MICROWAVE-ASSISTED ORGANIC SYNTHESIS an enabling technology with disruptive potential

Since the original publications on the benefits of conducting organic reactions in a microwave by Gedye[1] and Majetich[2] in the mid-80s, the uptake of this technique was sluggish at best for the next 12-14 years. However, the past few years have witnessed an explosion in the number of publications describing the utility of microwave synthesis, which can be directly correlated to the availability of instrumentation designed specifically for organic synthesis, allowing microwave reactions to be conducted in a safe and reproducible manner. This perspective will discuss the evolution of this technology, as well as its current use and untapped potential.

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Traditionally, organic synthesis at elevated temperature is carried out by conductive heating with an external heat source (electric plate heater, oil bath or heating mantle). This is a comparatively slow and inefficient method for transferring energy to the reaction since it depends on convection currents and the thermal conductivity of the various materials that must be penetrated, resulting in the temperature of the reaction vessel being higher than that of the reaction mixture. In addition, a temperature gradient can develop within the sample and local overheating can lead to product, substrate or reagent decomposition. In contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the solvent, reagents or catalysts presented in the reaction mixture. Since the reaction vessels are typically made out of microwave-transparent materials the radiation passes through the walls of the vessel directly into the whole reaction mixture volume. In typical microwave ovens, the magnetrons (microwave generators) produce a microwave wavelength of 12.25cm, which corresponds to a frequency of 2.45GHz. Microwave irradiation triggers heating by two main mechanisms: dipolar polarisation and ionic conduction[3]. By using closed microwave-transparent vessels, which can sustain higher pressures, the superheating effects are substantially magnified and it is possible to maintain solutions at temperatures much above their conventional reflux temperature. The higher purity of products often observed after

> "Scientific progress often does not consist so much of an advancement in science but rather in taking something that beforehand was not science and making it become a part of science itself."
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> *Sir Hermann Bondi*

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microwave irradiation can be largely attributed to the homogeneous and smooth *in situ* heating. The heating procedure is also highly controlled since the energy input starts and stops immediately when the power is turned on or off, respectively. It is important to point out that microwave energy cannot break bonds. Several recent books have appeared describing theoretical and practical aspects of microwave heating[5].

Commercial vendors of microwave equipment for chemistry

The past decade has seen the development of microwave equipment tailored specifically for chemistry, based on batch and flow processes. In particular, the advent of mono-mode microwave units has significantly increased the ease of use, as well as safety and reproducibility of microwave synthesis. The reaction volume dynamic range (0.1ml to 350ml) of mono-mode units provides tremendous flexibility in terms of scale, from reaction scouting to multi-gramme synthesis using minimal reaction re-optimisation. This ability to rapidly generate milligramme to multi-gramme quantities of intermediates and target compounds within a matter of minutes is an invaluable asset, and eliminates compound availability as the rate limiting step in biological evaluation. There are several vendors of equipment for batch as well as flow-based microwave-assisted organic synthesis, with Anton-Paar, Biotage, CEM and Milestone being a few of the larger providers. Details on the range of equipment available for medicinal and process chemistry as well as library synthesis applications are available on the company web pages (www.anton-paar.com, www.biotage.com, www.cem.com, www.milestonesci.com). In terms of microwaves for library synthesis, mono-mode microwave reactors for simultaneous parallel reactions with individual reaction temperature monitoring capability which capitalise on all the benefits of microwave synthesis described above (volumetric heating of reactants, quick on/off) are not yet commercially available.

The availability of reaction databases, which allow the user to rapidly identify microwave conditions has been a significant advancement. The addition of information on reactions performed specifically in mono-mode microwaves, reduces the uncertainty associated with trying to reproduce reactions performed using 'kitchen microwaves' (higher wattage, multimode units).

In recent years, flow chemistry has emerged as a viable means for performing many types of chemical transformations[5]. Flow chemistry involves driving liquids (normally reagent/substrate solutions) through a reactor which is often just a capillary or tubing. There is considerable interest in macro-scale (synthesis of active pharmaceutical ingredient synthesis), microscale (integrated 'lab-on-a-chip' type approaches where synthesis and biological screening are integrated) and meso-scale flow units. The key advantage to performing reactions in a flow reactor lies in the enhanced process controls when compared to batch synthesis – in a microfluidic reactor, for example, diffusive mixing of reagents is rapid, and the reaction conditions can be carefully controlled due to the high surface-to-volume ratio of the mixer. Additionally, conditions such as reaction time and temperature can be set and controlled with a high degree of accuracy and consistency across the entire reaction. Furthermore, it is a simple operation to run the reaction under pressure, which opens up the potential to superheat reactions in a manner similar to a batch microwave. One potential disadvantage associated with the rapid cooling of the reaction mixture on leaving the irradiation zone is crystallisation, providing a challenge in terms of reactor design, choice of reaction solvents and dilution. Information on commercial flow units can be found on the vendor websites (www.syrris.com, www.vapourtec.com, www.thalesnano.com). As a testament to the great interest in flow microwave chemistry, the Engineering and Physical Sciences Research Council (EPSRC), in partnership with GlaxoSmithKline and Pfizer, recently announced a research grant proposal programme aimed at increasing the volume of research in flow chemistry, as well as providing opportunities for technology and knowledge transfer between academia and industry.

