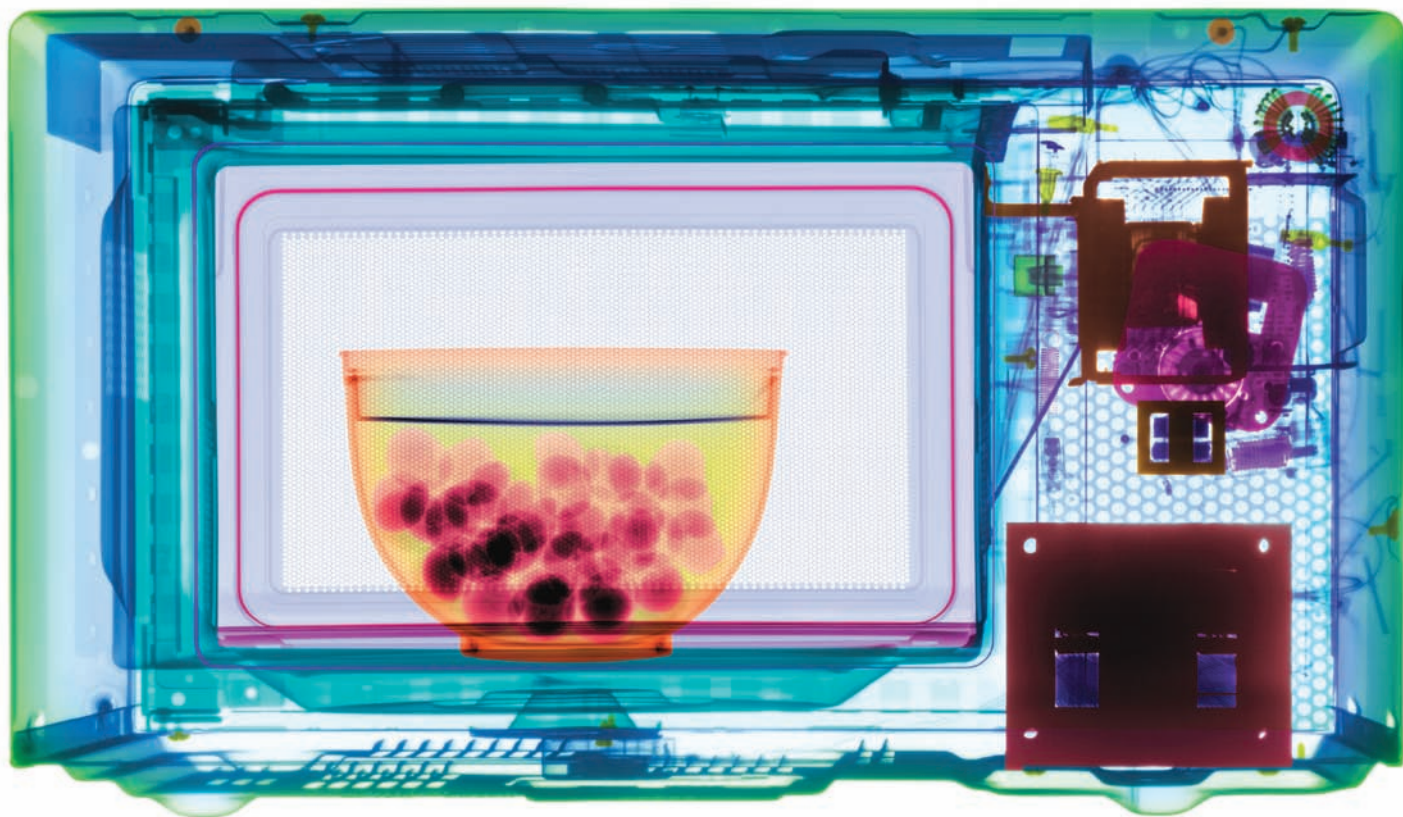


Microwaving myths

Microwaves are moving beyond organic synthesis, but there is still some confusion about what they do to molecules. Richard Van Noorden reports



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To a non-scientist walking into a modern synthesis laboratory, one tool among the alien glassware might seem familiar: the microwave oven. Just as domestic ovens heat up your dinner in minutes, so their scientific equivalents – with far greater safety and control – are famously convenient for speeding chemical reactions, where oil baths, isomantles or hot plates dawdle.

