Silicon and silicon oxide surface modification using thiamine-catalyzed benzoin condensations

Kelly A. Hoop, David C. Kennedy, Trevor Mishki, Gregory P. Lopinski, and John Paul Pezacki

Abstract: The benzoin condensation that involves the umpolung coupling of two aldehyde groups has been applied to the formation of functionalized silicon and silicon oxide surfaces using thiamine and other N-heterocyclic carbene (NHC) catalysis in water. This bioorthogonal conjugation of an aldehyde to a modified silicon or silicon oxide surface has been monitored and characterized using X-ray photoelectron spectroscopy and IR spectroscopy. NHC catalysis was found to be efficient in water mediating full conversion of the aldehyde functionalized silicon oxide surfaces at the interface.

Key words: "click" chemistry, benzoin condensation, silicon, surface functionalization.

Résumé : Dans le but de préparer des surfaces de silicium et d'oxydes de silicium fonctionnalisées, on a fait appel à une réaction de condensation de type benzoïne impliquant un couplage avec inversion de polarité de deux groupes aldéhydes, effectuée en solution aqueuse en présence de thiamine et d'autres carbènes N-hétérocycliques (CNH) utilisés comme catalyseurs. On a contrôlé la conjugaison bioorthogonale d'un aldéhyde à une surface de silicium ou d'oxyde de silicium modifiée et on l'a caractérisée en faisant appel à la spectroscopie photoélectronique des rayons-X et à la spectroscopie infrarouge. On a observé que la catalyse par des carbènes N-hétérocycliques est efficace dans l'eau pour conduire à une conversion complète des surfaces d'oxyde de silicium fonctionnalisées par un aldéhyde à l'interface.

Mots-clés : « chimie à clic », condensation de type benzoïne, silicium, fonctionnalisation d'une surface.

[Traduit par la Rédaction]

The development of organic reactions on silicon and silicon oxide surfaces is a highly active area of research because of the potential impact of the resulting new materials on applications in molecular electronics, biosensor development, and microarray technologies.[1] Considerable effort has been invested into building functional substrates onto silicon oxide surfaces at the nanoscale, leading to the development of several silicon oxide-bound systems for use on both particles and chips.[1,2] The most common techniques for the formation of monolayers on hydrogen-terminated silicon include: UV irradiation of alcohols and aldehydes, radical reactions of olefins using a radical initiator, or reactions with acylchlorides, which can then be further functionalized.[3] Silanes have been used for many years as a means to attach organic molecules to silicon oxide or glass and remain an important reagent in the fabrication of modified surfaces.[2] Currently, the techniques available to functionalize surfaces with biomolecules such as proteins are limited. Thus, there is a need to develop reactions that work well under aqueous conditions and that can be adapted to silicon surfaces.

Current strategies include physical, bioaffinity, and covalent immobilization.[4] Covalent immobilization, where a biomolecule such as a protein is directly attached to the surface via a newly formed covalent bond, offers advantages over other immobilization strategies. In particular, it allows for specific orientation of molecules at the surface and thus the generation of a homogenous surface. Also, unlike bioaffinity immobilization, the coupling partners employed in covalent immobilization can be relatively small, thus minimizing the chance that they will affect the structure and activity of the molecule being attached to the surface.

Covalent immobilization approaches for biomolecule attachment to silicon surfaces typically make use of highly specific bioorthogonal chemical reactions where functional groups not found in biology are used to specifically label and immobilize biomolecules.[4] While this approach offers many advantages, there exists only a handful of reactions that can be employed in a bioorthogonal manner.[4] The benzoin condensation, originally published in 1832 by Wöhler and Liebig,[5] represents a possible alternative for covalent coupling reactions onto silicon surfaces. The benzoin condensation involves the coupling of two aromatic aldehydes to form an α-hydroxy ketone via activation by cyanide.[5] The mechanism for this transformation was later elucidated by

