 kJ mol^{-1}),[14] stable towards attack by nucleophilic species such as water, alcohols, amines, *etc.* thus allowing the introduction of new functions into the network. In this strategy, functional alkoxysilanes of the general structure Y–R–Si(X)$_3$ where Y could represent a functional group (*e.g.* glycidyl, amine, halogen, isocyanate, *etc.*), R is an alkyl chain and X is an alkoxy group (*e.g.* methoxy, ethoxy, *etc.*) are very common.[15]

Whereas the alkoxysilane moiety can hydrolyze and condense with the growing silica network during the sol–gel process, the residue Y can be used for adding functionality or as a reaction center for functionalization. Among the wide range of available organosilanes, (3-glycidyloxypropyl)trimethoxysilane (GPTMS) is widely employed in the synthesis of class II hybrids and is particularly interesting for its reactive epoxy function. Three strategies are often reported (Fig. 1):[11,16]

(i) The organic and inorganic components are mixed with the functional alkoxysilane in hydrolysis conditions, often aqueous media or protic solvents, with a catalyst, thus triggering two reactions: silanol polycondensation and organic functionalization.[17]

(ii) The functional alkoxysilane is hydrolyzed and the resulting silanols create siloxane bonds, hence preserving the

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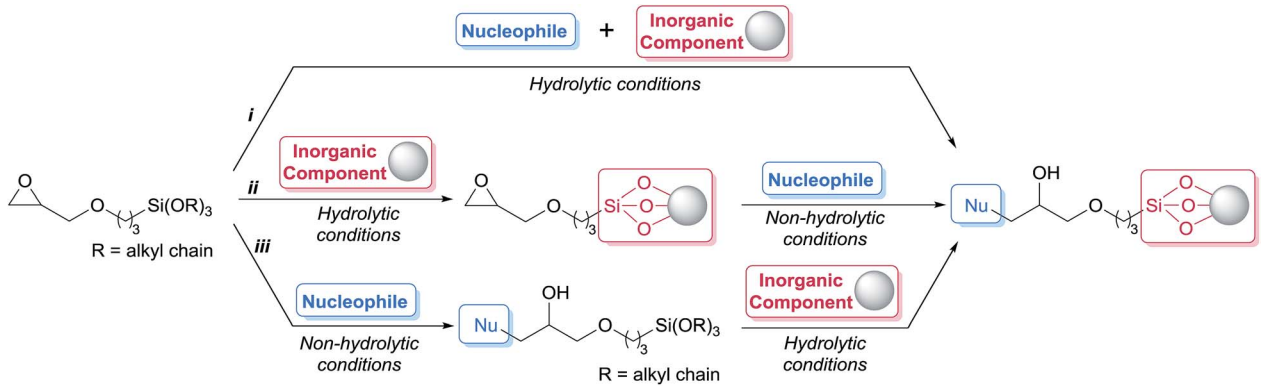


Fig. 1 Schematic representation of the three common strategies for the synthesis of hybrid materials from functional alkoxysilanes, using (3-glycidyloxypropyl)trialkoxysilane as the functional alkoxysilane.

electrophilic function for later use with an organic component.[15,18]

(iii) In contrast, the electrophilic group can first react with an organic reagent of interest (*e.g.* dyes, carbohydrates, *etc.*) to create a modified precursor bearing alkoxysilane functions that will be hydrolyzed in a second step.[19,20]

Based on these strategies, challenges and problems appeared due to the reactivities of both functions, which are highly dependent on the reaction conditions: solvent (aqueous, organic, ionic liquid media), temperature, concentration, catalyst, and acidic or basic conditions. All these parameters markedly influence the reactions taking place and complicate the formation of covalent links on both types of function on the silane, necessary in the synthesis of class II hybrids.

In the course of improving the properties of biomaterials, we were particularly interested in controlling the functionalization of substrates with glycidyl alkoxysilane derivatives.[7–10] However, the dual reactivity of functional alkoxysilanes and their sensitivity towards reaction conditions require a deeper understanding of their dynamics at the molecular level in order to design and rationally synthesize improved materials with well-defined structures.[6,21] Therefore, a thorough understanding of the reactivity of both epoxy and alkoxysilane functions was needed in order to finely control the functionalization process and the structures of the resulting materials.[22]

The dual reactivity of GPTMS has already been studied in both strategies i and ii by exploring the influence of the reaction such as: the role of Lewis acid boron trifluoride diethyl etherate on epoxide polymerization after a pre-condensation step with tetraethoxysilane (TEOS);[23,24] the impact of metal alkoxides such as $Zr(OPr)_4$ or $Ti(OEt)_4$;[25,26] the effect of an highly alkaline pH on the kinetics of reaction;[27,28] and the nature of the nucleophile in epoxy-amine systems.[29,30] More recently, the pH influence on the silica network formation *versus* epoxide-opening and the capacity of some simple nucleophiles to react with the epoxide at optimal pH conditions were investigated in aqueous media.[31,32] The functionalization reaction between GPTMS and chitosan in aqueous conditions was recently reported in the literature and revealed valuable elements for understanding the resulting hybrid structure using a combination of liquid and solid state NMR techniques.[33] In the meantime, we also carried out structural identification in hybrid synthesis based on the reactivity of nucleophiles in the presence of glycidyl silanes in organic media.

To the best of our knowledge, only a few studies have focused on fine characterization and structural elucidation for strategies ii and iii. An extensive characterization of products of the non-hydrolytic reaction between titanium(IV) chloride and GPTMS has been reported and some original structures have been suggested.[34] In a couple of publications, the reaction of primary amine with GPTMS was also examined but unfortunately the resulting structures were not fully characterized with NMR or MS techniques.[29,35–37]

Here, we sought to investigate the reactivity of GPTMS against simple nucleophiles in organic media with a focus on both the isolation and fine characterization of major products and the consequences in strategy iii. The amine, thiol and alcohol functions are well representative of nucleophiles often found in natural products or synthetic organic compounds used for hybrid materials (*e.g.* tissue engineering scaffolds made from hyaluronic acid, chitosan and other polysaccharides; chiral molecules for functionalized chromatography columns, *etc.*).[4,5] Another nucleophile, such as sodium azide, was alternatively selected due to the opportunity to access azide-based organic structures for click-chemistry functionalization.[38]

Our studies were focused on the reactivity in organic media of three glycidyl silanes: GPTMS, GPTES and PECS (Fig. 2) towards nucleophiles R–NH_2, R–SH, NaN_3 and R–OH. All these results were reported by subsection related to the nature of

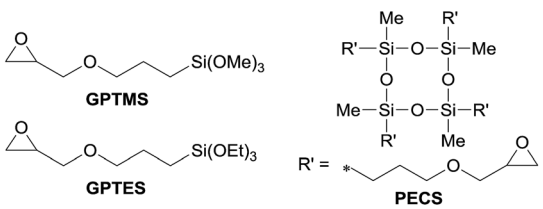
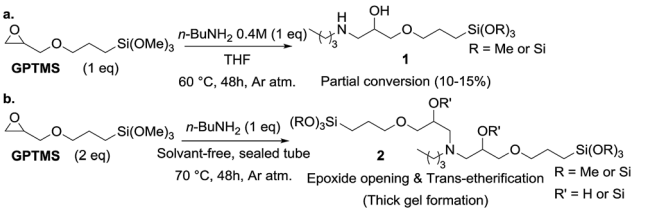


Fig. 2 Molecular structure of glycidyl silanes GPTMS, GPTES and PECS.

nucleophiles. Our investigations were dedicated to well identify and to better understand at the molecular level the reactivity of such nucleophilic species (R–NH_2, R–SH, NaN_3, R–OH) in presence of glycidylalkoxysilanes by using experimental procedures known in the literature.[22] Activation in the presence of bases or Lewis acids was investigated when needed. We also extended our study to the (3-glycidyloxypropyl)triethoxysilane (GPTES) and polyglycidylether cyclosiloxane (PECS) which exhibit higher stability.



Scheme 1 Reactions of *n*-butylamine with GPTMS: (a) in solution in THF, (b) in solvent-free conditions.