Yet, though microwaves dominate small-scale drug synthesis in the pharmaceutical industry, and are increasingly spreading into academic labs, some chemists remain reluctant to use them. 'It's become blatantly obvious to me that many chemists are incredibly conservative. Even though it's obvious from the literature that this is the way forward, they stick to heating up oil baths and doing their reactions overnight,' says Nicholas Leadbeater, who leads a microwave chemistry research group at the University of Connecticut, US.

What especially concerns the microwave community is others' lack of understanding about what the instrument does to molecules. For 15 years researchers have speculated that microwaves have special chemical effects, beyond their influence on heating. Although such confusion is gradually declining, the belief persists that there is some unexplained voodoo about running reactions in a 'black box' and waiting for the ping.

'Some claim that there's a lot of magic in microwaves. Actually it's just a great – and safe – way to do autoclave chemistry. It's not the last resort, it should be the first choice for any reaction that requires heat,' says Oliver Kappe, who leads the Christian Doppler Laboratory for Microwave Chemistry in Graz, Austria.

And microwave heating is finding uses far beyond its original remit. No longer are microwave reactions confined to sealed boxes at high temperatures and pressures. Researchers exploring how microwaves work are also expanding their uses beyond inorganic and organic chemistry. Microwaves are marching into the biosciences – already dominating areas like peptide synthesis – and are also being used to make nanoparticles and polymers.

Perhaps the only disappointment is that, despite being used in industrial processing for many years, microwaves still haven't broken into synthesis on a large



scale. It was hoped they'd be a greener, faster, cheaper way of making multi-kilogram batches of drugs or other compounds. That idea too apparently stemmed from insufficient consideration of how microwaves work, and where they could be used to advantage. With interdisciplinary teams of chemists and engineers now tackling the problem, though, microwaves might yet find their niche in scale-up.

It's getting hot in here

Whether heating up a mug of hot chocolate or accelerating a Suzuki coupling reaction, all microwave ovens work on the same principle. They inject energy directly into molecules, rather than warming the outside walls of a reaction vessel to spread heat by convection and conduction.

When irradiated at microwave frequencies (2.45 GHz in kitchen and commercial ovens), any dipoles in a reaction mixture – such as those in water molecules – wobble in an attempt to align themselves with the microwave's oscillating electric field. Charged particles, meanwhile, try to move under the field's influence. This frenzy of activity generates heat through collisions between molecules.

Solvents sealed inside a pot and microwaved can quickly

The kitchen microwave was once a novelty too

In short

● **Microwave heating is an established way to speed up organic syntheses, and dominates the pharmaceutical industry**
 ● **Confusion over what microwaves do to molecules remains, and they still haven't superseded conventional heating methods in mainstream laboratories**
 ● **As chemists understand more about how microwaves work, they are using them in nanoparticle and polymer synthesis, as well as in the biosciences**

superheat well above their boiling points, which is why reactions that take hours or days when heated conventionally can complete in minutes, or even seconds, in the microwave. Over 3000 research papers have documented this effect since microwaves were first reported to accelerate organic reactions in 1986. 'Any reaction that requires heat can probably be run faster, and more easily in a microwave,' says Leadbeater.

On a small scale, this convenience appeals to pharmaceutical chemists who have to generate libraries of compounds in a morning. 'In medicinal chemistry laboratories they have saturated the market. Virtually all new compounds now have their first synthesis in a microwave,' says Jonathan Moseley, of UK-based drug company AstraZeneca.

A faster reaction can also mean higher yields or greater selectivity for one product, as competing unwanted reactions have less time to kick in. It can save on reagents too: some organic coupling reactions proceed at such a lick in microwaves that only traces of metal catalyst are needed to get them going.

Modern equipment has increased the selection of microwaveable reactions. Leadbeater notes that recent innovations include running reactions under a gaseous atmosphere, to safely perform sealed-pot carbonylations or hydrogenations. 'You can also introduce reagents during a reaction, with a pump – we've done two-step reactions in one pot,' he adds.

And chemists no longer have to wait until a reaction has completed to analyse what they've got; Leadbeater and others have introduced spectroscopic techniques to monitor microwave reactions in real time. Kappe's group, meanwhile, are introducing silicon carbide plates on which many reactions can be run in parallel: unlike the 'hotspots' in your kitchen microwave, these plates are evenly heated throughout.

For those nervous of closing the door on their experiment, it's even possible to microwave open-top flasks or reflux equipment. Though you can't superheat solvents this way, microwaves still spread heat instantly and evenly through a sample in a way oilbaths can't match. This consistent heating profile is especially useful in nanoparticle synthesis. With temperatures high and constant through the whole

volume of a sample, particles all grow at roughly the same rate, leading to a controlled, narrow distribution of sizes.

