Chemistry at the square nanometer: reactivity at liquid/solid interfaces revealed with an STM

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For more than three decades the scanning tunnelling microscope (STM) has proven to be an indispensable tool to image molecules adsorbed at a surface at the highest detail possible. In addition to simply imaging molecules, STM can also be applied to monitor dynamic surface phenomena, including chemical reactions. By studying reactions at a surface at the single molecule level, unique information about reaction mechanisms can be obtained which remains hidden when conventional ensemble techniques are used. Many STM studies of chemical reactions have been performed in extreme environments like ultrahigh vacuum or high pressure chambers, but these are far removed from conditions in which most chemical and biological processes take place, i.e., in a liquid at ambient atmospheres. This feature paper highlights the developments in the relatively unexplored research area of investigating chemical reactions with an STM at a liquid/solid interface under ambient conditions. Covalent couplings between molecules, light-induced isomerisations, reactions under electrochemical control, and complex multistep processes and catalysis are discussed.

1. Introduction

At the centre of chemistry has always been the chemical reaction. To monitor the course of a reaction and elucidate the reaction mechanism, chemists have the availability over a myriad of analytical tools, such as NMR and mass spectrometry, UV-vis, infrared and fluorescence spectroscopy. Although these techniques can provide valuable information, they all have one important limitation in common: they analyse ensembles of millions of molecules and deliver a result which represents their averaged behaviour. This averaging may lead to incomplete or misleading conclusions, since it is possible that only part of the molecules under study are reactive, while others at the same time are completely inactive. For the development of efficient chemical processes and catalysts it is essential to fully understand their working mechanisms and performance at the highest detail possible. For this reason, during the past decade considerable interest has emerged in the application of methods that enable the study of chemical reactions at the single molecule scale. The stormy development of techniques that provide resolution at the extremely small scale, such as...
(confocal) fluorescence microscopy, high resolution electron microscopy, and various modes of scanning probe microscopy has further stimulated this new direction of research.

The importance of studying chemical reactions at a surface at the highest detail possible has been recognised by the awarding of the Nobel Prize in chemistry to Gerhard Ertl in 2007. As part of this research he has explored in detail the molecular mechanisms of the catalytic synthesis of ammonia over iron and the catalytic oxidation of carbon monoxide over palladium, both industrially relevant processes. Amongst others, he was also one of the pioneers to study such dynamic processes by imaging them at the atomic level using a scanning tunnelling microscope (STM). In particular the invention of this microscope in the early 1980s has opened up tremendous possibilities to image surfaces at an unprecedented lateral resolution. In comparison with (high resolution) electron microscopy, a major advantage of this relatively new technique is its ability to operate in a wide range of environments, varying from ultrahigh vacuum (UHV) to ultralow temperatures to high pressures to liquids in ambient atmospheres. As a result of this versatility, STM has been used in numerous studies in which surfaces and molecules adsorbed on them have been investigated in extreme detail. While STM is not only a unique technique because of its superior spatial resolution in topography, its tunnelling current also exhibits high sensitivity to electronic variations in the probed surface. It can provide a detailed picture of the local electronic density of states of molecules adsorbed onto a surface, and by carefully choosing the tunnelling conditions, various parts of a molecule can be identified, even if they are topographically obscured by other parts of the molecule.

Although the majority of STM studies of molecules on surfaces deal with their steady state characterisation of dynamic surface phenomena like Ostwald ripening, in the 1990s research was also started in which elementary chemical reactions were investigated by STM. Initially, all these research studies were carried out on small molecules under rather extreme UHV or high pressure conditions. In the past decade, reactions between larger organic molecules, mainly intermolecular couplings, have also been reported in such environments. However, such reaction conditions are far removed from the equilibrium conditions it allows dynamic and reversible mass transfer from the liquid phase to active sites at the surface; controlled variations in solute concentration can have an impact on the abundance of reactive species at the interface and affect reaction rates; and at a practical level, a liquid is easily accessible for the addition of reactants or the withdrawal of products. With regard to STM studies in this environment, the experimental setup is very simple and does not require the expensive UHV or high pressure chambers. A measurement can be started and processed rapidly, since it only requires the immersion of the STM tip into a solution of molecules onto an atomically flat surface.

The ability to understand chemical processes at liquid/solid interfaces has been identified as one of the biggest challenges of modern surface science, for example, in metal corrosion research and electrochemical processes related to battery development. Industrial synthesis routes often rely on a specific interplay between a solid support and a liquid phase, for example, to heterogeneously catalyse a reaction or to achieve product selectivity. A complete understanding about what is going on at liquid/solid interfaces, at the highest detail possible, is essential for the optimisation of these processes as well as for their improvement. Despite the importance of liquid/solid interfaces, so far relatively few chemical reactions have been investigated in this environment at the molecular level. Only in this century has fluorescence microscopy been applied to monitor chemical reactions carried out on crystal facets by single turnover counting, and mesoporous catalysts and enzymes on a surface. However, these techniques still lack the extremely high spatial resolution that can be achieved using STM and its appealing ability to visualise individual molecules and atoms in the course of a chemical reaction.

Although STM studies at the liquid/solid interface are very popular, the use of this technique to investigate chemical reactions in this environment is still rather in its pioneering stage. The majority of such studies have been carried out under UHV, which is an ultraclean and highly inert environment. It allows the use of a large variety of atomically flat surfaces, and precise temperature control from near zero to several hundreds of Kelvin. As a result, the mobility of atoms and molecules on the surface can be finely tuned and superior control over surface coverage can be achieved. Hence, the reactive properties of sub-monolayer structures, clusters of a limited number of molecules, or fully isolated single molecules can be studied. Compared to the UHV, working at a liquid/solid interface environment seems to be accompanied by quite some complications. While a vacuum provides ultimate control, a liquid phase is a dynamic environment, prone to evaporation, allowing only a limited temperature window between its melting and boiling points. The interaction of a liquid with the surface (wetting and dewetting) depends on both the nature of the surface and the liquid and is not always straightforward to predict. Deposition of molecules of interest typically occurs via self-assembly into close-packed 2D patterns from solution onto the liquid/solid interface.

The presence of a liquid is in particular a valuable asset when chemical reactions are carried out on a surface. At or close to equilibrium conditions it allows dynamic and reversible mass transfer from the liquid phase to active sites at the surface; controlled variations in solute concentration can have an impact on the abundance of reactive species at the interface and affect reaction rates; and at a practical level, a liquid is easily accessible for the addition of reactants or the withdrawal of products. With regard to STM studies in this environment, the experimental setup is very simple and does not require the expensive UHV or high pressure chambers. A measurement can be started and processed rapidly, since it only requires the immersion of the STM tip into a solution of molecules onto an atomically flat surface (Fig. 1).

