Applying Novel Technology in Microwave Synthesis

Introduction

Microwaves are important and powerful tools, found in laboratories across the world and applied across varying synthetic applications. With the ability to heat efficiently, precisely, and safely, laboratory microwaves have greatly benefited chemical synthesis. The Discover® 2.0, CEM Corporation's innovative laboratory microwave synthesizer, expands the capabilities and benefits of microwave reactors. Prior to discussion of the responsible developments and features, however, it is helpful to first understand the principles of microwave heating.

Microwave Heating Principles

Microwaves are low-energy electromagnetic waves, interacting with molecules via two modes of action: dipolar rotation and ionic conduction (**Figure 1**). In dipolar rotation, a molecule rotates back and forth constantly, attempting to align its dipole with the ever-oscillating electric field; in ionic conduction, a free ion or ionic species moves translationally through space, attempting to align with the changing electric field. In both cases: 1) the friction between the moving species results in heat generation and 2) the more polar and/or ionic a species, the more efficient the rate of heat generation.

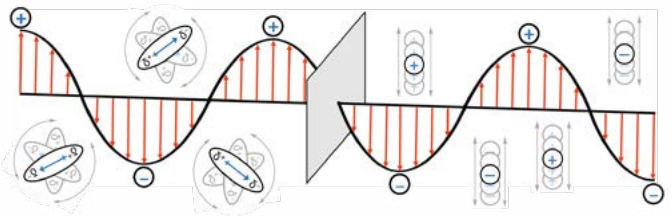


Figure 1. Mechanisms of Microwave Heating: Dipolar Rotation (Left) and Ionic Conduction (Right)

Because microwaves interact directly with the contents of a reaction mixture, energy transfer occurs more efficiently than with conventional heating techniques. Conventional heating techniques rely on thermal conductivity, a slow and inefficient method of heat transfer, limited by differing material's thermal conductivities. Microwaves instantly and directly heat a solution, resulting in a more efficient and more precise mode of heating.[1,2]

Benefits of Microwave Reactors

Dramatic reduction of total synthesis time is a great benefit of microwave heating in chemical synthesis. Though microwaves are able to heat a solution more efficiently than conventional means, there is a larger factor contributing to the enhanced reaction rates so frequently observed: the ability to operate at temperatures exceeding reflux while safely maintaining the consequent high-pressure atmosphere.

$$\text{At } T = T_0 + (10\,^{\circ}\text{C})x,\ t \approx \frac{t_0}{2^x} \quad \text{(Equation 1)}$$

A convenient generalization supported by the Arrhenius equation, is that a reaction rate will roughly double for every 10 °C the temperature increases. With this generalization, the approximation in Equation 1 can be derived, where T = microwave heating temperature, T_0 = conventional heating temperature, x = the temperature increase coefficient, t = microwave heating time and t_0 = conventional heating time. Traditional reactions that take hours conventionally, can be completed in minutes when employed in microwave reactors.[2]

Increasing Temperature Accuracy with iWave Temperature Monitoring

The ability to accurately measure and control reaction temperature is an important requirement for laboratory microwave reactors. Historically, there have been two major approaches to temperature measurement: standard IR sensors and fiber-optic probes. An innovative technology, the iWave® temperature sensor, has since proved a more valuable tool.

Previous Temperature Measurement Technologies

Standard IR sensors are robust and affordable, making them excellent candidates for microwave reactors. An added benefit of standard IR sensors is that they are non-invasive, fostering compatibility with auto sampler technologies and minimizing the number of components that require routine cleaning. Though a robust option, standard IR sensors are met with a few accuracy obstacles: 1) routine single-point calibrations are necessary, 2) delays in equilibrium between solution and vessel surface temperatures are expected and 3) volume-dependencies for instruments with side-mounted IR sensors (instead of bottom-mounted) must be considered (**Figure 2**).

