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Enzyme-Catalyzed Transetherification of Alkoxysilanes

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Abstract: We report the first evidence of an enzyme-catalyzed transetherification of model alkoxysilanes. During an extensive enzymatic screening in the search for new biocatalysts for silicon-oxygen bond formation we found that certain enzymes promoted the transetherification of alkoxysilanes when tert-butanol or 1-octanol were used as the reaction solvents.

Keywords: enzyme; biomimetic catalysis; transetherification; alkoxysilane.

1. Introduction

Biotransformations are chemical processes which occur under the influence of biological materials such as peptides and proteins. Amongst the myriad examples of bio-mediated transformations we have focused our attention on enzyme-catalyzed reactions at a silicon centre.

In the literature, there are several examples of organo-silicon biotransformations, such as the selective synthesis of organosilicon esters under mild reaction conditions [1], enzymatic silicone oligomerization catalyzed by a lipid-coated lipase [2], and the hydrolysis of silatranes catalyzed by an esterase obtained from the yeast Rhodotorula mucilaginosa [3]. In addition, nature provides the many...
examples reactions from simple to very complex with Si-substrates, where peptides and proteins are generally considered to be the undisputed arbiters [4, 5]. Examples include silica formation in diatoms and other silica-forming organisms [4, 5].

Our group has extensively studied silica precipitation [6] and the enzyme-catalyzed hydrolysis and condensation of alxokysilanes [7, 8, 9] under mild conditions. We have discovered several enzymatic candidates which were able to perform such reactions at room temperature and neutral pH and have investigated the potential involvement of their respective active sites in the biocatalyzed organo-silicon transformations.

In this contribution, we report a new enzyme-mediated reaction, namely the transetherification of alxoxysilanes, under mild conditions.

2. Results and Discussion

During our previous work on enzyme-catalyzed organo-silicon transformations, we were interested in siloxane-bond formation in the presence of biocatalysts both in aqueous and aqueous-organic media. Several monophasic and biphasic aqueous-organic systems were investigated as reaction solvents. One of the biphasic-aqueous organic systems employed during the alxoxysilane studies consisted of 1-octanol saturated with tris-buffered water. In addition to the enzyme-catalyzed hydrolysis and condensation of alxoxysilanes [9], the formation of the octylsilyl ethers as a result of transetherification and/or silanol-alcohol condensation/exchange was observed in this solvent whereas no equivalent reaction was observed in the negative control reactions (Scheme 1). The “side-product” octyl-silyl ether was identified as a new peak which appeared in the gas-chromatogram following reaction and work-up when compared to our standard set of peaks which arise from solvents (THF, ethanol and 1-octanol), unreacted starting material, hydrolyzed silanol, and the disiloxane condensation product.

The identity of the structure was further investigated by means of GC-MS (not shown) and was confirmed to be the alkoxyoctylsilyl ether.

**Scheme 1.** Enzyme-catalyzed transetherification and/or silanol-alcohol condensation.
The reactions were formulated with approximately 5:1 alkoxysilane to enzyme weight ratio in wet (water-saturated) 1-octanol (5:1 solvent to alkoxysilane weight ratio) and conducted in inert glass vials. After 24 hours of stirring at room temperature, the reactions were filtered and analyzed by GC-FID. The gas chromatography analysis was performed with an Agilent 6890 Series injector on an Agilent 6890 plus gas chromatograph with a flame ionization detector. Dodecane was used as an internal standard to quantitate the chromatographic analyses. The samples were prepared at ~1% (w/w) product in a THF solution containing 1% (w/w) dodecane. Based on triplicate measurements, the response factors for the analytes were calculated, and determined to be linear as a function of concentration over four orders of magnitude (i.e. 0.01-10% w/w).

**Scheme 2:** Chemical synthesis of the octyl-silyl ethers.

![Scheme 2](image)

R₁ = methyl or phenyl

octyl-silyl ether

In order to chromatographically quantify the trimethyloctyloxysilane and phenyldimethyloctyloxysilane products, the two compounds had to be synthesized, as they were not commercially available. The synthetic procedures are detailed in the Experimental Section. In general, the appropriate chlorosilane was refluxed with 1-octanol in THF in the presence of triethylamine (Scheme 2). The products were subsequently purified by vacuum distillation, characterized and used as standard references in the gas-chromatography analyses.

