Nucleophilic substitution on silica surfaces: Comparison of the reactivity of $\alpha$- versus $\gamma$-chlorosubstituted silanes in the reaction with sodium azide

Miriam KEPPELER,* Jürgen HOLZBOCK,* Johanna AKBARZADEH,** Herwig PETERLIK**, and Nicola HÜSING*,**,†

*Institute of Inorganic Chemistry I, Ulm University, Albert-Einstein-Allee 11, D-89069, Germany
**Faculty of Physics, University of Vienna, Strudlhofgasse 4, A-1090 Vienna, Austria
***Materials Chemistry, Paris-Lodron University Salzburg, Hellbrunner Str. 34, A-5020 Salzburg, Austria

Azido-group functionalized, hierarchically organized meso-/macroporous silica gels have been prepared through co-condensation of tetraalkoxysilane with chloromethyltrimethoxysilane or 3-(chloropropyl)triethoxysilane and subsequent conversion of the chloro groups. Azido functionalities have been obtained by nucleophilic substitution of the surface-bound chloro moieties with NaN$_3$ in N,N-dimethylformamide. A strong dependence of the later azide density (N$_3$ groups nm$^{-2}$) in the final material on the reaction conditions, such as temperature and time, but also on the spacer length (methylene versus propyl) of the organofunctional silane has been observed. In principle, the nucleophilic substitution benefits from higher reaction temperatures and times. However, while $\gamma$-azido groups seem to be stable over a wide range of reaction temperatures and longer reaction times, $\alpha$-azido moieties tend to decompose at temperatures above 60°C. The structural features of the monolithic gels and the azide functionalities on the surface were determined by IR-ATR-spectroscopy, elemental analyses, N$_2$-sorption analyses, small angle X-ray scattering and transmission electron microscopy.

Key-words : Sol–gel processing, Hybrid materials, Nucleophilic substitution, $\alpha$-silane, $\gamma$-silane, Azides

1. Introduction

Tailored porosity in inorganic–organic hybrid materials is of vital importance for a wide variety of applications, such as separation, adsorption, catalysis, energy storage, etc.¹⁻³ The combination of the structural characteristics of porous materials, such as high specific surface areas, uniform pore sizes, long range order of the pores or even tailored porosity on several length scales (micro-, meso- and macroporous size regime) with the possibility to deliberately and selectively functionalize the network to give inorganic–organic hybrid materials opens up almost unlimited possibilities.³ As the most prominent examples for hybrids, silica-based hybrid materials have been extensively investigated in the last decades.
iodopropyl-functionalities were converted to chloropropyl groups in such reaction conditions.\(^{17}\)

To get a versatile click-able material, the number and accessibility of introduced azides that belong to the most important functionalities for click reactions, is of great interest. Especially when a mesoporous material with pore diameters in the nanometer range is used, the spacer length between the silica surface and the azide functionality should be taken into account. Very short spacers are favoured for further modifications and reactions in such narrowly dimensioned pores. However, it has been shown that the spacer length might have a decisive influence on the chemical reactivity of a silane. The term \(\alpha\)-effect was introduced to describe the unique reactivity of \(\alpha\)-silanes at both the silicon atom and the functional group \(X\), however the \(\alpha\)-effect is not sharply defined and strongly depends on the nature of the substituents on the silicon atom.\(^{18-20}\)

In this study, we compare the reactivity of chloro-functionalized, porous and monolithic silica materials with a specific focus on the reactivity of the respective \(\alpha\)-chloro-functionalized silsesquioxane of the formula type \(\text{SiO}_{2/}\text{O}_{1/\text{SiCH}_{2}/\text{Cl}}\) compared to the analogous \(\gamma\)-silane based silsesquioxane \(\text{SiO}_{2/}\text{O}_{1/\text{Si(CH}_{3})_{2}/\text{Cl}}\) towards the nucleophilic substitution reaction in the presence of sodium azide. The influence of reaction temperature, reaction time, and surface chemistry (hydrophilic versus hydrophobic) will be investigated in detail.