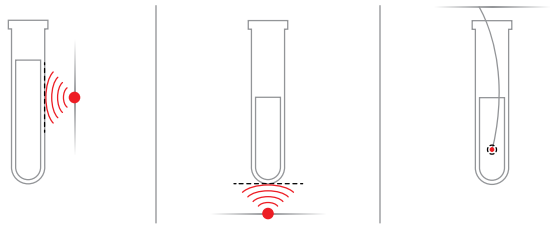


Figure 2. Side-Mounted Standard IR Sensor (Left), Bottom-Mounted Standard IR Sensor (Middle), And Fiber-Optic Probe (Right)

Fiber-optic probes offer better accuracy than standard IR sensors, but are not without their own challenges. Delicate and expensive, these probes require great care while handling, increased cleaning requirements, and are incompatible with auto samplers. Additionally, though more responsive than IR, this sensitivity is dampened when the probe is encased in a thermowell (necessary to prevent chemical wear). Lastly, though accurate, fiber-optic probes are limited to an isolated monitoring area rather than monitoring aggregate temperature.

iWave, An Innovative Technology for Temperature Monitoring

An innovative technology has emerged, however, addressing the deficiencies experienced by standard IR sensors and fiber-optic probes. The iWave temperature sensor (**Figure 3**) is a non-invasive temperature monitoring technology which can see through glass, Teflon® , and quartz, measuring solution temperature directly and with high precision and accuracy (40–300 °C).

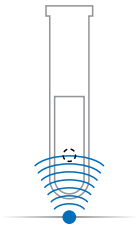
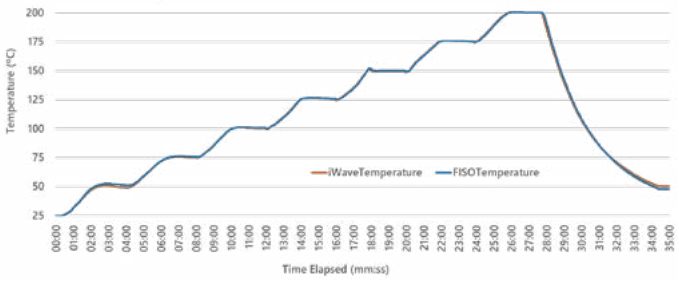


Figure 3. Non-Invasive, In-Situ Temperature Accuracy with iWave Temperature Monitoring

To verify performance of this novel technology, dual-temperature monitoring was equipped on the Discover® 2.0 and a multi-point heating experiment was conducted. Water was heated in increments of 25 °C from room temperature to 200 °C, while monitored by both the iWave temperature sensor and a fiber-optic probe (**Graph 1**). Temperature accuracy was retained during all ramping, holding, and cooling periods, displaying the iWave temperature sensor's applicability across wide temperature ranges (from a single-point calibration at 200 °C).

Graph 1. Heating Water from Room Temperature to 200 °C in 25 °C Increments



This *in-situ* accuracy of the iWave temperature sensor obsoletes fiber-optic probes, bypassing the need for fragile and expensive components, monitoring the entire reaction solution, and maintaining compatibility with auto samplers. Like standard IR sensors, the iWave temperature sensor is non-invasive, robust, and affordable; unlike standard IR sensors, no routine calibrations are necessary and no thermal response delays are observed. This iWave temperature sensor encompasses the strengths of both existing temperature monitoring technologies, offering a robust, non-invasive, accurate, and responsive solution for temperature monitoring.

Increasing Laboratory Safety with Activent Pressure Management

From chemical compatibility of reactor components to ensuring proper fume ventilation, and integrated stirring capabilities to vessel rupture containment, there is no doubt that laboratory microwave reactors are designed with safety at the forefront. A particularly important safety mechanism incorporated into some microwave reactors, however, is pressure maintenance and management.

Previous Pressure Measurement Technologies

Laboratory microwave reactors are equipped with pressure-monitoring capabilities to reduce the occurrence of vessel over-pressurizations. When a system detects pressures approaching the vessel's maximum limits, heating is terminated. If the pressure generated was solely attributed to vapor pressure, the pressure will return to ambient conditions upon cooling. If the pressure generated was due to gaseous byproduct formation, the elevated pressure levels will remain upon cooling (**Figure 4**).

Figure 4. Gaseous Byproducts Trapped within a Closed Vessel with Crimp-On Cap

Because many reactors utilize crimp-on caps or pneumatic sealing devices, the system operator must manually release this pressure, introducing opportunity where operator safety is compromised.

Activent Pressure Management, the Safest Technology for Pressure Handling and Venting

The Activent® pressure device was developed by CEM Corporation to not only contain and monitor internal pressure, but to vent gaseous byproducts generated. The pressure vessel caps utilized with the Activent pressure device require no tools (unlike crimp-on caps) and contain a small opening where excess pressure may be relieved (**Figure 5**).

