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PERSPECTIVE

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Recent advances in submolecular resolution with scanning probe microscopy

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Recently scanning probe microscopy has made tremendous progress in imaging organic molecules with high lateral resolution. Atoms and bonds within individual molecules have been clearly resolved, indicating the exciting potential of this technique for studying molecular structures, bonding within and between molecules, molecular conformational changes and chemical reactions at the single-molecule level. It turns out that the key step enabling such studies is an atomically controlled functionalization of the microscope tip. In this Perspective, the different techniques used for high-resolution molecular imaging, their implementations, advantages and limitations are described, and possible scientific areas of applications are discussed.

It has been a long-standing goal to image individual organic molecules with atomic resolution. Although atomic resolution is routinely obtained on many crystalline surfaces by scanning probe microscopy (SPM) methods, clear atomic resolution on molecules has only been achieved in the past two years by means of non-contact atomic force microscopy (NC-AFM)[1,2] and scanning tunnelling hydrogen microscopy (STHM)[3–5]. In these recent works aromatic molecules were imaged, and for the first time the individual atoms within the molecules were resolved. The obtained images directly visualize the molecular structure, for example, showing hexagons at the position of six-membered carbon rings. For both techniques, NC-AFM and STHM, an atomic functionalization of the sensor (that is, the placing of a well-defined atom or molecule at the tip of the scanning probe) was the key for achieving enhanced resolution. In the case of atomic force microscopy (AFM), the tip was modified by deliberately picking up a single carbon monoxide molecule, whereas in the case of STHM, the resolution was increased after bringing molecular hydrogen into the gap between the tip and the sample. Both techniques produce high-resolution images that closely resemble the molecular structure.

This improved resolution has immediately proved useful for applications to identify the molecular structure of natural compounds[2], to visualize intermolecular interactions in self-ordered molecular layers[5], and to investigate a novel molecular switch based on the reversible bond formation between an atom and a molecule[6]. Potential areas of impact are molecular surface chemistry and catalysis, molecular electronics and organic photovoltaics. In all these areas, SPM methods offer the possibility of investigating the relevant processes in real space and on the level of individual molecules. The broad spectrum of applications is made possible by the variety of scanning probe methods that access different properties. For example, the forces and energies associated with tip-induced molecular conformational changes[7] and lateral atomic manipulations[8] have been determined using AFM.

Using scanning tunnelling microscopy (STM) and spectroscopic methods, it was possible to map different properties of molecules with submolecular resolution, such as molecular orbitals[9], STM-excited fluorescence[10] and reaction rates[11]. Additional operation modes of NC-AFM capable of atomic resolution — such as Kelvin probe force microscopy (KPFM) for atomic charge state measurements[12], magnetic exchange force microscopy (MExFM)[13] and force spectroscopy with chemical sensitivity[14] — have yet to reach atomic resolution on molecules. This Perspective gives an overview of recent developments and their respective areas of application.

Atomic manipulation

Besides using the probe tip for a measurement, SPM offers the fascinating possibility of atomic manipulation techniques, as introduced by Eigler and co-workers[15]. Atoms and molecules can be pushed, pulled or slid on a surface[15,16] — referred to as lateral manipulation. Moreover, adsorbates can be picked up and dropped with the probe tip — referred to as vertical manipulation[17,18]. Using lateral manipulation, molecules can be placed with atomic precision to study them at certain adsorption sites[19–21]. Furthermore, their motion can be studied[22–24], and reactions can be induced by forming or breaking molecular bonds with voltage pulses from the STM tip[11,24–26]. Vertical manipulation can also be used for studying the contact of individual molecules with the STM tip[27,28]. These manipulation techniques have been known and refined in the STM community for almost 20 years. Notably, great progress has made with the AFM in recent years — both lateral[8,29] and vertical atomic manipulation[30] has been demonstrated with this tool.

Most important in the context of high-resolution imaging is the fact that vertical atomic manipulation can be used to functionalize the probe tip[17]. By approaching the tip to a certain adsorbate, for example an atom[17] or a molecule[18], and applying a voltage pulse when the tip is above it, the adsorbate can be transferred from the surface to the end of the tip. After the transfer, the tip is functionalized, and the imaging contrast crucially depends on the tip functionalization.