Results and discussion

The functional (3-glycidyloxypropyl)alkoxysilanes are of the most commonly used alkoxysilanes to synthesize class II hybrid materials. Our work was dedicated to reinvestigate the dual reactivity of these organofunctional silanes in presence of common nucleophiles because deeper understanding is needed. In fact, depending on their pK_a and nucleophilicity, nucleophiles can react on glycidyl silanes by ring-opening of the epoxide and/or polycondensation catalysis and/or alkoxy substitution with the alkoxysilane groups. For these reasons, particular attention was paid to the purification, recovery and extensive characterization (NMR and MS techniques) of the resulting products. In this context, it is important to note that purification of alkoxysilanes on silica-gel causes a loss of matter and is responsible for some of the low mass balances reported. A more detailed explanation, accompanied by small studies of the recovery rates for pure compounds, is given in the ESI† (part B).

Extensive characterization of the products (NMR and MS spectra), experimental procedures and other relevant data for the whole study are available in the ESI† to give structural evidence of the described compounds.

Primary and secondary amines as nucleophiles

Whereas the functionalisation of glycidylalkoxysilanes in presence of amines as organic reagents is well documented, we sought to reinvestigate this type of reactivity by using similar procedures of the literature and by rigorously identifying the structures of the resulting compounds by full spectroscopic characterization. In order to make the characterization of products easier, simple amines were used in the following studies. To begin, the reaction of *n*-propylamine (1 eq.) with GPTMS (1 eq.) in THF-d_8 (0.6 mL) at 40 °C was monitored by ^{1}H NMR with spectra acquisitions at 0.5 h, 1 h, 2 h, 3 h and 24 h. The spectra superposition (Fig. ESI_146†) demonstrated the increasing intensity of the methanol peak related to partial hydrolysis. In addition, no changes in the rest of the overall spectra and in the epoxy signal integrals at $\delta = 2.93$, 2.57 and 2.40 ppm were noted. Based on these observations, it is clear that under these reaction conditions, no epoxide-opening occurred.

According to the described procedure used for the synthesis of silsesquioxane film with pendant alkyl chains,[39] we reproduced the reaction of *n*-butylamine (1 eq.) at 0.4 M in freshly distilled THF in the presence of GPTMS (1 eq.) at 60 °C under argon atmosphere for 48 h (Scheme 1(a)).

After concentration of the reaction mixture, the unreacted *n*-butylamine was also evaporated under high-vacuum. Analysis by ^{1}H NMR (Fig. ESI_147†) revealed epoxide signals integrating for 0.85–0.87H each, meaning that only partial conversion (10–15%) occurred to yield the adduct **1**, characterized by the C*H*(OH) signal at $\delta = 3.82$ ppm integrating roughly for 0.12H.[40]

A similar synthesis has been reported without solvent in a sealed tube for the preparation of an oligomeric bridged silsesquioxane containing a pendant hydrophobic chain by reacting dodecylamine with GPTMS.[36] For sake of comparison, *n*-butylamine (1 eq.) was similarly reacted with GPTMS (2 eq.) in a dry tube sealed under argon atmosphere and left at 70 °C for 48 h (Scheme 1(b)). After 24 h, a significant increase in viscosity was observed as well as the appearance of a yellowish colour. After completion, the reaction mixture formed a thick gel (**2**). A fraction of this gel was dissolved under stirring for 16 h in a 0.1 M NaOD/D_2O (pH 13) to cleave the siloxane bonds was involved in the gelation.[41,42] The resulting ^{1}H NMR spectrum of the dissolved crude material revealed (Fig. ESI_148†) the total disappearance of the epoxy signals at $\delta = 3.00$ and 2.81 ppm (third signal masked by MeOH) and the appearance of the C*H*(OH) signal at $\delta = 4.01$ ppm (1H) related to complete ring-opening. Moreover, considering there was twice as much GPTMS as primary amine, our results confirmed the hypothesis of a second ring-opening since no epoxide signal remained.[36] This reaction was carried out following the above-described procedure and we reduced the reaction time (7 h) to avoid complete polymerization. The resulting product was obtained as a light yellow viscous oil, which could easily be solubilized in $CDCl_3$. After close examination of the ^{1}H NMR spectrum (Fig. 3), a conversion of around 80% was calculated from the epoxide signals at $\delta = 3.14$ and 2.79 ppm (integrating for 0.20H and 0.18H, respectively). Moreover, the MeO–Si signal, usually found at $\delta = 3.56$ ppm as an intense singlet, exhibited a change in its general appearance with the presence of smaller signals and an overall integration of 6H instead of 9H. As already suggested in the literature,[36] these observations are consistent with intra- and intermolecular trans-etherification reactions, which are responsible for the polymerization. These experiments can finally give structural evidence of this trans-etherification process, as confirmed by the spectroscopic data given in Fig. 3.

In addition, these preliminary studies showed clearly that the reactivity of a primary amine in the presence of GPTMS can afford ring-opening of the epoxide. Unfortunately, the resulting secondary alcohol can subsequently undergo intra- and

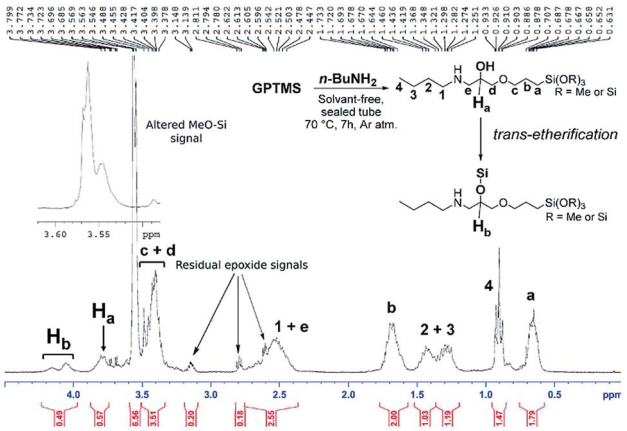
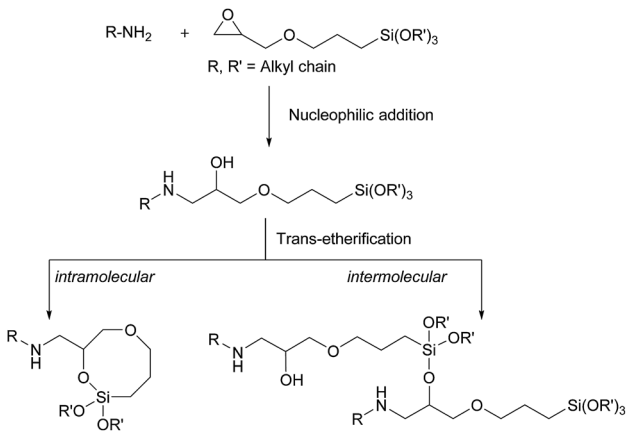


Fig. 3 ^{1}H NMR (300 MHz, $CDCl_3$) of the crude product of the reaction between *n*-butylamine and GPTMS after 7 h.



Scheme 2 Possible different reaction pathways for reactions between amine and (3-glycidyloxypropyl)trialkoxysilanes.

intermolecular trans-etherification with the alkoxysilanes (Scheme 2).

We then focused to similar procedures that are described in the synthesis of nanoparticles bearing different azamacrocyclic ligands by using GPTES instead of GPTMS. Interestingly, such reactions were not reported to produce side-reactions and the products were clearly described with full spectroscopic data (FTIR, ^{1}H and ^{13}C NMR and MS-ESI).[43] In this context, the reaction described in Scheme 3(a) was reproduced according to the described procedure. After hot dissolution of cyclam in toluene, a solution of GPTES in toluene was added and stirred for one day. The excess cyclam was removed by filtration at low temperature and the mother liquor was concentrated under vacuum to afford the crude azamacrocyclic ligand **3** in quantitative yield. The purity of the expected product was up to 95% and no further purification was needed. Following this protocol, the full characterization of the product we obtained (Fig. ESI_14–18†) is in accordance with the data provided in the literature.[43]

