SURFACE CHEMISTRY

A Swiss Army knife for surface chemistry

Voltage pulses offer a way to control single-molecule reactions on a surface

By **Igor Alabugin** *and* **Chaowei Hu**

To construct complex molecules and molecular devices, tiny, atomic-sized objects must be brought together and connected in a precise way. For better or for worse, this daunting task is still mostly done in a manner likened to putting Lego blocks in a washing machine and hoping that the quintillions of molecules somehow end up assembling themselves into the desired product, either by complete chance or under the guidance of other molecular-sized objects—i.e., catalysts. On page 298 of this issue, Albrecht *et al.* (*1*) show how a single molecule can be transformed into three distinct products depending on the voltage pulses from the tip of a scanning tunneling microscope (STM). Notably, the three products can be repeatedly interconverted with a high degree of control.

On-demand interconversion of molecules, or switching, can be done in many ways, such as chemically, photochemically, or electrochemically, depending on the chemical system and the intended goal. Recently, controlled transformations of individual molecules on surfaces have become possible (*2*–*6*). Although switching often relies on well-known processes, Albrecht *et al.* describe a distinct network of reactions that connects three exotic species, each of which would have limited stability under ambient conditions. These species defy the usual chemistry logic but are sufficiently stable on a sodium chloride (NaCl) surface to take part in multiple transformations and measurements, as demonstrated in 440 different reactions performed on five individual molecules. These processes revealed unusual chemistry that offers a large degree of control of reactivity and bond formation.

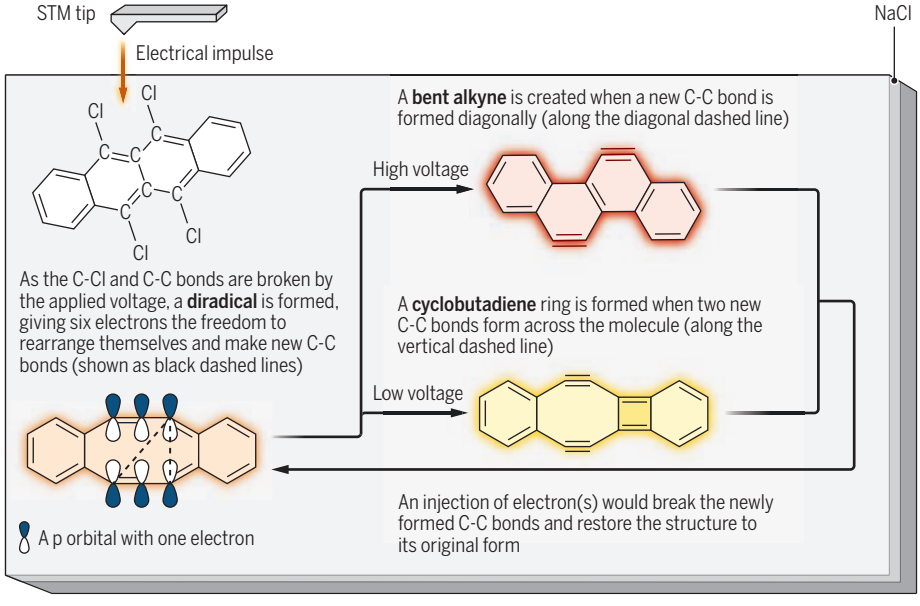
The sequence of transformations was set up by removing four chlorine atoms from the tetracyclic core to create the starting material, using an atomically sharp STM tip positioned above the particular molecule. As the chlorine atoms are removed, radical centers (i.e., an atom with one or more unpaired electrons) are created on the carbon atoms of the four carbon-chlorine (C-Cl) bonds. Two of the radical centers will then recouple by breaking one of the C-C bonds in the ring, but, after all the Cl atoms have departed, the system is still left with two unpaired electrons (i.e., a diradical). In this state, the two radical centers that are spread over two three-carbon sets of atoms are placed precariously, facing each other.

The usual chemical logic suggests that such a diradical would be transient and that the two unpaired electrons would immediately reconnect to make a C-C bond. However, in the unusual system reported by Albrecht *et al.*, the situation is quite different because of the presence of chemical frustration—i.e., the inability for the system to satisfy bonding requirements because of structural constraints (see the figure). Even though there are several ways to couple the electrons, the system is constrained structurally from forming the bond. The available choices are poor because one leads to an antiaromatic cyclobutadiene ring and the other forms a highly bent alkyne with a distorted C-C triple bond. Although the unpaired electrons can succeed in forming the C-C bonds needed for the products, the bonds are relatively weak and can be broken and remade at will by an applied voltage. Out of the two viable options, the unstable four-membered cyclobutadiene ring is preferred by the system because it is easier for the structure to form compared with the six-membered rings in the bent alkyne, which requires a greater distortion from its original geometry. However, the alkyne becomes the main product when a higher voltage is applied. This interplay between how quickly the product can be formed and its stability provides a way to selectively make either cyclobutadiene or bent alkyne by controlling the input voltage.

The reversion of two products back to the diradical requires energy and, hence, is unfavorable. Albrecht *et al.* made the back switching possible by inverting the relative stability of the diradical versus the cyclobutadiene and the alkyne by injecting electrons into the diradical using a voltage pulse. Because diradicals have a high likelihood of gaining an electron (*7*, *8*), their negatively charged states are suddenly more stable relative to the anionic states of the other two products. This change in the molecular energy landscape facilitates the conversion of anionic

Molecular shape-shifting enabled by electrochemistry

Albrecht *et al.* show how multiple reactions can be initiated and controlled by applying a voltage using a scanning tunneling microscope (STM) and demonstrate a way to interconvert between three distinct molecules.