For people working with SPM, it is reality that a large part of their time is spent on tip preparation, which can be exchanging, heating or sputtering tips, applying voltage pulses, or even crashing tips repeatedly into the sample surface. All this will affect the tip in certain ways, and after repeated preparation procedures and successive testing of the tip in SPM operation, sometimes a tip is found that shows good resolution. The problem with these tip preparation methods is that the resulting atomic structure of the tip is usually not known exactly.

Compared with these approaches, tip forming by means of controlled vertical atomic manipulation has two very important advantages. First, it is highly reproducible, and second, the atomic structure of the foremost part of the tip is known after the functionalization, which greatly aids interpretation of the data. The

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ideal atom or molecule for tip functionalization depends on the system under investigation and on the property that should be measured. The recent advances in molecular resolution achieved with NC-AFM are based on using vertical atomic manipulation to functionalize the tip of an AFM[1].

Non-contact atomic force microscopy

Atomic resolution on organic molecules was realized by means of NC-AFM at low temperatures (5 K) using a qPlus sensor. This sensor consists of a quartz tuning fork with one fixed prong and one free-standing prong that holds the tip[31]. The tuning fork is operated in frequency-modulation mode[32], that is, it is oscillated at its resonance frequency of about 30 kHz, and the signal measured is the shift of the resonance frequency Δf caused by the interaction between tip and sample. The large stiffness of the qPlus sensors cantilever ($k \approx 1{,}800\ \mathrm{Nm}^{-1}$) facilitates oscillation at small amplitudes (below 1 Å), an important prerequisite for measuring short-range forces to achieve atomic resolution[33].

To increase the resolution on organic molecules, the AFM tip was functionalized by picking up individual atoms or molecules by means of vertical atomic manipulation. Atomic resolution was achieved with carbon monoxide as well as with chlorine-functionalized tips, but not with Cu, Ag or Au terminations[1]. The best contrast was observed with CO functionalization, which revealed the atoms and bonds within molecules[1,2] and was even able to image C–H bonds, as shown in Fig. 1. The success rate for functionalizing a metallic tip with a CO molecule yielding high-resolution AFM images is about 30%. In the case of no success — that is, CO can not be picked up, or CO is picked up but afterwards the tip is asymmetric, unstable or shows no increased resolution — a new tip is formed by crashing the probe into the metal substrate (Cu in the shown examples) and the attempt to pick up a CO molecule is repeated. Figure 1a schematically shows how a pentacene molecule is imaged using a CO-functionalized tip. The tip model shows the CO molecule at its presumed adsorption site on the metallic (Au) tip with the carbon atom at the on-top site[18]. Figure 1b shows an AFM image of cephalandole A (its chemical structure is shown in Fig. 1c) also acquired with a CO functionalized tip.

Using density functional theory (DFT) these AFM measurements could be simulated with excellent agreement, the contrast mechanism could be well understood and the atomic contrast could be assigned to Pauli repulsion[1,2,34]. The longer-ranged attractive van der Waals and electrostatic forces show no atomic corrugation and give rise to the dark halo surrounding the molecule. The atomic features only become visible when working at small enough tip heights, that is, in the regime of Pauli repulsion between the CO molecule at the tip and the imaged molecule on the surface. The CO molecule can increase the resolution because of its small size and its chemical inertness, both of which facilitate its passing through the attractive interaction regime without bonding and finally entering the repulsive regime. The high-resolution images with the CO tip are usually obtained in the regime of maximum attractive forces between tip and sample. In this regime, the overall contributions from electrostatic and van der Waals forces are still larger compared with the Pauli repulsive forces. However, the attractive force components show little corrugation on the atomic scale and therefore only contribute an attractive background force. In the case of less inert tips, for example Au-, Ag- or Cu-terminated tips, the attractive forces became too large when trying to enter in the regime of Pauli repulsive forces, resulting in manipulating rather than imaging the molecule under investigation[1].

Non-contact atomic force microscopy has proved to be useful in the identification of natural compounds because the real-space data obtained is complementary to the information obtained by NMR and mass spectrometry. In the example reproduced in Fig. 1b, the imaged molecule could be successfully identified as cephalandole A by combining AFM, NMR, and DFT data[2].

