

MINIATURIZATION

Chemistry at the crossroads

The quest for miniaturization of chemical reactors is leading to a tangled web of reaction vessels, each formed at the junction of polymer nanofibres.

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Applied science often plays catch-up with nature. This has been true in fields as disparate as structural engineering, information technology and biochemistry. However, perhaps the best example of nature's superiority is in the handling of fluids and the manipulation of complex chemical reactions. The very fact that you are alive and able to read this article is due in no small part to a miraculous system of fluid pumping and distribution first characterized by William Harvey and Leonardo da Vinci^{1,2}. Moreover, the greater part of the mammalian circulatory system operates on the microfluidic level, a fact that often escapes notice.

In recent times, the field of 'artificial' microfluidics has been part of a general drive in chemistry and biology to harness the effects of small scales on the way matter behaves. In a manner similar to that proposed by Richard Feynman for information and electrical components³, chemists and biologists have been attempting, as it were, to inscribe the *Encyclopaedia Britannica* on the head of a pin. The potential benefits of such an approach are huge and indeed the scale on which chemical reactions are performed is getting smaller by the minute. Writing on page 80 of this issue⁴, Pavel Anzenbacher and Manuel Palacios of Bowling Green State University, Ohio, describe the possibility of harnessing attolitre volumes as discrete reaction vessels.

Reaction and analysis systems on a microfluidic scale are rapidly becoming mainstream tools in both academic and industrial research⁵. The success of microfluidic systems in molecular synthesis is largely a result of the ability to exploit atypical fluid behaviour in small-volume environments. The fact that fluid properties become increasingly controlled by viscous forces as reaction volumes diminish dictates that mixing can only be accomplished through diffusion. Nevertheless, at this scale diffusion is ideally suited to realizing both rapid and controlled mixing of fluids.

Although continuous-flow microfluidic systems have many applications, they do not fit all needs. In particular, it is hard to perform parallel reactions in isolated vessels under continuous flow. Recent investigation of segmented flow systems has provided

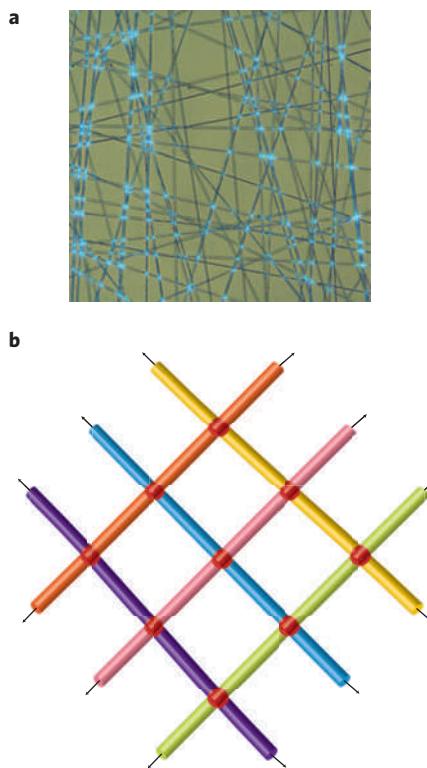


Figure 1 | The junctions formed between crossed polymer nanofibres when they are exposed to heat or solvent vapour can be used as attoscale chemical reactors. **a**, Crossed fibres impregnated with two different non-fluorescent reagents form a fluorescent product at the junction. **b**, The ability to impregnate different nanofibres with a variety of different reagents (represented by different colours) could lead to a method for ultra-high-throughput reaction screening.

some advances in this direction; picolitre-sized droplets can be formed spontaneously when multiple laminar streams of aqueous reagents are injected into an immiscible carrier fluid. These droplets can be generated at kilohertz frequencies and controllably dosed with varying amounts of reagents. They have been used to perform chemical and biological assays in high throughput^{6,7}.

The flow conditions in the microfluidic systems described above at least conform

to those that we might regard as normal in our everyday experience. However, once the characteristic dimensions become significantly smaller (below a few hundred micrometres) then molecular flow becomes dependent on both orientation and size⁸. To conduct reactions on an even smaller scale, it is necessary to leave conventional fluidic conduits behind and look to fibres, and it is just such an approach that is successful here.

The technique used is not without precedent. Indeed, it has been known for many years that fibres can interact with each other after production. This is particularly apparent in the case of watered or 'moiré' silk where complex patterns are created by the interaction of overlaid fibres. In their quest for 'attoreactors', Anzenbacher and Palacios have focused their attention on the interaction between electrospun polyurethane nanofibres that are deposited in a rectangular grid and overlaid in a cross-hatch pattern (Fig. 1). Orthogonal fibres, with diameters of around 200 nm, are doped with different reagents. The overlaid nanofibres are then softened either by the application of heat or by exposure to solvent vapours to join the fibres at the crossing points. The multiple junctions created during this process have a volume of a few attolitres and define discrete reaction vessels.

At first glance, such an interconnected network seems to be unsuitable for synthetic processing, but this overlooks the properties of polymers, which include the ability to readily adsorb hydrophobic compounds. To this end, Anzenbacher and Palacios impregnate warp and weft polymers with different analyte molecules and then observe the reaction at the crossing point. For example, mixing together two non-fluorescent components results in a fluorescent product, just as it would in a test tube or microtitre plate. Moreover, several other reaction systems, including the diazo-coupling of activated aromatics, Diels–Alder reactions and protein-labelling reactions, can be successfully performed in a highly controlled manner using the nano-grid technology.

