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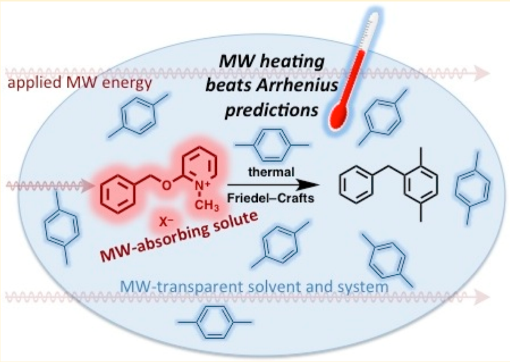
Microwave-Specific Acceleration of a Friedel–Crafts Reaction: Evidence for Selective Heating in Homogeneous Solution

Michael R. Rosana, Jacob Hunt, Anthony Ferrari, Taylor A. Southworth, Yuchuan Tao, Albert E. Stiegman, and Gregory B. Dudley*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390, United States

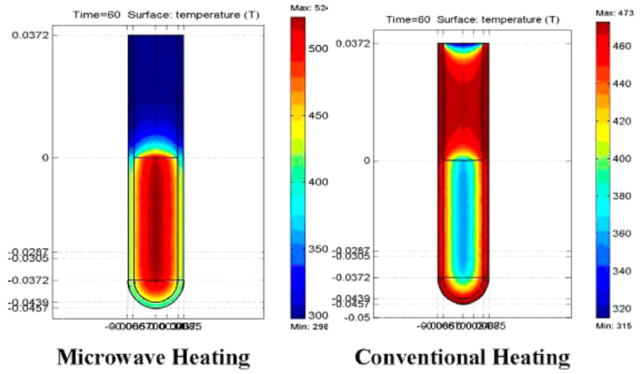
S *Supporting Information*

ABSTRACT: Thermally promoted Friedel–Crafts benzylation of arene solvents has been examined under both conventional convective heating with an oil bath and heating using microwave (MW) energy. Bulk solution temperatures—as measured by internal and external temperature probes and as defined by solvent reflux—were comparable in both sets of experiments. MW-specific rate enhancements were documented under certain conditions and not others. The observed rate enhancements at a given temperature are proposed to arise from selective MW heating of polar solutes, perturbing thermal equilibrium between the solute and bulk solution. *Central to MW-specific thermal phenomena is the difference between heat and temperature*. Temperature is a measure of the ensemble average kinetic molecular energy of all solution components, but temperature does not provide information about solute-specific energy differences that may arise as a consequence of selective MW heating. Enhanced chemical reactivity of the MW-absorbing solute can be described as a MW-specific "extra-temperature thermal effect", because the measurable solution temperature only captures a portion of the solute kinetic molecular energy. Experimental factors that favor MW-specific rate enhancements are discussed with an eye toward future development of MW-actuated organic reactions, in which the observed thermal reactivity exceeds what is predicted from temperature-based Arrhenius calculations.



INTRODUCTION

From the seminal observations of Gedye[1] and Majetich[2] that chemical reactions can be conducted in kitchen microwave ovens, synthetic chemists have been intrigued by the possibility that microwave heating can complement conventional heating and provide specific advantages for certain applications. Inspiration comes in part from food chemistry: certain foods and beverages such as popcorn, coffee, and bacon are often conveniently heated in a microwave oven, whereas people may prefer that other items such as toast, pancakes, and steak be prepared by conventional heating methods. Microwave ovens heat by fundamentally different mechanisms than conventional heat sources.[3] The different heating processes (cf. Figure 1) produce different outcomes in complex food chemistry systems, for example, prompting some to wonder if differences could likewise be observed in the comparatively simple systems involved in stepwise chemical synthesis.



Microwave Heating

Conventional Heating

Figure 1. Simulated thermal image adapted from the product literature of an early MW manufacturer[4] illustrating differences between MW and convective heating after 1 min.

