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Organic chemistry

Benzene rings reach their breaking point

Mark R. Crimmin

Benzene rings are almost unbreakable in typical reaction conditions. Chemistry has now been developed that selectively breaks these rings open, highlighting their potential as building blocks for making open-chain molecules. **See p.64**

Synthetic chemists are always searching for new ways to make chemical bonds. Methods for forging carbon–carbon (C–C) bonds are especially important, because they enable organic molecules to be built from scratch, step by step and piece by piece. Once constructed, C–C bonds are often considered to be 'untouchable' parts of the molecule that generally resist further chemical transformation. On page 64, Qiu *et al.*[1] challenge this preconception by reporting a reaction that breaks the strong C–C bonds of organic molecules known as aromatic compounds.

The term 'aromatic' was first used to describe organic compounds that have a pleasant smell, but now refers to a much broader categorization that encompasses entire classes of chemical. One of the simplest aromatic molecules is benzene, which contains six carbon atoms connected in a hexagonal ring. Benzene rings are exceptionally stable chemically, in part because of their ability to host six delocalized electrons. Aromatic molecules are some of the most useful building blocks of chemistry. They are common to the two main feedstocks — crude oil and biomass — from which chemicals are derived, and are found in materials, biomolecules and manufactured chemicals.

Carbon-based aromatic rings such as benzene are not usually thought of as easy to break apart. Instead, they tend to react in pathways that leave the ring — and its circular system of electrons — intact. Only under extreme conditions do benzene rings reach their breaking point. For example, a high-temperature (about 200 °C) process called hydroisomerization converts benzene into saturated hydrocarbons, including those that contain linear chains of carbon atoms[2] (Fig. 1a). Although the benzene ring is forced open, hydroisomerization is not selective and leads to a mixture of products. The approach can be likened to using a sledgehammer to break apart a marble — effective, but messy.

Nature has also found ways to split apart aromatic rings: benzene can be broken open by dioxygenase enzymes under biological conditions, to produce a compound called muconic acid[3] (Fig. 1b). In contrast to hydroisomerization, this multistep enzymatic process is highly selective, producing a single product through a precise and controlled pathway. Keen to follow nature's example, synthetic chemists have used high-energy molecules to force open benzene in reactions that add a metal atom (or atoms) directly to the ring[4–7]. However, these promising methods are still in development, and have not yet been applied to make useful new products.

Qiu *et al.* now report remarkable chemistry that selectively ruptures a single C–C bond in the aromatic ring of benzene derivatives. The reaction uses a strong chemical oxidant (sodium azide) in combination with a copper-based metal complex (Fig. 1c). The products of this ring breakage are linear atomic chains in which the six carbon atoms derived from the benzene ring are capped by two nitrogen atoms, at least one of which comes from the oxidant. In just a few more steps, these products can be converted into chemical building blocks that have a broad range of potential applications, including the synthesis of polymers.

The key to Qiu and colleagues' approach is to have a preinstalled group from a specific range of options on the benzene ring, to direct the reactivity of the starting material. The authors propose that this reactive group enables the formation of unstable reaction intermediates known as *bis*(nitrene) compounds, in which two nitrogen atoms are located at adjacent sites of the benzene ring. Previous studies have suggested that such substitution

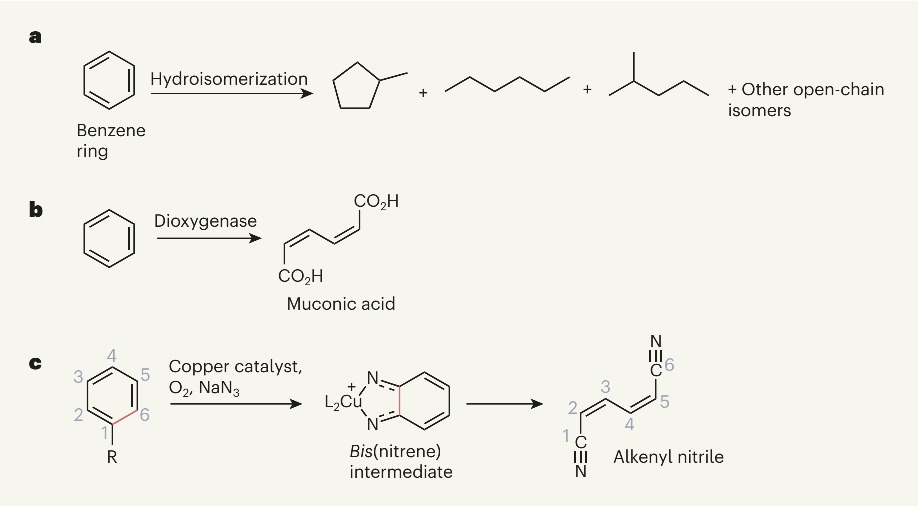

Figure 1 | Breaking benzene. Benzene rings are exceptionally stable, and few reactions were known to break them open. **a**, A process called hydroisomerization breaks benzene rings at high temperatures, but is unselective, producing a mixture of hydrocarbon products. **b**, Dioxygenase enzymes produce muconic acid as a single product under biological conditions. **c**, Qiu *et al.*[1] report a copper-catalysed reaction in which benzene derivatives react with oxygen and an oxidant (sodium azide; NaN_3) to produce alkenyl nitriles. The bond that breaks is highlighted in red, and the carbon atoms in the benzene ring are numbered to show how they translate from the starting material to the product. The reaction is proposed to proceed through an unstable intermediate called a *bis*(nitrene). R represents a range of reactive chemical groups; L is a ligand molecule; Cu, copper.

patterns could destabilize benzene and lead to the opening of the ring[8,9].