For STM experiments at liquid/solid interfaces, often non-conducting and non-volatile organic liquids are used. Although in principle a conventional ambient STM can also be used to acquire high resolution images in water and even in saline aqueous solutions, the performance of a so-called electrochemical scanning tunnelling microscope (EC-STM) is superior under these conditions. In an EC-STM (or in situ STM), two additional electrodes are employed to gain independent control over the electrochemical potentials of the tip and the sample. Instead of directly applying a bias voltage over these two electrodes, they are both set relative to a third electrode, the ‘reference electrode’.
electrolytes and ionic liquids. Possible operating environments of an STM, since one can occur through the systems significantly expands the range of surface. The complete control over potentials and currents that can drive the reactions that take place at the tip or the sample, thereby defining the third as a combination of the other two. The counter electrode can be considered as a supplier of electricity, which is at a (known) constant redox potential. The oxidising or reducing strength of both the tip and the sample, i.e. their ability to remove electrons from or add electrons to molecules adsorbed to the surface, can thus be controlled, and it is obvious that this possibility can be of great importance when chemical reactions are concerned. The bias potential $V_{\text{bias}}$ is determined by the difference between the potential of the surface relative to the reference electrode and that of the tip. In an EC-STM, two of these three potentials can be chosen independently, thereby defining the third as a combination of the other two. The counter electrode can be considered as a supplier of current to drive the reactions that take place at the tip or the surface. The complete control over potentials and currents that occur through the systems significantly expands the range of possible operating environments of an STM, since one can measure in conductive liquids like aqueous solutions, organic electrolytes and ionic liquids.

In this feature article we provide an account of the development of STM research dealing with the monitoring of chemical reactions at liquid/solid interfaces at room temperature in ambient atmospheres. First we will give a brief introduction about the pioneering STM work in monitoring reacting molecules in these environments, involving simple decomposition and isomerisation reactions. We will then discuss covalent couplings and polymerisations, highlighting the recent focus on constructing new materials such as two-dimensional covalent organic frameworks (2D-COFs). Light-induced isomerisation reactions of molecular switches will be described, followed by a section that elaborates on surface reactivity under potential control in an electrochemical STM setup. Finally, more complex systems that can carry out multistep reactions and catalysis will be discussed. A brief outlook will focus on the limitations and future opportunities of this new research area.

2. Chemical reactions investigated by STM

2.1 The first steps

In 1994, Rabe and De Schryver and coworkers were pioneers in investigating a chemical reaction at a liquid/solid interface by means of STM. They reported a phototransformation reaction in which 10-diazo-2-hexadecylantr hormone was converted to 2-hexadecyl-9,10-anthaquinone. The ex situ synthesised compounds were separately adsorbed onto the interface of 1,2,4-trichlorobenzene (TCB) and highly oriented pyrolytic graphite (HOPG), and were found to self-assemble into lamellar arrays with significantly different lamellar periodicities. When the reaction was carried out in situ at the liquid/solid interface, by illuminating the monolayer of the starting compound, STM showed the gradual disappearance of this monolayer and the appearance of a monolayer of the product. In another pioneering experiment, the cis-trans photoisomerisation of isophthalic acids containing an azobenzene moiety was investigated. When a monolayer of the trans-isomer at the 1-octanol/graphite interface was illuminated in situ, STM revealed that domains containing the trans-isomer were replaced by domains of the cis-product. Separate domains of the starting material and the product could be observed simultaneously in the same image. It was reasoned to be rather unlikely that this isomerisation reaction occurred in the two-dimensional confinement of the liquid/solid interface, due to steric constraints between the closely packed molecules in the monolayer. A more logical mechanism proposed was that irradiation of the system influences the equilibrium ratio of the cis- and trans-isomers in the supernatant solution. Since dynamic exchange can occur between the solutes and the molecules adsorbed at the interface, a change in equilibrium in solution also has an impact on the adsorption/desorption equilibrium between the solution and the interface. A decrease in the concentration of the trans-isomers will also induce desorption of these molecules from the interface, thereby paving the way for adsorption of the cis-isomeric product.

2.2 Covalent coupling reactions

The first STM study of a reaction that was truly confined to a liquid/solid interface was carried out by De Feyter, Müllen and De Schryver and coworkers. At a 1-undecanol/graphite interface they constructed a well-defined monolayer of diacetylene-containing alkyl chains equipped with isophthalic acid molecular recognition moieties. Via intermolecular hydrogen bonding between the isophthalic acids, lamellar arrays were formed in which the diacetylene moieties were oriented in an ideal geometry for an intermolecular topochemical polymerisation reaction at the interface. After illumination of the monolayer with UV light, clear changes in its structure could be observed by STM: the tunnelling contrast of the diacetylenes had changed, and the intermolecular spacing between the isophthalic acid headgroups had increased by 0.4 Å, indicating that the polymerisation had succeeded. In a follow-up work, the polymerisation of diacetylene-containing isophthalic acid (ISA-DIA, Fig. 2A) and terephthalic acid derivatives was investigated after monolayers of these compounds had been self-assembled by drop-casting their solutions at a HOPG surface. After illumination of the monolayer with UV-light, the appearance of the diacetylene parts in the STM images had significantly changed, in the sense that bright lines had become visible, likely corresponding to locally polymerised arrays of diacetylene moieties (Fig. 2B).
polydiacetylene wire to a C60 molecule.73
end was covalently linked to a phthalocyanine it encountered
monolayer, a polymer chain started to grow, whose reactive chain
applying a local voltage pulse to the diacetylene functions in the
process named ‘chemical soldering’ could be induced.72 By
confined to allow such a lifting of the chain.

It typically requires the single molecule resolution provided by
STM to investigate the occurrence of such highly local reactions
at a surface. In addition, the lamellar periodicities of the
polymerised parts of the monolayers had changed, as well as the
direction of the alkyl chains within these domains. In addition to irradiation with UV-light, also the STM tip could
induce topochemical polymerisation reactions by the application
of a bias voltage pulse of $-3.2 \text{ V.69,70}$

At the 1-phenyloctane/graphite interface, related diacetylene
molecules were found to slowly form a second layer and additional layers on top of the first monolayer.71 Because these
additional layers are not commensurate with the graphite
lattice and interacted poorly with the first monolayer of mole-
cules, their domains grew very large, up to the submicrometer
size. Interestingly, in a bilayer domain, only the diacetylene
molecules in the top layer were polymerised by applying a
voltage pulse. This observation was explained by assuming a
molecular conformation model in which the polymer backbone
is raised by 0.14 nm from the alkyl side chains. It was proposed
that such a lifting could only take place in a top layer, while
the molecules in the bottom layer were too much sterically
confined to allow such a lifting of the chain.

When on top of a self-assembled monolayer of diacetylene
derivatives small clusters of phthalocyanines were deposited, a
process named ‘chemical soldering’ could be induced.72 By
applying a local voltage pulse to the diacetylene functions in the
monolayer, a polymer chain started to grow, whose reactive chain
end was covalently linked to a phthalocyanine it encountered
on its path. Employing the same strategy, it is possible to link
a polydiacetylene wire to a C60 molecule.73

Recently the 1D polymerisation of diacetylenes in a self-
asssembled monolayer was expanded to the construction of 2D
grids, by employing rationally designed monomers that contain
diacetylene-containing aliphatic side-chains on both sides of a
monomer molecule.74 Synthetic variations in the location
and the spacing of the diacetylene moieties in the aliphatic
chains provided precise control over their position within a self-
asssembled monolayer. It was shown that only molecules
with specific distances between diacetylene units were able to
polymerise into cross-linked 2D grids.

Pursuing an analogous topochemical coupling concept, the
photodimerisation of cinnamate derivatives at the 1-octanol/
HOPG interface was also investigated.75 In that case, however,
no reaction was expected due to a topological mismatch of the
monomers at the surface, as was revealed by STM. Still, the
dimerisation reaction took place and evidence was provided by
STM that it occurred within the monolayer. This was attributed
to a relatively loose molecular packing in the dynamic liquid/
solid interface environment, which allowed sufficient mobility
of the molecules to enable an approach of their reactive sites.