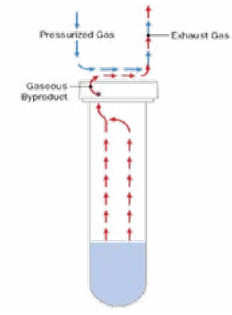


Figure 5. Gaseous Byproducts Released from a Microwave Vessel By the Activent Pressure Device

The Activent pressure device seals on top of the vessel cap, measuring internal pressure of the vessel (0–435 psi). Like previous technologies, the Activent pressure device will signal irradiation cessation as pressure limitations are approached; unlike previous technologies, however, the Activent pressure device can be programmed to vent gaseous byproducts before pressure limits are met and without stopping reaction irradiation. An inert carrier gas is applied each time the system vents, ensuring complete purging of (potentially flammable) gaseous byproducts from the system's lines. When a reaction is complete (and cool), any residual pressure is safely vented prior to releasing the microwave vessel.

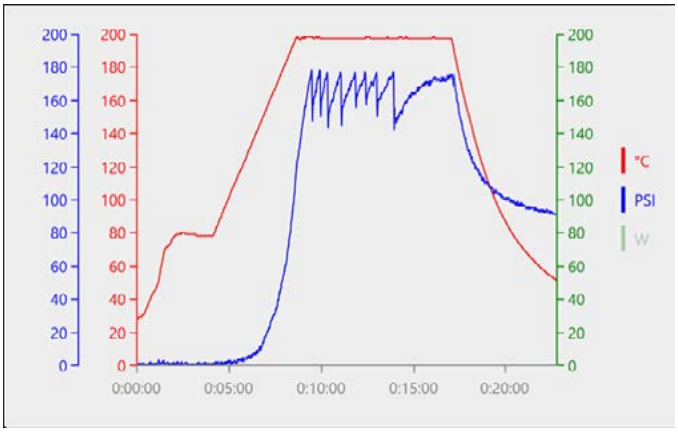


Figure 6. Temperature and Pressure Result Graph for a Wolff-Kishner Reduction Run on the Discover 2.0

To demonstrate the Activent pressure device's venting capabilities, a Wolff-Kishner reduction of benzophenone was performed in the Discover 2.0. The reaction required a 2-stage heating method (a shorter low-temperature reagent melt, followed by a longer high-temperature reaction period) and was programmed to vent 25 psi any time the internal pressure of the vessel exceeded 175 psi (due to N_2 generation from the reaction). The system vented 8 times in total during the reaction period, keeping the internal vessel pressure well within the maximum limits (**Figure 6**). The system vented the residual pressure after reaction completion and prior to vessel release, ensuring operator safety upon vessel retrieval and workup.

Increasing Chemical Exploration with Expansive Application Capability

Microwaves can be used for nearly any synthetic transformation, including those employing metallic reagents, from palladium catalysts to magnesium turnings. While metals in a kitchen microwave are a known safety concern, metal reagents (submerged in solvent) in a laboratory reactor are an everyday occurrence. From inert chemistry to transformations requiring gaseous reagents, or sub-ambient temperatures to flow chemistry, nearly any conventional synthetic transformation can be adapted to microwave irradiation.

Expanding Reagent Compatibility with Teflon Liners

Affordable and compatible with standard IR sensors, glass vessels are the industry standard for research-scale microwave reactors. Glass vessels, however, suffer chemical incompatibility with etching reagents like NaOH or HF. To address this shortcoming, Teflon® liners for insertion into standard glass microwave vessels have been developed (**Figure 7**). These liners, however, can impose significant effects on temperature accuracy with standard IR sensors due to increased thermal delay. Fortunately, development of the iWave temperature sensor obsoletes this issue, enabling use of otherwise prohibited reagents.