Qiu and co-workers' computational modelling suggests that, in their reactions, the *bis*(nitrene) intermediates can be formed on the copper atom of the catalyst, and are primed to break apart the benzene ring. They propose that the ring-opening step occurs through fracturing of the C–C bond between the two nitrogen atoms, which is brought about by the ability of these atoms to overload a molecular orbital that is associated with this bond with electrons.

In its current form, Qiu and colleagues' reaction will be challenging to translate to the manufacturing of chemicals. Sodium azide is both explosive and acutely toxic, and the copper catalyst is used in large amounts relative to the quantities of the reactants – which could make manufacturing-scale processes uneconomical, and might produce problematically large amounts of copper waste. The potential applications for synthesis in the laboratory, however, are fascinating. The authors show that their benzene-busting protocol can work on molecules with complicated structures, providing a new approach for chemically manipulating natural products, dyes and pharmaceuticals.

More generally, the development of methods that specifically destroy benzene rings could contribute to the emerging area of molecular editing[10] – the completely selective insertion, deletion or exchange of atoms in organic molecules – and provide new tools for chemical synthesis and the discovery of compounds needed for practical applications. Future methods could build on Qiu and colleagues' findings to find ways of breaking open benzene rings without the need for specific groups to be attached, or to incorporate atoms other than nitrogen into the carbon chain of the product. If a general approach can be found, synthetic chemists might look back and wonder why they did not search for benzene's breaking point sooner.

Mark R. Crimmin is in the Department of Chemistry, Molecular Sciences Research Hub, Imperial College London, London W12 0BZ, UK.
e-mail: m.crimmin@imperial.ac.uk

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Immunology

Fly immune defence finds a surprising way to sting

Cara West & Neal Silverman

Aspects of how immune defence processes evolved remain mysterious. Studies of the fly *Drosophila melanogaster* reveal previously unknown details of a defence pathway with echoes of, but key differences from, a human pathway. **See p.109 & p.114**

The detection of disease-causing agents by the rapidly responding branch of immune defences called the innate immune system relies on several classes of receptor. These detect molecular patterns associated with such agents, or the cellular damage that the agents cause. In particular, the surveillance of RNA and DNA is crucial to limit the replication of infectious organisms, especially intracellular microbes. Indeed, various sensors dedicated to the detection of nucleic acids have been characterized. Slavik *et al.*[1] (page 109) and Holleufer *et al.*[2] (page 114) now describe surprising defence functions for cGAS-like receptors (cGLRs) of the fly *Drosophila melanogaster*, and reveal that this class of receptor is more diverse than was previously anticipated.

Nucleic-acid-sensing receptors typically function by detecting nucleic acids in cellular compartments where these molecules should not reside in a healthy cell[3]. In mammals, the presence of DNA in the cytosol is a signature of infection by a DNA virus. This abnormality is detected by the enzyme cyclic GMP–AMP (cGAMP) synthase, which is also known as cGAS (Fig. 1). Double-stranded DNA binds to cGAS in a manner that is not sequence specific, and this binding triggers cGAS to make a cyclic dinucleotide molecule[4] called 2′3′-cGAMP.

STING, a transmembrane protein located on intracellular membranes, binds to 2′3′-cGAMP and then interacts with the kinase enzyme TBK1, which activates the transcription factors IRF3 and NF-κB (ref. 5). Interestingly, bacterially produced cyclic dinucleotides, such as cyclic-di-GMP, also bind to and activate mammalian STING[6]. Thus, STING serves as an indirect sensor of cytosolic DNA and a direct sensor of some bacteria, including *Listeria monocytogenes*[6].

The version of STING in *D. melanogaster*, dSTING, has been the focus of several studies, which found that it is also activated by cyclic dinucleotides and that it functions in defending against viral and intracellular bacterial infections[7–10]. Unlike mammalian STING, which responds to DNA viruses, dSTING has a crucial role in responses against RNA viruses, including the *Drosophila* C virus and Zika virus[7–10]. dSTING responds[10] to 2′3′-cGAMP, but the enzyme(s) and activation process responsible for synthesizing the activator of dSTING in fly cells was previously unknown. The *Drosophila* genome, and the genomes of insects in general, contains several genes that encode enzymes with a catalytic region called a nucleotidyltransferase domain that is similar to the catalytic domain of cGAS, but none of these enzymes contains the DNA-binding motif that is a component of cGAS.

Slavik *et al.* report that one of these cGAS-like proteins in *D. melanogaster*, called cGLR1, responds not to viral DNA but to double-stranded RNA (Fig. 1), which is a hallmark of viral infection. Interestingly, this recognition process depends on the length of the RNA, a system reminiscent of the RNA-recognition process used in mammalian innate defences[4] by the protein MDA5. Such a length-based mechanism would offer a way to avoid self-recognition of a type of short double-stranded RNA, called a small-interfering RNA, that is made during normal cellular processes.

Surprisingly, the cyclic dinucleotide that cGLR1 produces is 3′2′-cGAMP rather than 2′3′-cGAMP. The phosphate-bond positions of 3′2′-cGAMP are reversed compared with those of 2′3′-cGAMP. The authors show that this reversal arises through a switch in the order in which the cGAMP-forming nucleotides bind to the enzyme. In this system with echoes of the mammalian cGAS–STING pathway, the authors demonstrate that dSTING preferentially binds to 3′2′-cGAMP over 2′3′-cGAMP. This binding activates dSTING, which results in the activation of the NF-κB protein called Relish.

The ability to synthesize 3′2′-cGAMP seems to be unique to insects in the order Diptera, given that the authors found evidence for this biochemical activity in several species of *Drosophila*, but not in other orders of insects