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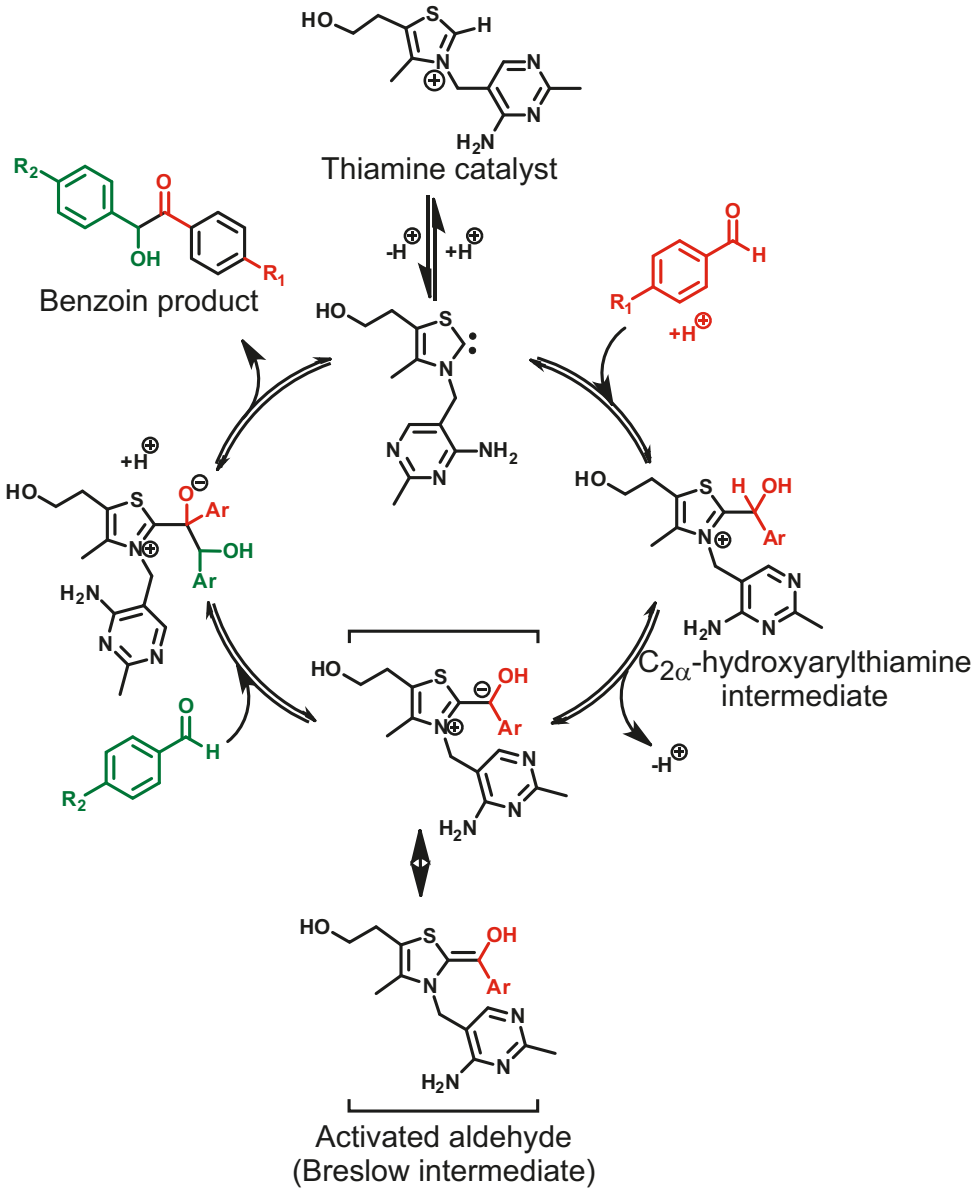
This paper is dedicated to Professor Ronald Kluger on the occasion of his 65th birthday.

Fig. 1. Catalytic cycle for thiamine-catalyzed benzoin condensation.



Lapworth in 1903.[6] Thiamine (vitamin B_1) is a naturally occurring water soluble compound that is also an effective catalyst for the benzoin reaction and was studied extensively by Breslow.[7] A reaction mechanism for the benzoin condensation catalyzed by thiamine is shown in Fig. 1. N-Heterocyclic carbenes (NHC) can also catalyze the benzoin reaction.[8–10]

Current research into benzoin-type reactions has shown that many NHCs similar to thiamine can also catalyze the reaction in polar protic solvents.[8,11,12] Moreover, recent advances have helped to make these transformations both asymmetric and also chemoselective for cross-coupled products.[9,10,13–17] Thiamine itself was also used to efficiently cross-couple different aldehydes as an enzyme complex with enzymes benzaldehyde lyase (BAL) and benzoylformate decarboxylase (BFD).[18] These findings suggest that the benzoin condensation may be a good candidate for further development as a reaction for covalent immobilization onto surfaces, since the catalysts are nontoxic, biocompatible, and aromatic aldehydes are functional groups not frequently found in commonly used model biological systems and offer an alternative to other click reactions.[19–37] A key nontrivial challenge is to determine the conditions under which the cross-coupling products are favoured in aqueous solution. We were interested in exploring conditions specifically for conjugating molecules to surfaces that have potential for future applications in biosensor and microarray functionalization. Herein, we describe the development of methodology using thiamine and NHC-catalyzed cross-coupling of aromatic aldehydes onto both hydrogen-terminated silicon and silicon oxide surfaces.

Results

Thiamine-catalyzed benzoin condensations were conducted on silicon oxide surfaces to determine the reactivity at the solid–liquid interface. Para-substituted benzaldehydes were used to test the electronic properties of the aldehydes for

rapid functionalization of the silicon surfaces. Benzaldehyde, 4-nitrobenzaldehyde, and 4-methoxybenzaldehyde were used in thiamine-catalyzed benzoin condensations on silicon oxide surfaces according to the sequence in Fig. 2 and are described in detail in the Experimental section. The optimal coupling involved reactions with 4-methoxybenzaldehyde by FTIR. No reactions were observed in the absense of catalyst or of 4-methoxybenzaldehyde.

FTIR analysis of samples

Thiamine was used to couple 4-methoxybenzaldehyde to the model surfaces of silicon oxide attenuated total reflection (ATR) chips to facilitate the measurement of changes in IR vibrational fequencies during the chemical reactions by FTIR. An ATR chip was prepared to afford the aldehyde surfaces shown in Fig. 2. Peaks in the FTIR spectrum (Fig. 3) of this surface agreed with the proposed bonding pattern with the peak at 1645 cm^{-1} corresponding to the imine C=N stretching mode,[38–40] the small peak observed at 1606 cm^{-1} associated with a vibrational mode of the phenyl ring, and the peak at 1703 cm^{-1} corresponding to the C=O stretching of the substituted benzaldheyde.[40] The ATR chip was then subjected to the benzoin condensation using the optimized reaction conditions with thiamine and 4-methoxybenzaldehyde and the reaction progress was monitored by FTIR (Fig. 3). After 4 h, the aldehyde peak at 1703 cm^{-1} was considerably reduced and, after 24 h, the aldehyde peak was no longer visible, whereas the peak at 1606 cm^{-1} had grown considerably, which is to be expected for the additional phenyl ring in the benzoin product. The carbonyl stretching vibration for the benzoin product[38,39] was masked by the imine peak of the linker. Control experiments were carried out where an imine-linker aldehyde surface ATR chip was immersed in benzoin reaction conditions including 4-methoxybenzaldehyde and TEA in water, but without the thiamine catalyst and separately without aldehyde. After 4 h under these conditions, the IR spectrum was unchanged, indicating that the changes in the IR spectra in Fig. 3 are the result of the benzoin condensation. The native oxide surface was exposed to the same reaction conditions to rule out nonspecific absorption. Again no new peaks were observed in the FTIR spectrum.