The combination of flow-chemistry and microwave synthesis was described in the pioneering work of Strauss in 1990[6], though somewhat surprisingly the first wave of reactors to be designed and readily accepted were the batch reactors. However, in recent years, several flow-based microwave reactors have been described, especially by Ley and Haswell[7]. Unlike batch synthesis, the ability to couple multiple modules containing reagents for multi-step synthesis or polymer-supported reagents is a tremendous advantage of this technique.

While the advent of microwave reaction databases has been an asset, the legacy of reactions conducted using conventional techniques is far greater. The recent advent of real-time reaction monitoring is aimed at allowing users a convenient way to ensure that reactions are conducted only for as long as required. Solvent interference is clearly an issue with real-time detection that must be dealt with, and there are a few techniques which have

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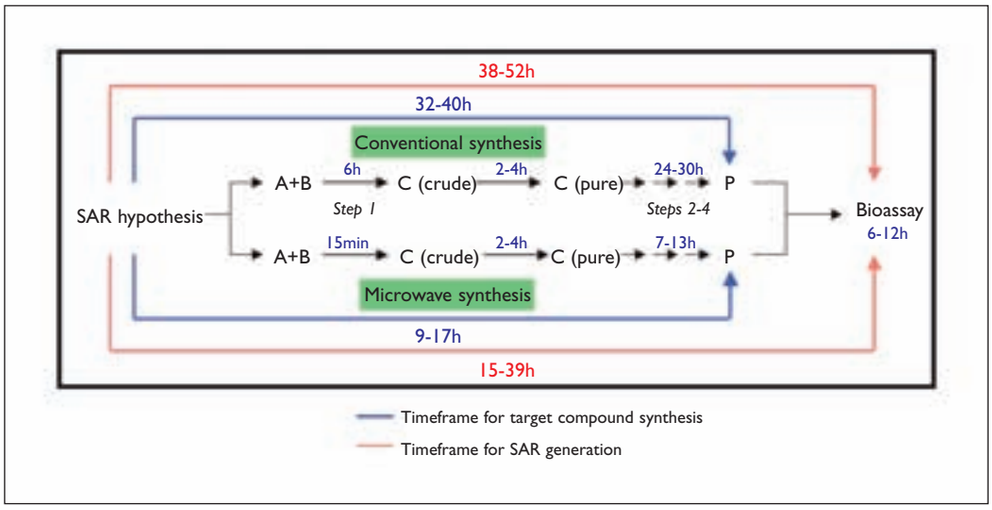

Figure 1: SAR Cycle, comparing conventional and microwave synthesis

been reported to address this. For example, UV/Visible spectroscopy has been used to monitor reaction progress even at dilute concentrations[8]. Vibrational spectroscopy techniques have historically proved to be very useful for monitoring chemical reactions. Taking into consideration the challenges associated with analysis of new samples as well as penetration of glass vessels, Raman spectroscopy is a particularly useful technique for *in situ* spectroscopy because it relies on light scattering and hence no mechanical interaction with the sample. The high information content obtained using this technique allows one to characterise intermediates, yielding increased mechanistic understanding, in particular when more efficient synthetic processes need to be developed[9]. While this is a technical advancement, the infrequent use of Raman spectroscopy as an analytical tool in medicinal chemistry laboratories may result in an inertia in the implementation of this technique.

Since closed vessel mono-mode microwave reactions are in the magnetron during the course of the reaction, it is not possible to visualise reactions, akin to conventional reactions. The recent disclosure of a microwave device with a source for illuminating the vessel and its contents, is an intriguing advance, enabling concurrent visual observation and infrared monitoring of microwave reactions[10].

