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Anne-Sophie Duwez awarded an ERC Advanced Grant for her project *Chemistry under Force*

Anne-Sophie Duwez, professor and head of the NanoChem laboratory at the University of Liège (www.nanochem.uliege.be) has been selected to receive an ERC Advanced Grant from the European Research Council for her *ChemForce* project. This prestigious funding –nearly 2.5 M€ over a period of 5 years– was awarded to develop research that aims to better understand how mechanical forces and chemistry affect each other by studying the rupture and reformation of basic chemical bonds at the single molecule level.

In 1952, Schrödinger wrote that we would never experiment with just one electron, one atom, or one molecule [1]. 40 years later, methods derived from scanning probe microscopies (SPMs) allowed us to manipulate single atoms and molecules, and even single bonds [2]. During the last three decades, physicists and biophysicists have largely exploited this opportunity to advance many fields of physics, nanotechnology, and biology. Single-molecule force spectroscopy (SMFS), which consists in trapping and stretching a molecule between an atomic force microscopy (AFM) tip and a surface, enables to probe (and/or to induce) molecular processes *in situ* and in real time through the application of mechanical forces. Such experiments have provided unprecedented insights into the structure and function of many biological systems, including DNA, proteins, enzymes, biomolecular machines, ...[3,4] Studying single molecules can reveal unexpected information. Even if the ~10^{23} molecules in a mole are identical in structure, random thermal fluctuations cause differences in their activities. Not all of them follow the same path through their reaction process. During any short-time interval, they are each unique. The ability to observe one molecule at a time allows us to ask and answer questions that are impossible, or extremely difficult, to approach by ensemble techniques [5].

Chemists did not fall into steps behind physicists and biologists and have benefited little from the advent of single-molecule experiments by SPMs. The use of SMFS for molecular recognition between two partner species has been exploited to some extent by chemists [6], but single-molecule mechanics, *i.e.* the study of intra-molecular mechanochemical processes, are much rarer. Despite some elegant examples in polymer science [7], SMFS remains largely under exploited in chemistry. A big question like *how forces and chemistry affect each other?* merits special attention. The mechanical activation of bonds is a ubiquitous process in nature. Strained molecular architectures govern many physiological processes, including enzyme activities, motion of molecular motors, division

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of cells, or muscle contraction [8]. Although mechanical forces are known to control rates of chemical reactions [9] and govern reaction pathways [10], they are little exploited in chemistry. Given the vector character of force, the reactions can follow specific pathways, yielding products that may differ from those of non-directional activation in solution (like thermal activation). Mechanical forces modify the free-energy surface of chemical reactions, enabling thermodynamically unfavourable reaction pathways, and yielding products that are either prohibited or too slow to obtain under thermodynamic control [8b,10a,11]. Even if mechanochemical synthesis by milling, grinding, or sonication, has provided some interesting information in this direction, this information remains very qualitative [12]. The mechanics of chemical bonds is still in its infancy and could largely benefit from SMFS. Major questions which could not be addressed so far, especially concerning the mechanical reversibility of chemical bonds and the bond lifetime under mechanical loads could be elucidated. SMFS offers remarkable opportunities to advance our fundamental understanding of chemical bonds. It can also open avenues for exploiting the capacity of mechanical loads to affect chemistry and guide the thinking in designing new materials, reactions and processes, in a framework other than thermodynamics in solution.

However, implementing single-molecule mechanics on small synthetic molecules remains a major challenge due to the very small scale of the involved processes compared to large biological systems. SMFS can be carried out by AFM, but also by optical tweezers (OT) or magnetic beads. Whatever the technique, the difficulty comes from the need to develop proper tools and prepare appropriate molecules that can be interfaced with the device, especially when one wants to probe bond reversibility. Over the last years, the group of Anne-Sophie Duwez have developed a range of pioneering approaches in SMFS [13] that now allow them to tackle this big question, which requires a considerable joint effort between synthetic chemists, chemical physicists, and engineers.