To test whether a bulkier group would be tolerated at the para position, a tether bearing electron-rich benzaldehyde 4-[2-(2-hydroxyethoxy)ethylamino]benzaldehyde was synthesized to mimic the electronics of the 4-methoxybenzaldehyde and to be a potential tether in future experiments. Thiamine was then used to catalyze the coupling of 4-[2-(2-hydroxyethoxy)ethylamino]benzaldehyde to the aldehyde-terminated ATR chip surface prepared according to Fig. 2. The reaction proceeded at a similar rate to that with 4-methoxybenzaldehyde. Again, the aldehyde carbonyl peak at 1703 cm^{-1} was greatly reduced after 4 h and no longer visible after 24 h (Fig. 4). A peak at 1605 cm^{-1} corresponding to the phenyl group was also present, as observed previously.

4-Fluorobenzaldehyde was also coupled to an aldehyde-terminated surface of an ATR chip using thiamine as a catalyst to test whether an electron-deficient aldehyde would affect the rate of the reaction. The reaction proceeded more slowly (Fig. 5), which was surprising given that it is more electrophilic. The reaction took approximately 6 times longer to reach completion. After 24 h the aldehyde carbonyl peak was no longer visible, and the remaining spectral features were consistent with those observed for the analogous reaction with 4-methoxybenzaldehyde.

A total of 11 NHCs,[3,7,41–46] all of which were already known catalysts of benzoin-type reactions in organic media, were tested in solution-based experiments towards the coupling of 4-methoxybenzaldehyde to the model surface. Of those tested, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (Fig. 6) was found to be the most efficient and was tested with the aldehyde surface in Fig. 2. Reaction conditions were adjusted to use only 1 equiv of base to fully deprotonate this NHC as opposed to the 2 equiv required with thiamine hydrochloride. After 4 h, the FTIR spectrum showed the reaction to be complete, since the aldehyde carbonyl peak at 1703 cm^{-1} was no longer visible and the phenyl peak at 1606 cm^{-1} had increased in intensity, corresponding to the increase of the second phenyl ring. The 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride catalyst appeared to be a better catalyst than thiamine for the cross-coupling of aldehydes at the solid–liquid interface.

X-ray photoelectron spectroscopy characterization of thiamine-catalyzed coupling reactions

The condensation of 4-fluorobenzaldehyde onto the surface was also monitored by using X-ray photoelectron spectroscopy (XPS). After 24 h under thiamine-catalyzed reaction conditions with 4-fluorobenzaldehyde, XPS scans of the imine-linker aldehyde surface (Fig. 5) showed the appearance of an F 1s signal at ~688 eV that is absent in scans of the surface prior to the reaction. A control experiment, where the surface was exposed to reaction conditions without thiamine, was carried out and detected fluorine at near background levels. To determine the amount of benzoin product formed on the surface, the N/F ratio of the final surface was determined. To calculate this ratio, sensitivity factors relative to carbon for both nitrogen (1.68) and fluorine (4) had to be considered.[47] The ratios were obtained by multiplying the observed intensity ratio from high-resolution scans by the inverse ratio of the sensitivity factors. The N/F ratio was found to be 4.7 for the benzoin-coated wafer (where the theoretical ratio should be 1) and 10.0 for the control wafer. The high N/F ratio indicates that not all of the terminal aldehydes reacted to form a benzoin product.

To enhance the fluorine reporter signal, 4-(trifluoromethyl) benzaldehyde was used in place of 4-fluorobenzaldehyde. In the survey scan of the reacted surface (Fig. 7), the F 1s signal at 688 eV was much larger than previously observed with 4-fluorobenzaldehyde. A high-resolution scan of the F 1s region showed that the reacted surface had a fourfold increase of fluorine emission over the control. The N/F ratio for the final functionalized surface was calculated to be 1.4 (the theoretical ratio should be 0.33) compared with 2.5 for the control wafer. Additionally, a high-resolution scan of the C 1s region showed an additional signal at 294 binding eV, which can be associated to a CF_3 carbon. An F/C_{CF_3} ratio of 3 was calculated (using sensitivity factors of 4 and 1 for F and C, respectively) which agrees with the theoretical value. Using the entire C 1s region between 282 and 295 binding eV, the calculated C/F ratio was 11.5 compared with a theoretical ratio of 6.3 for the benzoin product.

Fig. 2. Schematic of the reaction sequence for functionalizing silicon oxide surfaces using the thiamine-catalyzed benzoin condensation. The surfaces were first treated with 3-aminopropyltriethoxysilane (APTES) (step a), followed by reaction with 1 mmol/L aqueous terephthalaldehyde (step b), and benzoin condensation reactions were performed in an aqueous solution with substituted benzaldehydes, 1 equiv thiamine, and 2 equiv TEA with para-substituted aldehydes (substituents represented by X) as shown in step c.

