

Microwave Ring Expansion Reactions Performed at Sub-Ambient Temperatures

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Microwaves are traditionally thought of as extremely efficient heating instruments. Chemists first began to investigate microwave chemistry as a way to heat reactions to high temperatures quickly. As microwave chemistry was further explored, however, chemists discovered rate enhancements and cleaner products beyond that which could be repeated under conventional conditions, given the same temperature.¹

Sub-ambient synthesis is utilized for a variety of reasons, including reactivity, stability of products and/or intermediates, and low boiling points. Reactions run at low temperatures typically take a long period of time, because energy is not added to the system to help the reactants overcome the activation energy barrier. Traditionally, the only energy source available was thermal energy, the addition of which would increase the ambient or sub-ambient temperature beyond what the chemist desired.

Since it is known that microwave energy increases the rate of reactions beyond that which would be expected; given the measured bulk temperature, what would happen if microwave energy could be added to the system, but the measured, or bulk, temperature was kept low — ambient or below? In the past, moderate, simultaneous cooling while irradiating has been shown to promote cleaner transformations to the desired product with yields greater than that which occurs with only irradiation.² It seems logical, then that the same rate enhancements could occur at even lower temperatures.

How Microwave Energy Accelerates Organic Chemistry

In order to understand how these rate enhancements occur independent of the bulk temperature, one should have some familiarity with how a microwave interacts with organic molecules. A microwave, as shown in Figure 1, is a form of energy that falls at the lower end of the electromagnetic spectrum. It is defined in the 300 to about 300,000 megahertz (MHz) range. Microwaves only affect molecular rotation: they do not have enough energy to affect molecular structures directly. Of the four available frequencies for industrial, scientific, or medical applications, 2450 MHz is most commonly used because it has the right penetration depth (~1.75 inches) to be effective for laboratory scale samples.

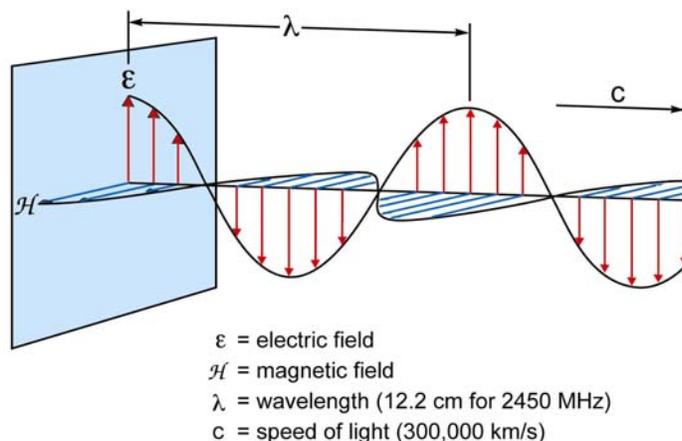


Figure 1. A microwave.

The electric field of the microwave interacts with organic molecules through either a dipole or ionic conductivity in the molecules themselves. As the electric field changes from positive to negative, the positive or negative ends of the dipole (or the positive or negative ion) seek to align with the opposite field. This causes molecular rotation. The rotational motion of the molecule as it tries to orient itself with the field results in a transfer of energy. The coupling ability of this mechanism is related to the polarity of the molecules and their ability to align with the electric field. There are a number of factors that will ultimately determine the dipole rotation coupling efficiency; however, any polar species (solvent and/or substrate) present will encounter this mechanism of energy transfer. Each transfer of energy is rapid, occurring every nanosecond (10^{-9} sec), while molecular relaxation occurs every 10^{-5} seconds, meaning the molecules are constantly stimulated and in a state of non-equilibrium, helping to drive the reactions to completion.