What is perhaps most remarkable is that because typical reagent concentrations

in the fibres after solvent evaporation are 500 mM, each 5-aL reactor contains on average just 1,500 molecules. The use to which this technology could be put is still unclear. A key short-term goal will surely be further downsizing to access single-molecule events. Molecular confinement in such small volumes allows access to perfect detection efficiencies and the prospect of stochastic analysis in a variety of chemical and biological systems. Furthermore, as the authors have already developed methods

for facile deposition of fibres containing a variety of reagents, ultra-high-throughput reaction screening is unquestionably an achievable target.

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ORGANOMETALLIC ACTINIDES

Now U=C it

A terminal uranium–carbon multiple bond has long been sought-after in actinide chemistry. Now, a complex featuring a dianionic carbon atom as part of a multidentate ligand brings actinide carbenes a little nearer.

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Transition-metal carbenes — organometallic compounds containing a metal–carbon double bond —have been prevalent in catalytic and synthetic chemistry since the 1960s. Yet for the actinide metal uranium, often referred to as ‘a big transition metal’, there are no compounds containing a simple uranium–carbon double bond. Researchers in France have just taken a step closer by using a simple chelating sulfur ligand to trap a central dianionic carbon atom into a double bond with uranium, showing us that a simple terminal U=C bond could one day be accessible¹.

Travelling across the *d*-block, complexes containing a double bond between the metal and the carbon of a bound organic fragment can be classified on a scale somewhere between two extremes. The more electropositive metals at the left hand side of the *d*-block (the early metals) form metal–carbon double bonds in which the metal orbitals are higher in energy than the carbon *p* orbitals, so the highest occupied molecular orbital is based primarily on the carbon atom, rendering it nucleophilic in character. The late metals (on the right-hand side) have electronegativities approaching that of carbon, and lower energy orbitals, so the bonding is oppositely polarized and the carbene carbon behaves as an electrophile. Many important catalysts for polymer and fine chemical synthesis rely on metal carbene complexes, and Dick Schrock, Robert Grubbs and Yves Chauvin were awarded the Nobel Prize in 2005 for their work on metal carbenes.

However, given the successes in transition-metal–carbon multiple bonds

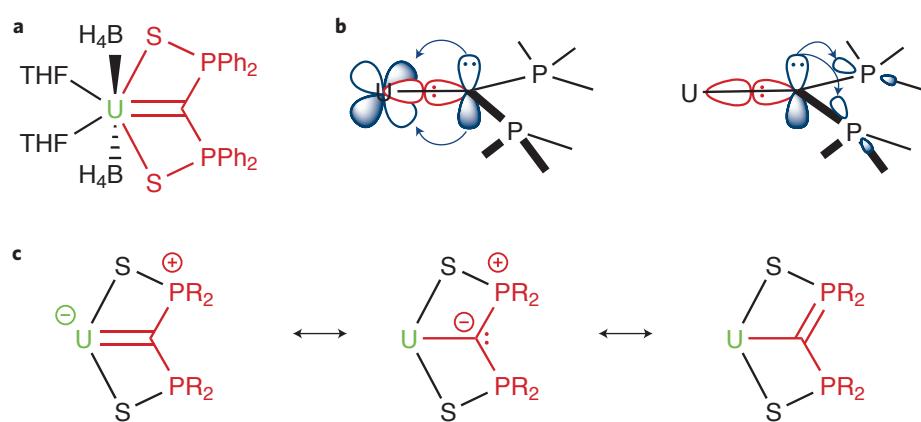


Figure 1 | Uranium carbene chemistry. **a**, A large planar multidentate SCS ligand allows a uranium carbene compound to be isolated, and its bonding and reactivity explored. **b**, The two electron-withdrawing P-substituents strongly stabilize the electron density on the carbene carbon, allowing the ylidic resonance forms (**c**) to contribute to the bonding description, in addition to a theoretically calculated donation into uranium 5f and 6d orbitals. ($R = C_6H_5$, THF = tetrahydrofuran).

it should have been only a matter of time before a molecule containing a genuine U=C bond was isolated. This has not been so. Advances in the organometallic chemistry of the lanthanides and actinides, collectively the *f*-block metals, have always lagged behind that of the *d*-block metals for a combination of reasons, but mainly because their large size and lack of orbital requirements for bonding make it difficult to stabilize kinetically inert complexes and to predict their reactivity.

Uranium has all the oxidation states between +3 and +6 available, and has no problem in using hybrids of *p*, *d* and *f*

orbitals to form double and even triple bonds to nitrogen and oxygen ligands. The majority of uranium compounds reported so far contain the linear dioxo cation $[UO_2]^{2+}$ in which the extremely strong uranium–oxygen bonds have a formal bond order of three. Many coordination complexes containing an organic imido group $U=N(R)$ have also been isolated, the most interesting being the direct analogue of the uranyl cation $[U(=NR)_2I_2(\text{THF})_2]$ (ref. 2). A molecular uranium–carbon multiple bond would be of interest because solid-state uranium carbide materials can be used in the new generation of safer nuclear reactors, but problems arise