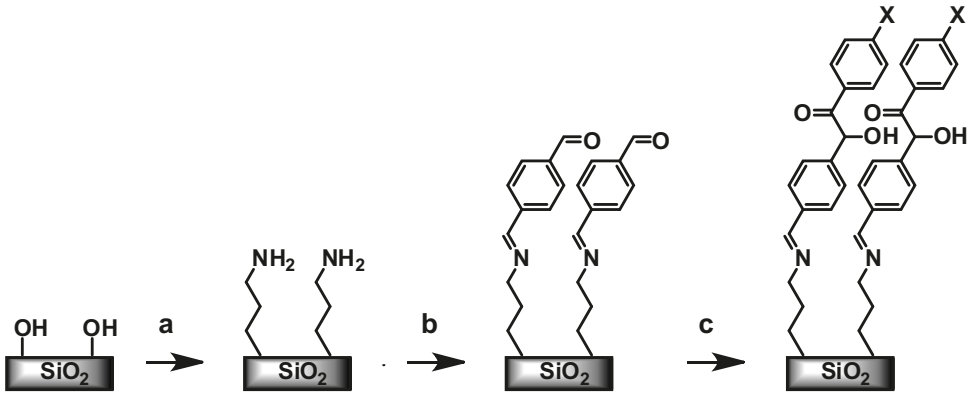


Fig. 3. FTIR characterization of thiamine-catalyzed coupling of 4-methoxybenzaldehyde to a model surface. Reaction progression at 0 h (bottom trace), 4 h (middle trace), and 24 h (top trace) of the conjugation reaction using thiamine as catalyst.

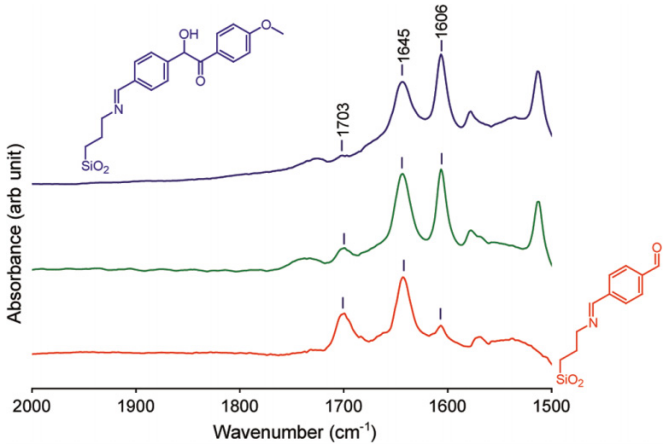
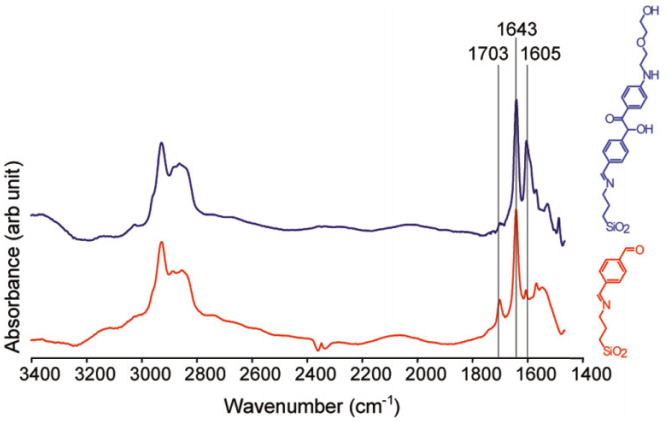


Fig. 4. FTIR characterization of thiamine-catalyzed coupling of 4-[2-(2-hydroxyethoxy)ethylamino]benzaldehyde to a model surface. Reaction progression at 4 h is shown.



Si(111) functionalization

Other surfaces were also tested to see whether the benzoin condensation reaction would be suitable for use in other applications where the use of glass or SiO_2 was not appropriate. A hydrogen-terminated (H-terminated) Si(111) ATR chip was prepared to provide the ether-linked aldehyde surface as in Fig. 8. Terephthaldialdehyde was directly attached to the H-terminated surface to yield the directly attached aldehyde to the Si(111) surface. The initial aldehyde-terminated surface provided a clean IR spectrum, with a peak at 1707 cm^{-1} corresponding to the C=O stretching of the benzaldehyde and a peak at 1612 cm^{-1} assigned to the phenyl. The directly attached

Fig. 5. Characterization of thiamine-catalyzed coupling of 4-fluorobenzaldehyde to a model oxide surface. (A) FTIR characterization at 0 h (bottom trace) and at 24 h (top trace). (B) X-ray photoelectron spectroscopy (XPS) survey scan(bottom trace: control, no catalyst; top trace: reaction after 24 h). The insert shows the XPS high resolution of the F 1s region (bottom trace: no catalyst; top trace: reaction after 24 h).