MW Effects and Controversy. With perhaps varying degrees of appreciation for the underlying dielectric loss processes, chemists began seeking experimental evidence of novel MW effects in organic synthesis. Certain early reports described rate accelerations of several orders of magnitude over conventional heating, leading to (probably unfounded) speculation that nonthermal coupling of MW radiation with molecules in solution can alter or reduce the activation energy of the reaction. However, there is no obvious quantum mechanical mechanism by which MW radiation can couple resonantly with a molecule in a way that could accelerate bond-changing events, as Stuerga thoroughly addressed in a series of early papers.[5] Many of the reported observations turned out to be compromised by flawed temperature measurements.[6] As synthetic chemists have come to appreciate the experimental

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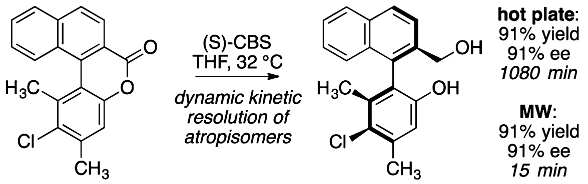
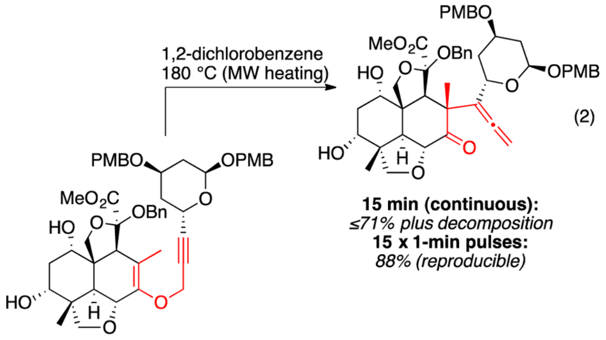
challenges associated with measuring temperature under MW heating, claims of dramatic and nonthermal rate accelerations have largely dissipated.[7] It is most reasonable to assume that MW energy must first be converted into thermal energy, and it is thermal energy (molecular motion) that drives chemical reactivity.

While claims of incredible MW effects recede from the organic synthesis literature, there remains an anecdotal lore associated with MW heating, as well as specific examples that are difficult to dismiss as artifacts of experimental error. The Yamada laboratory has reported several examples of enantioselective reactions in which MW heating has resulted in enhanced reactivity in comparison to conventional heating at the same temperature (eq 1).[8] The accuracy of their temperature measurements is underscored by the fact that they report similar enantioselectivities in both systems. Enantioselectivity and rate usually correlate inversely, but the rate/selectivity correlation is apparently somehow decoupled in the Yamada system.



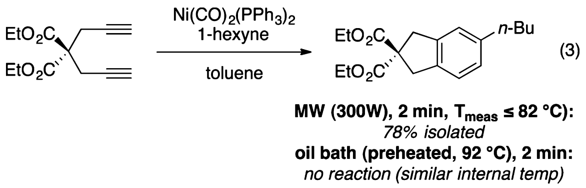
(1)

Pulsed MW heating (with intermittent cooling) proved advantageous in a key Claisen rearrangement in Ley's synthesis of azadirachtin.[9] Intermittent MW heating was more effective than continuous MW heating (eq 2), and MW heating was explored only after conventional heating options were exhausted. We have investigated the impact of pulsed MW heating on aryl Claisen rearrangements and found quantifiable traces of MW-specific thermal effects.[10]



(2)

Dieters reported a MW effect on metal-catalyzed alkyne trimerizations (eq 3).[11] MW-specific advantages for this and other metal-catalyzed processes, especially alkene metathesis reactions, have been described[12] and questioned.[13] MW effects have also been documented in the synthesis of metallic nanoparticles[14] and on solvent molecules in proximity to a metal surface.[15]



(3)