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Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306, USA.
Email: alabugin@chem.fsu.edu

forms of cyclobutadiene and bent alkyne back to radical anions. The experiments show that at least two electrons are needed for this to happen—one to provide energy for the reaction and one that is retained to open the ring. Furthermore, an observation of a transient dianion suggests that the extra electron may serve as a catalyst for the reaction (*9*, *10*) because the removal of the extra electron restores the neutrality and returns the system to its original state.

The control of voltage in conjunction with the possibility of electron injection enables a fully controlled interconversion between three isomeric, electronically unusual, and inherently unstable molecules. Albrecht *et al.* put a spotlight on these exotic species and illustrated how C-C bonds in carbon-rich species with weakly coupled electrons can be formed, broken, and reformed at will. Lessons from these newly discovered surface chemistry processes may be relevant for electron-catalyzed chemical reactions in chemistry and biology and may illuminate viable shortcuts for more efficient synthesis.

This molecular system can on-demand become one of three exotic chemical creatures, transforming between a diradical, an antiaromatic ring, and a highly bent alkyne. The potential to interact with a different set of partners makes this shape-shifting molecular system a Swiss Army knife with three distinct and useful chemical tools. For example, the diradical may participate in redox and radical reactions, the cyclobutadiene system can provide a potential binding site for a cationic transition metal, and the strained alkynes units can be used for various reactions such as cycloaddition (*11*) or nucleophilic attack (*12*, *13*). Future opportunities may arise from using the differences in electronic structures of the three species in molecular electronics, such as in molecular logic gates (*14*, *15*). ■

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NEUROSCIENCE

A cellular switchboard in memory circuits

Neurogliaform cells can direct the flow of information through the hippocampus

By **Michael T. Craig**[1] *and* **Jonathan Witton**[2]

The hippocampus is a brain region that is associated with memory. However, the hippocampus does not function alone, but rather operates within a wider network of brain regions (the extended memory network) including, among other areas, the prefrontal and entorhinal cortices and midline thalamic nuclei, such as nucleus reuniens (NRe) (*1*). Communication between these brain regions is important for many aspects of memory acquisition and consolidation, as well as for spatial navigation and decision-making. There are multiple routes through which information can flow through the extended memory network, with direct and indirect pathways converging on the hippocampus. The mechanisms by which information flow through these different pathways is prioritized have remained largely unknown. On page 324 of this issue, Sakalar *et al.* (*2*) report a cellular mechanism of information routing through the hippocampus.

Communication between neurons is thought to be enabled by neuronal oscillations—waves of rhythmic electrical activity that facilitate neural dialogue by creating temporal windows in which neuronal firing can be synchronized (*3*). By convention, neuronal oscillations are grouped into different frequency bands, with each band associated with specific cognitive processes. For example, theta oscillations occur at ~5 to 12 Hz and are associated with spatial navigation, whereas gamma oscillations occur between ~30 and 140 Hz and are associated with memory or high cognitive load (*4*). Gamma oscillations, often occurring alongside theta oscillations, can be further parsed into distinct subbands driven by different cellular mechanisms (*4*). This can be observed in the CA1 region of the hippocampus, where different types of gamma oscillation are found—specifically, a slow gamma oscillation ($gamma_S$; ~40 Hz) driven by input from neighboring CA3 and a faster midfrequency gamma oscillation ($gamma_M$; ~75 Hz) driven by input from the entorhinal cortex (*5*). $Gamma_M$ may be involved in the encoding of memory, whereas $gamma_S$ is likely to be important for memory retrieval (*5*).

Pyramidal neurons form the main computational unit of the hippocampus, with those in CA1 integrating inputs from multiple sources and sending signals to the subiculum and beyond through the generation of action potentials (also called spiking). Inputs to CA1 from CA3 arrive in stratum radiatum of the hippocampus, whereas those from the entorhinal cortex terminate in stratum lacunosum-moleculare of the hippocampus, providing an anatomical segregation of these different information streams (see the figure). There is also a functional segregation of CA3- and entorhinal-driven gamma oscillations: These different types of oscillation occur at different phases of the CA1 theta oscillation, potentially presenting a circuit-level mechanism that prevents the processes driven by different information streams (e.g., memory encoding versus retrieval) from interfering with each other (*5*). Whether the inputs to an individual pyramidal cell in CA1 can be actively switched between these different information streams has been unknown.

Within the hippocampus, inhibitory interneurons make up a diverse family of neurons, using γ-aminobutyric acid (GABA) as their neurotransmitter, with multiple subtypes providing exquisite temporal control over the spiking of excitatory pyramidal cells and other inhibitory interneurons (*6*). Neuronal oscillations are typically generated through a precisely coordinated balance between excitation and inhibition (*6*). Neurogliaform cells are an abundant class of inhibitory interneurons that reside in and project dense axonal arbors throughout stratum lacunosum-moleculare of the hippocampus. They are therefore well placed to inhibit the distal apical dendrites of CA1 pyramidal cells (*7*), but understanding their role in hippocampal information processing has remained elusive.

Sakalar *et al.* provide evidence that neurogliaform cells play an important role in

[1]School of Psychology and Neuroscience, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK. [2]Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, UK. Email: mick.craig@glasgow.ac.uk

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