2. Experimental Section

2.1 Materials

As silanes, tetraethyloxysilicate (TEOS, Fluka), 3-chloropropyl(triboxysilane (CPES, Aldrich), chloromethyl(trimethoxy)silane (CMTMS, Wacker Chemie AG), and chloro(trimethyl)silane (TMCS, Merck) were used without further purification. Ethylene glycol (EG, Aldrich) was purified by drying with \(\text{Na}_2\text{SO}_4\) and distillation from Mg. Pluronic P123 (\(M_w = 5800\)), \(\text{EO}_{2/\text{PO}_{10/\text{EO}_{20}}\text{(BASF), N,N-dimethylformamide (DMF, VWR) and Na}_{2/\text{N}}\text{(Merck) were applied without purification.}\)

2.2 Preparation of hexagonally organized mesoporous chloroalkyl-modified silica gels

Tetraethoxysilane (TEOS) was synthesized according to Brandhuber et al.\(^{21,22}\) Chloroalkyl-modified silica gels were prepared by co-condensation of TEOS and CMTMS or CPES in an aqueous reaction mixture containing Pluronic P123 as the structure-directing agent and \(\text{HCl}^{\text{(aq)}}\) as the catalyst. The percentage by weight ratio was \(\text{SiO}_{2/\text{P123/1M HCl/18/30/70 wt \%}}\) in which EGMS and CMTMS were used in a nominal molar ratio of either 9:1 (3.0 mmol CMTMS), 6:7:5 (4.5 mmol CMTMS) or 4:1 (6.0 mmol CMTMS) and EGMS and CPES in a nominal molar ratio of 9:1 (3.0 mmol CPES) according to Keppeler et al.\(^{15}\) The reaction mixture was homogenized for 1 min using a vortex stirrer to obtain a viscous white mixture, which was allowed to gel in a closed PE cylinder at 40°C and kept for 7 d at the same temperature for ageing. Removal of Pluronic P123, water and ethylene glycol was either conducted by immersion of the wet gels in a solution of 10 wt-\% of TMCS in petroleum ether (PE) for 24 h and subsequent washing with PE and ethanol; or simply by soaking in PE (3 times in 24 h), followed by washing with ethanol (3 times in 24 h).

2.3 Nucleophilic substitution

The wet chloroalkyl-modified silica gels were immersed into a saturated solution of Na\(_2\text{N}_3\) in DMF at different temperatures and several exposure times, and were subsequently washed by repeated immersion in water (five times within 24 h) and ethanol (three times within 48 h) to remove non-reacted Na\(_2\text{N}_3\). Drying of the wet silica gels was performed by simple evaporation of the solvent under reduced pressure.\(^{23}\)

2.4 Characterization

Specific surface areas were determined with \(N_2\)-sorption analyses on a NOVA 4000e (Quantachrome). Prior to analysis the samples were degassed at 60°C for 3 h. BET surface areas were evaluated using adsorption data in a relative pressure range from 0.05-0.30 with a 5-point-analysis. The amount of C, H and N on a percentage basis was determined by elemental analysis using an ELEMENTAR Varino. FT-IR-ATR (Fourier transform infrared spectroscopy in the attenuated total reflection mode) spectra were recorded on a Bruker Tensor 27. Small angle X-ray scattering (SAXS) measurements were performed with a Bruker Nano-Star using a pinhole camera with an X-ray generator (Cu \(K\alpha\) radiation monochromatized by cross-coupled Goebel mirrors, \(\text{U} = 40\text{ kV}, I = 35\text{ mA}\)). TEM investigations were performed on a Philips EM 400 (80 kV). The azide density \(N_2/\text{nm}^2\) on the surface was estimated by the specific surface area \(\text{SBET}\) and the percentage of nitrogen (assuming that the azide functionality is the only nitrogen-containing group in the sample) according to:

\[
\rho (\text{N}_2) = \frac{m_N \cdot N_A}{M_N \cdot 100 \cdot 3 \cdot \text{SBET} \cdot 10^{18}}
\]

Where \(m_N\) is the mass of nitrogen in 100 g of the silica gel, \(N_A\) is Avogadro’s constant, \(M_N\) is the molar mass of nitrogen and \(\text{SBET}\) is the specific surface area according to the Brunauer–Emmett–Teller (BET) model. The divisor 3 reflects that one azide group consists of three nitrogen atoms.