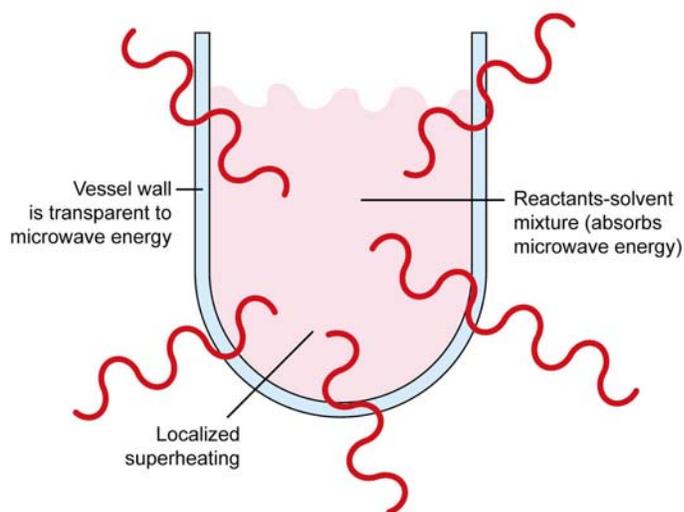
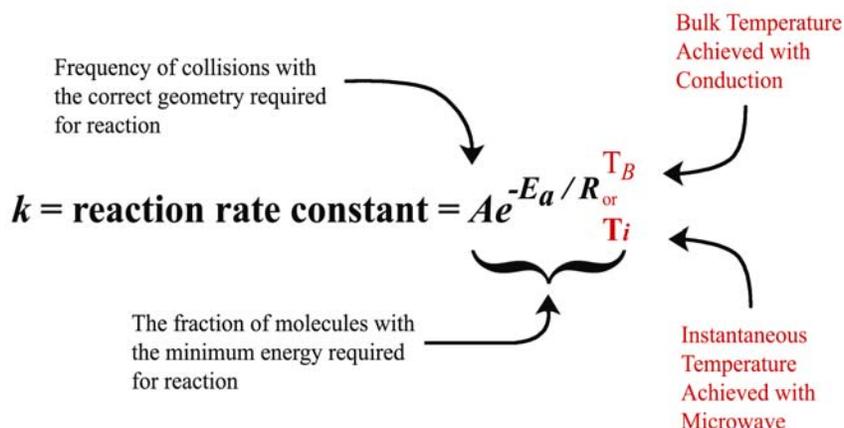


Figure 2. Schematic of heating with microwaves.

One of the advantages of using microwave energy, and the reason it can be utilized for sub-ambient synthesis, is that the rate enhancements are not dependent on thermal conduction. With conventional (conductive) heating, a hotplate is heated and the energy is then transferred to a beaker or round bottom flask. That heat must then be transferred again through each layer of liquid until the temperature is uniform, driving the reaction forward. Glass vessels are transparent to microwave energy, enabling the sample to absorb the energy directly and leading to more efficient energy transfers. Heat is not used to drive the reaction: energy is directly applied to the reacting species. Thermal energy is produced only as a byproduct. (Figure 2)

We know that microwave energy transfer is very rapid, while molecular relaxation is relatively slow. Microwaves will transfer energy in 10^{-9} seconds with each cycle of electromagnetic energy. The kinetic molecular relaxation rate from this energy is approximately 10^{-5} seconds. This means that the energy transfers occur faster than the molecules can relax, which results in the non-equilibrium condition and high instantaneous temperatures or T_i . In every reaction, the goal of energy addition is to surmount the activation energy barrier (E_a). Instantaneous temperatures simply help to drive the reaction over that barrier rapidly by adding more energy than is necessary to drive the transformation forward.

Looking at the Arrhenius equation provides a clearer picture:



The rate of a reaction is dependent on two parameters: the frequency of collisions with the correct geometry (A) and the fraction of molecules with the minimum energy required for the reaction (E_a/RT). With conventional heating, the temperature observed in a reaction, called the bulk temperature (T_B), determines the rate of the reaction. If the reaction needs to go faster, the temperature is increased. Under microwave conditions, the rate of the reaction is increased (illustrated by shorter reaction times). Looking at the Arrhenius equation, the collision geometry is not changed, the activation energy cannot be altered, and R is a constant, therefore, the temperature must be increased. Because microwave irradiation enables T_i , above that of the measured T_B , T_i controls the kinetics of the reaction. The rate is increased beyond that which would be expected of the measured bulk temperature. In addition, because the T_i is dependent upon the amount of power going into the reaction, increasing the amount of input power will, in turn, create higher reaction rates without the negative effects of thermal decomposition.