The *ChemForce* project, which has just been selected by the ERC for Advanced Grant funding, aims at broadening the scope of use of SMFS and adapt it to obtain a detailed picture of the interplay between mechanical forces and chemistry at the single molecule level. It proposes to solve a major failure of SMFS for the last 25 years concerning the extreme difficulty of probing bond reformation after its rupture. For this purpose, a series of tethered supramolecular and (dynamic) covalent bonds will be synthesized and probed to study their mechanical stability, including the time they can

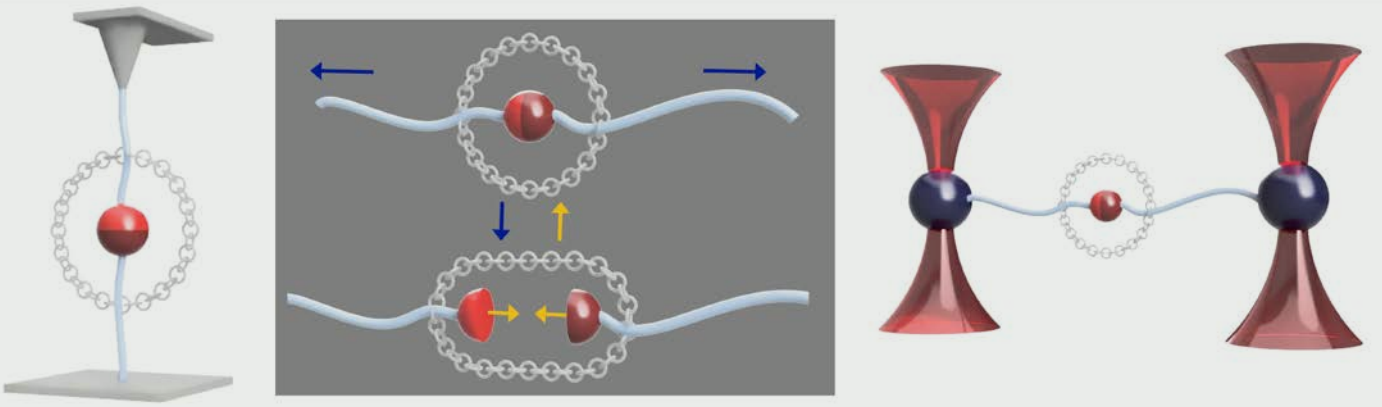

Figure 1: Schematic of the general objective of ChemForce. The concept of tethered bonds is shown in the central part. The partners of the bond stay in close proximity after being broken open and can rebind. Single-molecule force spectroscopy by AFM (left) or OT (right) is used to monitor the process in various environments (solvent, pH, presence of reagents, competitors, stimuli, …).

resist to a defined force, and their reversibility, in various geometries and chemical environments (Fig. 1). The tethered structure ensures that the components of the bond stay in close proximity after being broken open, leaving the possibility to reform the bond and to study how mechanical forces and proximity can trigger a chemical reaction. It will enable to obtain a detailed understanding of how mechanical forces can modify the free-energy surface of chemical reactions.

The bonds that will be under focus include Diels–Alder and click adducts, dynamic covalent bonds, and metal–ligand complexes. These experiments will enable to obtain unprecedented information about the mechanics of bonds, at the single molecule level, and about the possibility of forcing bond formation by proximity and mechanical force for species that normally require high temperature or another standard source of energy. Given the vector character of force, mechanical stability is an anisotropic property. The influence of the geometry and topology, which potentially affect the mechanics of the bonds, will also be investigated. The mechanical stability of a bond can largely differ from its thermodynamic stability. Bonds considered to be weak can turn out to be mechanically robust and on the contrary, strong bonds can turn out to be fragile when submitted to a mechanical load. The lifetime of a bond can be increased or decreased when subjected to a mechanical force [14]. The tethered mechanophores will incorporate these geometrical effects, and will be also embedded into more complex topological structures like mechanically interlocked molecules (MIMs, like catenanes, rotaxanes and knots), to modulate the mechanical activity of the bonds.

In summary, ChemForce aims at broadening the scope of use of SMFS and adapting it to obtain a detailed picture of the interplay between mechanical forces and chemistry at the single molecule level, thereby gaining in-depth understanding of the behaviour of chemical bonds under force, including their rupture, their dynamics, and their reformation. To reach this goal, a series of bonds have been selected, covering a broad range of characteristics (strength, lifetime, reversibility,…). These bonds were selected for their importance in various fields such as materials science, organic or supramolecular chemistry,… or, on the opposite, because they are relatively new and little understood. In both cases, there is a crucial lack of detailed information about their mechanical behaviour.

The originality of the project relies on its multidisciplinary approach (synthetic chemistry, advanced single-molecule mechanics and developments in AFM and OT) around timely important fundamental questions for chemistry in general, and for materials science in particular. The results obtained in *ChemForce* will help to understand how mechanical forces can be used to overcome activation barriers to chemical bond formation, enabling the use of less reactive starting materials. They will potentially guide the thinking in designing new materials, reactions and processes, to exploit the capacity of mechanical loads to affect chemistry.

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