Supramolecular Chemistry

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Feeling the Force of Supramolecular Bonds in Polymers

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Intermolecular forces control the self (and directed) assembly of molecular building blocks into organized supramolecular structures[1] and structural hierarchies. These forces are directional and relatively weak relative to the strength of the covalent chemical bonds that hold the building blocks together. Molecular geometry is equally important for building supramolecular materials, as without fitting and complementary molecular shapes specific recognition forces cannot bring about self-organization.

The complex and well-defined supramolecular equilibrium structures can self-repair themselves if the covalently bonded building blocks are forced out of their equilibrium position by external perturbations. However, as the strength of the operative interactions is on the order of k_BT, when supramolecular materials evolve towards their thermodynamic equilibrium, they may get trapped in metastable states, which prevents self-healing. Rational molecular design of the individual building blocks and supramolecular aggregates can yield materials with functions such as sensing and recognition, catalytic activity, molecular photonic and molecular magnetic properties, molecular delivery (dendritic cages), and self-healing properties (e.g., polymers).[2] It is also believed that understanding the interplay of interactions in supramolecular soft matter and the resulting organization will also bring us closer to understanding the origin of life.

The strength of intermolecular interactions and the corresponding intermolecular forces have been traditionally assessed by ensemble thermodynamic approaches with thermodynamic potentials (enthalpy, free energy). However, as a result of the growing interest in bottom-up molecular nanotechnologies, there is a growing need to know bond strengths and molecular stability from the single-molecule perspective, as well. As atomic force microscopy (AFM) techniques can now be used to manipulate molecules with nanometer precision[3] (in a direct one-to-one control of the individual species), adequate knowledge of supramolecular forces is also crucially important for molecular nanofabrication by AFM.

Chemical functionalization of AFM probe tips by self-assembled monolayers (by using, for example, ω-functionalized thiols for gold coated tips,[4] or functionalized silanes for oxidized Si tips[5]) introduced a new dimension to AFM, namely, chemistry. Tip functionalization approaches allow noncovalent molecular forces in supramolecular dimers, or polymers[6] to be mapped directly by measuring molecular forces as a function of distance between the AFM tip and the substrate surface. For this purpose, one of the interacting components of the supramolecular unit of interest is (usually covalently) attached to the AFM probe tip and the other to the substrate surface. The tip is then positioned such that the formation of specific supramolecular bonds between the tip-immobilized and the surface-immobilized complementary groups is established. Pulling the interacting molecules apart can lead to rupture of the supramolecular bonds of interest. AFM force–distance curves are measured while the tip is pulled, and at rupture the strength of individual supramolecular chemical bonds (or nonspecific surface-tip interaction forces, or the rupture of multiple bonds in parallel or in series) can be directly probed. If covalently bound spacer linkages, connected via supramolecular bonds, are inserted between the tip and the substrate, these will first be stretched prior to rupture. The entropic force contributions to molecular forces involved in chain alignment can also be assessed. This experimental approach is often referred to as AFM-based single-molecule force spectroscopy (AFM-SMFS). Force-extension relationships of supramolecular linkages (also possibly connected through covalent short-chain spacers) can be probed as a function of pulling speed (or force loading rate experienced by the bonds of interest), temperature, and solvent environment. Eventually, the weakest link in the molecular architecture connecting tip and substrate will rupture. Single biomolecules have been targeted for more than a decade by AFM-SMFS.[7] Binding potentials of receptor–ligand pairs, protein folding and unfolding pathways, DNA mechanics, DNA-binding proteins, and drugs have also been elucidated.

Although the concept of pulling and breaking seems simple, the adequate interpretation of AFM-SMFS data is full of challenges. For example, mechanical loading of supramolecular bonds increases bond dissociation rates relative to the mechanical stress-free case, as was first emphasized by Bell,[8] in situations far from equilibrium. This complicates the use of AFM-SMFS for complex molecular architectures, but also presents opportunities to study well-defined systems from new perspectives, as im-

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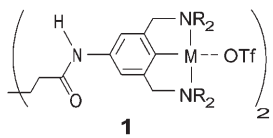
portant parameters of the potential-energy landscape along the unbinding reaction coordinate can be determined from loading rate dependencies.