Since the rate of reaction is now dependent on the microwave power going into the system, the bulk temperature can be kept low, while still experiencing the rate-enhancing benefits. Remember, the bulk temperature is not driving the reaction, the rapid transfers of kinetic energy are; therefore, the higher the T_i , as controlled by the power input, the more rapid the rate.

Conductive Heating	Microwave Synthesis	Sub-Ambient Microwave Synthesis
$T_B = T_i$	$T_i > T_B$	$T_i > T_B$
Kinetics are controlled by T_B	Kinetics are controlled by T_i	Kinetics are controlled by T_i
Thermal energy drives reaction	Thermal energy is created as a by-product	Unnecessary thermal energy is removed

T_i is dependent on T_B and Microwave Power
Higher Microwave Power Input creates Higher T_i

Table 1. Comparison of Conductive and Microwave Heating



Figure 3. Sub-ambient Reaction Accessory.

Sub-Ambient Reaction Vessel Design

Low-temperature microwave irradiation is most useful in reactions that are slow to proceed and temperature sensitive reactions. Just as with other microwave syntheses, reactions that require long periods of time to complete are prime candidates, because the efficiencies of microwave energy transfer will be the most dramatic and impressive in these cases. Many people do not think of microwave systems as being able to affect temperature-sensitive transformations, but due to the direct mechanism of energy transfer and the ability to cool the reaction during the energy transfer cycle, our technology enables chemists to create temperature-sensitive products by removing excess thermal energy. In addition, microwave energy will still greatly increase the yields in many of these low-yielding reactions. (Figure 3)

The apparatus utilized in these reactions has a working volume of 5 mL, or a total volume of 9 mL. The working temperature range for this particular vessel is from -70°C to $+30^{\circ}\text{C}$. The pump and jacketed design allows the microwave-transparent cooling media to flow outside the reaction mixture, enabling the low temperature point to be maintained. The use of an air line provides the inert atmosphere commonly associated with low temperature reactions. A fiber optic probe allows the measure of temperature in situ and is the most accurate device on the market for that purpose. Figure 4 shows a more detailed picture of the actual vessel used to perform low temperature reactions in a microwave. The two parts of the jacket, as well as the gas tubing and fiber optic probe can clearly be seen.



Figure 4. Sub-Ambient reaction

Preliminary Testing

To first test the system, DMF was heated with 150 W for 15 minutes in the jacketed vessel. DMF reached its reflux temperature in less than 15 minutes. The power of the cooling vessel can be seen below where the same volume of DMF was irradiated in the same vessel with 150 W for 15 minutes. Unlike the sample without cooling fluid, the presence of the cooling fluid enabled the bulk temperature, as measured with a fiber optic probe, to be held at -20°C . (Figure 5)