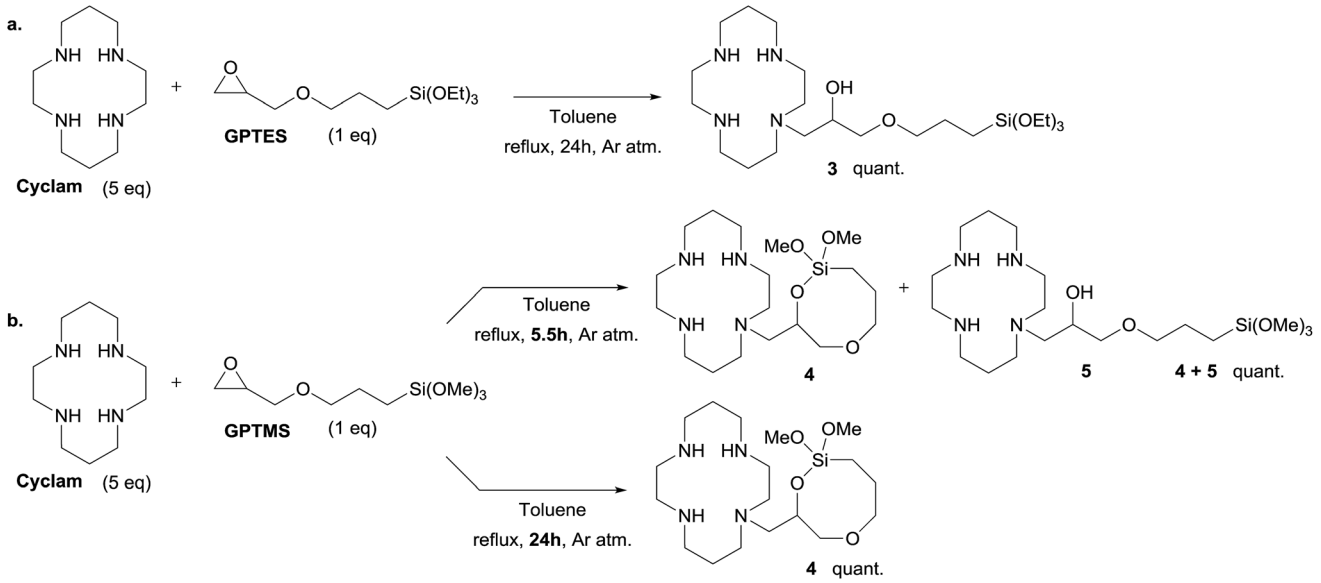
It is worth noting that neither hydrolysis nor trans-etherification between the generated secondary alcohol and ethoxysilane groups was observed. Therefore, different hypotheses could be postulated: (i) ethoxy groups increased the steric hindrance around the silicon atom sufficiently; (ii) the bulky character of the cyclam prevented side-reactions of the secondary alcohol with the silicon atom; (iii) a combination of the two previous hypotheses. In order to evaluate the steric effect of silicon substituents, we carried out the same reaction with GPTMS (Scheme 3(b)) using the published procedure.[43] No starting material was detected on TLC after 5.5 h and the reaction was stopped and treated as previously. A careful examination of the ^{1}H and ^{13}C NMR spectra revealed a complex mixture (Fig. ESI_149 and 150†). However, the main products could be identified from the MS-CI spectrum displayed in Fig. 4a (complementary spectra: Fig. ESI_151–152†).

In ascending order of *m*/*z*: a first peak at *m*/*z* 201.1 [M + H$^+$] (63%) and a low intensity peak at *m*/*z* 237.1 [M + H$^+$] (6%) correspond to residual cyclam and GPTMS, respectively; the highest peak at *m*/*z* 405.3 [M + H$^+$] (100%) matches the cyclic structure **4**, the last peak at *m*/*z* 437.3 [M + H$^+$] (21%) corresponds to compound **5** resulting from ring-opening of the epoxide. The structure of the compound **4** was also confirmed by NMR analysis (Fig. ESI_153 and 154†). As presented in Scheme 3, the cyclic compound **4** could arise from an intramolecular trans-etherification reaction from compound **5** between the secondary alcohol and a methoxysilane. Although the less favored intermolecular trans-etherification product was not observed, its formation might be possible under concentrated conditions.[36]

The same reaction was performed with a longer reaction time (24 h) to confirm that the intramolecular trans-etherification occurred after the substitution. The acquired ESI-MS spectrum presented in Fig. 4b revealed that the peak of the linear silane **5** at *m*/*z* 437.3 [M + H$^+$] was no longer present while the molecular peak at *m*/*z* 405.3 [M + H$^+$] (100%) of the cyclic silane **4** remained.

The conversion of the linear silane **5** over time seemed to favor the first hypothesis (i) highlighting that the steric hindrance around the silicon atom is a key factor for alkoxysilane stability. However, the second hypothesis (ii) cannot be completely ruled out at this point due to the particularly bulky structure of the cyclam molecule. Therefore, we carried out a complementary experiment with a simple amine to enable purification on silica-gel. Phenethylamine was selected and both reactions with GPTMS and GPTES were monitored. Whereas the reaction with GPTMS gave a complex mixture (Fig. ESI_155†), the reaction with GPTES showed full conversion after 18 h at reflux, as indicated by TLC (Fig. ESI_156†). After treatment, the reaction was immediately purified by flash chromatography to afford the two major products **6** and **7** as depicted in Scheme 4.[44]

In view of these results, some conclusions can be drawn about the reactions of amines in the presence of (3-glycidylpropyl)trialkoxysilanes. Firstly, it is important to point out that the reaction have to be carried out at reflux in toluene to proceed at a satisfactory rate. Secondly, the nucleophilic attack generated a secondary alcohol, which can be involved in intra- and intermolecular trans-etherification with the alkoxysilane



Scheme 3 Results for an excess of cyclam in reaction with (3-glycidyloxypropyl)trialkoxysilanes (a) on GPTES: chemoselective and efficient reaction leading to the azamacrocyclic adduct 3 in quantitative yield. (b) On the less stable GPTMS: loss of chemoselectivity and influence of the reaction time.

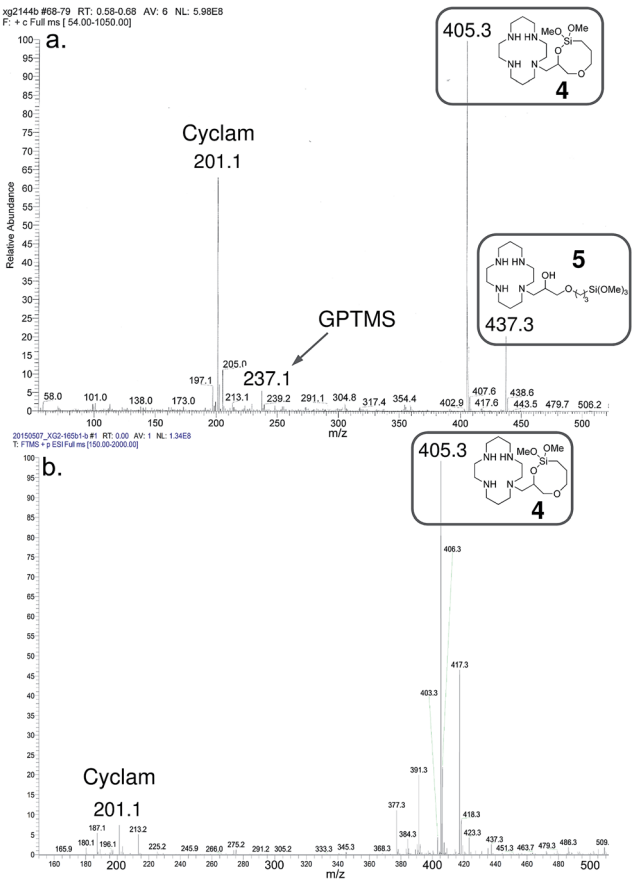
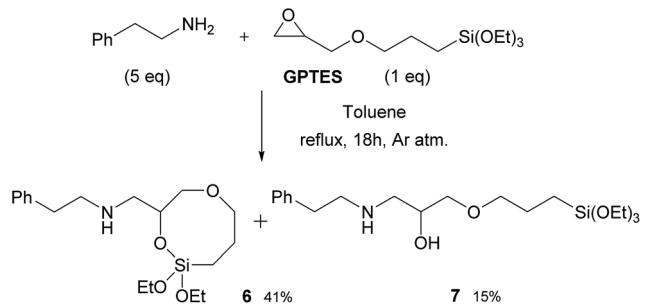


Fig. 4 MS spectra of the crude product of the reaction between cyclam and GPTMS after (a) 5.5 h and (b) 24 h.