Scanning tunnelling hydrogen microscopy

In 2008, Temirov *et al.*[3] demonstrated atomic resolution on molecules using STM. They also increased the resolution by 'inserting' a certain molecule between tip and sample. A spectacular enhancement of the resolution was observed after admitting molecular hydrogen (or deuterium[4]) into the system — a technique therefore dubbed scanning tunnelling hydrogen microscopy. Figure 2a shows a high-resolution image of PTCDA (3,4,9,10-perylene-tetracarboxylic-dianhydride; its chemical structure is shown in Fig. 2b) obtained by STHM — the six-membered rings constituting the molecule are clearly visible. The underlying imaging mechanism was also assigned to Pauli repulsion[4]. The hydrogen molecule physisorbs in the tunnelling junction and changes its position owing to Pauli repulsion, resulting in a change of the tunnelling current. The hydrogen molecule is thus believed to act as an uncalibrated transducer between the force and the tunnel current. However, because of its complexity, this imaging mechanism is not yet understood completely and so far no STHM images have been simulated by theory.

Scanning tunnelling hydrogen microscopy was applied to the investigation of molecular monolayers[3,5]. In this case, the high accuracy of measuring the molecular orientation is very important,

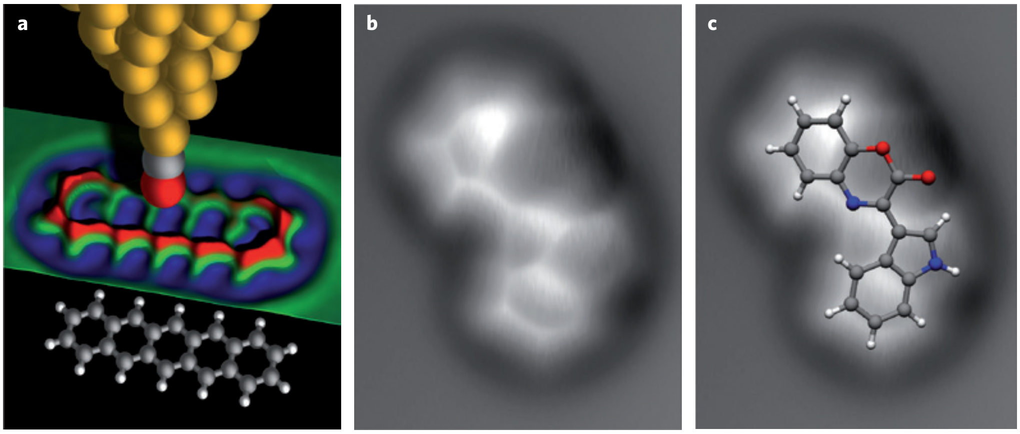

Figure 1 | Molecules imaged with atomic resolution using NC-AFM. Constant-height NC-AFM measurements using CO-functionalized tips. **a**, Model of a CO-functionalized tip above a pentacene molecule. The measured AFM data is shown as a colour-coded map (Δf = −7 Hz (blue) to −2 Hz (red); oscillation amplitude A = 0.02 nm; measurement data taken from ref. 1). **b**, Cephalandole A. Image size 1.6 nm × 1.9 nm; A = 0.05 nm; grey scale from −7 Hz (dark) to +2 Hz (bright). **c**, The same image as (**b**) with the molecular model of cephalandole A overlaid. Images **b** and **c** reprinted with permission from ref. 2, © NPG 2010).