Dramatic MW-specific effects in heterogeneous systems (cf. food chemistry) are common, including heterogeneous synthesis and catalysis. Two significant examples are presented here (Figure 2). The first is a study by Hulshof et al.,[16] in which MW electromagnetic radiation was shown to accelerate formation of Grignard reagents by magnesium surface energy-transfer events that cannot be duplicated by conventional heating. The second was a recent examination of the industrially relevant Boudouard reaction:[17] $C + CO_2 \leftrightharpoons 2CO$. The highly endothermic (ΔH = 41 kcal/mol) production of CO becomes exergonic at high temperatures due to favorable entropy; the equilibrium concentration of CO exceeds that of CO_2 only at temperatures above 643 °C (916 K). Stiegman and co-workers reported that MW heating of the solid carbon surface selectively accelerates the forward reaction and lowers the temperature at which CO becomes the major component to 213 °C (486 K).[18] MW-specific carbon surface activation events were postulated. These examples illustrate the potential of MW energy to improve chemical reaction processes in ways other than by bulk heating of the system, but the macroscopic heterogeneity of these systems was critical to the effects in both cases. *Our objective is to observe and quantify similar effects in macroscopically homogeneous systems.*

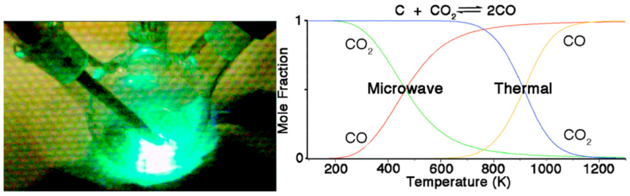


Figure 2. (left) Arcing of Mg turnings exposed to MW irradiation, reproduced from ref 16b. This energy-transfer event is not caused by convective heating. (right) MW-specific alteration of observed thermodynamic equilibration between CO and CO_2 in the Boudouard reaction; reproduced from ref 18.

What many of these processes have in common is a MW-absorbing catalyst or substrate in a less absorbing system, a combination that was recognized early on as being of some interest.[19] This common profile of several systems for which MW heating apparently provides an advantage is consistent with (and in some cases helped guide) the design of the focal reaction system of our study. It is also consistent with current theory on the mechanisms of MW heating:

MW Theory. The conversion of microwave energy into thermal energy requires a medium that interacts with and absorbs MW electromagnetic radiation in such a way that heat is generated.[3]

For a dielectric (i.e., nonconductive, nonmagnetic) material, the MW → thermal energy conversion is macroscopically related to its frequency-dependent permittivity. Bulk permittivity—ε, the ability of a substance to transmit an electric field—is expressed as the sum of its real and complex components: $\varepsilon = \varepsilon' - i\varepsilon''$. If no absorption is occurring ($\varepsilon'' = 0$), then the real component ε' is equal to the dielectric constant, ε. The imaginary component ε'' characterizes the dielectric loss, which is the source of heat. The dielectric loss tangent—tan δ, the portion of the electric field that is lost to heat—is quantified as the ratio of the imaginary and real components of the permittivity function: $\tan \delta = \varepsilon''/\varepsilon'$. The value of tan δ varies with temperature and the frequency of the applied field. It is typically reported at 2.45 GHz, the standard frequency used in kitchen microwave ovens. (It is important to bear in mind that the energy associated with this frequency is insufficient to promote bond-cleavage events.[5] As noted above, MW energy generally must first be converted into thermal energy to promote reactivity.)

For molecules in solution, classic Debye theory[20] addresses the MW energy loss processes that result in volumetric heating. Molecular dipoles in solution rotate in response to the oscillating electric field of the incident radiation. However, due to collisional processes in solution, the frequency of the molecular oscillations is out of phase with that of the electric field. This results in loss processes—often thought of as frictional—that generate heat. The quantity of heat generated is related to the frequency of the applied field, the size and dipole of the absorbing molecule, the viscosity of the solution, and other factors.

For a homogeneous (and efficiently stirred) solution, such loss processes occur uniformly throughout the system, enabling the rapid and efficient volumetric heating that is so intimately associated with MW chemistry.[21] For pure liquids (single-component solutions), all molecules are identically suited to interact with the applied field, and selective MW heating is not observable.[22] The same is effectively true for multicomponent solutions in which the solvent (major solution component) strongly absorbs MW energy, such as reactions conducted in high tan δ solvents like DMSO and NMP. Given proper stirring, thermal homogeneity should be maintained throughout the system.