Scheme 4 Reaction between less sterically hindered phenethylamine and GPTES.

groups, as previously demonstrated by the fully characterized experiments. However, it appeared that the steric hindrance of either the amine or the alkoxysilanes is a parameter that greatly influences the levels of trans-etherification. Therefore, silicon substituents could be interchanged with bulkier alkoxy groups, which could provide a useful tool to reach functionalized amines without altering the silane moiety.[45]

Thiols and thiolates as nucleophiles

The thiol function is often found in both natural products and synthetic compounds and can act as a potent nucleophile. In view of the results obtained with the amine series, their reactivity was similarly investigated with glycidyl alkoxysilanes.

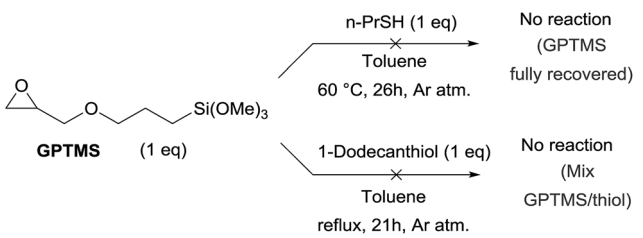
Thiols are known to be better nucleophiles than their homologous alcohols since the sulfur electrons are more easily polarizable. This nucleophilicity could potentially be strong enough to enable epoxide-opening according to various published studies but these results did not report any spectroscopic data to characterize the resulting compound of the reaction.[46,47]

For instance, precursors of hybrid materials containing lanthanide have been prepared by reaction of 4-mercaptobenzoic acid with GPTMS in DMF at 80 °C for 4 h. Another example is the synthesis of bridged precursors of mesoporous silica by reaction of (3-mercaptopropyl)triethoxysilane with GPTMS in toluene at 80 °C.[48] For better understanding of the reactivity of nucleophiles in presence of alkoxysilanes, we reinvestigated the behaviour of simple thiols derivatives with GPTMS under reaction conditions inspired by the literature (Scheme 5).[48]

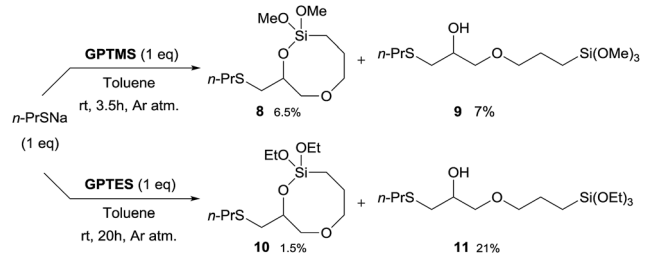
To explore the nucleophilicity effect, we selected *n*-propanethiol to react with GPTMS, as it is easy to eliminate under vacuum due to its volatility. The mercaptan was reacted with GPTMS in toluene at 60 °C instead of 80 °C, due to the boiling point of *n*-propanethiol (bp 67–68 °C). After 26 h, no reaction had occurred as indicated by TLC monitoring, so the reaction was stopped and the volatiles were removed by rotary evaporation. The ^{1}H NMR spectrum of the obtained crude oil was identical to that of GPTMS, with only trace amounts of other signals in the background. It could be firstly thought that the lower temperature prevented the required activation energy from being reached. Hence, the experiment was repeated with *n*-dodecanethiol, which has a higher boiling point (bp 266–283 °C), enabling heating at toluene reflux (110 °C). After 21 h, no reaction had occurred, as indicated by TLC monitoring; the reaction was stopped and the toluene removed by rotary-evaporation. By means of ^{1}H NMR analysis (Fig. ESI_157†), the resulting crude oil was found to be the simple superposition of the NMR spectra of the two starting materials: neither epoxide-opening nor alkoxysilane hydrolysis had occurred.

These data suggest questioning about previously described results in the literature and are consistent with the following two facts:[22] (i) alcohols, which have close reactivity (albeit less nucleophilic), do not react on the glycidyl pattern without activation; (ii) the ^{1}H NMR spectrum presented in the original reference shows the epoxide signals (DMSO-d_6, δ = 3.09, 2.71 and 2.50 ppm), which seem to be incorrectly assigned. The ^{1}H NMR spectrum displayed in this original reference is in accordance with our results, revealing a superposition of the two starting reagents.[22]

Since the ring-opening of the epoxide by the thiol group failed in these conditions, we decided to go further by studying their conjugated bases (thiolates), known to be better nucleophiles. Thus, sodium propylthiolate was reacted smoothly at room temperature in stoichiometric conditions with GPTMS or



Scheme 5 Reactions of thiol compounds in the presence of GPTMS.



Scheme 6 Reaction of sodium propylthiolate with (3-glycidyloxypropyl)trialkoxysilanes.

GPTES. After 3.5 h for GPTMS and 20 h for GPTES, no starting material was detected by TLC monitoring and the corresponding compounds **8**, **9** for GPTMS and **10**, **11** for GPTES, were obtained (Scheme 6).[49]

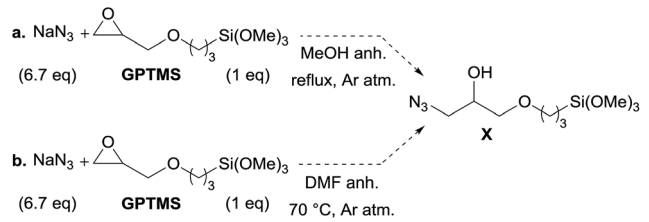
The ^{1}H NMR spectra of both reaction crude products (Fig. ESI_158 and 159†) displayed the C*H*(OH) signal at $\delta \approx$ 3.8–3.9 ppm for the linear silane and at $\delta \approx$ 4.1 ppm for its cyclic sub-product, confirming that a nucleophilic substitution had occurred. After purification by flash chromatography, these compounds were isolated as pure products, which were representative of the species observed in the ^{1}H NMR spectra of the crude. The low yields reported were due to a loss of material during the purification step. The structures of these compounds suggested a similar reaction pattern to the one previously described in the amine series. In fact, for the GPTMS reaction, the cyclic silane **8** and the corresponding former alcohol **9** were obtained in similar quantities. Concerning the GPTES reaction, the linear silane **10** was recovered in a much higher amount than its corresponding cyclic byproduct **11**, which was isolated in trace amounts. Once again, these results suggest that the nature of the alkoxy groups is determinant for the selectivity of the reactions using GPTMS or GPTES reagents.

Sodium azide as nucleophile

The copper-catalyzed Huisgen azide-alkyne cycloaddition is one of the most popular reactions in the click-chemistry field and has found several applications in the synthesis of hybrid materials.[50–52] As the availability of azido trialkoxysilanes is very limited, the introduction of the azido group into functional alkoxysilanes is of particular interest to give access to azido-functionalized precursors for hybrid synthesis. The use of sodium azide as a nucleophile is one of the most reported synthetic routes to introduce the azido function into organic compounds.[38] We investigated the epoxide ring-opening of glycidyl alkoxysilanes with sodium azide in homogeneous conditions (Scheme 7).

Based on the heterogeneous conditions in the literature (silica/NaN_3/GPTMS),[50] we carried out the reaction of GPTMS in the presence of an excess of sodium azide in homogeneous conditions without silica (Scheme 7a and b). Methanol was selected as solvent according to the source paper, and another attempt was tried with DMF to favor nucleophilic addition.

However, in both cases, the crude mixture could not be treated because of the degradation of the materials during



Scheme 7 Reaction of glycidyl alkoxysilanes in the presence of sodium azide in homogeneous conditions.

concentration under vacuum. Therefore, no crude analysis could be conducted. In order to overcome this limitation, the reaction was sampled regularly and monitored by ^{1}H NMR (Fig. 5a and b). Thus, methanol was substituted by deuterated methanol (CD_3OD) and for the DMF a pre-saturation technique was used to reduce its signals ($\delta = 2.65$ and 2.54 ppm).

Regarding the use of methanol as solvent, the ^{1}H NMR monitoring (Fig. 5a) revealed that, after only five minutes at reflux, the MeO–Si signal of starting GPTMS (an intense singlet at $\delta = 3.57$ ppm (9H)) had completely disappeared and a new methoxy signal integrating for 9H was observed at $\delta = 3.35$ ppm related to methanol release. Since the chemical environment of the silicon atom has significantly changed, the CH_2–Si signal also changed its appearance as the reaction progressed. These observations could be due either to substitution of all silicon substituents with azide anions or by trans-etherification with deuterated methanol.