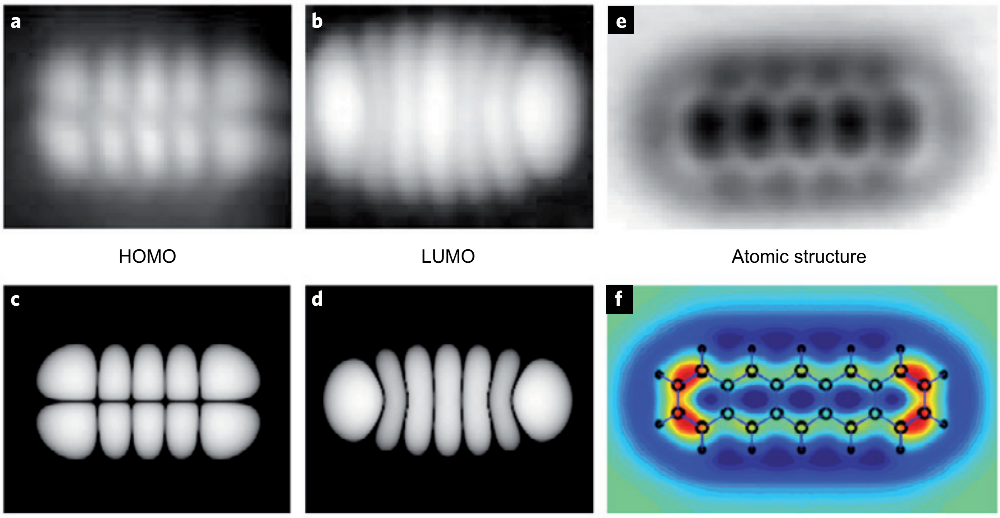

Figure 3 | Pentacene imaged with STM and NC-AFM. a,**b**, Molecular orbital images of pentacene on two monolayer NaCl on Cu(111) obtained by STM using a pentacene-terminated tip. Image size 2.5 nm × 2.0 nm; constant current. The HOMO (**a**) was imaged by setting the sample voltage to the first resonance at negative bias at V = -2.5 V, thus tunnelling out of the molecular orbital. The LUMO (**b**) is imaged by electrons tunnelling from the tip into the orbital at positive bias V = +1.7 V. **c**,**d**, Contours of constant orbital probability distribution of the HOMO (**c**) and LUMO (**d**) of the free pentacene molecule obtained by DFT. **e**, NC-AFM image of pentacene on two monolayer NaCl on Cu(111) obtained using a CO-functionalized tip. Image size 2.2 nm × 1.4 nm; oscillation amplitude A = 0.07 nm. **f**, Computed frequency shift for an intermolecular distance d = 0.475 nm between CO and pentacene. Reprinted with permission from: **a**–**d**, ref. 9, © 2005 APS; **e**, ref. 1, © 2009 AAAS; **f**, ref. 34, © 2010 IOP.

and it is even possible to visualize intermolecular hydrogen bonds[5] (as shown in Fig. 2c and Fig. 2d) indicating the great potential of this technique for the investigation of molecular networks.

When comparing STHM and AFM, the most important difference is that AFM offers the possibility of measuring forces and energies quantitatively. Measuring them is the key to many applications in surface science because interaction forces and potential maps can be obtained directly and, furthermore, a quantitative comparison with DFT calculations is possible. In STHM, the unknown conversion between force and current renders a quantitative extraction of forces and the simulation of measurements extremely challenging.

Although both techniques, AFM and STHM, can image atoms and bonds within individual molecules, there are differences in the contrast they deliver. In AFM, a halo surrounding the molecules is observed originating from van der Waals and electrostatic forces. Furthermore, the intramolecular C–H bonds are clearly resolved with AFM. STHM has so far been applied to adatom dimers[4] and molecular monolayers, where it could also resolve intermolecular bonds, but individual isolated molecules have not yet been investigated. A general advantage of AFM is its applicability on insulating substrates, whereas an advantage of STHM is its ease of use. The technically demanding overhead to perform NC-AFM (sensor implementation, oscillation detection, control of oscillation amplitude and frequency) is not needed, and STHM can easily be implemented in existing low-temperature STM systems by admitting molecular hydrogen or deuterium[4].

Conventional scanning tunnelling microscopy

Scanning tunnelling microscopy is highly sensitive to the molecular electronic structure, and its capability of imaging molecular orbitals has been demonstrated[9,35]. However, STM images electron densities with energy selection given by the applied voltage, which usually restricts STM to energy levels near the Fermi energy, that is, to the frontier orbitals. Accordingly, STM (unless performed as STHM) does not image the atomic structure, but can resolve molecular orbitals. Therefore, AFM or STHM, with their capability of resolving atoms, nicely complement STM. All this information has been measured for pentacene and yielded a complete dataset for this molecule, shown in Fig. 3. The experiments were performed on a thin insulating film (two monolayer) of NaCl grown on a Cu substrate to decouple the molecules from the metal and to reduce hybridization and broadening of the molecular orbitals. The decoupling by an insulating layer is useful for studying orbitals and electronic structures in general, as also demonstrated in many other experiments[9–12,36–43]. Note that for the molecular orbital imaging with STM, vertical manipulation was used to increase the resolution by functionalizing the tip with a pentacene molecule[9]. The highest occupied molecular orbital (HOMO) and the lowest

