Single-Molecule Recognition and Manipulation Studied by Scanning Probe Microscopy

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Hydrophilic → non-sticky
Hydrophobic → sticky


MTAN-inhibitor

Scanning Probe Microscope (SPM): Basic aspects

- Surface
- Tip
- Motion
- Atmosphere

Even-COOH vs. even-COOH

m1, m2
Scanning

- Principle of piezo element. The applied voltage makes the element longer or shorter.

- The combination of three piezo elements makes it possible to move the STM tip in the X-, Y-, and Z-directions.

- In most modern scanning probe microscopes, one uses a tube geometry.
Local structures without periodicity can be understood only by scanning probe microscope.
Resolution

**Instrument**

- Mechanical Profiler
- Optical Profiler
- Atomic force microscope (AFM)
- Scanning tunneling microscope (STM)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Depth Resolution</th>
<th>Lateral Resolution</th>
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<tr>
<td>Mechanical Profiler</td>
<td>0.5 nm</td>
<td>0.1-25 μm</td>
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<tr>
<td>Optical Profiler</td>
<td>0.1 nm</td>
<td>0.35 - 9 μm</td>
</tr>
<tr>
<td>Atomic force microscope (AFM)</td>
<td>0.01 nm</td>
<td>0.1 nm</td>
</tr>
<tr>
<td>Scanning tunneling microscope (STM)</td>
<td>0.001 nm</td>
<td>0.1 nm</td>
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</table>
Scanning Probe Microscope (SPM)

General experimental approach-
Monitor a physical quantity which is dependent on separation between a probe tip and a sample surface.
→ Use Current (I) and Force (F)

• Scanning Tunneling Microscope (STM)
• Atomic Force Microscope (SFM)

SPM techniques provide unique information-

Local - probes topographic and electronic structure on an atomic scale
Real space - information is collected through a direct measurement
STM-monitors a tunneling current.

\[ I \propto U e^{-\left(k d \sqrt{\Phi}\right)} \]

- I - tunneling current
- U - sample bias
- k - transmission coefficient
- d - tip sample separation
- \( \Phi \) - average work function

- conductive sample
- tunneling current: pA~nA
- lateral resolution: 0.1nm
- depth resolution: 0.001nm
PRINCIPLE of STM

$I(d) \propto \exp\left(-\text{const.} \times \sqrt{\Phi d}\right)$

Pd(111)
STM Tip
PVBA/Pd(111)
Molecular Orientation and Chiral Recognition of a Single Chiral Molecule

Adsorption Preference of PVBA on Pd(111)
(Submitted to PRL, July 2003)

Model Potential $V(r)$ between a Carbon Atom and fcc(111)

$V(r) = \begin{cases} 
0 & \text{at a top-site}, \\
1 & \text{at a hollow site}
\end{cases}$

(Fourier Expansion of Surface Reciprocal Lattice)

$V(r) = \frac{2}{3} - \frac{2}{9} \sum_{n=0}^{2} \cos \omega_n \cdot kr$

$r$ : position coordinate, $\omega_0=(0,1)$, $\omega_1=(-\sqrt{3}/2, -1/2)$, $\omega_2=(\sqrt{3}/2, -1/2)$, $k = 4\pi/\sqrt{3} a.$
Binding Energy

Summation of each potential value for all atoms of two rings as a function of angle for each chirality ($\chi$)

\[\begin{array}{cccccc}
\text{Energy (a.u.)} & \text{Angle (°)} & \lambda & & \delta & \\
5 & 0 & 60 & 120 & 180 & \\
10 & 0 & 60 & 120 & 180 & \\
15 & 0 & 60 & 120 & 180 & \\
\end{array}\]
Orientation and Chiral Recognition of PVBA on fcc(111)

Pd(111) Orientation

Ag(111) Orientation

No Chiral Recognition

Chiral Recognition
AFM-Monitors interfacial forces

\[ F \propto \left(\frac{1}{d}\right)^x \]

F-interfacial force
d-tip sample separation
x-power law of acting force

Interfacial forces include:
- repulsive forces (contact AFM)
- van der Waals forces (noncontact AFM)
- electrostatic forces (EFM)
- magnetic forces (MFM)
- chemical forces (CFM)

- interfacial forces: \( pN - nN \)
- lateral resolution: 0.1- 10nm
- depth resolution: 0.01 – 0.1nm
Atomic Force Microscopy (AFM)

AFM has made it possible to view living biomolecules with atomic resolution in physiological environment.
AFM Tip and Cantilever

• Tip radius: 4 nm
Surface Forces on Switchable Bioactive Surfaces Studied by Interfacial Force Microscope

Thermally-Activated Surfaces: Tethered PNIPAM Films

Probing of Biomolecular Interaction

Hydrophilic $\rightarrow$ non-sticky

Hydrophobic $\rightarrow$ sticky

Force-Distance Curve
Single Molecular Force Spectroscopy
Enzyme-inhibitor interaction

Bomb Fishing

Hook and Bait Fishing
5’-methylthioadenosine/S-adenosylhomocysteine nucleosidase (MTAN)

**Substrate**

\[ \text{S-Adenosylhomocysteine (SAH)} \]

**Inhibitor**

\[ \text{Homocystinyl Immucillin A (HIA)} \]

This enzyme-inhibitor pair is an important one, owing to its potential for antibiotic development.
MTAN-inhibitor interaction

\[ \text{Epoxy group forms a covalent bonding with } -\text{NH2 group} \]
→ Statistical analysis enables to probe intermediate states between an enzyme and an inhibitor for a new drug design
Temperature Controlled Reversible Switching in Tethered pNIPAM films

Graph showing the relationship between temperature and advancing contact angle, with notable thicknesses and hydrophilic/hydrophobic states indicated.

Chemical structure of poly(n-isopropylacrylamide) shown.
PNIPAM+Microhotplate = Reversible Protein Trap

PNIPAM coating on silicon nitride membrane (200 μm wide)

Hot plate can be programmed to heat PNIPAM above transition

Heating promotes protein adsorption. Cooling promotes protein desorption
Variable Temperature Studies Reveal Sharp Transition for PNIPAM
-ODTS Coated Tip

Behavior of PNIPAM under water
1) All surfaces experience long-range repulsion consistent with “anti fouling” behavior
2) The repulsion collapses at a sharp transition temperature
3) Above the transition, PNIPAM surface become sticky after contact is made, consistent with protein adsorption.
Tip-PNIPAM Interactions

Below Transition Temperature

Chain Hydration (2 nm thick)
1) Promotes swelling
2) Inhibits adhesion

Above Transition Temperature

Disruption of Hydration Layers
1) Allows collapse
2) Promotes adhesion
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