Another valuable information was that the characteristic signals of the epoxide ring at $\delta = 3.13$, 2.78 and 2.59 ppm slowly

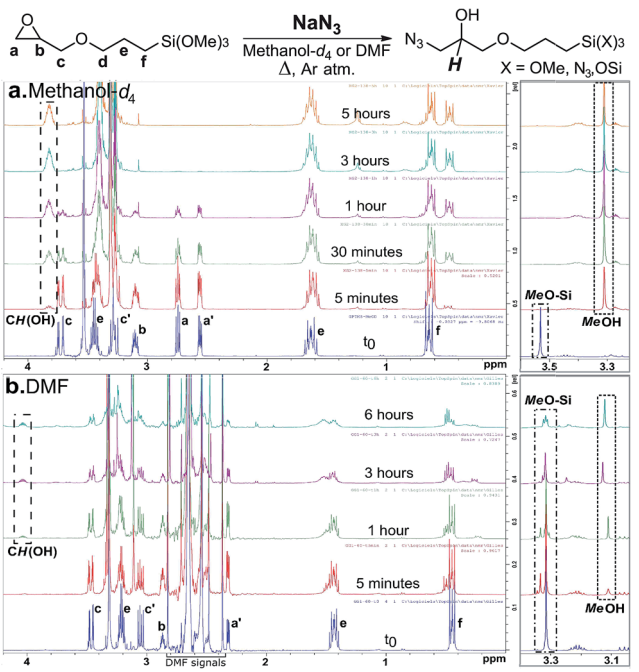


Fig. 5 ^{1}H NMR monitoring of the reaction between GPTMS and NaN_3 in (a) CD_3OD and (b) DMF with an inset of their corresponding methoxy areas.

decreased and finally disappeared after 5 h (Fig. ESI_160†). In the meantime, the distinctive C*H*(OH) signal ($\delta = 3.82$ ppm) was increasing to reach a maximum after the same time. These observations confirmed that the epoxide was slowly opened by an azide anion, as expected.[53]

In the case of DMF as solvent, ^{1}H NMR spectra (Fig. 5b) were acquired regularly over a period of 6 h. Similar changes to those observed in methanol were noticed, suggesting that the nucleophilic addition by azide anion had occurred. The epoxide signals at $\delta = 2.87$ and 2.32 ppm disappeared slowly while the C*H*(OH) signal at $\delta = 4.04$ ppm increased. During the reaction process, the MeO–Si signal at $\delta = 3.31$ ppm decreased as much as the methanol signal at $\delta = 3.11$ ppm increased, associated with methoxysilane hydrolysis.

Regarding our attempt in methanol-d_4, further ^{13}C NMR and MS analyses were carried out on the final solution to determine the structure of the newly formed compounds. Based on the ^{13}C NMR techniques, we observed a septuplet at $\delta = 48.70$ ppm, which is in accordance with the expected shift for CD_3O–Si (Fig. ESI_162†). This signal confirmed that the methoxysilane moieties were still present on the structure. Since the ^{13}C sequence is not a quantitative method, we could not determine the degree of substitution of silicon.

To complete the analysis and gain further insight into the structural identification, the experiment was carried out again in classic methanol and analyzed with MS techniques. Regarding the mass spectroscopy (ESI) analyses of the crude reaction, several species were identified from the spectrum displayed in Fig. 6 (complementary spectra: Fig. ESI_163–166†). The structures of the four main species (**C**, **D**, **F**, **G**) were identified and confirmed by HRMS. Multiple sub-species (**A**, **B**, **E**, **H**, **I**, **J**) were also identified.

Surprisingly, all these identifications showed that most of the exhibited structures suggest that the formation of azidosilanes is possible starting from alkoxysilanes (except for E and H). These results were quite unexpected because azidosilanes are more commonly prepared from halogenosilanes or from silane with a highly reactive trifluoroacetate intermediate.[54–56]

The addition of an excess of sodium azide was also achieved in the presence of the more stable glycidyl silane GPTES. After 5 h under the same reaction conditions, the mixture was analyzed by mass spectrometry (Fig. ESI_167†). The same peaks and species presented in Fig. 6 were found on the ESI-MS spectrum of the final mixture. The large excess of methanol probably induced a complete trans-etherification of ethoxysilane groups, leading in the first minutes to a GPTMS-like intermediate that reacted as previously described.

With PECS as reagent, the same reaction conditions also led to the rupture of the disiloxane bonds, thus destroying the square-like pattern and affording azido-substituted trimeric, dimeric and monomeric species (Fig. ESI_168–171†).

To summarize, the expected nucleophilic addition of an azide anion on the epoxide ring of the glycidyl silanes (GPTMS, GPTES and PECS) could be processed with an excess of sodium azide. However, mass spectrometry analyses revealed that the silane moieties can be affected by azide anions, giving rise to azidosilane derivatives. Since the

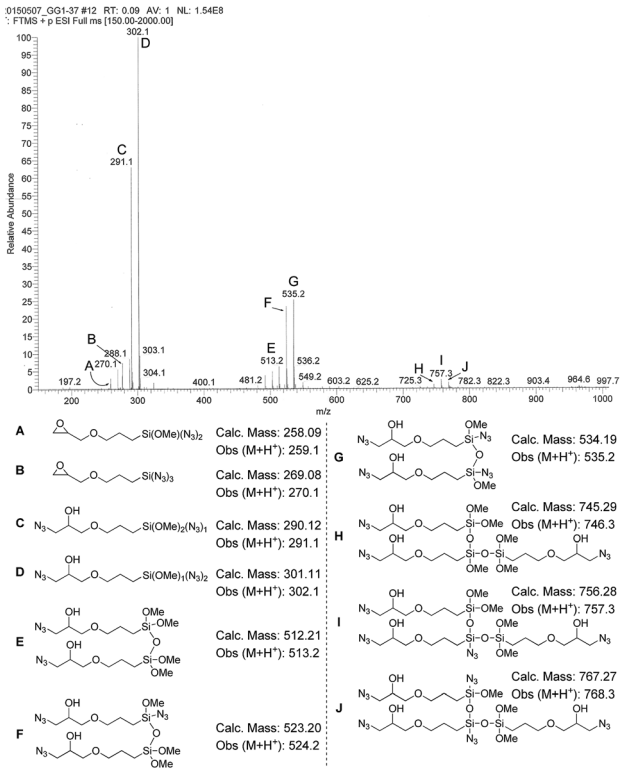


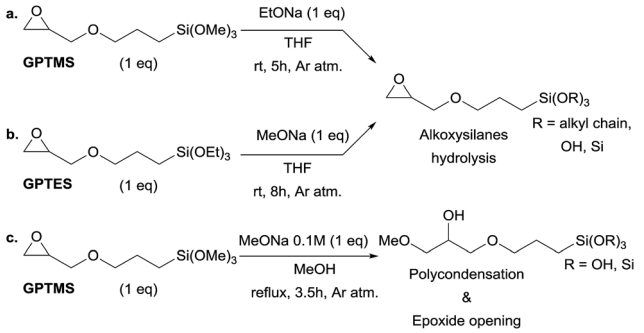
Fig. 6 ESI-MS spectrum of the reaction mixture after 5 h and the molecular structures of identified species.

formation of azidosilanes from alkoxysilanes has never been reported in the literature, further explorations could be considered to reveal a valuable strategy for the preparation of azidosilanes.

Alcohols and alkoxides as nucleophiles

Alcohols are probably the most reported nucleophiles in reactions with functional alkoxysilanes GPTMS and GPTES for the synthesis of nanostructures based on network formation around the silicon atom and functionalization of the epoxide moiety.[57–60] This dual reactivity could complicate the characterization of the reaction products and lead to missing or misinterpreted data analyses (NMR, MS) of their structures in the literature.[22] It is well known that alcohols are too weak nucleophiles for epoxide ring-opening reactions without activation.[32,61] Thus, the use of alkoxide reagents or activation of epoxide by acidic conditions is needed, but those conditions are potentially unsuitable for reagents bearing alkoxysilane moieties. We investigated the different procedures, and the structures of the products resulting from this type of reaction, with alcohol derivatives.