Selective advantage

The most astounding microwave heating effects arise because not all molecules convert microwave radiation to energy with the same efficiency. Apolar solvents like toluene are transparent to microwaves and don't heat up at all; while ionic liquid solvents can shoot up by more than 10°C a second under irradiation, and can be added in small amounts as heat dopants to speed slow reactions.

This selective heating permits some remarkable organic transformations. Shainaz Landge, working with Bela Torok at the University of Massachusetts, US, uses microwaves to aid the enantioselective synthesis of organofluorine compounds – using organocatalysts at –25°C. The microwaves inject energy only into the molecules involved in the delicate reaction, while a pre-chilled, non-microwave-absorbing solvent acts as a refrigerator in an outer jacket.

Selective heating may also be behind microwaves' surge of popularity in the biosciences, according to Mike Collins, head of the US-based microwave company CEM. Dedicated microwave instruments for making peptides were only introduced a few years ago but already dominate the field.

In peptide synthesis, amino acids are coupled to a peptide chain growing on a solid support, using automated, repetitive reactions. A growing peptide chain tends to fold back on its end after six or seven couplings, leading to unwanted side reactions, Collins explains, but this seems less of a problem during microwave-assisted synthesis. That's partly because bursts of energy are transferred to the chain quickly enough to disrupt its back-folding. One partial explanation, still hotly debated, is that the peptide chain is itself a polar molecule – so, wobbling like a 'macro-dipole' in the applied field, selectively converts microwave irradiation to kinetic energy quicker than conventional heating allows.

'The big growth area will be in biosciences over the next few years,' Collins predicts. 'We see microwaves used in any bioscience process where energy is beneficial



Oliver Kappe leads the Christian Doppler Laboratory for microwave chemistry

OLIVER KAPPE, UNIVERSITY OF GRAZ, AUSTRIA

– for example, to synthesise any solid phase biopolymer such as DNA and RNA, or to speed cell assays.' Mike Lally, vice-president of business development for Sweden-based scientific instrument providers Biotage, also sees microwaves' future in biological applications that go beyond synthesis, including the processing of enzymes and antibodies. In proteomics, microwaves are already used to speed enzyme digests of proteins (for computational analysis) from hours to minutes. Microwaves can heat digests to modest temperatures which don't denature enzymes, and may also selectively inject energy into polar proteins, meaning they fragment more readily.

Past the mythology

Such is the buzz that the microwave literature is stuffed with speculation: do

microwave fields have a special influence on molecules beyond the thermal effects already described – perhaps influencing the orientation of individual polar bonds to favour particular transition states and reaction pathways?

Kappe and other researchers say they've shown these ideas are wrong. They're invoked because researchers don't correctly measure how hot microwaved components actually get during a reaction. Kappe has heated reactions to those same high temperatures with oilbaths, and got much the same yields and product profiles as with a microwave. Still, the speed, consistency and selectivity of microwave heating can't be exactly matched by oilbaths or hot plates. In the synthesis of large biomolecules the debate over non-thermal microwave effects is still raging, but Kappe says he wouldn't be surprised if all the benefits there turn out to be thermal too.

'It is remarkable, considering how well we understand the basics of the heating mechanism, how many contrasting opinions are still aired as to the exact origin of rate accelerations in microwave-assisted reactions. The problem is, it takes precision, the right equipment and a lot of work to establish the absence of specific non-thermal microwave effects and so many claims

Open-top reactions can now be run in microwaves



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– accepted by others in the community – are unsubstantiated and unsupported with rigorous data,’ says Mark Bagley, a chemist at Cardiff University, UK.