Model for Selective MW Heating in Solution. Richert and co-workers offer a model for selective heating in slow-moving liquids using a low-frequency electric field.[22] Their model includes transient domains in which solute configurational temperature can be increased faster than the measurable bulk solution temperature (Figure 3). The energy of the electric field does work on the polar solute within the transient domain, creating kinetic molecular energy that eventually propagates through the liquid as heat.

We apply their model to MW heating of multicomponent solutions in which the solvent is nonabsorbing and a specific solute (minor solution component) is strongly MW-absorbing; the transient domain is defined by the absorbing solute within its solvent cage. Multicomponent solutions are macroscopically homogeneous, *but solvent cages produce transient heterogeneity at the molecular level.* According to Richert, "local heating can occur in cases where absorptivity is a spatially varying quantity".[22c] As the solute absorbs MW radiation and converts it into thermal energy, thermal equilibrium between the transient solvent cage domains and the bulk solution is perturbed. The solvent cage domain temperature will be higher than what can be thermometrically recorded as the bulk temperature. *The temperature inside the solvent cage will be effectively higher than the measurable temperature of the bulk solution.*

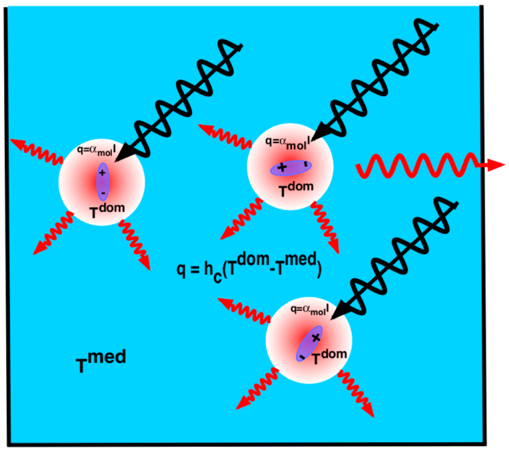


Figure 3. Graphical illustration of the "transient solvent cage domain" model for selective MW heating of strongly MW absorbing solutes in an otherwise MW-transparent system. Interactions between the solute and MW radiation generate heat within transient solvent cages, perturbing thermal equilibrium between solute and solvent. Heat flows from the domain to the bulk solution and then out of the system.

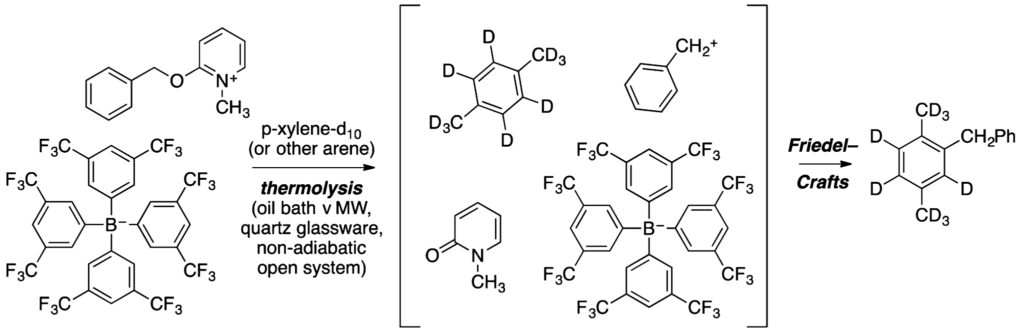
This local heating model is conceptually similar to "temperature sculpting in yoctoliter volumes" using laser photoexcitation of gold nanoparticles, as described last year by Reiner et al.,[23] and it rationalizes the previously cited concept of molecular radiators,[24] in which MW-specific heating of a polar solute results in bulk heating of the otherwise nonabsorbing solution. We define a **molecular radiator** in the context of MW chemistry as *a strongly absorbing solute that converts applied MW energy into thermal energy, generating heat in an otherwise poorly MW-absorbing system.* As heat from the molecular radiator flows to the bulk solution and eventually out of the system to the surroundings, there will necessarily be a thermal gradient in which the molecular radiator (e.g., within its solvent cage) is effectively hotter than the bulk solution, which in turn is hotter than the surroundings. The simple analogy is using a radiative space heater to heat a room: the radiator must be hotter than the room to serve its purpose. *This MW-specific heating effect cannot be duplicated using convective heating.*