First, the reactions of alkoxides in the presence of (3-glycidyloxypropyl)trialkoxysilanes (GPTMS or GPTES) were performed by using protocols in organic solvent inspired from the literature.[58–60] These reactions were carried out in order to monitor by NMR analysis any substituent exchanges occurring on the silicon atom (Scheme 8).



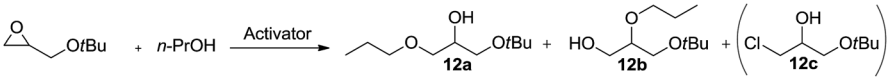
Scheme 8 Reaction of sodium alkoxide with GPTMS and GPTES.

To begin with, relatively mild conditions were tested (Scheme 8a and b). Thus, equimolar amounts of silane and sodium alkoxide were stirred in THF, at room temperature, and the reaction was monitored by TLC. After relatively short times in both cases (5 h and 8 h), the starting silanes were no longer detected by TLC analysis and the reactions were stopped. ^{1}H NMR spectra of the crude mixtures (Fig. ESI_172 and 173†) were very similar and exhibited no changes in the epoxide signals (δ = 3.14, 2.78 and 2.60 ppm). However, significant differences in the methoxysilane and ethoxysilane signals were noticed. For GPTMS, the MeO–Si integration value dropped from 9H to 4.6H and presented three major singlets. Moreover, no ethoxy signal was present on the spectrum. For GPTES, the EtO–Si integration values dropped from 9H and 6H to 6.6H and 4.4H and presented multiple signals. Moreover, no methoxy signal was present on the spectrum. All these observations suggest that no ring-opening occurred but that hydrolysis of the alkoxysilane groups took place. Next, GPTMS was reacted with sodium methoxide in refluxing methanol (Scheme 8c).

After 3.5 h at reflux and in stoichiometric conditions, a solid in suspension was observed and the crude ^{1}H NMR analysis (Fig. ESI_174†) showed the almost complete disappearance of the MeO–Si peak (δ = 3.56 ppm, 1.7H), with epoxide signals (δ = 3.13, 2.78 and 2.60 ppm) integrating for around 0.2H. The appearance of two multiplets at δ = 4.18 and 3.94 ppm integrating for 0.13H and 0.67H, respectively, was characteristic of the newly formed C*H*(OH) motif resulting from the ring-opening of the epoxide. Thus, the epoxide-opening reaction finally occurred but only after complete hydrolysis of the methoxysilanes.

Consequently, these homogeneous reaction conditions, leading simultaneously to functionalization of the epoxide and polycondensation, provided a viable alternative in specific cases (*e.g.* heterogeneous synthesis with silica).[50] However, these conditions were not appropriate for chemoselective ring-opening of the epoxide function with alcohols. Following these requirements, we looked at another alternative to favour epoxide ring-opening without affecting the alkoxysilane moieties by screening several Lewis acids as efficient catalysts for the ring-opening reaction. Boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) as well as other Lewis acids (*e.g.* $Al(OTf)_3$, $ZnCl_2$, $TiCl_4$, *etc.*) are all described in the literature as performing epoxide ring-opening efficiently.[62–67]

Table 1 Activated ring-opening reaction of *tert*-butylglycidyl ether in the presence of *n*-propanol



Entry	Activator	Reaction conditions	Ratio	Yields[a] [%]
1	$Cu(BF_4)_2 \cdot xH_2O$ (1 mol%)	Epoxide (1 eq.), ROH (1 eq.), PhMe, rt, Ar atm., 16 h	**12a : 12b** = 3.5 : 1[b,d]	**12a:** 13 and **12b:** 3
2	$Cu(BF_4)_2 \cdot xH_2O$ (1 mol%)	Epoxide (1 eq.), ROH (5 eq.), PhMe, rt, Ar atm., 16 h	**12a : 12b** = 4.3 : 1[b,d]	**12a:** 16 and **12b:** 4
3	$Cu(OTf)_2$ (10 mol%)	Epoxide (1 eq.), ROH (1 eq.), CH_2Cl_2, rt, Ar atm., 2 h	—	—[e]
4	$Al(OTf)_3$ (1 mol%)	Epoxide (1 eq.), ROH (1 eq.), PhMe, rt, Ar atm., 16 h	**12a : 12b** = 1 : 0[d]	**12a:** 14 and **12b:** 0
5	$BF_3 \cdot Et_2O$ (1 mol%)	Epoxide (1 eq.), ROH (1 eq.), CH_2Cl_2, rt, Ar atm., 0.5 h	**12a : 12b** = 4.3 : 1[b,d]	**12a:** 28 and **12b:** 5
6	$BF_3 \cdot Et_2O$ (1 mol%)	Epoxide (1 eq.), ROH (5 eq.), CH_2Cl_2, rt, Ar atm., 0.5 h	**12a : 12b** = 2.6 : 1[c]	**12a:** 69 and **12b:** 27
7	$ZnCl_2$ (60 mol%)	Epoxide (1 eq.), ROH (1 eq.), CH_2Cl_2, rt, Ar atm., 16 h	**12a : 12c** = 1 : 2.1[c,d]	**12a:** 21 and **12c:** 45
8	$ZnCl_2$ (100 mol%)	Epoxide (1 eq.), ROH (5 eq.), CH_2Cl_2, rt, Ar atm., 16 h	**12a : 12c** = 1 : 1[b]	**12a:** 21 and **12c:** 17
9	[EMIM][BF_4] (3.3 eq.)	Epoxide (1 eq.), ROH (1 eq.), 50 °C, Ar atm., 16 h	—	—[e]

[a] Yield of isolated product. [b] Ratio obtained from ^{1}H NMR integrations of the crude mixture. [c] Ratio calculated on isolated products. [d] Partial conversion. [e] ^{1}H NMR of the crude presented unchanged epoxide signals.

In this context, we carried out the ring-opening reaction in a model series using the commercially available *tert*-butylglycidyl ether in the presence of Lewis acids ($BF_3 \cdot Et_2O$, $ZnCl_2$, $Cu(BF_4)_2 \cdot xH_2O$, $Cu(OTf)_2$, $Al(OTf)_3$) (Table 1). The activated ring-opening reactions using copper- or aluminium-based catalysts were not successful resulting only in no or low conversion (entries 1–4). It is worth noting that the $BF_3 \cdot Et_2O$ catalyst afforded the best results in terms of conversion and yield (entries 5–6). Our first attempt using stoichiometric conditions of alcohol/epoxide in the presence of 1 mol% of Lewis acid (entry 5) afforded clean partial conversion and gave rise to both regioisomers **12a** and **12b** with an encouraging yield of 36%. By increasing the amount of alcohol (5 eq., entry 6), full conversion was observed after only 0.5 h and a quantitative yield was obtained (>95%). The regioselectivity seems to favour the secondary alcohol **12a**, resulting from the attack on the less sterically hindered position of the epoxide.

In the case of $ZnCl_2$ (entries 7–8), the reaction showed complete conversion with 100 mol% of the activator and the regioselectivity of the ring-opening reaction was excellent since the primary alcohol **12b** was not detected by NMR in the crude of the reaction. However, this method of activation unfortunately gave rise to the side-product **12c** from the nucleophilic attack of chloride on the epoxide. Because of the Lewis acid character of ethylmethylimidazolium tetrafluoroborate (EMIM BF_4), this ionic liquid was also used as solvent (entry 9), but no reaction was observed.