In the past decade, a considerable number of STM studies
on covalent molecule–molecule couplings have been reported
on metallic surfaces under UHV,27–44 often also at ultralow
temperatures. Under less extreme conditions, Müllen and Rabe
and coworkers carried out an intramolecular coupling within
hexa(4-dodecyl)phenylbenzene ([HDPB]) molecules (Fig. 3).76 By
adding a solution of FeCl$_3$ in nitromethane to a self-assembled
monolayer of this compound at the TCB/HOPG interface, an
oxidative cyclodehydrogenation reaction occurred to yield fused
hexa-peri-benzocororone derivatives, which after the reaction
could again be imaged. However, due to the presence of the
salts as a reactant, the coupling reaction could not be followed
in situ by means of STM since significant Faradaic currents
interfered with the tunneling current. This example illustrates
that if one wants to monitor the course of a coupling reaction at
a liquid/solid interface using STM, the used conditions should
not be too harsh or incompatible with the technique.

In recent years, imine couplings, involving the formation
of reversible covalent bonds between aldehydes and amines,
have become increasingly popular reactions at a liquid/solid
interface.77–84 They occur under mild acidic conditions and at
relatively slow rates, allowing real-time monitoring by STM. By
careful choice of aldehyde and amine components, robust 1D
and 2D covalent organic frameworks (COFs) can be formed
which may have possible applications as structurally stable
porous surfaces that can serve as nanosized reaction vessels,
separation membranes, or host–guest data storage materials.

Li et al. showed that a self-assembled monolayer of 1,3,5-
tris(4′-formylphenyl)benzene (TFB) at a 1-octanoic acid/HOPG
interface undergoes a structural transformation after the addition of 5-amino-isophthalic acid (AIPA) over the course of 24 h (Fig. 4). TFB self-assembles into lamellar arrays that consist of paired molecules (Fig. 4B). After the addition of a solution of AIPA, STM revealed the slow degradation of the initial network and from the resulting disordered surface assembly slowly a novel, porous network evolved, consisting of clearly larger triangular-shaped molecules (Fig. 4C). These were assigned to the tris-imine product, based on the in situ obtained STM images as well as a direct comparison with STM images of the ex situ synthesised compound. Although the formation of the new self-assembled porous network could be imaged over time with an STM, intermediate species in which one or two imine bonds were formed were not observed. Apparently only the trisubstituted product can form a stable and well-organised network at the liquid/solid interface.

The construction of ordered 2D covalent imine networks at the liquid/solid interface is seemingly easy, but may suffer from some problems that hinder their application as, for instance, novel electronic materials. Lack of dynamics in imine bond formation can produce COFs with relatively small domain sizes and many defects, or allow the formation of different isomeric structures at different temperatures. Recent advances have therefore focused on increasing the reversibility of the coupling reaction, leading to systems under full thermodynamic control that allow self-repair, minimising the occurrence of defects. It was found that some monomers can be polymerised simply at the liquid/solid interface, while others require predeposition of one of the principle components, before the second component is introduced in an autoclave at elevated temperatures, together with the water-releasing agent CuSO₄·5H₂O. This complex acts as a regulator and ensures that thermodynamic equilibrium can be reached, although this equilibrium can yield a significant amount of hemiaminal bonds, an intermediate in the imine formation.

Recently, Lei and coworkers recognised the importance of the concentration of aldehyde and amine components in the supernatant solution for the successful formation of well-defined 2D COFs over large areas on the surface. Upon carrying out imine coupling reactions employing trialdehyde TFB and a series of linear terminal bis-amines, STM revealed that the use of low concentrations resulted in the formation of large domains of regular honeycomb networks, while at higher concentrations closer packed patterns and disordered domains were formed, in which incomplete reaction products were also present. A typical example of this concentration effect is evident from the reaction between TFB and 4,4-diamino-p-terphenyl (DATP), shown in Fig. 5. Thus, COF formation follows the same ‘concentration-in-control’ principle as coined by De Feyter and Tobe, and which has been observed for many self-assembled systems at liquid/solid interfaces. At low concentrations of the reactants, porous networks are allowed to form, while at higher concentrations the adsorption energies (both surface–adsorbate and adsorbate–adsorbate) of the reactants and coupling products become higher, resulting in the formation of closer packed structures.
This also highlights the importance of working at a liquid/solid interface, since the properties of the solution can provide direct control over the structure and reactivity of the formed network at the surface.

Samori and Lehn and coworkers studied with an STM the dynamics and in particular the reversibility of imine bond formation at the liquid/solid interface in more detail. First, a monolayer of 4-(hexadecyloxy)benzaldehyde (HDB), in which the molecules are arranged in lamellar arrays (Fig. 6A and B), was constructed at the 1-phenyloctane/HOPG interface. Upon adding a solution of an aliphatic 2-aminododecane on top of that layer, a double imine coupling reaction occurred and the disubstituted bisimine product completely replaced the HDB lamellae at the liquid/solid interface (Fig. 6C in the case of the C2-bisimine product). Due to steric congestion at the interface, the process involves the desorption of HDB, subsequent reaction in the supernatant, and readsoption onto the surface. Interestingly, the reaction at the interface was found to proceed 10,000 times faster than in solution, which was attributed to an increased concentration of the reactants and a lowering of the activation barrier of the reaction in the quasi-2D confinement near the interface. In addition, it can be envisioned that dehydration during imine formation is promoted by the proximity of the hydrophobic surface. After a monolayer of HDB had been transformed into the bisimine product by the addition of 1,2-diaminoethane, subsequent addition of 1,6-diaminohexane prompted another transformation. Because of the reversible nature of the imine bond, the monolayer at the liquid/solid interface converted completely to the C6-coupled product (Fig. 6D). A similar replacement was observed when 1,12-diaminododecane was added to either a C2 or C6-bisimine monolayer. The reverse reaction, however, in which a shorter diamine is added to a preformed bisimine network, turned out to be much more difficult. For example, the addition of 1,6-diaminohexane to a C12-bisimine network did not evoke any structural transition. Only after the addition of 200 eq. of the diamine and several hours of reaction time the lamellae of the C6-bisimine started to appear at the interface. This behaviour was related to a difference in adsorption energies of different bisimine products. Bisimines with a longer spacer between the imine moieties adsorb stronger at the interface than those with shorter spacers, due to the difference in the number of molecule–surface and molecule–molecule interactions. For this reason, the trans-imination reaction is always driven towards the ‘longer’ product. Further support for this was obtained from the observation that from a solution containing an equimolar mixture of ex situ synthesised bisimines with, respectively, C2, C6 and C12 spacers, only the compound with the C12 spacer was adsorbed onto the surface.