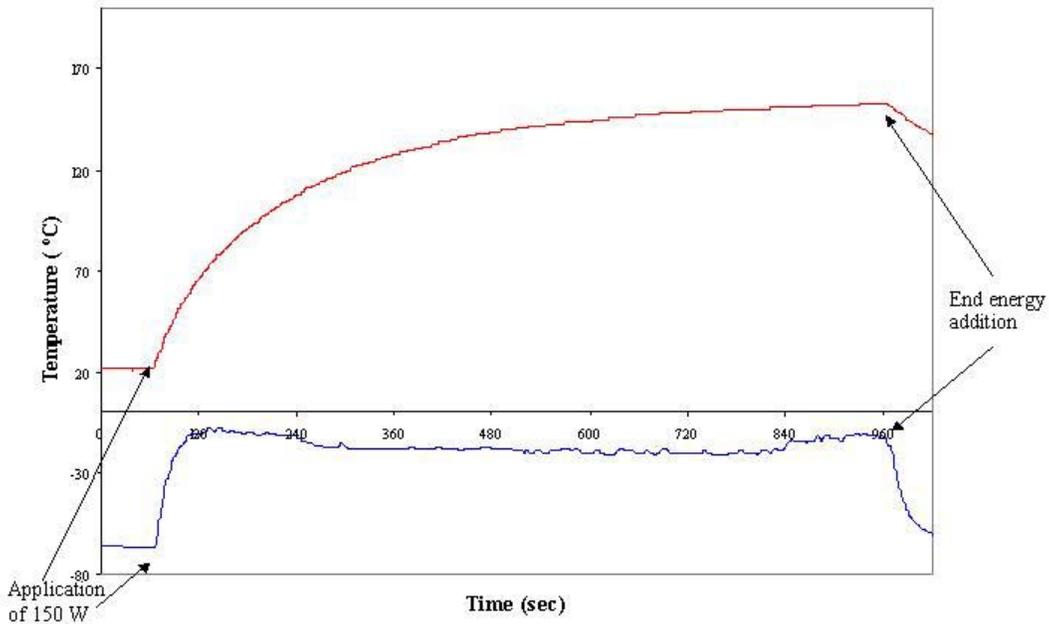


Figure 5. Comparison of DMF Irradiation with and without cooling fluid

For the first reaction, the starting material in Figure 6 was synthesized via a substitution reaction from 1,4-dichloro-2-butene and potassium phenoxide. Conventionally, the reaction takes 21 hours from 0 to 20°C (75%).³ Using the cooling method with microwave irradiation, it took 35 minutes at 30°C (87%).

The *cis*-diphenoxy-2-butene was then used to perform a base-promoted elimination reaction to yield the phenoxydiene. Conventionally, this reaction takes 2.5 hours at 0-25°C (78%).³ Using the Sub-Ambient Microwave Apparatus, the reaction was performed at -60°C, substantially below the conventional temperature, in only 5 minutes (81%). This example in particular, highlights the use of instantaneous temperatures to increase the rate of the reaction.

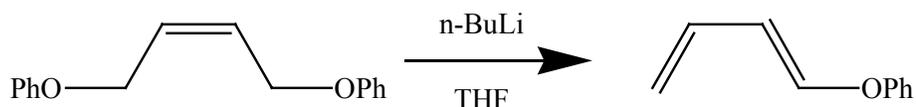


Figure 6. Elimination Example

Ring Expansion Reactions

Ring expansion reactions are useful tools in synthetic chemistry. They allow the formation of larger rings in situations that are very difficult otherwise, without disrupting the rest of the ring. A significant number of these expansions require low temperatures due to the instability of the intermediate formed or reactivity of the starting materials. They also generally take from one hour up to several days to perform. With the advent of the sub-ambient microwave synthesis system, these reactions can now be performed in less time at low temperatures.

Conventionally, the reaction in Figure 7 takes 4 hours in an ice bath to give a ratio of 85:15 for the two isomers.⁴ It was tried in a microwave for 1 minute, with a power of 150 W. The temperature started at -45 and over the 60 seconds, rose to +12 °C. The yield of the two possible products was found to be 98%, in a 84:16 ratio, very similar to that using the conventional conditions.