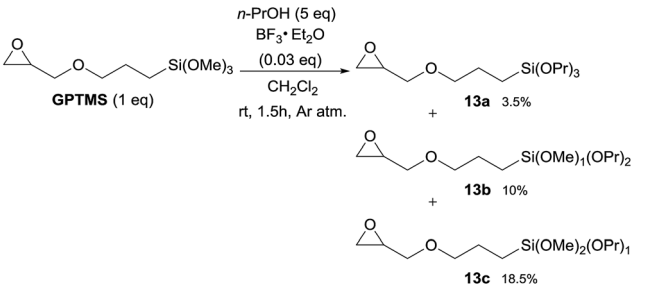
According to these preliminary studies on the glycidyl model, the ring-opening reaction of glycidyl alkoxysilanes was investigated in the presence of the Lewis acids $Cu(BF_4)_2 \cdot xH_2O$, $ZnCl_2$ and $BF_3 \cdot Et_2O$. Whereas the reactions with glycidyl silanes in the presence of $Cu(BF_4)_2 \cdot xH_2O$ afforded only intermolecular trans-etherification reactions (silicon substituent exchange) for GPTMS and GPTES, the use of $ZnCl_2$ revealed ring-opening reactions analogous to the results of the model series. In fact, the reactions afforded a mix of chlorine and alcohol adducts with various modified alkoxysilane moieties.[68] Interestingly, the reaction of *n*-propanol with glycidyl alkoxysilanes (GPTMS, GPTES, PECS) in the presence of $BF_3 \cdot Et_2O$ gave rise to the following results.

Catalytic activity of $BF_3 \cdot Et_2O$ with GPTMS as reagent

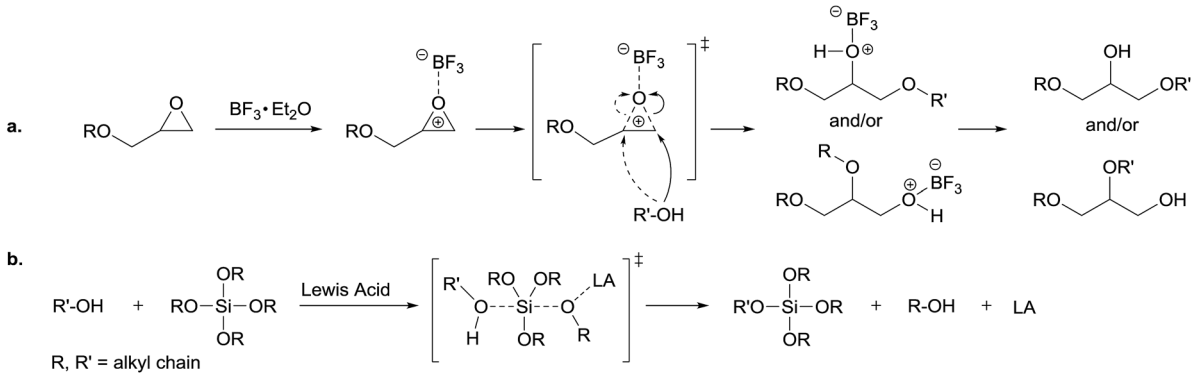
The reaction of GPTMS with *n*-propanol in the presence of $BF_3 \cdot Et_2O$ was carried out and the expected ring-opening of the GPTMS epoxide by *n*-propanol was not observed (Scheme 9).

The ^{1}H NMR spectrum of the crude mixture (Fig. ESI_175†) showed clearly that the epoxide signals remained unchanged. However, the ^{1}H NMR spectrum also exhibited changes in the methoxysilane signal intensity and the presence of propoxy signals. Three products **13a**, **13b** and **13c** were identified in the crude mixture and were fully characterized by NMR and HRMS after flash chromatography.[69] The resulting low yields are explained by partial decomposition of the compounds during silica-gel purifications.

Regarding the chemical structures of the compounds **13a**, **13b** and **13c**, these $BF_3 \cdot Et_2O$-catalyzed-reactions appeared to promote only trans-etherification reactions leading to mixed alkoxysilane derivatives (methoxy and propoxy). When the amount of catalyst was increased (up to 20 mol%), the reaction conditions favored the formation of (3-glycidyloxypropyl)



Scheme 9 Reaction of *n*-propanol with GPTMS in the presence of $BF_3 \cdot Et_2O$ catalyst.

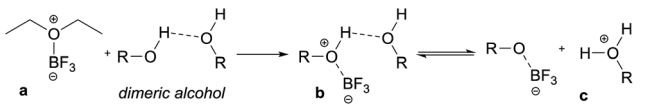


Scheme 10 (a) Classic mechanism for $BF_3 \cdot Et_2O$-catalyzed addition of alcohol on epoxide. (b) Lewis acid-catalyzed trans-etherification of alkoxysilanes through a penta-coordinated silicon transition state.

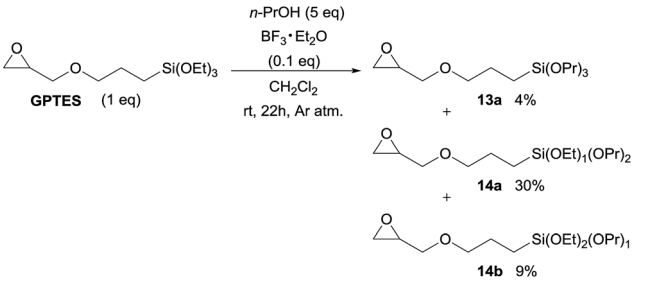
tripropoxysilane **13a** as sole compound, as attested by the ^1H NMR spectrum of the crude mixture (Fig. ESI_176†).

Based on the classic $BF_3 \cdot Et_2O$-catalyzed ring-opening reaction of epoxide (Scheme 10a), the BF_3 formed a complex with the epoxide oxygen, which consequently increased the ring electrophilicity. Then, the nucleophile (ROH in this case) could attack preferentially on the less hindered carbon. Obviously, this mechanism cannot explain the trans-etherification observed for compounds **13a–c**. However, the formation of these structures can be explained by plausible mechanisms of activation of epoxy functionalized alkoxysilanes by $BF_3 \cdot Et_2O$. In fact, trans-etherification reactions catalyzed by Brønsted or Lewis acids have already been described in the literature,[70,71] and involve the nucleophilic attack of the alcohol *via* a penta-coordinated silicon transition state (Scheme 10b). Rather than activating the epoxide ring, $BF_3 \cdot Et_2O$ might activate preferentially the alkoxysilane moiety. Furthermore, the activation mechanism of $BF_3 \cdot Et_2O$ in aprotic solvent has recently been reported.[72,73] According to these studies, BF_3 might react preferentially with the nucleophile in aprotic solvent giving rise to two complexes: $(ROH)_2 \cdot BF_3$ (Scheme 11 (complex **b**)) and $ROH \cdot BF_3$, the first one being more stable.

Hence, this activation pathway could lead to a catalytic amount of oxonium species (Scheme 11(c)) that could be considered strong acid. For instance, the conjugated acid of trifluoroethanol (CF_3–CH_2–OH_2^+) exhibits a calculated acidity in the range of H_2SO_4 and triflic acid, and thus showed to be a moderate superacid.[73] Since strong acids in anhydrous conditions (triflic acid, anhydrous HCl) could catalyze silicon alkoxide trans-etherification very efficiently, the *in situ* generation of catalytic amounts of these transient acidic species could promote the observed trans-etherification.[70]



Scheme 11 Suggested $BF_3 \cdot Et_2O$-catalyzed activation mechanism of alcohols in aprotic solvent involving (a) $BF_3 \cdot Et_2O$ (b) dimeric complex $(ROH)_2 \cdot BF_3$ and (c) acidic oxonium species ROH_2^+.



Scheme 12 Reaction of *n*-propanol with GPTES in the presence of $BF_3 \cdot Et_2O$ catalyst.

Catalytic activity of $BF_3 \cdot Et_2O$ with GPTES as reagent

Moreover, the $BF_3 \cdot Et_2O$-catalyzed reaction was similarly achieved using GPTES as the glycidyl silane (Scheme 12). Compared to GPTMS, larger amounts of catalyst (from 3 mol% up to 10 mol%) and longer reaction times (~20 h) were required to reach complete GPTES consumption. These observations could be attributed to an increased steric hindrance around the silicon atom as it is known that bulkier alkoxysilanes have significant consequences on trans-etherification levels.[42,71] In the case of 10 mol% $BF_3 \cdot Et_2O$ (Scheme 12), the results were very similar to the experiments with GPTMS. In fact, three compounds **13a**, **14a** and **14b** (representative of the crude) were isolated. Each compound resulted from a trans etherification reaction and no species presenting an opened epoxide was identified in the crude or after purification.