In a related work, the influence of the surface on imine coupling reactions was further explored by comparing both the surface and supernatant solution compositions. Terephthalaldehyde TA was reacted with mixtures of amines A1 and A2 to yield imine-coupled products P1–P5 (Fig. 7). While in benzene-d6 solution no imines were formed, the addition of an excess of porous graphitic carbon (PGC) to the solution resulted in an almost full conversion of the starting materials into coupling products, indicating an enhanced effect of PGC on the condensation reaction. Moreover, imines containing one or two octadecyloxy chains (P2, P4 and P5) were preferentially formed over imines containing only tert-butylphenyl groups (P1 and P3). Separate STM experiments of pure P2, P4 and P5 indeed revealed the self-assembly of these compounds into well-defined layers at the 1-phenyloctane/HOPG interface, while the compounds containing tert-butyl groups did not form stable adsorbed layers. These results indicate a substantial degree of chemoselectivity, mediated by the added carbon surface. The imine products that adsorb onto PGC are removed from the solution, and since all the condensation reactions are equilibrated these are amplified towards forming P2, P4 and P5 at the expense of P1 and P3. To investigate if the added surface could exhibit additional chemoselectivity in forming P2, P4 and P5, its added amount was decreased stepwise in order to induce competition of different products for adsorption. A shift towards a mono-imine product...
P2 was observed and the yields of P4 and P5 were reduced to zero, indicating that P2 successfully competes with the other two products for adsorption onto the PGC surface. This competition effect was confirmed when the same reaction was carried out on a HOPG surface in an STM setup: mono-imine P2 was observed to preferentially self-assemble into ordered monolayers over bis-imine P4, which is attributed to a more efficient packing of the former compound at the liquid/solid interface. Interestingly the chemoselectivity of the reaction was also observed when non-graphitic surfaces such as amorphous carbon and (hydrophilic) silica were used. On these surfaces the compounds do not self-assemble in large areas of high order, suggesting that this is not a prerequisite for product enhancement and that just the presence of materials with large surface areas is sufficient.

When imine coupling and hydrolysis are carried out in aqueous solutions, an extra control factor comes into play: the rate of both reactions is highly dependent on the pH of the system. At low pH, imine formation is slow due to protonation of the amine, but imine hydrolysis is fast since this process is acid catalysed. At high pH, imine coupling dominates. The moderate pH range (pH values between 2 and 5) is of particular interest, since imine coupling and hydrolysis rates may be such that they allow the formation of oligomers and polymers, while the reactions are still dynamic in nature.

Kunitake and coworkers employed an electrochemical scanning tunnelling microscope (EC-STM, see also Section 2.4) to image imine coupling reactions between a large variety of bis-aldehydes and bis- and tetra-amines at the interface of an Au(111)/iodine surface and aqueous solutions with a pH just below the pKₐ of the used amine component. Depending on the building blocks, ordered adlayers of extended 1D aromatic polymers were obtained. The polymer chains terminated at the domain boundaries, which is evidence of a surface propagation polymerisation mechanism, rather than polymerisation in solution followed by deposition at the interface. An example of 2D polymerisation following this approach, using the tetra-amino-functionalised porphyrin TAPP and the bis-aldehyde TPA, is shown in Fig. 8. At a pH of 3.52, the formation of mesh-like COF structures was observed by EC-STM (Fig. 8C). The reversible nature of the imine bonds between the TPA and TAPP building blocks could be directly imaged, at single linker resolution, in consecutive STM images (Fig. 8D and E), which revealed the disconnection and restoration of the linkers between two porphyrin moieties.

The principles that govern the formation of 2D COFs not only apply to imine bond formation, but can also be extended to other chemical motifs as well. 1,4-Benzene diboronic acid polymerises into a hexagonal network through the formation of boroxine rings (B₃O₃), a reaction that produces water and is reversible. The groups of Lackinger and Wan more or less
simultaneously showed the preparation of such COFs on a graphite surface, and imaged the product with an STM at either the liquid/solid or the air/solid interface (Fig. 9). While the hexagonal boroxine network could be imaged, its preparation had to occur ex situ since high humidity and temperature conditions were required. The network could be formed directly at the liquid/solid interface by heating, or by dropcasting a suspension of preformed boroxine oligomers followed by annealing. STM revealed that the predeposition method produced tiny domains of branched boroxine oligomers, or small hexagonal domains with a typical size below 10 nm. After annealing in a humid atmosphere, the surface showed significant ripening and large hexagonal domains. In a follow-up work, Lackinger and coworkers showed that the method for 2D boroxine COF formation could be extended to a larger set of aryldiboronic acids, which provided control over the pore size of the hexagonal network. The COFs can serve as supramolecular hosts that can bind C60 molecules both inside the pores and on top of the boroxine network.

Lei and coworkers designed a boroxine 2D COF based upon an azobenzene-containing diboronic acid. After synthesis of the network at the HOPG surface, STM shows a hexagonal network with only little defects. After UV-irradiation, the surface coverage of the network decreased to as low as 11% after 2 h of exposure. It was proposed that trans–cis isomerisation of the azobenzene moieties strains the hexagonal ring structure until one of the B–O bonds in the ring breaks. A simple annealing step resulted in regeneration of the destroyed surface network. UV-irradiation and consequent destruction of the network released copper phthalocyanine molecules that were previously adsorbed within the porous structure.

2.3 Isomerisation reactions

As was described in Section 2.1, cis–trans isomerisation of a diazobenzene moiety was one of the first chemical reactions that was studied at the submolecular level in a liquid-STM setup. Since then, the investigation of such isomerisation reactions and their impact on the structure of self-assembled monolayers has continued to be an area of interest. Previous examples of azobenzene-type isomerisations had to occur in densely packed 2D monolayers, where the molecules have limited space to undergo spatial reorganisation within a confined space. For this reason it was proposed that the molecules isomerised in the supernatant solution, followed by their re-adsorption at the liquid/solid interface.

In an attempt to confine these isomerisation reactions to the liquid/solid interface, a trifluorene-azobenzene derivative TFAB (Fig. 10) was designed in which the azobenzene moiety is decoupled from the surface when the molecules are adsorbed. At the 1-phenylpentane/HOPG interface the trans-isomer of TFAB self-assembled into a rather disordered monolayer in which bright protrusions were present that were assigned to the azobenzene moieties. Although the size of these protrusions did not correspond with the molecular structure, this was explained by the extra degrees of freedom of the azobenzene moiety which is not adsorbed directly onto the surface. When the monolayer was exposed to UV light, a full structural reorganisation occurred within one hour. A much larger surface area per molecule was observed, and the previously present bright protrusions now extended over the entire molecules. From these observations it was concluded that the cis-TFAB isomers were successfully formed. Remarkably, exclusively, the cis-isomer was present on the surface, while in the supernatant solution it was found.
to be the minor constituent (max. 34%) due to incomplete isomerisation. A higher adsorption energy of the monolayer of the cis-isomers could account for this observed difference. The isomerisation at the liquid/solid interface turned out to be fully reversible, as was demonstrated by exposing the monolayer of cis-TFAB to visible light. After 10 minutes, a mixed domain of both the cis- and trans-isomers could be observed. Prolonged irradiation resulted in desorption of the cis-isomers, while the trans-isomer domains grew via deposition of the molecules from solution.