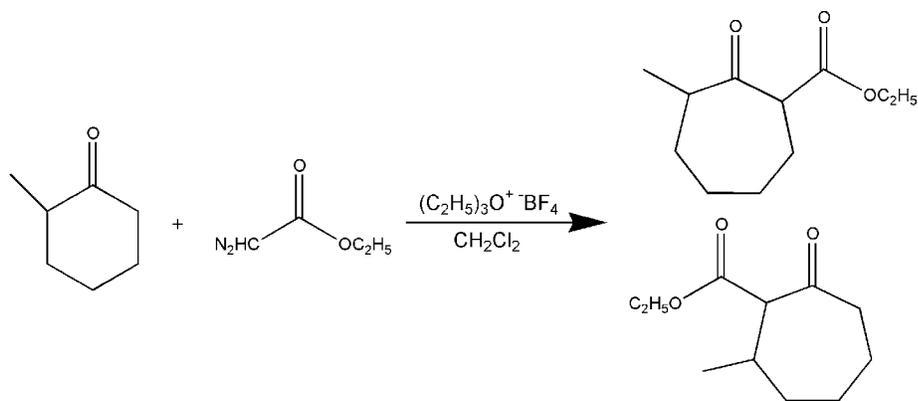


Figure 7. Ring Expansion Example 1

The reaction shown in Figure 8 involves the formation of a cyclohexanone or cycloheptanone ring derivative. Conventionally, this reaction takes 4 hours in an ice bath.⁴ Just as with the previous reactions, it was completed in 1 minute with 150 W. If you notice, the yield for the cyclohexanone is significantly greater than the conventional yield. This is due to the formation of large molecular weight side products (possibly the result of aldol condensations) formed in the conventional reaction⁴. In a microwave, because the reaction is so fast, these side products were not formed, thus generating more of the product.

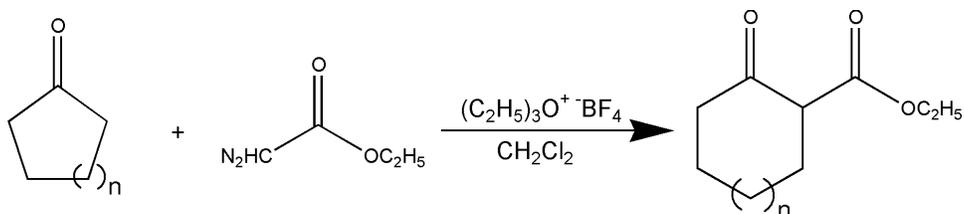


Figure 8. Ring Expansion Example 2

n = 1	Conventional	Microwave	n = 2	Conventional	Microwave
Time	240	1	Time	240	1
Temp.	0 °C	-45 – 2 °C	Temp.	0 °C	-45 – 0 °C
Yield	38%	65%	Yield	90%	95%

Table 2. Results

The first reaction (Figure 7) was reexamined to determine how rapidly it was being converted to product. By applying 50 W for only 15 seconds, 99% conversion to the two products was achieved in a ratio of 87:13. To ensure this was not simply a rapid reaction, the reaction was cooled down to $-50\text{ }^{\circ}\text{C}$ and allowed to warm to $-40\text{ }^{\circ}\text{C}$ without microwave irradiation, the same temperature range over which it was irradiated. The amount of conversion in 5 minutes was less than 10%.

Conclusion

Because microwave energy directly activates molecules in a reaction, it allows excess thermal energy to be removed from the solution, while shortening reaction times and increasing yields. The new vessel technology, which enables the introduction of a cooling medium in the outer jacket while the inner vessel holds the reaction being heated by microwave energy, allows the removal of the excess thermal energy that causes degradation in temperature-sensitive reactions, improving yields and decreasing side reactions. This opens the door to all types of new chemistries never before thought possible in a microwave.

References:

1. a) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (d) Majetich, G.; Hicks, R. *Radiat. Phys. Chem.* **1995**, *45*, pp. 567-79. (e) Loupy, A. (Ed.) *Microwaves in Organic Synthesis*, Weinheim, Wiley-VCH, 2002.
2. a) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873. b) Humphrey, C. E.; Easson, M. A. M.; Tierney, J. P.; Turner, N. J. *Org. Lett.* **2003**, *5*, 849. c) Katritzky, A. R.; Zhang, Y.; Singh, S. K.; Steel, P. J. *ARKIVOC* **2003**, (xv), 47. d) de Pomerai, D. I.; Smith, B.; Dawe, A.; North, K.; Smith, T.; Archer, D. B.; Duce, I. R.; Jones, D.; Candido, E. P. M. *FEBS Lett.* **2003**, *543*, 93.
3. Roversi, E.; Monnat, F.; Vogel, P.; *Helv. Chim. Acta*, **2002**, *85*, 733.
4. Mock, W.L.; Hartman, M.E.; *J. Org. Chem.*, **1977**, *42*, 459.