The "transient solvent cage domain" model provides an opportunity to design and exploit MW-specific thermal effects in solution. If the MW-absorbing solute within its solvent cage is also a reactant in a chemical process, and if thermally promoted reactivity can occur more quickly than thermal equilibration of the solution,[25] then selective MW heating of the absorbing solute and MW-specific reaction rate enhancements should be observable. The observed reactivity would occur as a function of the effective temperature within the domains, which would be greater than the measurable temperature of the bulk solution. The term "effective temperature" (T_{eff}) is used here to describe the average kinetic molecular energy of the MW-absorbing solute molecules. T_{eff} cannot be measured directly; it must be inferred by studying chemical behavior (e.g., reaction kinetics).

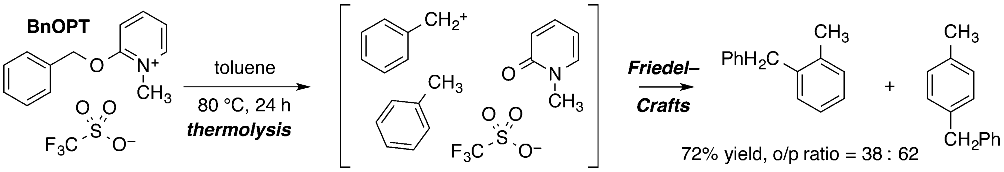
Central Hypothesis. Our central hypothesis is that chemical reactivity of a MW-absorbing solute in an otherwise-non-absorbing system can be **MW-actuated**: accelerated using applied MW energy to rates that cannot be duplicated by conventional heating to similar reaction temperatures.[26]

Central to this hypothesis is the distinction between thermal energy (heat) and temperature. Temperature, an intensive property, describes the ability of a substance to transfer heat; heat is an extensive property.[27] For solution-phase chemical reaction systems, temperature reflects the ensemble average kinetic molecular energy of the solution components. The relationship between solution temperature and solute kinetic energy applies uniformly *only if the solute and solution are at thermal equilibrium.* The experiments described herein are designed to perturb thermal equilibrium such that the average kinetic molecular energy of the MW-absorbing solute is higher than what would be expected on the basis of the macroscopically observable bulk solution temperature.

Scheme 1. Thermal Friedel–Crafts Benzylation, the Focal Reaction of This Study, with Key Experimental Design Parameters



Scheme 2. Previously Reported Thermal Friedel–Crafts Reaction[29]



We envisioned testing our central hypothesis using a reaction system in which the reactant of interest is highly and uniquely capable of absorbing MW energy, and any heat generated within the system would emanate from this focal reactant. We designed a system (cf. Scheme 1) in which an ionic benzyl-transfer reagent[28] undergoes thermolysis, nominally to a phenylcarbenium species, which then reacts with the nonpolar aromatic solvent in a Friedel–Crafts substitution process. Ionic species are typically strongly MW absorbing, and our system was carefully designed to exclude any other potential MW-absorbing materials. We ultimately selected nonpolar *p*-xylene as the solvent (and Friedel–Crafts coupling partner), employed custom-made reaction vessels constructed out of MW-transparent quartz, and otherwise took efforts to moderate bulk solution temperature while maximizing the selective heating of the MW-absorbing solute. All of the reaction mixtures were *macroscopically homogeneous and vigorously stirred throughout all of the experiments* described in this report unless otherwise noted.