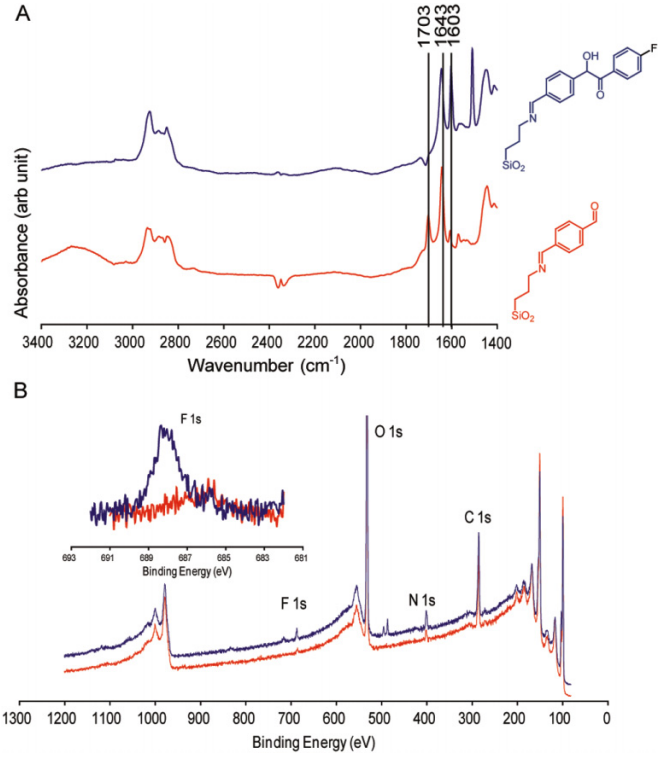


Fig. 6. Molecular structures 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride.

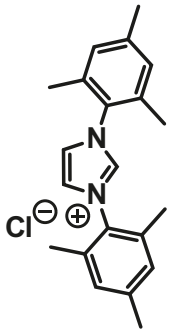
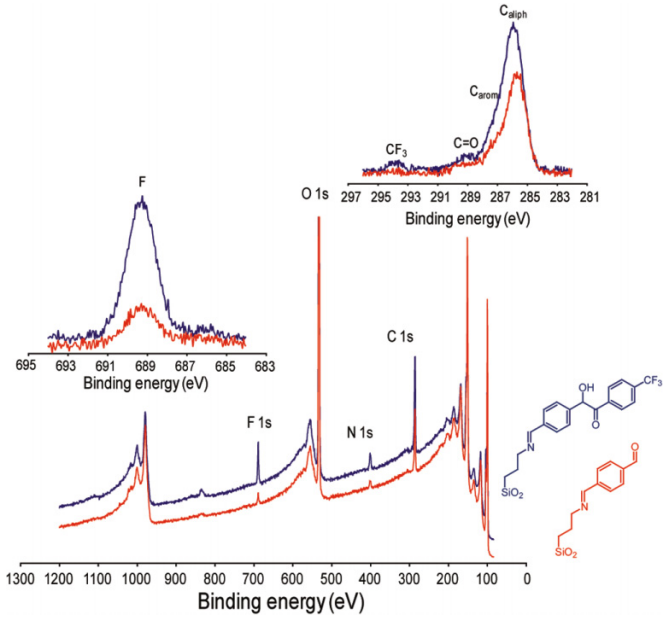


Fig. 7. X-ray photoelectron spectroscopy (XPS) characterization of thiamine-catalyzed coupling of 4-(trifluoromethyl)benzaldehyde to a model surface (bottom trace: control, no catalyst; top trace: reaction after 24 h). The spectrum from 1200 to 0 eV is shown. The upper left insert shows the F 1s region. The upper right insert shows the C 1s region.

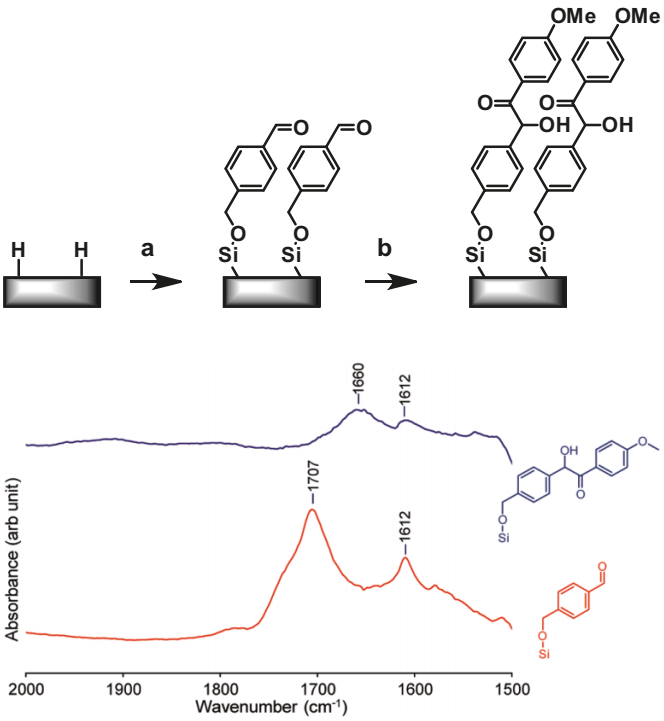


aldehyde surface was submitted to the same reaction conditions that were used to couple 4-methoxybenzaldehyde to silicon oxide surfaces using thiamine catalysis and monitored by FTIR (Fig. 8). After 4 h, the aldehyde carbonyl peak at 1707 cm^{-1} was significantly reduced and a new peak at 1655 cm^{-1} appeared, which was assigned to the C=O stretching of the benzoin carbonyl group. After 24 h, the aldehyde peak was no longer visible and only peaks assigned to the benzoin product remained.

Discussion

The thiamine-catalyzed benzoin condensation reaction was used to attach model aldehydes to surfaces. The reactions were generally observed to be faster and more chemoselective than those in solution. We hypothesize that the solid–liquid interface concentrates the organic reactants and acts similar to phase-transfer catalysis.[48–50] SiO_2 was chosen as the base substrate, since it is a common substrate in microar-

Fig. 8. FTIR characterization of thiamine-catalyzed coupling of 4-methoxybenzaldehyde to hydrogen-terminated Si(111) surfaces. Directly attached aldehyde surface and reaction progression at 0 h (bottom trace) and 24 h (top trace).



rays and has been extensively studied in such applications. Also, aldehyde coupling reactions provide new methods for bioconjugation given that a number of new methods exist for incorporating unnatural aldehyde groups into peptides and proteins.[51–54] Another advantage for performing methodology development on SiO_2 is that the surface also lends itself well to many spectroscopic techniques, including FTIR and XPS that were used extensively to characterize our modified surfaces.