3. Results and discussion

As the silica source tetraethoxysilane (TEOS) was applied for two reasons: on one hand, the released glycol shows a better compatibility to the liquid crystalline phases of the structure-directing agent P123 compared to monoalcohols, such as ethanol from e.g. tetraethyl orthosilicate, and on the other no compatibilizing solvent is necessary and hydrolysis and condensation reactions can take place in a purely aqueous solution.\(^{13,14,21}\) For a better visualization, the resulting monoliths are presented in the ESL Fig. 1 for a pure silica example. For the investigation of the influence of the spacer chain length on the nucleophilic substitution reactions, chloro-substituted silica gels were prepared by a co-condensation approach.\(^{15}\) In principle several pathways could lead to azido-functionalized silica surfaces: 1) the surface grafting agent (3-azidopropyl)trialkoxysilane could be synthesized prior to sol–gel processing from 3-chloropropyltrialkoxysilanes.\(^{22}\) However, the \(\alpha\)-analogue has not been reported so far and a stronger influence of the azido moiety on the phase separation process and thus on the hierarchically organized network structure is expected; 2) Sol–gel processes could be catalyzed by HI instead of HCl to facilitate the formation of the azido functionalized surface in the nucleophilic halide-azido exchange. In this case a strong influence on the final network structure can be expected as has been shown recently by using HBr or HNO\(_3\) as the sol–gel catalyst.\(^{24,25}\) 3) The iodopropyl-derivatized silanes could be applied, but again in the presence of HCl halide exchange reactions are expected.\(^{17}\)

In our previous work, we already observed during sol–gel processing significant differences between the respective chloro-functionalized \(\alpha\)-silane, (\(\text{MeO}_{3/\text{SiCH}_2/\text{Cl}}\) (CMTMS), and the analogous \(\gamma\)-silane, (\(\text{EO}_{3/\text{Si(CH}_3)_2/\text{Cl}}\) (CPES), reflected in the
structural characteristics of the gel. Gels modified with chloromethyl groups typically exhibit higher specific surface areas (S\text{\text{BET}}) and larger mesopores with a narrower size distribution than samples prepared from chloropropyl-modified gels. Gels prepared with the γ-silane (EtO)\text{SiCH(CH}_3\text{)}Cl show a drastically decreased pore volume and a lower specific surface area compared to the CMTMS analogues. This can probably be attributed to a) the different reactivity towards hydrolysis and condensation, but b) also to the different polarities of the molecules. Nucleophilic substitution of chloride into azide in saturated solutions of NaN_3 in DMF either at 65°C for methylene-spacered samples or at 80°C for propylene-spacered samples have been conducted successfully. For the following discussion all data are taken from samples prepared from gels with a starting EGMS/CMTMS ratio of 6.75:1 and EGMS/CPES ratio of 9:1, except otherwise mentioned. This implies that the number of chloro-functionalities is intrinsically lower for the gels containing the γ-spacered function.

In our previous report we also observed a high tendency of the α-azide to degrade. In this study a more detailed investigation of the influence of reaction temperature (20, 40, 60, 80 and 100°C) and time (1, 2, 3, 4, 5 and 6 d) on the yield of the nucleophilic substitution reaction (SN-reaction) is presented. One has to keep in mind that in our case, the reaction with the azide is performed directly on the functionalized, highly porous monolithic body, thus limitations due to diffusion or accessibility of the active sites are expected and are accounted for by longer reaction times and higher temperatures than typically used. The samples that have been obtained after nucleophilic substitution with NaN_3 in DMF are azidomethyl- and azidopropyl-modified hierarchically organized silica gels comprising meso- and macropores (schematically shown in Fig. 1). These gels have been treated with trimethylchlorosilane (TMCS) in order to remove reactive silanol groups, extract the structure-directing agent (P123), and facilitate drying of the monoliths. Opaque, crack-free monolithic materials have been obtained as shown in Fig. 1, right.

The first part of the manuscript is devoted to the influence of the reaction temperature. Compared to a iodo functionality the chloro moiety is a suboptimal nucleofuge, requiring higher temperatures for the nucleophilic substitution. The reaction temperature was optimized with respect to the highest azide yields for both precursor gel systems. Lower reaction temperatures resulted in incomplete reaction, while higher reaction temperatures led to degradation of the functional units and thus, again to lower yields. In principle, the successful transformation of the chlorides into azides has been confirmed for all samples by IR-ATR spectroscopy (exemplarily shown for two samples in Fig. 2). A new vibration band at approximately 2100 cm\text{\textsuperscript{-1}} is detected by the antisymmetric stretching vibration of the cumulated double bond of the terminal azido groups.