As shown in Figure 1 and detailed in Tables 1-2, selected enzymes such as trypsin, *Rhizopus Oryzae* lipase (ROL) and lysozyme were able to catalyze the formation of the octyltrimethyl-silyl ether (Figure 1, top) and/or the octylphenyldimethylsilyl ether (Figure 1, bottom) after 24 hours at room temperature. In similar conditions, no condensation was observed in the negative control reactions.

**Figure 1:** Enzyme-catalyzed transetherification and/or silanol alcohol condensation/exchange study between trimethylethoxysilane (top figure) or phenyldimethylethoxysilane (bottom figure) with 1-octanol (blue bars) or tert-butanol (red bars), after 24 hours at 25 °C.
Figure 1 shows percentage yield of octyl-ether formation based on the quantitative chromatographic data, the mass balance being completed by either unreacted alkoxysilane, silanol formed by simple hydrolysis, or the corresponding disiloxane from the condensation product with another molecule of silanol (see Scheme 1). Notably, in the absence of any biocatalyst (negative control), no octyl-silyl ether was observed, denoting the critical role of the enzyme in the alkoxysilane transetherification transformation.

Table 1. Enzyme-catalyzed transetherification reactions between trimethylethoxysilane and 1-octanol or tert-butanol after 24 hours at 25 °C.

| Reaction                                           | % yield (normalized) |
|----------------------------------------------------|----------------------|
| negative control, 1-octanol                        | Me₃SiOEt¹ 91.3       |
| negative control, 5% water in tert-butanol         | Me₃SiOH² 5.3         |
| Rhizopus oryzae lipase, 1-octanol                  | HMDS³ 3.4            |
| Rhizopus oryzae lipase, 5% water in tert-butanol   | Me₃SiOR⁴ 0.0         |
| bovine pancreatic trypsin, 1-octanol               |                      |
| bovine pancreatic trypsin, 5% water in tert-butanol|                      |

¹ Me₃SiOEt = trimethylethoxysilane
² Me₃SiOH = trimethylsilanol
³ HMDS = hexamethyldisiloxane
⁴ Me₃SiOR = trimethyloctyloxysilane and trimethyl tertbutoxysilane in the 1-octanol and tert-butanol reactions, respectively
Table 2: Enzyme-catalyzed transetherification reactions between phenyldimethyethoxysilane and 1-octanol or tert-butanol after 24 hours at 25 °C.

| Reaction | PhMe₂SiOEt² | PhMe₂SiOH³ | (PhMe₂OSi)₂-O⁴ | PhMe₂SiOR⁵ |
|----------|-------------|-------------|----------------|-------------|
| negative control, 1-octanol | 100.0 | 0.0 | 0.0 | 0.0 |
| negative control, 5% water in tert-butanol | 88.8 | 11.2 | 0.0 | 0.0 |
| Rhizopus oryzae lipase, 1-octanol | 66.8 | 21.5 | 0.0 | 11.7 |
| Rhizopus oryzae lipase, 5% water in tert-butanol | 95.8 | 4.2 | 0.0 | 0.0 |
| chicken egg white lysozyme, 1-octanol | 3.2 | 55.0 | 0.0 | 41.8 |
| chicken egg white lysozyme, 5% water in tert-butanol | 71.5 | 28.5 | 0.0 | 0.0 |

1% Yield = qualitative (i.e. area percent) values

² PhMe₂SiOEt = phenyldimethyethoxysilane
³ PhMe₂SiOH = phenyldimethylsilanol
⁴ (PhMe₂OSi)₂-O = phenyldisiloxane
⁵ PhMe₂SiOR = = phenyldimethyloctyloxysilane and phenyldimethyltertbutoxy-silane in the 1-octanol and tert-butanol reactions, respectively

To our knowledge, this is the first case of an enzyme-mediated transetherification reaction of an organo-silicon substrate under mild conditions. It is apparent that there is advantage in using an enzyme at room temperature over the conventional synthetic procedure the synthesis of the octyl-silyl products by avoiding the use of harsh chemicals and elevated reaction temperature.