■ RESULTS AND DISCUSSION

First Attempts. We had previously reported thermal Friedel–Crafts benzylation of aromatic solvents.[29] A heterogeneous mixture of 2-benzyloxy-1-methylpyridinium triflate (BnOPT) in solvent was heated with stirring at 80 °C in an oil bath (e.g., Scheme 2). The salt dissolved upon heating, and degradation of the salt coupled with benzylation of the solvent reached full conversion typically within 24 h. Thermal ionization of BnOPT to produce a phenylcarbenium-type species, 2-methylpyridone, and triflate, followed by Friedel–Crafts alkylation of the solvent, was postulated as the mechanistic pathway.

Considering the ionic reagent and nonpolar solvents employed in this study, we imagined possibly accelerating this reaction process by substrate-selective MW heating in homogeneous solution. However, the initial mixture is heterogeneous. Selective MW heating of heterogeneous systems is common, and in this case the ionic reagent selectively heated and rapidly decomposed without ever going into solution. We needed a more soluble version of our benzyl-transfer reagent.

Making a Soluble Salt. A series of analogues was prepared and crudely screened for enhanced solubility.[26] The salt was stirred in toluene at either room temperature or at 35 °C and then allowed to settle to the bottom of the flask. An aliquot was then removed and concentrated under reduced pressure, and the mass of residue was then correlated crudely with solubility. The commercially available triflate salt (BnOPT) was sparingly soluble in toluene at 35 °C. Increasing the size (and hydrophobicity) of the heterocycle (e.g., quinoline derivatives)[30] correlated with enhanced solubility in toluene, but the counteranion seemed to have a larger effect. Whereas the tetrafluoroborate salt of 2-benzyloxy-1-methylpyridinium was practically insoluble, the larger and more hydrophobic tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate counterion (BArF)[31] enhanced solubility to the point at which homogeneous solutions in toluene and other aromatic solvents could be achieved by stirring in a warm water bath.

The experiments described below involved heating identical solutions of 2-benzyloxy-1-methylpyridinium tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate (BnOPB, Figure 4) in either a preheated oil bath or a MW reactor. In each case, the mixture of salt and solvent was warmed with stirring until a homogeneous solution was obtained before starting the comparative heating experiments. In this manner we were able to circumvent MW-specific but unproductive decomposition of the ionic substrate in the initial heterogeneous mixture and focus on MW-specific effects on the homogeneous solutions.

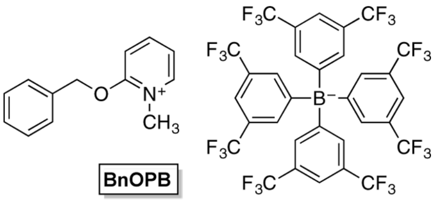


Figure 4. 2-Benzyloxy-1-methylpyridinium tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate (BnOPB), the reactive and MW-absorbing solute employed in these experiments.

Preliminary Experiments at Constant Temperature: Observations and Complications. Our initial experiments involved heating homogeneous solutions of BnOPB in *p*-xylene-d_{10} at 80 °C in either a MW reactor or an oil bath. We monitored the reaction progression over time by analyzing small aliquots by ^{1}H NMR spectroscopy. We chose *p*-xylene as the solvent because of its symmetrical structure and convenient chemical properties (reactivity, boiling point, etc.). Due to its symmetrical structure, *p*-xylene is nonpolar and less MW-absorbing that nonsymmetrically substituted arenes, and it reacts with phenylcarbenium to produce a single product, which simplified the analysis.

Our initial observations were intriguing but problematic. Figure 5 (top) illustrates reaction conversion over time for an experiment in a preheated oil bath (80 °C) and one in a CEM Discover MW reactor programmed to heat at 80 °C (constant temperature mode). The MW reactor automatically employs a feedback loop that varies MW power to establish and maintain the prescribed temperature. In the MW experiment we saw evidence of dramatically enhanced reactivity at the early stages of the reaction, but attempts to repeat this reactivity profile produced erratic and variable results. We could not draw concrete conclusions from these experiments.