Perspective on current use

Prior to microwave-assisted synthesis, it can be argued that combinatorial chemistry was the last major advancement in terms of a chemistry-based breakthrough technology in the pharmaceutical industry. The powerful potential of combinatorial chemistry, bringing together multiple facets of polymer and synthetic chemistry coupled with biological screening of large numbers of compounds resulted in rapid uptake and great expectations in terms of the potential to transform the future of drug discovery. While it is possible that the true impact of this core technology has not yet been realised in a pharmaceutical setting in terms of new molecular entities (NMEs), in general it is widely accepted that this technique has failed to live up to the hype. Having said that, concepts, which have their roots in combinatorial chemistry, continue to prosper in fields such as material science and dynamic combinatorial chemistry. While the reasons for the failure of combinatorial chemistry to deliver on the hype are beyond the scope of this article, on a philosophical note, the introduction of this technique was bandied as a breakthrough, disruptive technology, leading to the veritable 'peak of inflated expectations'[11]. On the contrary, the introduction of microwave synthesis in drug discovery has not suffered this peak, presumably since it has been viewed as an enabling technology so far.

A brief discussion on how microwave technology has influenced the Structure Activity Relationship (SAR) cycle in medicinal chemistry is shown in **Figure** 1. The following assumptions have been made:

Average reaction time using conventional heating: 6hr
Average reaction time using microwave heating: 15min
Average number of linear synthetic steps/target molecule: 4

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Average purification time regardless of heating technique: 2-4hr
Average time for a biological assay: 6-12hr

It is clear that in terms of the time taken purely for the synthetic steps, microwave synthesis provides a tremendous advantage compared to conventional heating techniques (1hr compared to 24hr). If one assumes that reactions performed using both techniques proceed with similar purity and post-synthetic transformations, use of microwave-assisted synthesis results in procurement of target compounds 2-5-fold faster than conventional synthesis. If one includes biological evaluation to enable a true measure of impact on the overall purpose of compound synthesis, microwave-assisted synthesis can expedite an SAR cycle up to 3-fold. Needless to say, if one were to include parallel synthesis using either convection heating or microwave heating, the SAR cycle above would need to be modified accordingly.

Future directions

So where does microwave synthesis go from here? What will it take for this technology to make the transition from an enabling technology with significant impact on SAR cycles to transforming the ability to evaluate multiple hypotheses in parallel? Clearly the ability to couple expedited product purification is and should continue to be an area of intense focus to maximise the benefits of compressed reaction times. Currently, there is no convenient *in situ* work-up and purification procedure available for reactions performed in batch microwaves that do not involve significant manual intervention. On the other hand, flow reactors are ideally suited for expedited purification by attaching various modules containing polymer supported reagents reactions, and in fact there are several elegant publications describing this approach[5].

The applications of microwave synthesis to biological applications such as the exposure of antigens for immunohistochemical staining in embedded tissue samples, increased catalysis of enzymatic and chemical cleavages for peptide mapping and increased removal of PTMs for improved protein characterisation raises intriguing possibilities in terms of further shortening the SAR cycle (**Figure 1**)[12]. Obviously, the temperature sensitivity and polar nature of enzymatic reactions should be kept in mind prior to subjecting them to superheating. That could be the reason why there are no reports linking chemical synthesis and biological testing utilising microwave irradiation. However, the concept of microwave fluidics[13] in which low power microwaves are used to move fluids on a disposable device, without heating the fluids *per se* could be an extremely valuable technology because it is a 'noncontact' method, sparing sensitive biological systems. This concept has been applied to expedite bioanalytical reactions, but an extension of this to pharmacological bioassays, especially in conjunction with microwave synthesis and expedited purification, could provide a breakthrough in terms of shortening the SAR cycle from days to a matter of hours!

In terms of microwave technology itself, there are several exciting avenues, which are in their early stages of utilisation:

Reactions at sub-ambient temperature: Because microwave energy is transferred kinetically, not thermally, microwaves can accelerate reactions maintained at low temperatures[14]. Due to the direct mechanism of energy transfer and the ability to cool the reaction during the energy transfer cycle, this technique should enable the synthesis of temperature sensitive products by removing excess thermal energy. Just as with other microwave syntheses, reactions that require long periods of time to complete are prime candidates, though there have been limited examples in the literature, despite the availability of commercial equipment. It is possible that additional studies are required to carefully measure the temperature of these reactions prior to widespread use.

Green chemistry: Another underexplored avenue of investigation is the area of 'green chemistry'. Also known as sustainable chemistry, green chemistry is defined by the EPA (www.epa.gov/gcc/) as 'the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances'. While there are several criteria which determine the classification of reactions as 'green', the potential to use (supercritical) water as a solvent for microwave synthesis is a tremendous advantage, eliminating the use of traditional organic solvents[15]. The combination of ionic liquids and microwave heating allow scientists to open new unexplored functionalisations of complex systems. Due to their high polarity and stability at elevated temperatures, ionic liquids are attractive solvents or co-solvents in microwave synthesis[16]. Additionally since they have melting points close or near to room temperature, negligible vapour pressure and are immiscible with a range of organic solvents, reaction products can be removed post-reaction and the ionic liquid recycled.