Interestingly, the enzymatic screening conducted during the hydrolysis and condensation study of monoalkoxysilanes in wet tert-butanol (see [9] and Figure1) did not lead to any tert-butylsilyl ether product formation. This may be due to the steric hindrance of tert-butyl groups, as opposed to the longer but more flexible octyl chains, which may be more accessible to the enzyme cavities. Notably, ROL was observed to catalyze both octyl ether formation. Lipases normally interact with long-chain alcohols and/or carboxylic acids as natural substrates. Our results show that ROL catalyzes the formation of octyl-silyl ethers. Conversely, the lipase was not able to catalyze the formation of tert-butyl silyl ethers. This is in agreement with the natural substrate-selectivity of the ROL, and suggests the involvement of the active site during the catalysis. Trypsin was a good biocatalyst for trimethyloctyl silyl ether formation, and this is in line with our previous studies on the alkoxysilane hydrolysis and condensation reactions [7, 9]. Lysozyme, which was already observed to be a good siloxane-bond biocatalyst [8], produced the highest yield of the phenyldimethyloctyl silyl ether in this study. The reason for the unusual selectivity of this glycoside hydrolase is not yet understood and will be the subject of further investigations. The work proves the potential of the use of (bio-)macromolecules as catalytic aids on unusual substrates under facile and mild reaction conditions.
3. Experimental Section

3.1. Materials

3.1.1. Synthesis of Trimethyloctyloxysilane

1-octanol (31.25g, 0.24mol) and triethylamine (24.28g, 0.24mol) were dissolved in anhydrous THF (300ml) under nitrogen in a 3-necked round-bottomed flask, and a solution of chlorotrimethylsilane (15.21g, 0.14mol) in anhydrous THF (100ml) was added dropwise to the mixture over one hour. After gently refluxing at approximately 70°C, a white solid precipitated (triethylammonium chloride). The solid was filtered off and the filtrate recovered. The solvent and excess triethylamine were removed using a rotary evaporator, and the transparent liquid purified by distillation at 120 °C and approximately 85 mbar. The product was characterized by NMR spectroscopy and GC-MS, and it was used as a GC-standard in order to understand the product distribution during the enzyme-catalyzed transesterification studies. Yield 67%. 1H NMR (CDCl3, 300 MHz): δ 3.45 (t, 2H, J 7.4, O-C\textsubscript{H}_2), 1.41 (m, 2H, OCH\textsubscript{2}-C\textsubscript{H}_2), 1.16 (m, 10H, OCH\textsubscript{2}CH\textsubscript{2}-(C\textsubscript{H}_2)_5), 0.77 (3H, t, J 7.4, O(CH\textsubscript{2})_7-C\textsubscript{H}_3) and 0.0 (s, 9H, Si(C\textsubscript{H}_3)_3) ppm. 13C NMR (CDCl3, 75.45 MHz) δ 63.2 (O-C\textsubscript{H}_2), 33.2 (OCH\textsubscript{2}-C\textsubscript{H}_2), 32.3 (OCH\textsubscript{2}CH\textsubscript{2}-C\textsubscript{H}_2), 29.8 (O(CH\textsubscript{2})_3-C\textsubscript{H}_2), 29.7 (O(CH\textsubscript{2})_4-C\textsubscript{H}_2), 26.3 (O(CH\textsubscript{2})_5-C\textsubscript{H}_2), 23.1 (O(CH\textsubscript{2})_6-C\textsubscript{H}_2), 14.5 (O(CH\textsubscript{2})_7-C\textsubscript{H}_3) and 0.0 (Si-(C\textsubscript{H}_3)_3) ppm. 29Si NMR (CDCl3, 79.3 MHz): δ 17.5 ppm. Mass m/z (EI) 202 (M^+), 187 (M^+-CH\textsubscript{3}). NMR data were consistent with those reported [10].