As previously described, methylene-spacered samples tend to adsorb higher amounts of nitrogen during nitrogen sorption, have larger pore diameters (D\text{\text{H}N\text{D}B}) and slightly higher specific surface areas (S\text{\text{BET}}) compared to the propyl-spacered samples. The structural parameters for azido-modified silica gels obtained after exposure to DMF/NaN_3 for 2 d at different temperatures are exemplarily given in Table 1 (a complete overview of the structural parameters of azidoalkyl-modified samples synthesized with different exposure temperatures and times are listed in Table 1/ESI).

All samples exhibit isotherms with H1-hysteresis loop (ESI, Fig. 2) according to the classification of Sing, which is characteristic for mesoporous materials with a well pronounced long range ordering of the mesopores. These data indicate that the reaction temperature of the nucleophilic substitution reaction up to 60°C has no significant influence on the structural features of the hybrid silica gels. Above 80°C, the pore volumes and specific surface areas areas are slightly increasing. The hexagonal arrangement of the mesopores (especially for the CMTMS samples) is still unchanged as detected by TEM and SAXS measurements. TEM images illustrate the typical honeycomb structure of the pore entries or the long-ranged 2-dimensional pore channels. The SAXS pattern show higher order reflections with the characteristic sequence for a 2-dimensional hexagonal ordering of 1:3\textsuperscript{1/2}:2 \ldots (Fig. 3).

The final functionalization density with azido groups was determined by elemental analysis (Table 2). For the monolith sample treated for 2 days two different trends can be observed: Whereas the number of inserted azides per nm\textsuperscript{2} for propyl-spacered samples increases with increasing S\text{\text{BET}}-reaction temperature, a clear dependence on temperature for methylene-spacered samples is observed. Samples from CPES show an azide density of about 0.15 N_3 \text{nm}\textsuperscript{-2} at 20°C that is increased to 0.94 N_3 \text{nm}\textsuperscript{-2} by a S\text{\text{BET}}-reaction temperature of 100°C. For samples from CMTMS the obtained azide density for a reaction temperature of 20°C is in the range of 0.18 N_3 \text{nm}\textsuperscript{-2}, reaches a maximum at
60°C with 1.04 N₃ nm⁻² and lowers to 0.39 N₃ nm⁻² at 100°C. More information on samples treated with other exposure temperatures and times are listed in Table 2/ESI.

To obtain a better understanding of the influence of the reaction time, the number of treatment days for the SN reaction was varied from 1 to 6 days (see Table 1, ESI). Again, very clear trends, supporting the data obtained for a reaction time of 2 days, are obtained. For the γ-azides, the number of inserted γ-azides exhibits a saturation behavior at approximately 80°C (Fig. 4, left). Whereas for methylene-spacered samples a maximum of the α-azide density is obtained at the range of 60°C and 3 d, where an α-azide density of 1.18 N₃ nm⁻² is reached and a decrease of the α-azides density is observed at higher SN-reaction temperatures (Fig. 4, right). In addition, for the series at 100°C, the α-azide density continuously decreases with prolonged reaction time in the order of 0.39 (2 d), 0.27 (3 d), 0.19 (4 d), 0.15 (5 d) and 0.11 (6 d) N₃ nm⁻². To exclude an influence of the reaction medium (sodium azide in DMF), it has been exchanged to a fresh solution of saturated NaN₃ in DMF in one sample after two days. However, no influence on the yield of azides was observed. This indicates that γ-azides on nanostructured silica surfaces are more stable compared to α-azides; the latter ones tend to decompose, probably facilitated through higher temperatures and presumably due to a destabilization caused by the close proximity to the silicon center (γ-effect). It can be expected that in analogy to carbene formation from diazoalkanes, nitrenes are formed via thermolysis of the azide function, followed by further reactions.²⁸)

However, there is a great interest to synthesize azidomethyl-modified silica gels with a sufficient γ-azide density, because spacers as short as possible are favoured for further modifications and reaction in such narrowly dimensioned pore systems. The α-azide density can also be increased by simply applying a larger CMTMS concentration in the co-condensation reaction and thus provide a larger number of chloro-moieties for the reaction. The hexagonal arrangement of the mesopores and the high degree of order can be fully maintained by extending the CMTMS concentration up to 6.0 mmol.