Examples of AFM-SMFS targeting synthetic, supramolecular dimers and polymers with well-defined, "designer" molecular structure and architecture are still relatively sparse compared with the number of studies on complex biological molecules. Some examples for synthetic supramolecular structures encompass studies of host–guest interactions in inclusion complexes, quadruple H-bonded complexes, and metal-mediated coordinative complexes.[6] A landmark contribution to this area is offered by the recent work of Craig and co-workers, who systematically explored the use of reversible bonds consisting of metallic pincer Pd^{II}–pyridine-based complexes[9] (Scheme 1) in supramolecular networks[10] and polymers.[11,12]



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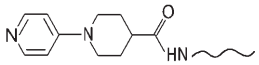
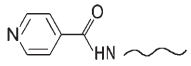


2a



2b

Scheme 1. Transition-metal-based pincer (**1**) and pyridine ligand (**2a,b**) structures studied by Craig and co-workers[12] by AFM-SMFS. See text for the choice of R and M in **1**. OTf = trifluoromethanesulfonate.

In networks consisting of poly(4-vinyl pyridine) through coordination with bis(M^{II}–pincer) complexes (**1**, M = Pd, Pt),[10] the bulk rheological response was initially probed under the same thermodynamic conditions by varying the R group (R = Me, Et). This simple structural variation significantly alters the dynamics of the complex (i.e., the rate constants for ligand exchange), and thus the lifetimes of the supramolecular cross-links change by several orders of magnitude while the value of the equilibrium constant remains essentially unchanged. Faster dynamics (methyl substitution) weakens the mechanics of the ensemble, which is manifested by a dramatic decrease of solution viscosities. Thus, it is in this case ligand-exchange dynamics, rather than thermodynamics, that determine the bulk viscoelastic properties of the corresponding supramolecular network.

Main-chain reversible linear supramolecular polymers can assemble, for example, by self-assembly of covalently linked, 2-ureido-4[1*H*]-pyrimidinone (UPy) moieties, which form quadruple H-bonded linkages along the supramolecular chain, as first described by Meijer and co-workers.[13] The unbinding forces of single, quadruple H-bonding $(UPy)_2$ complexes, as observed by AFM-SMFS,[14] exhibited the loading rate dependence anticipated in nonequilibrium conditions for loading rates in the range of 5 to 500 nN s^{-1} at 301 K in hexadecane. By contrast, these rupture forces were independent of the loading rate from 5 to 200 nN s^{-1} at 330 K. These results indicate that the unbinding behavior of individual supramolecular complexes can be directly probed under both thermodynamic nonequilibrium and quasi-equilibrium conditions.[14] In H-bonded supramolecular polymers, however, the effects of thermodynamics and dissociation dynamics are strongly anticorrelated, since association and diffusion rates have similar magnitudes. However, linear supramolecular chains composed of two covalently linked organometallic pincers **1** and two pyridine-based ligands connected to the substrate and the AFM tip, respectively, offer the advantage that for R = Et (if compared with R = Me) the exchange rate slows down whereas the ligand association thermodynamics is influenced to a much smaller degree.[11] Values of ligand association constants and dissociation rates of the pincer–pyridine complexes (without linkers) can be quantitatively determined by NMR spectroscopy for R = Me, Et, etc., as well as for ligands with different affinities (**2a**, **2b**). This variation allowed Craig and co-workers to correlate main-chain dissociation dynamics and ensemble dynamic mechanical behavior (solution viscosity and effective hydrodynamic size of the associating supramolecular polymers).

However, chemical variation is not the only means of changing the apparent (effective) dissociation rate (complex lifetime). Dissociation under mechanical loading can exhibit far-from-equilibrium kinetics if the values of the mechanical bond-loading rate (r_f) during the AFM-SMFS experiment and the values of the dissociation rate have similar magnitudes. In such cases, as mentioned earlier, the most likely rupture (detachment) force depends on the loading rate.