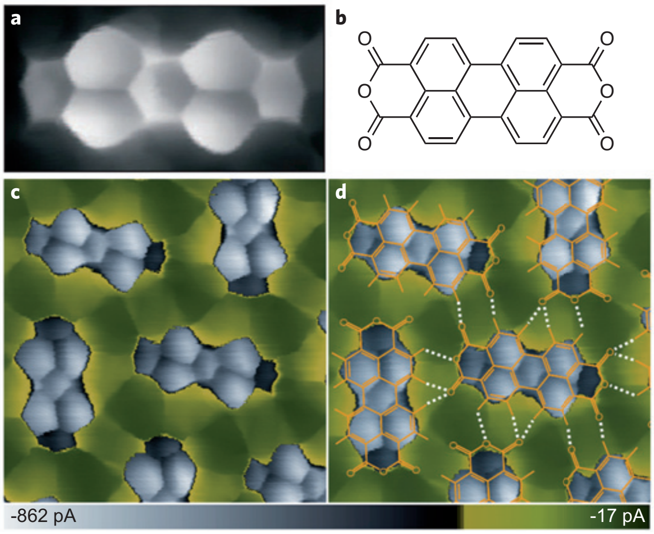

Figure 2 | PTCDA monolayer imaged with STHM. a, STHM image of PTCDA on Au(111). Image size 1.3 nm × 0.7 nm; constant height, V = 5 mV. **b**, Chemical structure of PTCDA. **c**, STHM image of the herringbone phase of PTCDA on Au(111). Image size 2.5 nm × 2.5 nm; constant height, V = -2 mV. **d**, The same image with the molecular structures and possible hydrogen bonds indicated. Reprinted with permission from: **a**, **b**, ref. 4, © 2010 APS; **c**, **d**, ref. 5, © 2010 ACS.

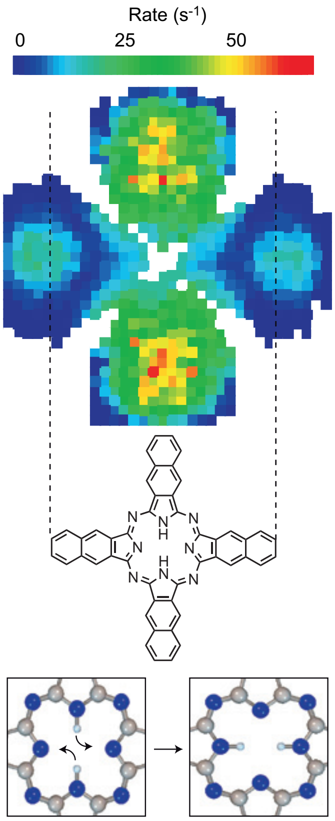

Figure 4 | Measuring reaction rates with submolecular resolution. Spatial map of the switching rate for the hydrogen tautomerization reaction (shown in the insets below). The reaction rate is measured using STM time traces at each pixel for a tunnelling current of 1 pA at a bias of 1.825 V. For reference, the structure of the molecule is displayed to scale. Reprinted with permission from ref. 11, © 2007 AAAS.

unoccupied molecular orbital (LUMO) were imaged with STM by selecting the respective voltage as shown in Fig. 3a and Fig. 3b. The AFM measurements on pentacene shown in Fig. 3e were performed with a CO-modified tip as described above. Additional DFT calculations were carried out to corroborate the interpretation of the STM data[9] (Fig. 3c,d) and the AFM data[1,34] (Fig. 3f).

Additional scanning tunnelling microscopy modes

To discuss the prospects of SPM for molecular imaging it is important to also take a look at the spectroscopic techniques and STM modes that assess different measurement signals. Various modes of scanning tunnelling spectroscopy (STS) have already proved their value in revealing highly interesting properties of molecules on the submolecular scale. For example, imaging by inelastic electron tunnelling spectroscopy (IETS) was used to probe the excitation of vibrational modes with submolecular resolution[43–45].

