



Insights into Dynamic Covalent Chemistry at Surfaces

Journal:	<i>ChemComm</i>
Manuscript ID	CC-COM-08-2015-006970
Article Type:	Communication
Date Submitted by the Author:	19-Aug-2015
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COMMUNICATION

Insights into Dynamic Covalent Chemistry at Surfaces

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,

Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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The potential of surface confined self-assembly to influence the chemical equilibrium of Schiff base formation and bias the yield and distribution of reaction products is explored.

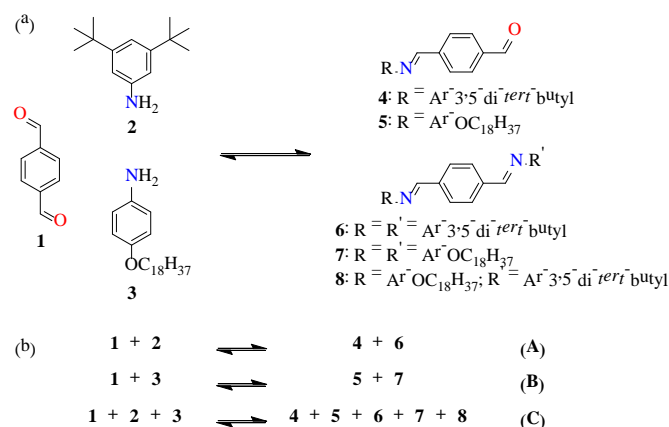
In recent years, dynamic covalent chemistry (DCC) has taken a central role in organic synthesis due to its ability to form products which are otherwise not easily accessible through classic synthetic routes.^{1,2} DCC is a versatile approach that allows harvesting one desired product out of the combinatorial library through selection of well-defined and controlled equilibrium conditions.³ The formation of imine-bonds (via Schiff base reaction) is a simple yet efficient reaction which is extensively used in DCC due to its reversibility under mild conditions.⁴ Among the various ways to influence the equilibrium in DCC reactions, adsorption of reagents or reaction products on solid substrates is a potentially promising approach. In particular, the selective adsorption of one or few of all possible reaction products promises to be an elegant approach to have an impact on the product distribution. In a recent publication, Samori et al.⁵ found that highly oriented pyrolytic graphite (HOPG) has an enhancement effect on the formation of Schiff bases. They also have demonstrated chemoselective synthesis of specific bis-imines from a mixture of different bisamines.

HOPG is a high-quality graphite substrate with large atomically-flat terraces. It is well-known that this substrate templates the self-assembly of many organic molecules into well-ordered physisorbed two-dimensional (2D) crystals at the liquid-solid interface, most often as monolayers.⁶ Molecule-molecule and molecule-substrate interactions, as well as external parameters (e.g. solvent, solute concentration or temperature) have an impact on the substrate coverage and the structural characteristics of the adlayer.^{7,8} Moreover, the principles beyond competitive adsorption when two or more building blocks are present at the interface, are well understood.^{9,10} The above insights were obtained with the help of scanning tunneling microscopy (STM). With this scanning probe microscopy technique, it is possible to visualize very thin films, typically monolayers, at the interface

between a liquid and an atomically flat conductive substrate such as HOPG, with submolecular resolution, and to reveal the structural properties of these films. There is plenty of evidence that many alkylated molecules self-assemble at the liquid-HOPG interface into regular patterns. STM is also the technique that Samori et al. used for the successful nanoscale analysis of the surface-supported monolayers - for convenience we refer to it as surface composition - where they demonstrated the preferential adsorption and formation of one of the several reaction products. While STM proved to be very valuable in this case focusing on the surface composition, it does not give any direct information on the relation between surface composition and solution composition, including the reaction yield and product distribution, nor does it reveal the importance of the nature of the surface or the potential catalytic action of the surface. Furthermore, the information that can be obtained via STM is biased as due to its low temporal resolution, highly dynamic disordered phases will remain unnoticed.

In this Communication, for the first time we address both the solution composition and surface composition of a DCC reaction, i.e. a Schiff base reaction, using STM and NMR and shine light on how a surface influences the solution composition. Furthermore, we report on the catalytic or enhancement effect of surfaces on DCC reactions.