Combination with other forms of energy: While there are no commercial units enabling microwave and ultrasonic irradiation, reports in the literature using 'jerry rigged' units have reported tremendous rate accelerations using this combination[17]. In particular, for heterogeneous reactions in water, the integrated application of microwave and ultrasound irradiation has been shown to be highly advantageous, combing the effects of superior reaction rates and green chemistry.

Similarly, there are only a few reports studying the effects of combining microwave irradiation with photochemistry[18]. Since the energy of microwave radiation is substantially lower than that of UV radiation, photochemical irradition would be responsible for initiating the chemical transformation, with microwave irradiation subsequently affecting the course of the reaction via coupling with the highly reactive, electronically excited molecules. The use of Electrodeless Discharge lamps provides a unique opportunity to combine these technologies in a facile manner, enabling photochemical reactions at high temperature to be conducted in a 'contained' environment. While the possibility of expanding the use of photochemistry via combination with microwaves is a worthy pursuit, special attention needs to be paid to the safe design of robust microwave photochemistry units prior to extensive uptake in the pharmaceutical industry. The recent introduction of equipment for microwave-assisted UV digestion utilising electrodeless Cd lamps could facilitate the uptake of this technology.

An elegant scientific breakthrough in terms of the application of microwaves to the synthesis of quantum dots has recently been reported[19]. Using commercially available starting materials, scientists at the NIST were able to synthesise highly uniform and efficient quantum dots for a range of frequencies and show them to be stable in aqueous solutions for longer than four months. The applications of microwaves in the field of peptides and glcopeptides is a burgeoning field of active interest as well[20].

Concluding thoughts

The desire for rapid and efficient synthesis of target molecules in a drug discovery setting is overwhelming. Most medicinal/drug discovery chemists have far more creative hypotheses than time to investigate them. The 'SAR cycle' (**Figure 1**) comprising conception, synthesis, purification, biological evaluation and back to conception, however, can often take days to weeks. The advent of instrumentation enabling safe and reproducible microwave synthesis has provided drug discovery scientists the

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opportunity to evaluate several chemical hypotheses in the same time it used to take to evaluate a single one. As a result, the creativity of drug discovery scientists can be harnessed to provide companies a tangible competitive advantage. However, the uptake of this technique is still not as widespread as it could be. A few factors that will be important to its continued role in impacting drug discovery are:

Access: Despite the tremendous improvements in reaction rate, microwave units are significantly more expensive than equipment for conventional heating equipment, making the concept of 1 microwave, 1 chemist an expensive proposition. To truly harness the intellectual prowess of medicinal chemists, ready access to microwave units has to be paramount.

Scalability: This is less of an issue now than it was a few years ago, with the increased scale of batch microwave units, allowing for minimal reaction optimisation in generation milligramme and multigramme quantities of product. The uptake of flow microwave units in medicinal chemistry setting continues to lag, but given the significant timesavings possible with on-line purification, it is anticipated that the scenario will change in the coming years.

Reaction information: As mentioned previously, the wealth of information available on reactions conducted using conventional heating dwarfs that with microwave heating. The continued growth of reaction databases along with the familiarity of users will result in less uncertainty about using this technique as a method of first choice. Additionally, with microwaves now making their way into the undergraduate and graduate curriculum, one imagines the first question the new breed of chemists entering the pharmaceutical industry ask is 'where's my microwave'?!

Continued emphasis on safety: As new add-on software and hardware features continue to be introduced, especially in larger scale reactions and ultrasonic and photochemistry coupled microwave synthesis, the continued attention to safety is essential.

Creative ways to shorten the SAR cycle: The earlier discussion highlighted the significant improvements brought about by microwave-assisted synthesis compared to conventional heating techniques. However, it also suggests that the overall rate improvements in the SAR cycle are only a fraction of the tremendous shortening of reaction time. The combination of polymer supported reagents for purification of batch microwave synthesis as well as other innovative ways to reduce post-synthetic manipulations will be essential to maximise the time-savings. The untapped potential of coupling microwave synthesis, purification and biological evaluation in a streamlined manner will provide the maximal timesavings, even if it is for a limited number of bioassays. The ability to reduce the SAR cycle from days to hours could determine whether microwaves make the transition from an enabling technology to a disruptive technology.

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