3.1.2. Synthesis of Phenyldimethyloctyloxysilane

1-octanol (28.65g, 0.22mol) and triethylamine (22.26g, 0.22mol) were dissolved in anhydrous THF (250ml) under nitrogen in a 3-necked round-bottomed flask and a solution of chlorodimethylphenylsilane (20.48g, 0.12mmol) in anhydrous THF (100ml) added dropwise to the mixture over one hour. After gently refluxing at approximately 70°C for 2 hours, the triethylammonium chloride was filtered off and the filtrate collected. After removing the solvent and excess of triethylamine using a rotary evaporator, the product was purified by distillation at 142 °C and approximately 85 mbar. The product was characterized by NMR spectroscopy and GC-MS and it was used as a GC-standard in order to understand the product distribution during the enzyme-catalyzed transesterification studies. Yield 44%. 1H NMR (CDCl3, 300 MHz): δ 7.22-7.02-7.01 (m, 5H, aromatic H), 3.26 (t, 2H, J 6.6, O-CH\textsubscript{2}), 1.17 (m, 2H, OCH\textsubscript{2}C\textsubscript{H}_2), 0.90 (m, 10H, OCH\textsubscript{2}CH\textsubscript{2}-(C\textsubscript{H}_2)_5), 0.51 (t, 3H, J 3.0, O(CH\textsubscript{2})_7-C\textsubscript{H}_3) and 0.0 (s, 6H, Si(CH\textsubscript{3})_2) ppm. 13C NMR (CDCl3, 75.45 MHz): δ 138.1-133.4-129.5-127.7 (aromatic C), 63.0 (O-CH\textsubscript{2}), 32.6 (OCH\textsubscript{2}C\textsubscript{H}_2), 31.8 (O(CH\textsubscript{2})_3-C\textsubscript{H}_2), 29.4 (O(CH\textsubscript{2})_3-C\textsubscript{H}_2), 29.2 (O(CH\textsubscript{2})_4-C\textsubscript{H}_2), 25.7 (O(CH\textsubscript{2})_5-C\textsubscript{H}_2), 22.6 (O(CH\textsubscript{2})_6-C\textsubscript{H}_2), 14.0 (O(CH\textsubscript{2})_7-C\textsubscript{H}_3) and -1.7 (Si-(CH\textsubscript{3})_3). 29Si NMR (CDCl3, 79.3 MHz): δ 7.5 ppm. Mass m/z (EI) 264 (M^+), 249 (M^+-CH\textsubscript{3}). NMR data were consistent with those reported [11].
3.2. Enzyme-Catalyzed Transetherification Reactions

The reactions were formulated with a 5:1 alkoxysilane (100mg) to enzyme (20mg) weight ratio in 0.5 g of alcohol (water-equilibrated 1-octanol or tert-butanol containing 5% (v/v) buffered water). Prior to analysis, the reactions were filtered through a Whatman Autovial® 5 0.45-µm Teflon® filter. The closed (screw capped) two-phase reactions were conducted in inert glass vials at 25 °C with magnetic stirring for 24 hours. The reaction products were isolated and analyzed by GC-FID (quantitative) and GC-MS (qualitative).

Control reactions are defined as non-enzymatic reactions. Specifically, experiments conducted in the absence of a protein are defined as negative control reactions.

3.3. Gas Chromatography-Flame Ionization Detection

The gas chromatography (GC) analyses were performed with an Agilent 6890 Series injector on an Agilent 6890 plus gas chromatograph (GC) with a flame-ionization detector (FID).

| Table 1: GC-FID experimental parameters. |
|----------------------------------------|
| Parameter                                | Setting                                                      |
| Carrier gas                             | 99.9995% Ultra high purity helium (UHP)                      |
| GC inlet, split                         | 250 °C, split ratio=100:1, constant flow (rate = 1.0ml/min.) |
| Detector                                | Flame ionization detector at 275 °C, H₂ = 40ml/min, Make up N₂ = 45ml/min. |
| GC column                               | HP-5MS crosslinked 5% phenylmethylsiloxane film (30m x 0.25mm, 0.25 µm film) |
| GC temperature program                  | 50(2) → 250 (8) @ 10 °C/min, 30 min total run time           |
| Internal standard                       | ~1%(w/w) dodecane in THF                                     |
| Data system                             | Agilent Technologies ChemStation                              |

The system was configured as detailed in Table 1. Dodecane was used as an internal standard to gravimetrically quantify the chromatographic analyses. The samples were prepared at ~1% (w/w) product in a THF solution containing 1% (w/w) dodecane. Based on triplicate measurements, the response factors for the analytes were calculated (Equation 1), and found to be linear as a function of concentration over four orders of magnitude (i.e. 0.01-10% (w/w) (Table 3).