Tahara et al. incorporated the photochromic switching behaviour of the azobenzene moiety into a porous network of alkoxylated DBA derivatives (Fig. 11). Three of the six alkyl chains of these molecules were end-functionalised with a diazobenzene moiety containing two carboxylic acids, and as a result a honeycomb network was obtained at the 1-octanoic acid/HOPG interface in which the photochromic groups were present inside the pores. This partial pore occupation restricted the space for the binding of additional guest molecules inside the pores. In the presence of coronene, STM revealed that 96.5% of the remaining porous space was filled with a single coronene molecule, while the other 3.5% of the pores contained two or three of these guests. The presence of hexakis(phenylethynyl)benzene, a guest with large affinity for HOPG, did not influence the binding of coronene within the porous structure, apparently due to its poor fit in the small pores. To investigate the photochromic behaviour of the adsorbed diazobenzene-functionalised DBAs and its effect on the 2D network structure, the monolayer was irradiated with UV light. After the addition of the coronene guest molecules to the supernatant solution, a clear difference in the number of adsorbed guests in the pores was observed. Now, 19% of the pores contained more than one adsorbed coronene guest, significantly more than 3.5% of the pores observed before irradiation. This increased ability to host guests was attributed to a trans-cis isomerisation of several of the azobenzene moieties within a pore, resulting in an increase in the pore size. To investigate if this isomerisation really occurred at the liquid/solid interface and not via the supernatant solution, an experiment was conducted in which half of the sample was masked from UV irradiation. After irradiation, the masked area showed similar guest binding properties as the non-irradiated sample, whereas the irradiated area showed a significant increase in the number of pores that bound two or more guests. These results confirm that the isomerisation reactions indeed occur confined to the liquid/solid interface.

Stilbene derivatives can also undergo isomerisation reaction under the influence of UV light. Liao et al. investigated the photochromic behaviour of self-assembled monolayers of E-stilbene derivatives with three ester-terminated alkyl chains at the 1-phenyleoctane/HOPG interface. When a monolayer of compound S1 (Fig. 12A), which self-assembles at the liquid/solid interface in parallel rows of dimers (Fig. 12B), was irradiated with UV light, it fully transformed into an ordered kagomé network (Fig. 12C). Analysis of the bright aromatic cores of the molecules of S1 within the network, associated with the benzene rings in the stilbene moieties, revealed a 0.2 nm decrease in distance, which is consistent with an isomerisation of the E-isomer to the Z-isomer. A similar E-stilbene derivative S2, containing three C10 instead of C4 alkyl spacers, also self-assembled into rows at the liquid/solid interface, but now into motifs containing two pairs of molecules in the unit cell. Irradiation of this network again caused a dramatic change in the molecular arrangement. Domains of pairs of Z-stilbene isomers were formed, in which the dimeric partners were oriented with respect to each other in either a head-to-head or a head-to-tail fashion (Fig. 12D). Interestingly, prolonged irradiation of the network led to a follow-up [2+2] cycloaddition reaction that occurred exclusively between molecules of the head-to-head-oriented dimers, generating cyclobutane derivatives. Since in this product the conjugation between the benzene rings is lost, it appears slightly dimmer in STM images than the still present non-reacted Z-stilbene isomers that are arranged in a head-to-tail fashion (Fig. 12E).

Light-induced phase transitions at the liquid/solid interface are not solely restricted to azobenzene or stilbene-derived photo switches. Also diarylethene-based systems have been widely studied, both in solution and at the liquid/solid interface. Diarylethene switches can quickly isomerise between two or more metastable states under the influence of light. Illumination-induced isomerisation drastically changes not only their molecular structure, but also their shape and flexibility. Confinement of such molecules to a surface may therefore result in light control over the structure of 2D self-assembled networks.

Matsuda and coworkers investigated the photochromic behaviour of a wide range of diarylethene derivatives. Compound DE1 (Fig. 13A) consists of a pyrene moiety to which two
thiophene-based diarylethene groups are connected. The diarylethenes can exist in two stable states: a flexible open isomer and a closed rigid one, which can be reversibly switched using UV or visible light. Since the two switches are connected via the pyrene moiety, the system has 3 possible configurations: open–open (o–o), open–closed (o–c), and closed–closed (c–c).
The pure open–open isomer was found to self-assemble at the 1-octanoic acid/HOPG interface into ordered lamellar arrays with a 5.6 nm periodicity (Fig. 13B). After irradiation of this network with UV light for 5 seconds, STM revealed the formation of a new domain type at the surface. This process was reversible, as irradiation with visible light restored the original o–o-isomer network. When the structure of the newly formed domain was compared to the network structures of the ex situ prepared open–closed and open–open isomers of the compound, the open–closed isomer monolayer structure strongly resembled that of the open–open isomer, albeit with a slightly smaller lamellar periodicity of 4.7 nm. The closed–closed isomer also self-assembled into well-ordered arrays, but with a much smaller periodicity of only 1.9 nm. This spacing matched the periodicity of the domain formed after in situ irradiation of the open–open isomer. In order to determine the relative adsorption energies of various network structures, a solution of all isomers in a ratio of 45:33:22 (o–o:o–c:c–c) was applied to the liquid/solid interface. While the closed–closed isomer was the minor constituent in solution, STM revealed that the surface was predominantly covered by this isomer, implying a larger adsorption energy compared to those of the other isomers.

Prolonged irradiation of the closed isomer of thiophene-based diarylethene switches can lead to the formation of a third stable isomer. When a self-assembled network of the open diarylethene isomer DE2-o (Fig. 14) was investigated with an STM at the 1-phenyloctane/HOPG interface, it was found that as a result of the internal flexibility of the molecule the two thiophene rings were not oriented in a sufficiently close position to undergo ring-closing isomerisation upon irradiation with UV light. Instead, the molecules desorbed into the supernatant solution to isomerise, after which the closed-isomers DE2-c readorsbed in a different pattern at the liquid/solid interface. This isomerisation was fully reversible, since irradiation with visible light regenerated the network of DE2-o molecules. Prolonged irradiation of the network of DE2-c induced the formation of the photoirreversible annulated product DE2-a. Interestingly, when a solution of a mixture of DE2-c and DE2-a (ratio 98:2) was deposited on HOPG, STM revealed the presence of only the annulated isomer. Theoretical modeling of the thermodynamic parameters of the adsorption processes showed that this by-product had a significantly larger adsorption energy than those of the other isomers, confirming the capacity of HOPG as a selector in amplifying the abundance of a component, which is present in minor concentrations in solution, onto the surface.

Even more sophisticated switching behaviour was observed for assemblies of a terthiophene derivative with three bis-alkoxybenzene rings (Fig. 15A) at the TCB/HOPG interface. Because of the photochromic nature of the terthiophene core and the concentration-dependent behaviour of the compound at the liquid/solid interface, this molecule can act as a switch with four possible states. The open terthiophene isomer TTP-o was capable of forming two different 2D polymorphs, the relative abundance of which on the surface was strongly dependent on the concentration of the compound in solution. Below 40 µM, the a-type polymorph is dominant, while at higher concentrations predominantly the higher density b-polymorph is found (Fig. 15B-2 and 3). The closed isomer TTP-c did not form an ordered monolayer (Fig. 15B-1). In solution, further UV irradiation of TTP-c led to the formation of the annulated isomer TTP-a, which self-assembles at the surface into a hexagonal porous honeycomb network over a wide concentration range (Fig. 15B-4). All isomerisation steps were also performed in situ in the STM setup, by irradiating the networks at the TCB/HOPG interface. Initially, a solution of TTP-c (conc. = 78 µM) was placed at the HOPG surface. After illuminating the surface with visible light for 30 min, part of the molecules isomerised to TTP-o, and an ordered monolayer that mainly consisted of the a-polymorph was observed. This is an indication that the amount of TTP-o in the supernatant solution is below 40 µM, since this is the threshold for the formation of the b-polymorph. After illuminating for 60 min, a sufficient amount of TTP-o had formed to surpass the concentration threshold of 70 µM at which the b-polymorph is exclusively present at the surface. This polymorph could be switched further by illuminating the sample with UV light. After 10 minutes, TTP-a started to form as was evident from the formation of small disordered domains within the monolayer. After 30 min of irradiation, no more b-type domains were observed, but only small islands of TTP-a. The ordering of this network could be further improved by annealing the sample at 50 °C for 10 min, after which the extended honeycomb domains were observed by STM.