Whereas for propyl-spacered samples a strong influence on the structure of the gel network is observed with increasing amount of CPES (the limit is around 3.0 mmol), this is not the case for the...
CMTMS modified silica samples. An increase of the CMTMS concentration in sol–gel processing from 3.0, 4.5 to 6.0 mmol CMTMS leads to the expected increase of the α-azide density, indicating, that there is a good accessibility of the chloro groups in the filigree nanostructured network (Fig. 5). Exemplarily, for silica gels prepared from a silica precursor solution containing 3.0 mmol CMTMS and subsequent SN-reaction at 60°C an α-azide density of 0.66 N₃ nm⁻² has been obtained. This value is increased to 1.34 N₃ nm⁻² by use of a silica precursor solution containing 6.0 mmol CMTMS and keeping the temperature of the SN-reaction constant at 60°C (Table 3). An interesting additional trend is that with increasing amount of CMTMS on the silica surface, the degradation of the α-azide is not as pronounced anymore, which is reflected by the absence of the maximum that was found for the samples with 3.0 mmol CMTMS at 60°C reaction temperature.

The latter point let us to have a closer look on the surface chemistry of the silica gels. Typically the gels are treated with TMCS, which reacts with free surface silanols to give a trimethylsilylated and hydrophobic surface. Simultaneously, the structure-directing agent is extracted from the gel body and drying upon preservation of the filigree structure is facilitated. However, it can be assumed that the inserted trimethylsilyl groups reduce the azide density, because of steric hindrance during the conversion of the chlorides into azides, which is especially true for methylene-spacered samples. Therefore, a close look has been given to samples, in which the template has been removed by extraction with ethanol and DMF. Here, a polar surface carrying a large amount of silanol groups and less sterically hindered α-chloro-functionalities is obtained. For these samples a slightly higher α-azide density has been found after nucleophilic substitution compared to the TMCS treated samples supporting the above made assumptions. Upon optimized synthesis conditions it is possible to generate a hexagonally organized mesoporous silica network modified with an α-azide density of more than 2.0 N₃ groups nm⁻² (6.0 mmol CMTMS, 60°C, template removal: extraction, Table 3).
The approach containing chloroalkyl-precursors and subsequent SN-reaction conditions in order to achieve the highest possible reactivity of the chloro- but also the stability of the inserted azide functionalities on the nanostructured surface strongly depends on the SN-temperature \( \text{[°C]} \). Over 100°C, the azidomethyl groups tend to decompose above propylene-based spacers. While azidopropyl groups are stable in these conditions, in addition to that a slightly increased trimethylsilyl groups is avoided.

**Table 3.** \( \alpha \)-Azide density depending on CMTMS concentration and the method of template removal (TMCS or extraction)

<table>
<thead>
<tr>
<th>( S_0 )-temperature [°C]</th>
<th>3.0 mmol CMTMS</th>
<th>4.5 mmol CMTMS</th>
<th>6.0 mmol CMTMS</th>
</tr>
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<tbody>
<tr>
<td>TMCS</td>
<td>extraction</td>
<td>TMCS</td>
<td>extraction</td>
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<tr>
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<td>0.59</td>
<td>0.61</td>
<td>0.69</td>
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<tr>
<td>50</td>
<td>0.63</td>
<td>0.70</td>
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<tr>
<td>55</td>
<td>0.69</td>
<td>0.76</td>
<td>1.11</td>
</tr>
<tr>
<td>60</td>
<td>0.66</td>
<td>0.77</td>
<td>1.20</td>
</tr>
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<td>70</td>
<td>0.74</td>
<td>0.92</td>
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**4. Conclusion**

In summary we could successfully demonstrate the synthesis of hexagonally organized mesoporous, azidoalkyl-functionalized silica gels (alkyl = methylene and propyl) via a co-condensation approach containing chloroalkyl-precursors. The reactivity of the chloro-, but also the stability of the inserted azide functionalities on the nanostructured surface strongly depends on the CH\(_2\)-spacer length, which was varied between methylene and propylene-based spacers. While azidopropyl groups are stable in these conditions, in addition to that a slightly increased trimethylsilyl groups is avoided.

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**References**