Single-molecule switching mechanisms have been studied extensively by STM and STS[11,24,42,46], motivated by future applications in molecular electronics[47]. A molecular switch that has been investigated in great detail is the STM-induced hydrogen tautomerization reaction of naphthalocyanine[11]. The switching rate was mapped as a function of the lateral tip position, as shown in Fig. 4. This map shows that the switching can be directed toward a certain outcome by choosing the exact tip position for the current injection above the molecule. For this measurement the tautomerization reaction has been induced about 100 times at each pixel on average, giving in total ~75,000 switching events of this molecule, demonstrating the reliability of the process[11].

Recently, a switch based on the reversible bond formation between a PTCDA molecule and a Au atom on a thin insulating film was investigated using both STM and NC-AFM[6]. Whereas STM was used for the operation of the switch and its electronic characterization, NC-AFM provided the exact geometric conformations of the atom–molecule complex.

Further information can be obtained by combining STM with optical spectroscopy in STM-induced photon emission from single molecules[13,36]. Chemical recognition based on fluorescence and phosphorescence spectra has been demonstrated[36], as well as submolecular resolution in fluorescence spectra[10] and photo-induced resonant tunnelling[37,38].

Furthermore, the magnetic properties of molecules are also of interest, especially for future technologies including classical and quantum computation. Spins can be investigated on the single-atom and molecular level using spin-polarized (SP-)STM[48–50] and spin-flip spectroscopy[39–41,51]. Nanosecond time resolution has recently been demonstrated, using spin-flip spectroscopy to measure spin-relaxation times in FeCu complexes[41]. SP-STM has been demonstrated with impressive intramolecular resolution on Co–phthalocyanine, revealing large variations of the spin polarization above a molecule that range from amplification to inversion with respect to the underlying Fe film[50].

Additional atomic force microscopy modes

In NC-AFM, spectroscopic methods are also very interesting and can be exploited to access many different properties. In fact, to obtain forces (that is, the tip–surface interaction force) and energies (that is, the tip–surface interaction energy) from the measured frequency shift Δf, one already has to perform force–distance spectroscopy. The force can then be computed by integrating Δf with respect to the vertical tip height, with some corrections for the finite oscillation amplitude[52], and three-dimensional force maps can be obtained[53]. Atomic resolution in the force maps of molecules was demonstrated by Gross and co-workers[1], and Moll *et al.*[34] showed that at specific tip–sample distances, Δf, force and energy maps are comparable and show similar atomic resolution and contrast above molecules.

Moreover, using force–distance spectroscopy, chemical contrast was demonstrated on semiconductor surfaces, whereby three different species of atoms could be clearly distinguished by comparing the maximum attractive force — see Fig. 5 (ref. 14). Remarkably, this experiment was even performed at room temperature, unlike the other data shown in this Perspective, which all were obtained at cryogenic temperatures. However, for several reasons, the application of this technique to obtain chemical contrast on molecules remains challenging. First, the atomic distances in molecules are smaller than for the experiment shown here, for example, the length of a C–C bond is only one fourth of the nearest-neighbour distance in the example shown in Fig. 5. Second, in molecules, atomic species can appear in different coordination and with different bond order, and therefore atoms with different hybridization might appear differently in NC-AFM. Further challenges arise from the fact that molecules are usually not planar, and even small deviations from a planar geometry complicate both measurement and analysis and have to be taken into account in the interpretation of the data, as shown in the case of cephalandole A (ref. 2). Furthermore, when imaging a semiconductor surface the AFM tip interacts with the directed dangling bonds of the atoms in the topmost layer. Such dangling bonds are absent in the case of hybridized molecular orbitals. Finally, adsorbed molecules are usually less stable than atoms in crystal surfaces, and care must be taken not to manipulate the molecule during imaging. Nevertheless, a possible route toward chemical sensitivity on molecules is the use of different tip functionalizations and comparison of the resulting interaction forces. The change