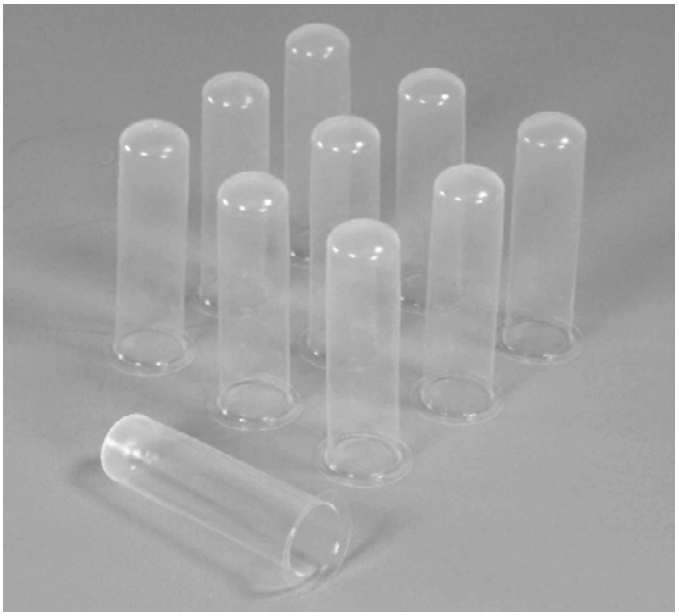


Figure 7. Teflon Liners for Insertion into Standard Glass Microwave Vessels

To demonstrate the utility of Teflon liners, reaction conditions typical in zeolite synthesis[3] (10% NaOH heated to 170 °C for 6 h) were performed in glass vessels with and without the liners. As expected, significant vessel etching was observed when no liner was employed and no vessel etching was observed when a liner was employed (**Figure 8**).

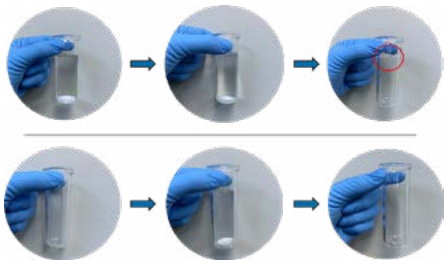
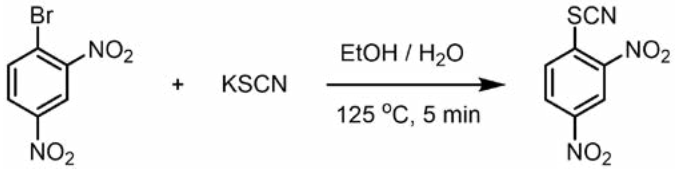


Figure 8. Significant Vessel Etching When No Teflon Liner Was Employed (Top) and No Vessel Etching When Teflon Liner Was Employed (Bottom).

Increased Scalability and Workflow Efficiency

A common limitation in single-mode microwave reactors (reactors where the cavity is no larger than 12.2 cm in diameter; intentionally designed for one standing wavelength) is maximizing microwave vessel volume capacity. Historically, microwave vessels have been limited to around 30–35 mL total volume (with a maximum working volume of 20–25 mL), typically capping product yields at around 1 g. Recently, however, CEM Corporation has developed a large-scale, 100-mL vessel capable of withstanding high temperature and pressure conditions for use in the Discover 2.0, offering a working volume scale of 0.2–70 mL and enabling product yields from the milli- to multigram scale.

To demonstrate the increased synthetic scale capabilities, the nucleophilic aromatic substitution of 1-bromo-2,4-dinitrobenzene with potassium thiocyanate was performed in the three Discover 2.0 standard vessel offerings: 10-mL, 35-mL, and 100-mL vessels (**Figure 9**); product yields were 270 mg, 1.1 g, and 2.7 g, respectively, though over 5 g of product could have been synthesized if the 100-mL vessel was utilized to its maximum working volume (70 mL).



Vessel Size	10-mL	35-mL	100-mL
Isolated Yield	270 mg	1.1 g	2.7 g

Figure 9. Isolated Product Yields For The Nucleophilic Aromatic Substitution Of 1-Bromo-2,4-Dinitrobenzene With Potassium Thiocyanate

Conclusion

CEM Corporation's Discover 2.0 is a research-scale laboratory microwave synthesizer utilizing novel developments and technologies to maximize the capabilities of synthetic exploration. Whether increasing temperature accuracy with iWave temperature monitoring, laboratory safety with the Activent pressure device, or chemical exploration with expansive application capability, the Discover 2.0 is an invaluable tool for any synthetic laboratory.

References

[1] Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233–238.

[2] Brittany, H. (2002). *Microwave Synthesis: Chemistry at the Speed of Light*. Matthews: CEM Publishing, pp.11-27.

[3] Nasser, G. A.; Muraza, O.; Nishitoba, T.; Malaibari, Z.; Yamani, Z. H.; Al-Shammari, T. K.; Yokoi, T. *Ind. Eng. Chem. Res.* **2019**, *58*, 60-68.

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