As a model system we chose to explore reactions between terephthalaldehyde **1** and anilines **2** and **3**. These reagents should yield stable fully aromatic Schiff bases allowing their isolation and characterization (Scheme 1). They were also selected in anticipation of the differences in affinity for graphitic substrates among the reagents and possible reaction products. The bulky tert-butyl groups on parent aniline **2** as well as on its mono- and bisimine reaction products should disfavour their adsorption and self-assembly on surfaces due to steric hindrance. In contrast, *n*-alkoxy groups are known to interact in a favourable way with graphite and promote self-assembly¹¹, therefore a stronger affinity of aniline **3** and its reaction products, in particular bis-imine **7**, to graphite was anticipated.



Scheme 1: (a) Chemical structure of reactants and products, and (b) studied equilibrium reactions.

First, in order to explore the affinity of reagents and reaction products for graphite and their potential to form an ordered monolayer, self-assembly of reagents **1**, **2** and **3** and ex-situ synthesized products **5**, **6**, **7** and **8** was investigated with STM at the 1-phenyloctane/HOPG interface. While as expected, compounds **1**, **2** and **6** did not show any sign of monolayer formation on HOPG, STM-experiments confirm that compounds **3**, **5**, **7** and **8**, however, self-assemble into well-ordered 2D networks (Figure S1-4).

With this in mind, we designed an experiment that allowed us to probe the solution composition of reaction **C** (scheme 1b) in the presence of an excess of high surface area porous graphitic carbon (PGC) using NMR spectroscopy. Upon mixing **1**, **2**, and **3** in a 1:2:2 ratio, we expect that the position of the chemical equilibrium will be affected by the presence of a substrate, i.e. a graphitic substrate. According to the principle of Le Chatelier¹², the favored adsorption of the alkylated reaction products **5**, **7** and **8** removes them from the reaction mixture while promoting their formation. In the experiment, 6.5 mg PGC was added to a reaction mixture of aldehyde **1** and anilines **2** and **3** ($c_1 = 3.68$ mM, $c_2 = c_3 = 7.36$ mM, $V = 0.5$ ml) in benzene- d_6 and the progress of the reaction was studied using ¹H-NMR. The reaction mixtures are stirred continuously at 60°C to make sure full equilibration of the reaction has occurred and promote exchange of solution within the porous material. The selected amount of PGC has approximately 4 m² of free surface available for adsorption. This is enough to adsorb ~ 12 μmol of bis-imine **7**, meaning that an excess of surface will be available for adsorption, given the low concentrations used in the experiments, so competitive adsorption is not expected to be important.

In the absence of PGC, no sign of imine-bond formation is observed in the NMR spectra after 1 hour of reaction at 60°C.

However, when PGC is added to the samples, 99 % of the original amount of **1** is converted to a mixture of products, indicating an enhancement effect of PGC in the formation of aromatic Schiff bases. To ensure that the samples had equilibrated completely, we performed control experiments where analysis was done after 24 hours. The product distribution in these samples was comparable to the samples analysed after 1 hour. The composition of the reaction mixture is given in Table 1 (a detailed version of the table and analysis can be found in the ESI, table S1-3).

Table 1. Compound distribution in reaction C (% in reaction mixture; numbers between brackets is the fraction adsorbed on PGC for that specific compound), in the presence of different amounts of PGC, 1 h after mixing the reagents. The numbers correspond to the yield of a given reaction product based on **1.**

Product	6.50 mg	0.50 mg	0.25 mg
1	1 ± 1 (0)	0 ± 1 (0)	1 ± 1 (0)
Mono-imine 4	7 ± 2 (0)	11 ± 2 (0)	15 ± 2 (0)
Bis-imine 6	13 ± 3 (0)	8 ± 3 (0)	5 ± 3 (0)
4 + 6	20 ± 7 (0)	19 ± 5 (0)	20 ± 5 (0)
Mono-imine 5	16 ± 5 (15)	48 ± 5 (44)	79 ± 5 (62)
Bis-imine 7	48 ± 5 (48)	33 ± 5 (33)	0 ± 5 (0)
5 + 7	64 ± 5 (63)	81 ± 5 (77)	79 ± 5 (62)
Mixed-imine 8	15 ± 5 (15)	0 ± 5 (0)	0 ± 5 (0)