The average rupture force was predicted by Evans and Ritchie to depend linearly on $\ln(r_f)$ with a slope that is related to the barrier height of the free energy from the minimum to the transition state projected in the direction of the external force[15] (Figure 1). The intercept with the x axis yields the value of the rate constant k_{off} for breaking of the stress-free supramolecular bond. Craig and co-workers determined the values of the most probable rupture forces for two pincer-ligand complexes with different ligand dissociation kinetics (different equilibrium thermal off rates). The pyridine ligands were attach-

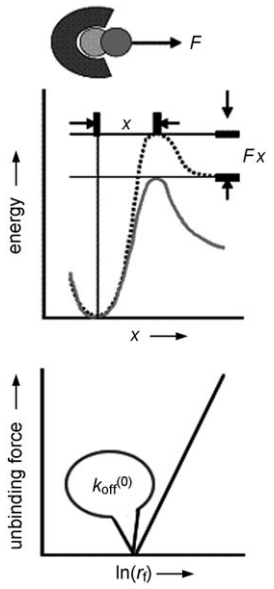


Figure 1. Top: Dissociation pathway of a supramolecular bond over a single, sharp energy barrier. The barrier height in AFM-SMFS is decreased by the applied constant force F with a magnitude of Fx. Bottom: The magnitude of the most probable unbinding force obtained by AFM-SMFS as a function of the natural logarithm of the loading rate $\ln(r_f)$, and the extrapolated thermal dissociation constant k_{off}.

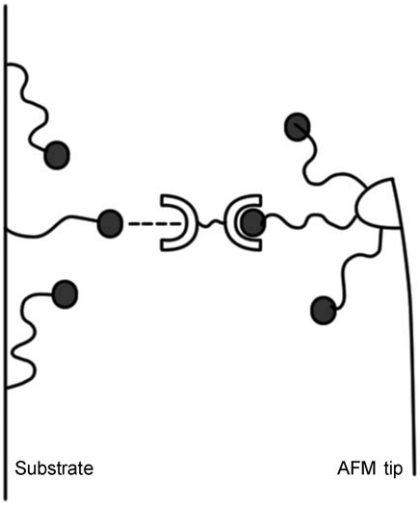


Figure 2. AFM-SMFS experiment and supramolecular bond rupture upon pulling.[12] The AFM tip (right) and the substrate (left) are covalently functionalized with pyridine (black circle). Rupture of a bifunctional pincer (in DMSO) is shown.

ed to the AFM tip and to a substrate surface, and a solution of **1** in DMSO was added (Figure 2).

The structures **1**-(**2a**)$_2$ and **1**-(**2b**)$_2$ showed essentially identical barrier heights (identical slopes for the rupture force vs. $\ln(r_f)$ relationship within experimental error) from AFM force-spectroscopy data, which clearly indicates the same unbinding mechanism for the different complexes. However, owing to differences in the thermal off rates, the x-axis intercepts of the most likely rupture forces (estimates for the stress-free off-rate constants) yielded different values. The estimated rate constants from AFM-SMFS data showed an excellent agreement with the thermal off-rate values obtained from NMR spectroscopy (the value for **1**-(**2a**)$_2$ is greater by a factor of approximately 20–30 than that of **1**-(**2b**)$_2$). A master plot of rupture force versus scaled loading rate (loading rate normalized to the corresponding equilibrium dissociation rate measured by NMR spectroscopy) of the two complexes showed a single line. This study represents the first quantitative comparison of rupture dynamics of well-characterized supramolecular bonds from independent AFM-SMFS and NMR data, and the excellent agreement between the two results is truly a milestone in single-molecule nanoscience. It constitutes a significant step towards a molecular-level understanding of the bulk mechanical behavior of supramolecular polymers on the basis of rupture and mechanical behavior of single supramolecular bonds under stress.

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