2.4 Reactions under electrochemical control

An electrochemical STM (EC-STM) provides control over the oxidising or reducing strength of both the tip and the sample.
With the help of an EC-STM, the formation of conductive polymers has been imaged at submolecular resolution. 3-Butoxy-4-methylthiophene (BuOMT) was electropolymerised at an interface of Au(111) and dichloromethane in which molecular iodine was dissolved. When voltage pulses of 1.4 V were applied to the Au(111) surface, the formation of highly organised linear wire structures became apparent in the STM images (Fig. 16). These wires appeared to be single polythiophene chains, and at higher magnifications the constituting thiophene monomers could be detected as a zig-zag arrangement within the chains, with a 0.38 nm repeating distance. The wires were organised along three specific directions on the surface, which indicates an epitaxial relationship with the underlying Au(111) lattice. It was found that both the surface coverage and the length of the chains increased when more voltage pulses were applied (Fig. 16A–C). The maximum observed chain length was 75 nm, which corresponds to ~200 monomer repeat units. The presence of iodine in the system appeared to be essential, since in its absence no well-defined polymer growth was observed at the surface. In iodine-containing dichloromethane, STM images of parts of the Au(111) surface where no polymer chains were present revealed a hexagonal pattern of iodine atoms. Apparently, these adatoms assist in the formation or attachment of the well-defined polymer wires at the surface. The polymerisation mechanism was unveiled by applying a stepwise procedure (Fig. 16D). When BuOMT was dissolved in the iodine-containing dichloromethane solution, UV-vis spectroscopy indicated the formation of trimeric thiophene species, presumably via an oxidation reaction mediated by the dissolved iodine. Subsequently, a voltage pulse of 0.77 V was applied to the solution, which oxidised the trimers to radical cations. These charged species were proposed to subsequently function as nuclei at the iodine-covered Au(111) surface, from which propagation occurs to form the polythiophene wires.

EC-STM imaging was also used to reveal the structure of a monolayer of aniline molecules at the 0.1 M aqueous H$_2$SO$_4$/Au(111) interface, and its subsequent polymerisation to give polyaniline (Fig. 17). When the surface potential of the gold surface covered with aniline was shifted to 1.05 V (vs. RHE), oxidative polymerisation of the adsorbed aniline molecules occurred, which had a clear impact on the surface topography: elongated line structures were formed, which were identified as aligned polyaniline chains. Magnification of the lines revealed an internal zig-zag ordering of the constituting monomers (inset in Fig. 17C). The distinct preferential alignment of the monomers in the [1 2 1] direction of the Au(111) surface is responsible for the strong anisotropic polymerisation observed in STM images. On rougher Au(111) surfaces, the polyaniline chains exhibited a higher degree of curvature, which supports the indication of the well-defined polymer wires at the surface. The polymerisation mechanism was unveiled by applying a stepwise procedure (Fig. 16D). When BuOMT was dissolved in the iodine-containing dichloromethane solution, UV-vis spectroscopy indicated the formation of trimeric thiophene species, presumably via an oxidation reaction mediated by the dissolved iodine. Subsequently, a voltage pulse of 0.77 V was applied to the solution, which oxidised the trimers to radical cations. These charged species were proposed to subsequently function as nuclei at the iodine-covered Au(111) surface, from which propagation occurs to form the polythiophene wires.
that the polymerisation is a surface-confined process. Similar polymerisation reactions of aniline were observed at different types of liquid/solid interfaces.99,100 With absolute control over the potential of the surface, an EC-STM can be used as an electrochemical cell in which the microscope can provide information about processes occurring at the electrode/liquid interface. The EC-STM is therefore an ideal tool to detect and identify molecules that can change their oxidation state.

Borguet and coworkers did extensive research on redox processes of the tetrapyridyl porphyrin derivative TPyP (Fig. 18).101,102 These porphyrin molecules self-assembled at the 0.1 M aqueous H2SO4/Au(111) interface in a reduced P(C) state when a slightly negative surface potential (−0.1 V vs. SCE) was applied.102 When the surface potential was increased for a short while, by applying a 0.3 V voltage pulse, dark porphyrin signatures appeared within the monolayer. Since the number of these dark signatures was dependent on the duration and magnitude of the pulse, they were assigned to oxidised TPyP species. At a pulse voltage of 0.2 V, the oxidised species showed a random surface distribution, while with a 0.3 V pulse they appeared to cluster in larger patches. The nearest-neighbour distribution of these oxidised species shows a deviation from random statistics, although the reason for this is not yet clear. Consecutive STM images showed only little change in the number of oxidised molecules after the voltage pulse was applied, however, their location changed constantly. Previous studies had revealed that the interaction between the oxidised species and an Au(111) surface is so strong that an ordered monolayer cannot form. Hence, the authors suggest that the observed mobility is caused by electron transfer from molecule to molecule instead of simple diffusion or desorption and adsorption.

The mechanism of porphyrin reduction at the 0.01 M aqueous HClO4/Au(111) interface was further investigated on adsorbed tetra(4-carboxyphenyl)porphyrin molecules.103 When the surface potential was gradually lowered from 0.15 to 0 V, molecules with a brighter contrast started to appear. These signatures were assigned to reduced protonated porphyrins, H4P(−II) species.

![Fig. 16](image1)

![Fig. 17](image2)

![Fig. 18](image3)
When the pH of the supernatant solution was decreased (to 0.1 M and 1 M aqueous HClO₄), lower surface potentials were required (0.05 V and 0.15 V, respectively) before the bright signatures were observed. This is an indication that protonation of the porphyrin disfavours the reduction reaction.

The electrochemical properties of viologens (4,4'-bipyridinium derivatives), which exhibit rich redox behaviour in solution, have also been investigated with an EC-STM. Dibenzyl viologen (dBV²⁺) does not form ordered structures at a 0.3 M aqueous KCl/HOPG interface, but when the surface potential was lowered to 0.38 V a lamellar structure appeared. This close-packed structure was proposed to consist of edge-on-orientated dBV⁺ radical cations, as their presence at this potential was observed by electrochemical solution experiments. Favourable face-to-face π–π stacking interactions between these molecules were proposed to stabilise this layer. More recently, the properties of the closely related diphenyl viologen (dPhV²⁺, Fig. 19A) were investigated at the same liquid/solid interface in more detail. Cyclic voltammetry (CV) showed two redox processes. A reduction occurring at a negative surface potential, which was assigned to the reaction of dPhV²⁺ to dPhV⁺, resulted in a transition from a gas-like adlayer to an ordered 2D structure at the surface, as was observed using an EC-STM (Fig. 19B). Arrays of edge-on-oriented dPhV⁺ molecules were observed, similar to the assembly of dBV⁺. The second redox process, which occurred at a positive potential, was related to a reversible order–disorder phase transition at the surface. Chloride ions were proposed to form a stable adlayer at the liquid/solid interface, which was confirmed by electroreflectance and CV experiments. Subsequently, dPhV²⁺ molecules assemble onto this layer. The EC-STM at a positive surface potential indeed showed an ordered arrangement of face-to-face-oriented dPhV²⁺ molecules (Fig. 19C). No imaging of the chloride ions could be achieved, but it is safe to conclude that an electrolyte may play a non-innocent role in adsorption processes of redox-active organic molecules (Fig. 19D).