For the PGC 6.50 mg case, 78 % of the original amount of **1** adsorbs on the substrate in the form of mono-imine **5**, bis-imine **7** and mixed-imine **8** while 22 % remains in solution as free aldehyde **1**, mono-imine **4** and **5**, and bis-imine **6**. 63 % of the adsorbed products can be ascribed to **5** and **7**, while in solution **4** and **6** account for 20 % of the products. The total amount of alkoxyated products is thus 3 times higher compared to the products containing the di-*tert*-butyl-groups, indicating chemoselectivity aided by the substrate. Control experiments where two-component mixtures (reaction **A** and **B** in scheme 1b) are studied, show that the ratios between mono- and bis-imines **4:6** and **5:7** are comparable (table S11). However, for reaction **C** this is no longer the case. The products derived from reaction with aniline **2** show a distribution of 7 % mono-imine **4** and 13 % bis-imine **6**. The products derived from reaction with aniline **3** show a distribution of 16 % mono-imine **5** and 48 % bis-imine **7**. This can most likely be attributed to the formation of mixed-imine **8**, which is present in a 15 % yield, and once it is formed, gets removed from the reaction mixture through adsorption on PGC. In this way the ratio between mono-imine **5** and bis-imine **7** can be changed.

All three alkylated products **5**, **7** and **8** seem to adsorb on PGC when there is an excess of surface available. This means that there is not enough difference in affinity for the substrate between these compounds. However, it can be expected that when the amount of PGC is decreased, competitive adsorption between these alkoxyated products will be of importance to the position of the chemical equilibrium. Therefore, we studied the effect of smaller amounts of PGC (0.50 and 0.25 mg) in reaction **C** (table 1 and ESI, table S4-7). Both samples show a product distribution of about 20 % di-*tert*-butyl-group-containing products and 80 % alkoxyated products. For the alkoxyated products there is a shift in product distribution in favor of mono-imine **5** when the amount of available surface is decreased. In case of 0.25 mg PGC, no bis-imine **7** is formed, while 62 % of mono-imine **5** adsorbs on PGC and 17 % remains in solution. The 0.50 mg experiment has 33 % bis-imine **7** and 44 % mono-imine **5** adsorbed on the surface, while now only 4 % mono-imine **5** remains in solution. Mixed-imine **8** is not formed in these experiments due to competitive adsorption between the alkoxyated products.

The presence of PGC has a significant impact on the outcome of the studied reaction. In all cases, due to adsorption of alkoxyated products on the substrate, the formation of these products is favored. Decreasing the amount of PGC induces competition between compounds **5**, **7** and **8**. In the regime of competitive adsorption, compound **5** is the favored product, leading to a 4 times higher yield of alkoxyated products compared to products containing di-*tert*-butyl-groups.

To gain more insight into the surface composition when reaction **C** occurs in the presence of a graphitic surface, we performed STM experiments using an HOPG substrate. Due to the different experimental set-up, it is necessary to change the solvent. We chose phenyloctane because it is compatible with requirements for STM imaging in liquids, i.e. low vapor pressure, and it is comparable with benzene which was used for NMR experiments (both are non-polar). To exclude any concentration effect on the reaction outcome, we used the same concentrations that were used in the NMR studies. Since the HOPG surface is approximately 1 cm² large, this leads to an excess of molecules and a situation where competitive adsorption between different compounds will be relevant.