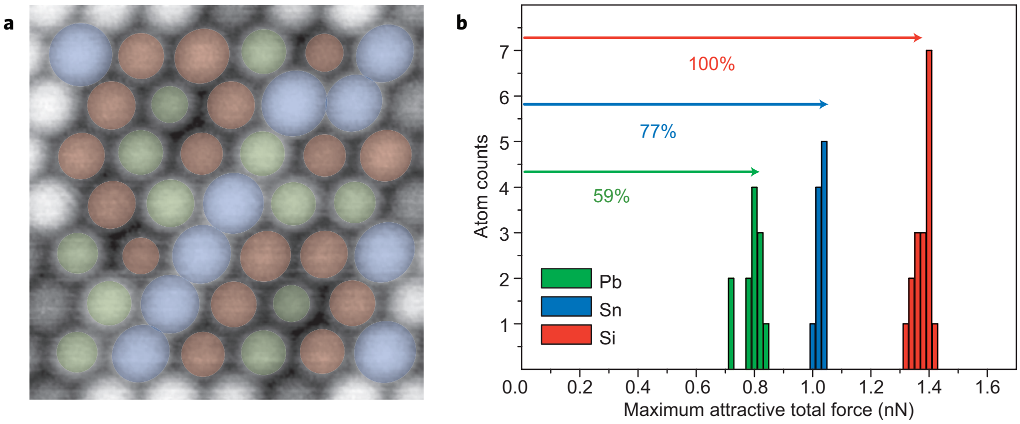

Figure 5 | NC-AFM with chemical sensitivity. a, NC-AFM image of a surface alloy composed of Si, Sn and Pb atoms blended in equal proportions on a Si(111) substrate. The colour coding corresponds to the chemical species as determined by force distance spectroscopy: Si, red; Pb, green; Sn, blue. **b**, Atom counts as a function of the maximum measured attractive force above the Pb, Sn and Si atoms. The three different atom species are clearly distinguished by their respective maximum forces. Reprinted with permission from ref. 14, © 2007 NPG.

in contrast due to different tip terminations could yield chemical contrast for certain elements as pointed out by Gou *et al.* in a recent theoretical study[54].

Atomic force microscopy experiments on molecules demonstrate the capability of this technique to directly measure forces and energies. For example, the energy associated with the conformational switching of a single molecule was directly measured using force–distance spectroscopy[7], and for a CO molecule on Cu(111) a map of the interaction potential could be measured directly by manipulating the CO molecule with the AFM tip[8].

Other operation modes of AFM have so far only shown limited intramolecular resolution, but give rise to expectations for the future. In particular KPFM and MExFM could provide interesting information if they reach atomic resolution on molecules. KPFM — which can be performed as bias spectroscopy with the NC-AFM — has been shown to measure the local contact potential difference with atomic resolution on both semiconductors[55–58] and insulators[59]. This technique is extremely sensitive to charges, and recently the measurement of atomic charge states was demonstrated[12]. KPFM could be suitable for measuring the charge states and even charge distributions on individual molecules or complexes[60]. Such information would be valuable in investigating charge transport in molecular electronics[47] and single-electron devices[61,62] as well as for charge separation in organic photovoltaics. Furthermore, important insight into catalytic processes could be gained as the charge state also governs the catalytic reactivity of adsorbates.

Magnetic exchange force microscopy detects the short-range magnetic exchange force between tip and sample spins, and atomic resolution in measuring the spin contrast on thin antiferromagnetic films has recently been achieved[13,63]. MExFM, like SP-STM and spin-flip spectroscopy, has promising applications in research focusing on the combination of molecular electronics and spintronics[64].

Outlook

In general, STM and AFM measure different properties, and their results can complement one another as shown in the example of pentacene, where molecular orbitals and molecular structure were resolved with STM and AFM, respectively. Recent improvements in NC-AFM and STHM have resulted in clear atomic resolution on individual molecules, mainly achieved owing to defined tip functionalization. In the near future, several offspring techniques of STM and AFM are expected to reach atomic resolution on molecules. In terms of molecular-structure identification, the application of AFM spectroscopic techniques for increased chemical sensitivity is promising. Moreover, additional parameters will be measured with submolecular resolution using STM-induced light emission, spin-flip spectroscopy, SP-STM, KPFM and MExFM. In all these cases it can be expected that atomically defined tip functionalization will again be a key step to further increase the resolution and sensitivity of these techniques on molecules.

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Additional information

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ERRATUM

Recent advances in submolecular resolution with scanning probe microscopy

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In the version of this Perspective originally published, the arrows in Fig. 5b were too short, and should have appeared as shown here. This has now been corrected in the HTML and PDF versions.