\[ RF_{analyte} = \left( \frac{[analyte]}{Area_{analyte}} \right) \times \left( \frac{Area_{IS}/[IS]}{RF_{IS}} \right) \]  

where \( RF_{analyte} \) = response factor for the analyte, \([analyte] = concentration of the analyte, Area_{analyte} = peak area of the analyte, Area_{IS} = peak area of the internal standard, [IS] = concentration of the internal standard, \( RF_{IS} = response factor for the internal standard = 1 \). Equation 1 was then solved to quantitatively calculate the concentration of an analyte in the presence of an internal standard (Equation 2).
\[ [\text{analyte}] = (R_f^{\text{analyte}} \times \text{Area}^{\text{analyte}}) \times ([\text{IS}] / \text{Area}^{\text{IS}}) \]\hfill (2)

4. Gas Chromatography-Mass Spectrometry

The gas chromatography-mass spectrometry (GC-MS) analyses were performed with an Agilent 6890 Series injector on an Agilent 6890 plus gas chromatograph with a 5973 MS detector. The MS detector was autotuned with perfluorotributylamine (PFTBA) prior to analysis. The system was configured as detailed in Table 4.

Table 3: GC-FID analyte retention times and response factors.

| Analyte\(^1\)       | Retention Time (m) | Average | Standard Deviation | RSD\(^2\) |
|---------------------|--------------------|---------|--------------------|-----------|
| Me\(_3\)SiOEt       | 2.75               | 2.00    | 0.007              | 3.3%      |
| Me\(_3\)SiOH        | 2.63               | 2.35    | 0.091              | 3.9%      |
| HMDS                | 3.22               | 2.01    | 0.052              | 2.6%      |
| PhMe\(_2\)SiOEt     | 10.37              | 1.35    | 0.007              | 0.5%      |
| PhMe\(_2\)SiOH      | 9.92               | ND      | ND                 | ND        |
| phenyl disiloxane   | 17.42              | ND      | ND                 | ND        |
| PhMe\(_2\)SiO(CH\(_2\)_7)CH\(_3\) | 17.48           | 2.02    | 0.038              | 0.2%      |
| Me\(_3\)SiO(CH\(_2\)_7)CH\(_3\) | 10.97           | 2.15    | 0.027              | 1.3%      |
| dodecane            | 11.11              | 1.00    | ---                | ---       |

\(^1\) Me\(_3\)SiOEt = trimethylethoxysilane, Me\(_3\)SiOH = trimethylsilanol, HMDS = hexamethyldisiloxane, PhMe\(_2\)SiOEt = phenyldimethylethoxysilane, PhMe\(_2\)SiOH = phenyldimethylsilanol, phenyl disiloxane = diphenyltetramethyldisiloxane, PhMe\(_2\)SiO(CH\(_2\)_7)CH\(_3\) = phenyldimethyloctyloxysilane, Me\(_3\)SiO(CH\(_2\)_7)CH\(_3\) = trimethyloctyloxysilane, dodecane = internal standard.

\(^2\) RSD = relative standard deviation

Table 4: GC-MS Experimental Parameters.

| Parameter                   | Setting                                      |
|-----------------------------|----------------------------------------------|
| Carrier gas                 | 99.999% high purity helium                   |
| GC inlet, split             | 250 °C, split ratio= 50:1, constant flow (rate = 1.0 mL/min.) |
| GC column                   | HP-5MS crosslinked 5% phenyl methylsiloxane film (30m x 0.25mm, 0.25 um film) |
| GC temperature program      | 50(2) \(\rightarrow\) 250 (8) \(@\) 10 °C/min, 30 min total run time |
| GC-MS transfer line temperature | 350 °C                                      |
| MS ionization               | electron impact                              |
| MS full scanning mass range | 15-500 amu, 1 scan/sec                       |
4. Conclusions

The use of wet 1-octanol as a solvent system for the enzyme-catalyzed hydrolysis and condensation of alkoxysilanes led to the observation that some enzymatic candidates promoted the transetherification and/or alcohol exchange of alkoxysilanes. To our knowledge, this is the first example of a biocatalyzed process leading to the synthesis of a new alkoxysilane. The route offers a clear example for further expanding the potential of bio-catalyzed reactions at a silicon centre and would offer several advantages with respect to conventional chemical procedures, such as benign reaction conditions and the use of non-toxic catalysts. Further studies with different alcohols and in the absence of water are planned to explore the full potential of this novel biomimetic transetherification.

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Conflict of Interest

The authors declare no conflict of interest.

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