Interestingly, we observed reactivity patterns that were different from those observed for NHC-catalyzed aldehyde cross-coupling reactions in solution. Usually electron-withdrawing substituents are favored for cross-coupling of benzaldehyde derivatives.[9,10,13–17] However, there are examples of analogous thiamine catalyzing cross-coupling reactions in water with methoxy-substituted benzaldehydes, where the thiamine catalyst is bound as a co-factor to an enzyme.[18] Interesting donor–acceptor relationships were established under these reaction conditions.[18] Others have postulated that differences between thiamine-dependent enzymatic catalysis and enzyme-free thiamine catalysis in solution may be due to desolvation and orientation of the thiamine co-factor on the enzyme.[55] A similar phenomenon may be happening for the catalysis on silicon surfaces where aromatic aldehydes are oriented with respect to the plane of the surface and where solvent behaviour is quite different from bulk solution.

(3-Aminopropyl)triethoxysilane (APTES) was chosen as the attachment molecule as it is a commonly used aminosilane for such purposes.[56,57] Although it is commonly used, it also has a complex reactivity profile because of its three reactive ethoxy groups. It can undergo the desired reaction of

covalent attachment with the surface through one, two, or three of the ethoxy groups; however, either vertical or horizontal polymerization are also possibilities with this substrate.[58] The latter, horizontal polymerization, can still be useful in surface functionalization, since it is possible that there is one ethoxy group still present and able to react with the SiO_2 even once it is polymerized and anchor the preassembled layer to the surface. APTES can also form hydrogen bonds to orient itself in several different arrangements on the surface.[58] This complex reactivity results in a nonhomogeneous surface and monolayers of APTES on SiO_2 that are difficult to consistently reproduce.

It has been previously shown that APTES quickly reacts with the surface at ambient temperature and pressure, without the need for any additional reagents or solvents.[59] An advantage to using ambient temperature and pressure vapour deposition is that we did not have to worry about excess water in the solvent causing uncontrollable polymerization of APTES. Reaction of the surface with APTES resulted in an amine-terminated surface. The terminal aromatic aldehyde was then installed by reacting the surface with an aqueous solution of terephthaldialdehyde as previously reported.[40] This provided an efficient means of reaching the terminal aldehyde without excess reagents, and the peak for the aldehyde (at ~1703 cm^{-1}) was clearly visible in the resulting IR spectrum of the surface.

The reaction progress between the aldehyde surface described in Fig. 3 and 4-methoxybenzaldehyde was followed by monitoring of the intensity of peaks of important functional groups in the FTIR spectrum. The shrinking of the aldehyde carbonyl peak at 1703 cm^{-1} was used to report on the consumption of the initial aldehyde-functionalized surface. The peak at 1606 cm^{-1} (a ring vibrational mode) was present in the initial aldehyde, but its intensity increased considerably upon formation of the benzoin product with the addition of a second phenyl ring on the surface. The peak at 1643 cm^{-1} (C=N stretching mode of the imine) remained unchanged after the benzoin reaction, evidence that the imine-linker was still intact. This suggests that the benzoin product was indeed being formed on the surface and giving rise to the observed changes in the IR spectrum.

It is interesting to note that, whereas the carbonyl peak for the benzoin products was not visible for the silicon oxide surfaces, the 4-methoxybenzoin surface derived from Si(111) did include a peak at ~1660 cm^{-1} that was assigned to the benzoin carbonyl peak. This suggests that the carbonyl peak of the benzoins on the model silicon oxide surfaces was in fact masked by the imine signal at 1643 cm^{-1}.

When 4-[2-(2-hydroxyethoxy)ethylamino]benzaldehyde was used, the reaction proceeded on the same time scale as the initial experiment; however, when 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride was used in place of thiamine, the 1703 cm^{-1} peak was no longer detectable after only 4 h (compared with 24 h with thiamine). This may be due to the increased stability and reactivity of the carbene formed after the deprotonation of the C_2 hydrogen. The presence of a phenyl ring on both heteroatoms as compared with only one with thiamine provide additional electron density to the C_2 site, stabilizing the resulting carbene.[12] The same system was also tested using an electron-poor aldehyde, 4-fluorobenzaldehyde. Fortuitously, we did see a reduction of the 1701 cm^{-1} peak and the emergence of a peak at 1603 cm^{-1}, which was assigned to the additional phenyl ring; however, this change in the spectrum was only apparent after 24 h. This observation does support our initial hypothesis that the electronics of the benzaldehydes play a role in determining the speed at which the reaction progresses. More evidence that the activated aldehyde species is forming with the electron-rich aldehyde is that when the imine-linked aldehyde-terminated surface is reacted with only catalyst and base, there is little change in the surface spectrum, where the 1703 cm^{-1} is only slightly decreased, but no additional peaks are observed.