2.5 Multistep reactions and catalysis

The reactions in an ambient STM discussed so far mainly involved the visualisation of reacting molecular components on a surface. Following a different approach, our group started research in which molecular catalysts were adsorbed at a liquid/solid interface. Such catalysts can serve as centres for multiple reaction steps, and quite often it is not completely clear which mechanisms are at work at the active site. We reasoned that STM might be a tool complementary to the ensemble techniques for revealing mechanistic information at the single catalyst level. For this specific research we built a dedicated catalysis-STM setup, equipped with a bell-jar and an inert liquid-cell. These features made it possible to add or withdraw chemicals to or from the liquid during scanning, and to work under any desired atmosphere.

As part of ongoing research on porphyrin-catalysed epoxidation reactions, we adsorbed manganese porphyrin catalysts MnP (Fig. 20A) at the η-tetradecane/Au(111) interface. These catalysts are efficient in oxidising alkenes with molecular oxygen. When the self-assembled network of MnP molecules was imaged in the bell-jar filled with inert argon, nearly all molecules had a similar appearance in the STM images (Fig. 20B). When the argon was replaced by molecular oxygen, molecules with a much larger apparent height became visible (Fig. 20C), which suggested...
a reaction between the manganese porphyrins and oxygen.\textsuperscript{107} However, such a reaction was unexpected, because Mn(III) porphyrins in solution are inert towards oxygen; they first need to be activated by reducing their metal centres from Mn(III) to Mn(II).\textsuperscript{108} Specific changes in reflection UV-vis spectra recorded on the monolayer of MnP at the liquid/solid interface indicated that such a reduction took place spontaneously at the moment the catalysts were adsorbed at the Au(111) surface. The spectra also indicated that the higher appearing signatures were stable Mn(IV)O species, which are known to be highly reactive in epoxidation catalysis (Fig. 20E). To investigate this, a small droplet of the alkene cis-stilbene was carefully added to the liquid phase while scanning was continued. STM images showed that the moment the alkene reached the liquid/solid interface, the number of Mn(IV)O species abruptly decreased (Fig. 20D). During follow-up scans, STM revealed the continuous formation of new Mn(IV)O species and their rapid disappearance, suggesting catalytic turnover. After 4 days of reaction time an aliquot of the liquid was analysed by gas chromatography, which revealed the formation of both cis- and trans-stilbene oxide, with strong selectivity to the cis-isomer. This result confirmed that the catalytic reaction had taken place. When a large number of STM images of the second reaction step, i.e. the reaction of MnP with O\textsubscript{2}, were statistically analysed, it turned out that the Mn(IV)O species were preferentially formed at adjacent locations at the surface. This cooperative effect, which can only be elucidated by employing single molecule studies at the superior lateral resolution provided by STM, suggested that each molecule of O\textsubscript{2} oxidised two adjacent catalysts (Fig. 20E). Based on this observation, a homolytic dissociation of O\textsubscript{2} was proposed, which is the only mechanistic pathway that can explain the generation of two identical Mn(IV)O particles.

To further elucidate the oxidation mechanisms involved with this type of catalyst, and in particular the Mn(III) → Mn(II) reduction step, the behaviour of the related tetraphenyl-substituted manganese porphyrin Mn1Cl (Fig. 21A) was investigated.\textsuperscript{109} A self-assembled monolayer of this compound at the 1-octanoic acid/HOPG interface showed nearly identical Mn1Cl molecules when it was imaged with an STM at positive

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**Fig. 20** (A) Manganese porphyrin catalyst MnP and the reaction it catalyses in which cis-stilbene is oxidised to cis- and trans-stilbene oxide. (B–D) STM images of a monolayer of MnP catalysts at the n-tetradecane/Au(111) interface during the multistep reaction. Tunnelling parameters: $V_{\text{bias}} = -200$ mV, $I_{\text{set}} = 10$ pA. (B) System under argon; note the two pairs of oxidised catalysts (red dots) between the native catalysts (yellow dots). (C) The same interface after the introduction of O\textsubscript{2} into the system. (D) The same interface after the addition of cis-stilbene to the liquid phase. (E) Proposed catalytic cycle showing changes in the porphyrin catalyst which were concluded from the observations in STM images. Reproduced with permission from ref. 107.

**Fig. 21** (A) Structure of the manganese porphyrin catalyst Mn1Cl. (B) STM image of a monolayer of Mn1Cl at the 1-octanoic acid/Au(111) interface under an argon atmosphere. (C) STM image showing four different signatures and their assignments of the manganese porphyrin complexes in air. Tunnelling parameters: $V_{\text{bias}} = -800$ mV, $I_{\text{set}} = 10$ pA. (D) STM image showing the cooperative formation of signature Mn1-C. Reproduced with permission from ref. 109.
or moderately negative surface bias voltages in an argon atmosphere (Fig. 21B). When the surface bias voltage was decreased below a threshold of ~600 mV in air, porphyrin signatures with varying apparent heights started to emerge. Within 10 minutes, four distinct manganese porphyrin species could be detected, labeled \( \text{Mn1-A}, \text{Mn1-B}, \text{Mn1-C} \) and \( \text{Mn1-D} \) (Fig. 21C). These signatures were assigned by carrying out a series of rational design STM experiments, in combination with thorough statistical analyses of the resulting images. Signature \( \text{Mn1-A} \) was assigned to the native \( \text{Mn1Cl} \) molecules, since it was the most abundant species at the beginning of the experiment. The assignment of signature \( \text{Mn1-C} \) was deduced from STM experiments in different atmospheres. In an inert argon atmosphere, less than 3% of \( \text{Mn1-C} \) signatures were observed in the monolayer, while in a reactive oxygen atmosphere their abundance increased to >20% surface coverage within a couple of hours. In addition, similar to the case of the previously described \( \text{MnP} \) molecules, \( \text{Mn1-C} \) signatures were also preferentially generated in pairs at the surface (Fig. 21D). The oxygen-dependent formation of \( \text{Mn1-C} \), as well as the observed cooperativity, therefore led to its assignment as an \( \text{Mn(IV)} = \text{O} \) porphyrin complex. When the evolution of \( \text{Mn1-C} \) was monitored in a large number of experiments, consecutive STM images revealed that \( \text{Mn1-C} \) was formed four times more often from a \( \text{Mn1-B} \) than from a \( \text{Mn1-A} \) precursor. For this reason, signature \( \text{Mn1-B} \) was assigned to an activated \( \text{Mn(II)} \) porphyrin. A similar activation mechanism for manganese porphyrins as was described for \( \text{MnP} \) is proposed. Whilst for the latter catalyst adsorption of the porphyrins at the liquid/solid interface, which is attributed to activation of the cobalt centres by their adsorption onto the polarised cobalt–oxygen bond.