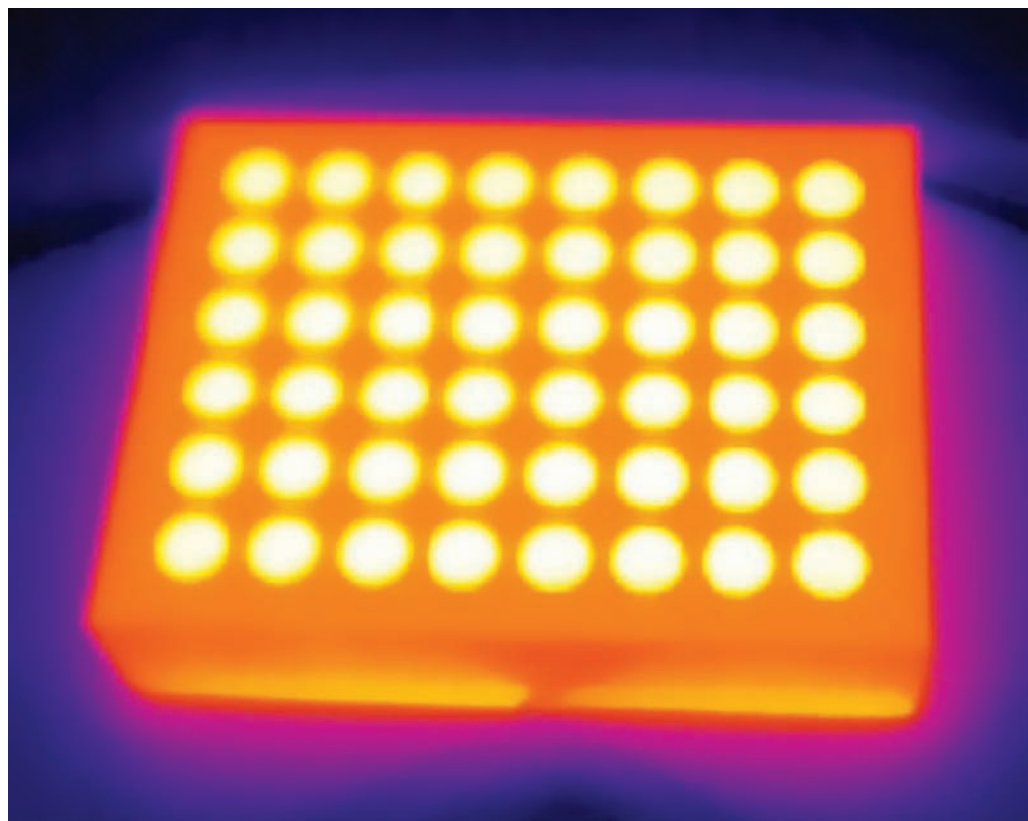
And chemists are still a long way off being able to switch on the microwave and predict what will happen to their reaction. Reactions are optimised by trial and error, rather than by design. For example, microwaves are known to enhance free radical polymerisation, a complicated process where a number of reaction steps (initiation, propagation, termination) are going on simultaneously. But no-one understands exactly why that is, so they can’t systematically improve on polymer yield or polydispersity. Researchers at Nottingham’s National Centre for Industrial Microwave Processing are hoping to be more precise. ‘We measure the individual dielectric properties [dictating how a material reacts to electromagnetic fields] of all the individual components and how they change with temperature,’ explains Nottingham’s John Robinson. ‘That should tell us how and when to apply microwave energy to improve the reaction.’

Already the team has found that, contrary to what’s claimed, microwaves have no effect on the first step in polymerisation reactions: the splitting apart of an initiator, AIBN (azobisisobutyronitrile), into free radicals that will help to propagate growing polymer chains. By measuring the dielectric properties of AIBN, they’ve shown its absorption of microwaves is negligible and doesn’t change with temperature: it’s only the free radicals, formed when AIBN dissociates, that absorb microwaves more strongly.

Desperately seeking scale-up

This sophisticated understanding may help break the glass ceiling of microwave synthesis: making drugs on a large scale. At the moment, says Merck chemist Joe Pawluczyk, ‘Medchem make the compounds quickly using microwave-assisted reactions; then the process team have to re-design those reaction steps because they can’t use microwaves on a multi-kilogram scale.’

What’s the problem? After all, microwaves have been used at industrial scales to help dry and process materials for some decades, as the Nottingham team stress. The



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team is, for example, now using microwaves to break apart mineral ores, and to remove oil from the gravel remnants of industrial drilling – both processes where microwaves heat faster and more selectively than other methods.

But this doesn’t apply to drug synthesis. Throw large amounts of liquid chemicals into a batch reactor, and you immediately hit a ‘penetration depth’ problem: microwaves are absorbed after passing through a few centimetres of water at room temperature, for example. That’s fine for a reaction in a 250ml flask: but in a 5 litre reactor filled with liquid, microwaves just heat slightly beyond the outer edges of the glassware. You have to stir your solution to get the heat convecting through the sample – and then you might as well use an oilbath.

The alternative is to get reagents to flow past microwaves in thin pipes, so that electromagnetic fields can penetrate the whole sample. This ‘flow’ concept has already been trialled, by French company Sairem, in the scale-up synthesis of a cosmetic, Laurydone. Microwaves heated reagents that were cycled through a thin pipe from a storage tank. But the reactor – never anything more than a proof of principle – has now been

An infrared image of a silicon carbide chip used to microwave many reactions in parallel

dismantled. Bert Hulshof, who works for DSM in the Netherlands and has seen the Laurydone trial, says it was the flow chemistry system that provided claimed advantages in productivity and energy efficiency, not the microwaves. Conventional heating on that system would have worked just as well.