The XPS data obtained from reactions involving aldehydes with fluorine substituents (4-fluorobenzaldehyde and 4-(trifluoromethyl)benzaldehyde) suggests that the main pathway for the incorporation of the fluoro signal at 688 eV is from the formation of the benzoin product on the surface. With reactions involving 4-fluorobenzaldehyde, the observed N/F ratio of 4.7 shows that under the reaction conditions, approximately one in five amines carried a benzoin product. The presence of a small F peak in the control can be attributed to either cross contamination or to 4-fluorobenzaldehyde reacting with free amines from unreacted APTES. With 4-(trifluoromethyl)benzaldehyde, the observed N/F ratio of 1.4 corresponds to approximately one in four amines carrying a benzoin product, which was very similar to the results in the previous system. The additional signal at 294 eV corresponding to the carbon of the CF_3 group and the observed F/C_{CF_3} ratio of 3 confirms that the entire F signal is associated with the incorporation of 4-(trifluoromethyl)benzaldehyde onto the surface. When considering the entire carbon region, the observed C/F ratio of 11.5 was much higher than the theoretical ratio of 6.3 for the benzoin product and much higher than the ratio of 3.7 for imine formation between unreacted APTES at the surface and 4-(trifluoromethyl)benzaldehyde. Since unreacted terminal aldehyde will increase the carbon content, this could indicate that only about 50% of the terminal aldehydes undergo benzoin condensation. The higher C/F ratio also indicated that the direct coupling of unreacted APTES at the surface and 4-(trifluoromethyl)benzaldehyde must be a negligible reaction pathway.

Conclusions

The benzoin condensation is an effective bioconjugation reaction to functionalize silicon and silicon oxide surfaces that proceeds using thiamine and NHC catalysts in water. Although we were able to demonstrate the condensation reactions using APTES-functionalized silicon oxide surfaces, more stable surfaces will be required to fully exploit this chemistry. Surfaces such as those generated by the reaction of terephthalaldehyde on H-terminated silicon surfaces, where the aromatic aldehyde is attached directly to the silicon surface through an Si–O–C bond, are stable and easily functionalized by the benzoin condensation. This method provides a new entry into the chemistry for functionalizing surfaces with biomolecules and has the potential to be exploited in the development of bioassays and in other applications.

Experimental

Materials and methods

Thiamine chloride hydrochloride, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, triethylamine, solvents, inorganic salts, and all benzaldehydes were used as received from Sigma-Aldrich unless otherwise stated in the text. Nuclear magnetic resonance spectra were recorded on a Bruker DRX-400 using a frequency of 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C and using a broadband direct detection probe. High-pressure liquid chromatography – mass spectrometry/mass spectrometry (HPLC–MS/MS) were carried out on a Waters system consisting of a Waters 996 photodiode array Ddetector, an Alliance HT – Waters 2795 separations module, and a Waters Micromass Z_{Q2000} unit equipped with a pneumatically assisted electrospray ionization source. Samples were run on a Waters Sunfire C18 (100 × 2.10 mm, 3.5 μm) column with a gradient of 10%–95% acetonitrile / 0.1% formic acid in H_2O / 0.1% formic acid over 15 min with a flow rate of 0.2 mL/min. MS data were collected in single-ion recording mode and processed using Masslynx. Attenuated total reflection Fourier transform IR (ATR-FTIR) spectra were recorded using a Nicolet MAGNA-IR 860 spectrometer at 4 cm^{-1} resolution. The ATR crystals were mounted in a purged sample chamber with the light focused normal to one of the 45° bevels. Background spectra were obtained using a blank surface (oxide surface or H-terminated surface depending on the experiment). XPS was performed on a PHI 5500 instrument using monochromated Al KR (1486 eV) radiation with detection on the surface normal. Spectra were fitted with Gaussian profiles using standard procedures. The positions of all peaks were normalized to C 1s at 285.0 eV. Experimental details for the benzoin compounds and the surface design are given in the Experimental section.

Silicon oxide elements

ATR elements were cleaned with piranha solution at 120 °C for 20 min and then rinsed with deionized water. To form the imine-linker aldehyde surface, the ATR element was exposed to APTES vapour for 10 min at room temperature. Once the free amine layer was formed, the ATR element was washed by sonicating in ethanol for 10 s, followed by rinsing with ethanol and then placement in a 1 mmol/L solution of terephthalaldehyde in water for 30 min at room temperature. The ATR element was then removed from the terephthalaldehyde solution and washed by sonicating in ethanol for 10 s, followed by rinsing with ethanol.

Silicon elements (H-terminated)

ATR elements were cleaned with piranha solution (96% H_2SO_4 and 30% H_2O_2, 3:1) at 120 °C for 20 min and then rinsed with deionized water. Samples were H-terminated by etching in degassed ammonium fluoride for 15 min, followed by a brief rinse in degassed water. To form the directly attached aldehyde surface, a 0.2 mol/L solution of terephthalaldehyde in toluene was degassed by bubbling with argon in a glass Schlenk tube for 10 min, followed by addition of the ATR element and heating of the solution at 90 °C for 1 h. The solution was cooled to room temperature and the ATR element removed and washed with 1,1,2-trichloroethane (TCE) in a Soxhlet extractor for 15–20 min and then further reacted as previously described.

Benzoin condensation on surfaces

Typically, 0.1 mmol of catalyst was dissolved in 1 mL of distilled water. To this, triethylamine (TEA) (27 μL, 0.2 mmol (with thiamine) or 18 μL, 0.1 mmol (with imidazolium catalyst)) was added. Para-substituted benzaldehyde (0.1 mmol) was added, and the solution was thoroughly mixed to form an emulsion. The reactions proceeded more slowly at lower catalyst concentrations and did not proceed at all in the absence of catalyst. The aromatic aldehyde-terminated ATR element was immersed in the solution and gently shaken. The reaction progression was monitored by ATR-FTIR. Gentle to vigorous washing was used as needed before scans to remove any noncovalently bound material.