In the experiment, a mixture of the three reagents (**1**, **2**, **3** in ratio 1:2:2; $c_1 = 3.68$ mM, $c_2 = c_3 = 7.36$ mM) in phenyloctane was dropcasted on HOPG. STM revealed the formation of a self-assembled monolayer at the 1-phenyloctane/HOPG interface composed of two different networks. One of the networks corresponds to the self-assembled monolayer formed by **3** (Figure S1). The 2nd network is shown in Figure 1a. The bright protrusions grouped in rows correspond to the aromatic cores while the darker regions show the typical characteristics of parallel aligned alkyl chains. The white arrows correspond to the alkyl chains in each separate group of molecules. Usually three chains can be seen next to each other, but sometimes we observe 2 or even 4. These defects disturb the periodicity within a lamella, making it impossible to determine the unit cell parameters in a reliable fashion. However, by comparing interlamellar distances in the STM-images, the network observed in Figure 1a matches with that of mono-imine **5** synthesized ex situ (Figure 1b). The interlamellar distance for mono-imine **5** is 6.65 ± 0.13 nm whereas it is 6.58 ± 0.10 nm for the product observed in the STM-experiment. The observed defects can most likely be attributed to co-adsorption of small amounts of bis- and mixed-imine **7** and **8**. As mentioned previously, unreacted **3** is also present on the surface but from consecutive STM-images it can be seen that these domains slowly disappear in time and are replaced by the observed mono-imine **5** network (Figure S11).

These observations are congruent with the NMR experiments where competitive adsorption is evident. Possible reasons for the absence of bis-imine **7** on the surface can be a less favourable adsorption (compared to **5**), a lower yield of formation in solution, or the combination of both. In a series of control experiments, we could show that **5** preferentially adsorbs in favour over **7** (table S12 and figure S12), revealing indeed that competitive adsorption is operative. A possible explanation for the preferential adsorption of mono-imine **5** over bis-imine **7** can be given by the packing density of the monolayers for both compounds. The density for mono-imine **5** is 0.47 molecules/nm² while it is only 0.28 molecules/nm² for bis-imine **7**, making the assembly into monolayers of mono-imine **5** more efficient.

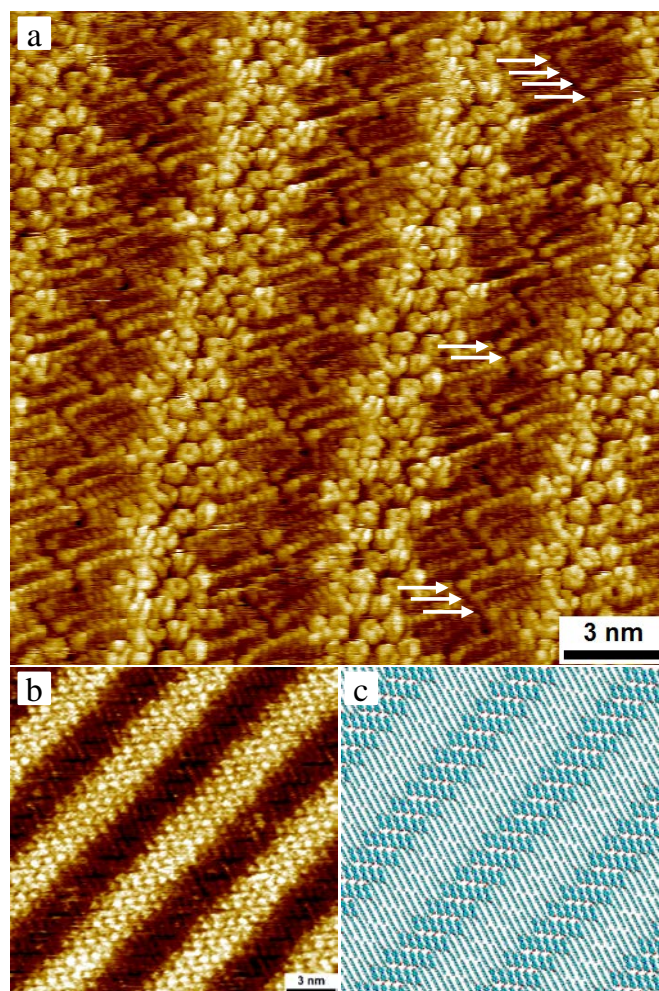


Figure 1: (a) STM-image of products in a monolayer formed after a mixture of **1**, **2** and **3** in 1-phenyloctane, a typical solvent for STM imaging in liquids, is dropcasted onto HOPG. (b) STM image of a monolayer of mono-imine **5** at the 1-phenyloctane/HOPG interface and (c) corresponding tentative molecular model.