So the difficulty, as Oliver Kappe stresses, is that it’s hard to see where microwaves actually add an advantage in scale-up reactors. ‘I’m far less optimistic about using microwaves in large-scale organic synthesis than I was a few years ago,’ he says.

Nottingham’s chemists say that researchers looking to scale up reactions should pick out candidates that take advantage of what microwaves offer beyond conventional heating. For example, conventionally-heated flow chemistry doesn’t cope well with viscous solutions, since they don’t transfer heat quickly. But microwaves would solve that problem: in a thin enough pipe, a viscous solution would heat instantly all the way through. That is why Nottingham’s team hopes that polymerisation reactions, with their rubbery solutions, will benefit from microwave heating on larger scales. The selective heating effect of microwaves might also come into

‘Some people think there’s a lot of magic in microwaves’



CHRIS DODDS, UNIVERSITY OF NOTTINGHAM, UK

play in pharmaceutical synthesis – for example, by lining a pipe with metal catalysts that rapidly absorb microwave energy, Hulshof speculates.

Whatever the solution, it will have to be a reactor custom-designed for a particular process. ‘And you’ll need to bring together a multidisciplinary team of chemists, microwave experts, process engineers, electrical engineers and end users,’ says Derek Irvine, one of the Nottingham team.

‘Unless there is some unique advantage for a particular process, I don’t think scale-up is where microwaves will have a major impact: 1kg is as far as they’ll go,’ says CEM’s Collins. But other chemists such as Leadbeater maintain that there’s still a lot of potential for scale-up. For the emerging fields of peptide and nanoparticle synthesis, however, ‘scale-up’ means only a kilogram or hundreds of grams, and the products can be of extremely high value. ‘We’ll be developing products to allow scale-up here,’ Collins adds.

Changing mindsets

Beyond scale-up, top of microwave chemists’ wish-list is seeing the technology saturate academic laboratories. Reluctance partly stems from the costs of commercial

microwave equipment; tens of thousands of pounds. All very well for medicinal chemists under pressure to quickly generate libraries of compounds, but perhaps a stretch for an academic lab. It certainly seems a lot compared to a hotplate, but compares reasonably to the cost of an analytical instrument, Kappe points out. In the biosciences, microwave peptide synthesisers cost little more than their equivalents that use conventional heating.

Confusion about what microwaves can do is the main problem, Kappe thinks. ‘I’ve seen instruments collecting dust because the research group has used them for the wrong things, with the wrong mindset about what they can do – and then microwaves in that lab get a bad name,’ he says. Collins feels that the perception that microwaves had to be used in sealed vessels also blocked progress. ‘Now chemists know they can run open reactions and still get benefit in microwaves, that’s a real driver for take-up,’ he says. Biotage’s product manager Pell Lidström says the company’s microwave sales rose 24 per cent last year, with 36 of 200 university sites making their first ever orders.

Nottingham researchers use microwaves on a large scale in industrial processes

The way to gain wider acceptance, Leadbeater says, is to train undergraduates to use microwaves. ‘A reasonably funded teaching lab could buy a microwave and have a carousel for multi-loading samples – and that would widen the scope of what undergraduates can do. They could waste their time on reactions requiring 10–15 hours of reflux, or do them in five minutes,’ he says.

Bagley says standard procedures and teaching lab experiments are already available. ‘I don’t think the mantle heater will ever be discarded – goodness, look at how long the Bunsen burner has prevailed. But we will see increasing introduction of technological alternatives,’ he adds. And with the biosciences, materials, polymer science and nanotechnology joining the fray, microwaves could soon become a staple in many more laboratories – no magic involved.

‘Chemists still can’t turn on a microwave and predict what will happen to a reaction’

Further reading

- C O Kappe, *Chem. Soc. Rev.*, 2008, **37**, 1127 (DOI: 10.1039/b803001b)
- J M Collins and N E Leadbeater, *Org. Biomol. Chem.*, 2007, **5**, 1141 (DOI: 10.1039/b617084f)
- For information on the upcoming conference: Enabling Technologies in Drug Discovery and Process Research – Microwaves, Flow, and Beyond. Antigua, 28–31 January 2009: www.zingconferences.com/z.cfm?c=46