Methoxybenzoins

Distributed among four 1.5 mL eppendorf vials, thiamine chloride hydrochloride (328 mg, 0.984 mmol) was dissolved in distilled water (2.4 mL) along with TEA (280 μL, 1.968 mmol). 4-Methoxybenzaldehye (160 μL, 0.984 mmol) and benzaldehyde (120 μL, 0.984 mmol) were added to the solution and the solution was shaken vigorously to form an emulsion. The vials were then placed in a centrifuge and spun for 3 days at 1400 rpm. The reactions were combined and 10 mL of water and 10 mL of ethyl acetate were added. The organic phase was isolated and the aqueous phase extracted 2 times with 10 mL of ethyl acetate. The organic fractions were combined, dried with magnesium sulfate, filtered, and concentrated. The resulting oil was purified by silica gel chromatography (4:1, hexanes – ethyl acetate, R_f = 0.32) to isolate the desired benzoin product as a mixture of regioisomers (3:1 based on NMR). The isomers were then separated by preparative HPLC (NovaPak C18 19 × 300 mm, iso 30% MeCN in H_2O, 20 min) in 41% total isolated yield.

2-Hydroxy-1-(4-methoxyphenyl)-2-phenylethanone[38]

Yield: 20 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.93 (2H, d, J = 9.0 Hz), 7.39–7.25 (5H, m), 6.88 (2H, d, J = 9.0 Hz), 5.91 (1H, d, J = 5.8 Hz), 4.67 (1H, d, J = 6.0 Hz), 3.84 (3H, s). MS (positive ESI, M + 1) m/z 243.

2-Hydroxy-2-(4-methoxyphenyl)-1-phenylethanone

Prepared as previously described.[38] Yield: 8 mg (8%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.00–7.86 (2H, m), 7.54 (1H, dd, J = 4.3, 10.5 Hz), 7.42 (2H, t, J = 7.7 Hz), 7.30–7.24 (3H, m), 6.87 (2H, d, J = 8.7 Hz), 5.93 (1H, d, J = 6.0 Hz), 4.50 (1H, d, J = 6.0 Hz), 3.78 (3H, s). MS (positive ESI, M + 1) m/z 243.

4-[2-(2-Hydroxyethoxy)ethylamino]benzaldehyde

Prepared as previously described.[60] A mixture of 4-bromobenzaldehyde (925 mg, 5 mmol), 2-(2-aminoethoxy)ethanol (725 μL, 7.5 mmol), K_2CO_3 (1.38 g, 10 mmol), CuI (95 mg, 0.5 mmol), and L-proline (23 mg, 1 mmol) in 3 mL of DMF (dry) was heated to 80 °C for 48 h in a sealed flask under Ar. The cooled mixture was diluted with ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and con-

centrated. The residual oil was loaded on a silica gel column and eluted with ethyl acetate to afford 200 mg of the corresponding aniline (19% yield). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 9.75 (1H, s), 7.72 (2H, d, J = 8.7 Hz), 6.66 (2H, d, J = 8.7 Hz), 4.80 (1H, s), 3.80 (2H, s), 3.78–3.72 (2H, m), 3.69–3.57 (2H, m), 3.44 (2H, q, J = 5.3 Hz), 2.01 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ: 190.56 (CH), 153.45 (C), 132.54 (CH), 126.90 (C), 112.19 (CH), 72.49 (CH_2), 69.44 (CH_2), 62.01 (CH_2), 43.04 (CH_2). MS (positive ESI, M + 1) *m*/*z* 210.3; (negative ESI, M – 1) *m*/*z* 208.3.

4-Formyl-N-*[2-(2-hydroxyethoxy)ethyl]benzamide*

4-Carboxybenzaldehyde (1.015 g, 6.76 mmol) was dissolved in 16 mL of toluene. Once the aldehyde was dissolved, *p*-toluenesulfonic acid (38 mg, 0.20 mmol) and ethylene glycol (415 μL, 7.44 mmol) was added. The reaction was refluxed with a Dean–Stark apparatus overnight. Once the reaction was complete, the toluene was evaporated and the residual oil was dissolved in ethyl acetate (30 mL) and washed once with water (30 mL) and once with brine solution (30 mL). The organic phase was collected, dried over Na_2SO_4, and concentrated. The protected acid was recrystallized from hexanes – ethyl acetate to afford 1.22 g of 4-[1,3]dioxolan-2-yl-benzoic acid (92% yield). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.02 (2H, d, J = 8.0 Hz), 7.49 (2H, d, J = 8.4 Hz), 5.78 (1H, s), 3.99 (4H, m). 4-[1,3]Dioxolan-2-yl-benzoic acid (123 mg, 0.633 mmol) was dissolved in 5 mL of DMF. Once the acid was dissolved, 2-(2-aminoethoxy)ethanol (7 μL, 0.697 mmol) was added along with DCC (196 mg, 0.950 mmol) and HOBt (128 mg, 0.950 mmol) and the reaction was allowed to stir at room temperature overnight. Once the reaction was complete, the mixture was dissolved in 10% sulfuric acid (5 mL) and left to stir at room temperature for 2 h to deprotect the aldehyde. Once the reaction was complete, the product was purified by flash chromatography (5%–10% methanol in dichloromethane) to afford 64 mg of the aldehyde (43% yield). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 10.05 (1H, s), 7.92 (4H, s), 3.76 (2H, m), 3.69 (4H, m), 3.62 (2H, m). MS (positive ESI, M + 1) *m*/*z* 238.3; (negative ESI, M – 1) *m*/*z* 236.1.

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