A related example of the difference in the properties of metal–porphyrins in solution and those adsorbed at a liquid/solid interface was recently reported for the coordination of an axial ligand to the nickel analogue of \( \text{CoOEP} \), \( \text{NiOEP} \). While \( \text{NiOEP} \) in solution does not coordinate to imidazole, the ligand readily complexes with the porphyrin when the latter is adsorbed at the 1-phenyloctane/HOPG interface. In this particular case, the imidazole binds to the nickel centre as a \( \pi \)-acceptor of the 1-phenyloctane/HOPG interface, and they were able to extract the thermodynamic parameters related to this process.\(^{111}\)
charge that is donated from the HOPG surface to NiOEP. DFT calculations revealed that the surface-adsorbed nickel porphyrins are in the singlet state, whereas in solution they are in a triplet state and require σ-donor-type ligand binding. This is again evidence that adsorption onto a substrate may dramatically influence the chemical properties of functional molecules.

Phthalocyanines structurally resemble porphyrins and have often been found to readily self-assemble at liquid/solid interfaces. Wan and coworkers investigated the oxygen reduction reaction of iron phthalocyanine (FePc, Fig. 23A) complexes at the 0.1 M HClO₄/Au(111) interface in an EC-STM setup. When the FePc monolayer was imaged by EC-STM at surface potentials higher than 0.3 V under an ambient atmosphere, the molecules appeared in two distinct contrast modes (bright and dark), approximately in equal amounts. Under an inert nitrogen atmosphere the dark signature was predominantly observed, while under a pure oxygen atmosphere the bright signature was dominant. Based on the oxygen-dependent behaviour and theoretical calculations, the dark signatures were assigned to the native FePc molecules and the bright ones to FePc-O₂ complexes. When the surface potential was lowered in situ under an oxygen atmosphere, the oxygen reduction reaction was initiated, and the bright signatures associated with the FePc-O₂ complexes were immediately converted to dark ones (Fig. 23B). The process was found to be fully reversible. Under a nitrogen atmosphere no changes in molecular contrast were observed and all molecules remained in their dark state, associated with native FePc. CV experiments of the Au(111) electrode covered with FePc showed a shift in the offset potential for the oxygen reduction reaction, indicating catalytic behaviour of the monolayer.

3. Conclusions and outlook

Beyond just imaging steady state situations or dynamics of molecules, the in situ monitoring of reactivity at a surface with an STM provides a new dimension to scanning probe research and a new technique to investigate chemical reactions at a superior resolution. In addition to obtaining information about the proceeding mechanism of a reaction at the ensemble level, single molecule behaviour can be monitored in a highly appealing way: by visualisation. Being pioneered under rather extreme conditions like UHV, low temperature, or high pressure, the current developments in monitoring reactions with an STM at a liquid/solid interface bring single molecule studies closer to the realistic environments encountered in a chemical laboratory – ambient temperature, pressure and atmosphere – and the possibility of easily adding or withdrawing reactants and products without the need to interrupt the scanning. Compared to reactivity at surfaces under UHV or in air, the liquid/solid interface provides a much more dynamic environment in which reacting molecules at the surface can benefit from interaction with the liquid phase. Their self-assembled structures are allowed to reorganise and self-repair, either remaining confined to the interface or via desorption and readsoption via the supernatant. They can be exposed to variations in pH, temperature and reactant concentration, as a result of which reaction rates may be controlled. And in an electrochemical environment, precise control over the redox properties of adsorbed species can be obtained.

The new technique to study chemical reactions is, however, also accompanied by limitations, the most important one being time resolution. Typically, scanning a surface of several tens of square nanometres with an STM takes at least multiple seconds, which is very slow when compared to the time frame of most chemical reactions. Faster scanning is in principle possible, but is typically also accompanied by a poorer resolution. Although efforts have been undertaken to develop STMs which operate at video-rates, they have not yet been routinely applied in reactivity studies at the liquid/solid interface. Therefore, when it comes to studying reactivity with an STM one of the major challenges will be to obtain increased time-resolution. Alternatively, a careful choice of the reaction under study might still yield valuable results. When a reaction proceeds only slowly, STM snapshots at certain time intervals can provide very valuable information about reaction mechanisms.

One should also always keep in mind that scanning by the STM tip is not necessarily innocent; apart from mechanical effects it can also have electronic effects on the adsorbed molecules, since close to the tip a strong local electric field is present. For that reason it is advisable, if possible, to always correlate results obtained by STM with results obtained by complementary techniques. Here one can, for example, think about surface analysis methods like reflection UV-vis or Raman spectroscopy, or analysis of the supernatant solution by conventional analysis techniques.

Despite its limitations, a bright and exciting future can be foreseen for STM as a new tool to study reactivity at a liquid/solid interface. Many reactions from the bulk are waiting to be investigated at the single molecule scale at a surface, and without doubt STM will reveal new insights about reaction mechanisms and possibly be able to identify meta-stable reaction intermediates, simply by their visualisation. Fundamentally new
insights can be expected when it really becomes possible to relate the surface structure and chemical reactivity at the nanoscale. For example, from heterogeneous catalysis and sustainability points of view it is essential to know why certain parts of a catalytic surface are more reactive than others, and STM can deliver the required resolution to address such questions. It will also be of interest to investigate the mechanisms by which chirality is transferred from a chiral surface, or a monolayer of chiral catalysts, to an enanti-selectively formed reaction product. The increased interest in STM studies of chirality at liquid/solid interfaces can serve as an excellent basis for such investigations.17

New insights obtained from STM research might also lead to novel approaches towards the bottom-up construction of functional self-assembled networks. The recent boost in developing nanoporous surfaces and 2D-COFs, which can serve as two-dimensional hosts for one or more guest molecules, paves the way for introducing compartmentalisation in surface-confined catalysis and molecular electronics research.118,119 Pores of several nanometers in size can serve as nanoscale reaction vessels, in which in a liquid environment highly selective reactions may be carried out between a limited number of molecules. Obviously, an STM will be the instrument of choice to study such reactions. Finally, it will be of particular interest to obtain full control over surface-confined reactions. In this respect it can be foreseen that EC-STM will become an important monitoring tool, since it allows control over redox states of molecules adsorbed at the liquid/solid interface. In this way, it becomes possible to start and stop reactions, by inducing reactive and inert states in molecules.

For future advances in single molecule reactivity at liquid/solid interfaces, additional STM device modifications can be envisaged that allow more control over the structure and reactivity in these environments. Precise temperature control is a very important ability that will allow the extraction of kinetic and thermodynamic parameters from interface-based processes. The possibility of controlling atmospheric composition and pressure, as well as to exchange liquids at a liquid/solid interface in a non-invasive way, will further widen the scope of this research area. In this context it can be foreseen that in the near future STMs will become an integrated module of reactor-type platforms that operate under full (micro)fluidics, atmosphere and temperature control.

At this moment, the study of chemical reactions with an STM is an area of research which is still in its infancy. But given the importance of active surfaces in industry and everyday life, fundamentally new insights into reactivity at the highest resolution possible might lead to new directions in catalyst development, and to the rational design of increasingly efficient functional materials that operate in the dynamic environment of a liquid/solid interface.

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