According to our results, we provided a better understanding of the covalent functionalization of (3-glycidyloxypropyl)trialkoxysilanes (GPTMS and GPTES) based on their dual reactivity. In fact, their reaction using the Lewis acid $BF_3 \cdot Et_2O$ afforded only trans-etherification compounds without altering the epoxide function. Consequently, some molecular structure reported in the literature could have been wrongly attributed to the corresponding macromolecules, as exemplified by a recent study of $BF_3 \cdot Et_2O$-catalyzed addition with *n*-octadecyl alcohol in the presence of GPTMS.[69,74]

Catalytic activity of $BF_3 \cdot Et_2O$ with PECS as reagent

In this context, we explored an alternative preparation of these glycidyloxypropylsilane derivatives using more chemoselective

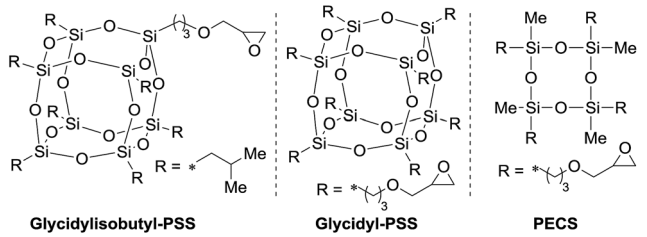


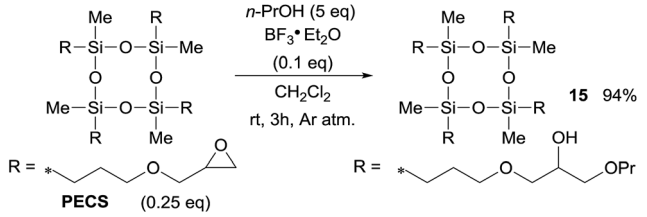
Fig. 7 Molecular structure of glycidyl polysilsesquioxanes (PSS) and polyglycidyl ether cyclosiloxane (PECS).

reactions. Thus, the functional polyhedralsilsesquioxanes (PSS) have a glycidyl function and could enable more selective reactions because of the better stability of disiloxane bonds compared to alkoxysilane groups. PSS are prepared by controlled polycondensation resulting in the replacement of alkoxysilane groups by disiloxane bonds. As depicted in Fig. 7, both valuable glycidyl functionalized PSS and the polyglycidyl ether cyclosiloxane (PECS) are represented. Because of its very close structural similarity to the two aforementioned PSS, PECS was selected in our study due to its commercial availability at a reasonable price.

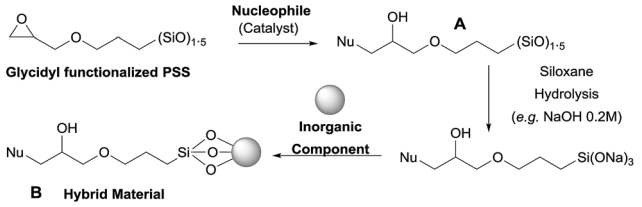
Whereas the $BF_3 \cdot Et_2O$-catalyzed epoxide self-polymerization of a pre-reacted sol of GPTMS and TEOS has already been reported,[23,24] we sought to exploit the stabilization of the silicon atom provided by disiloxane bonds to perform intermolecular nucleophilic addition reactions. In this context, the addition reaction of *n*-propanol with PECS was investigated in the presence of $BF_3 \cdot Et_2O$ as Lewis acid (Scheme 13).

PECS was reacted with an excess of *n*-propanol in the presence of 10 mol% of $BF_3 \cdot Et_2O$ at room temperature for 3 h and afforded the tetra alcohol-substituted cyclosiloxane **15** with a 94% yield after purification on silica-gel. The structure was confirmed by NMR and HRMS techniques (Fig. ESI_135–142†).

Whereas the trans-etherification reaction was predominantly observed in the (3-glycidyloxypropyl)trialkoxysilane series, the reaction with PECS showed exclusively ring-opening of the epoxide moiety. This confirmed the interest of having stable disiloxane bonds instead of alkoxysilane groups for the $BF_3 \cdot Et_2O$-catalyzed addition of alcohol on the epoxide function. These results could be of great importance for potential applications in hybrid synthesis with pre-grafted glycidyl alkoxysilanes (on inorganic material, *e.g.* mesoporous silica) or glycidyl PSS. The latter are advantageous since they could be purified after the functionalization and thus be unambiguously characterized.



Scheme 13 Reaction of *n*-propanol with PECS in the presence of $BF_3 \cdot Et_2O$ catalyst.



Scheme 14 Potential synthesis of hybrid materials using PSS derivatives.

Moreover, since siloxane bonds are sensitive to hydrolysis under certain conditions, a three-step strategy for the synthesis of well-defined organic–inorganic architectures with functional PSS as the starting reagent could be explored (Scheme 14).

In contrast to the usual one-pot heterogeneous synthesis, the advantage of this strategy would be the formation of an intermediate functionalized PSS (Scheme 14A), which could be well characterized by NMR and/or MS techniques. Therefore, this method would give greater confidence in the molecular structure of the final hybrid material (Scheme 14B).

Conclusions

Due to the challenge for the production of (3-glycidyloxypropyl) silane-based hybrid materials, the reactivities in organic media of three selected glycidyl silanes (GPTMS, GPTES, PECS) towards common nucleophiles were investigated in details by focusing on the purification and full characterization of the resulting compounds of the reaction. From the information gathered herein, the nucleophile properties combined with the mode of activation showed a great influence on the reaction outcomes in homogeneous conditions.

Specifically, the primary and secondary amines were shown nucleophilic enough to carry out epoxide-opening on (3-glycidyloxypropyl)trialkoxysilanes without catalytic activation, although intra- and/or intermolecular trans-etherification could occur depending on the structure of both entities. The steric hindrance around the silicon atom and the secondary alcohol generated by the ring-opening of the epoxide were the main factors controlling the level of intra- and/or intermolecular trans-etherification.

In contrast, it was demonstrated that thiols were not strong enough nucleophiles either to open the epoxide ring, even at high temperature, or to lead to side-reactions on the alkoxysilanes. In this context, it was necessary to use their conjugated bases to perform regioselective nucleophilic opening on the epoxide. A consecutive intramolecular trans-etherification leading to cyclic species was subsequently observed.

In the case of sodium azide as a strong nucleophile, a close monitoring study by ^1H NMR of homogeneous reactions in methanol and DMF demonstrated the ring-opening of the epoxide by azide anions but also showed major changes in the silicon atom environment. In addition, thorough ^{13}C NMR and MS analyses of the methanolic mixture revealed that these reaction conditions might lead to unexpected structures, with many identified species displaying at least one azide linked to the silicon.

Lastly, since alcohols could not perform the epoxide-opening, it was necessary to use their corresponding alkoxides. Nevertheless, polycondensation started to occur prior to the ring-opening reaction of (3-glycidyloxypropyl)trialkoxysilanes by alkoxides.

Our studies with Lewis acids were performed with the aim of functionalizing the epoxide without altering the alkoxysilane moieties. After screening different Lewis acids in a model series, $BF_3 \cdot Et_2O$ was selected as the most efficient catalyst. We demonstrated that reactions catalyzed with $BF_3 \cdot Et_2O$ led only to trans-etherification reactions on glycidyl alkoxysilanes and the plausible mechanisms of the reaction were discussed. Finally, in the case of glycidyl polysilsesquioxane, it is worth noting that $BF_3 \cdot Et_2O$ could catalyse efficiently and selectively the ring-opening of the epoxide by an alcohol with quantitative yield.

In summary, the dual reactivity of glycidyl alkoxysilanes could greatly complicate the reactions in the presence of nucleophiles: ring-opening *vs.* trans-etherification *vs.* polycondensation.

The choice of the nucleophile was crucial to perform ring-opening of the epoxide of glycidyl moieties and an additional activation was often needed: higher temperatures, more nucleophilic species (alkoxide instead of alcohols, for instance) or addition of Lewis acid.

The stability of the alkoxysilane function in the reaction conditions was critical to access pure compounds or well defined structures in hybrid materials.

Finally, original structures and unreported results have emerged from our studies that should be taken into consideration when looking at previous work in the literature.[22,69] The control of reactions involving glycidyl silane derivatives depended on key parameters that needed to be taken into account to reveal further molecular structures in hybrid synthesis. These key parameters enabled to improve the fine chemical control in our syntheses of biomaterials for tissue engineering.

Acknowledgements

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