The enhancement effect by PGC is peculiar. Since PGC is known to have acidic impurities on its surface¹³ and the formation of Schiff bases can be acid-catalyzed, we performed a series of control experiments. First acetic acid was added to the solutions in different quantities, in the absence of PGC, to observe any catalytic effect. Three samples containing 10 %, 25 % and 50 % acetic acid with respect to the number of aldehyde molecules were prepared (Table S13). However, the addition of acid does not give rise to the same fractional yield as observed in presence of PGC. The reaction stops at the formation of both mono-imine **4** and **5** without any sign of bis-imine products. A large fraction of **1** remains unreacted in solution. As a second control, a basification procedure to PGC was performed by exposing it to a 10% NaOH-solution for 1.5 hours (Figure S13). Similar conversion rates compared to untreated samples were obtained indicating that this procedure has no effect on the enhancement effect of PGC, and that this effect is not caused by acidic impurities.

In order to probe the effect of the graphitic nature of the substrate on the enhancement effect, two other high surface area substrates were compared: amorphous carbon and silica. Similar to PGC, amorphous carbon is hydrophobic but lacks the characteristic graphitic patches,

while silica is hydrophilic. Both substrates do not support self-assembly of reagents and/or reaction products into ordered areas. However, both substrates show similar fractional yields in reaction **A**, **B** and **C** when compared to PGC (Table S14-15) and therefore the nature of the substrate has apparently no impact on its enhancement effect.

This leads us to conclude that the high specific surface area of the substrate is responsible for the enhancement effect and thus two mechanisms can be proposed. The first mechanism involves an on-surface reaction of terephthalaldehyde with the adsorbed aniline. The second possibility presumes that the reaction occurs in solution within the close vicinity of the substrate, where continuous adsorption/desorption processes increase the local concentration of molecules. Which of the 2 processes is dominant probably depends on the building block and specific experimental conditions (concentration, temperature, etc.). For example, formation of imine covalent organic frameworks (COFs) at gas/solid interface is undoubtedly happening via the first pathway¹⁴, while in the case of imine COF formation in aqueous solution the initial reaction, i.e. nucleation, happens in solution while growth and ripening is happening on surface.¹⁵ Based on the design principles, i.e. **3** has a higher affinity for the substrate than **2**, a larger fraction of **3** than **2** will react via the first pathway. However, both compounds undergo adsorption/desorption processes and therefore can also react through the second pathway.

After confirming the generality of the enhancement effect for three high surface area substrates, we also investigated how the position of the chemical equilibrium in reaction **C** is influenced through adsorption on these substrates (Table S15) when an excess of surface is available. The total amount of mono-imine **4** and bis-imine **6** in solution remains equal, however there is some variation in the product distribution between different substrates. Adsorption of products **5**, **7** and **8** accounts for 73 % (amorphous carbon) and 70 % (silica) of the original amount of **1** while this was 78 % on PGC. This small decrease in affinity of alkylated products towards the substrate is in line with the observed increase of mono-imine **5** (4 % for amorphous carbon, 6 % for silica) and unreacted **3** in solution. However, these differences in adsorption behaviour between the substrates remain insufficient to induce substantial changes in the product distribution.

In summary, we have demonstrated that the formation of aromatic Schiff bases is catalyzed in presence of various high surface area substrates. In case of HOPG, we could show that molecular self-assembly and competitive adsorption is at play. A combination of adsorption processes with dynamic covalent chemistry leads to a shift in the position of the chemical equilibrium thus favoring the formation of the adsorbed products. In this way, we were able to obtain a 4:1 ratio in favor of the adsorbing products. In general, adsorption based processes can enhance chemical reactions and bias reaction product distribution. Future research will focus in more detail on the mechanistic aspects.

This work was supported by grants from the Fund for Scientific Research – Flanders (FWO – Vlaanderen). The research leading to these results has also received funding from KU Leuven (GOA 11/003), Belgian Federal Science Policy Office (IAP-7/05), and the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC Grant Agreement no. 340324.

Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [Synthesis of reference compounds, STM data and NMR spectra of these compounds, dynamics of reaction at liquid/solid interface studied by STM, experimental and analytical details of NMR-spectra, control experiments to check acidity of PGC, and details on the use of different substrates can be found in the ESI]. See DOI: 10.1039/c000000x/

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