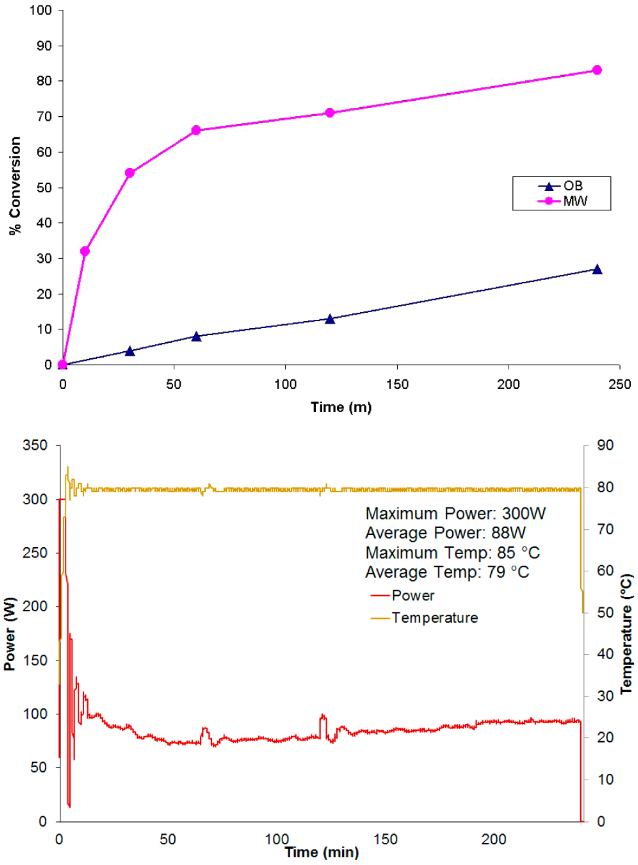


Figure 5. (top) Reaction conversion over time for experiments heated at 80 °C using the MW in constant-temperature mode (pink circles) and a preheated oil bath (navy triangles); reproduced from ref 26. (bottom) MW power and recorded temperature as a function of time in the MW experiment.

The reproducibility problems with this MW experiment stem from using variable MW power to try to achieve a prescribed reaction temperature. Constant-temperature mode is convenient for MW-assisted organic synthesis, particularly when adapting procedures developed under conventional heating conditions. However, overreliance on constant-temperature mode has likely contributed to prior confusion over possible MW effects.[6] It also turns out that the constant-temperature mode is not ideal for observing MW-specific thermal effects.[10]

Power and temperature profiles for this experiment are given in Figure 5 (bottom). The system is subjected to high MW power at the outset to generate heat and raise the temperature as rapidly as possible, and then the power is reduced once the desired temperature is achieved. If reactivity correlates with MW power in any way, then any MW-specific reactivity would most likely be observed in the early stages of the reaction, while the power is high and the temperature is increasing. However, the power and temperature profiles reveal fluctuations in recorded temperature, including spikes as high as 85 °C. In response, the MW reactor automatically adjusts the power; this adjustment takes the form of a series of progressively smaller pulses of applied MW power. The exact temperature and power profile is nearly impossible to replicate across multiple experiments. Moreover, because of lag time in the thermometric recordings, it is likely that temperature swings are greater than what is recorded: i.e., the temperature spike was probably higher than the recorded temperature of 85 °C.

These observations suggested to us that there might be observable reactivity differences between oil bath and MW heating in this system, but better control over the MW heating profile is needed to support any firm conclusions. One can achieve such control by setting a prescribed MW power profile. Here, we prescribed a fixed and constant MW power, which eliminates the potential for rapid and MW-specific temperature fluctuations. (We have also been examining pulsed MW power sequences, which perhaps better mimic the power profile in the early stages of the experiment illustrated in Figure 5, as described in an accompanying report.[10])

MW-Specific Thermal Effects at High MW Power. We examined the effects of MW heating at high constant power (300 W) on the thermal reactivity of our system. As described previously, identical homogeneous solutions of BnOPB in *p*-xylene-d_{10} were vigorously stirred and heated either in the MW or in a preheated oil bath. The MW reaction system was designed to minimize heat formation other than by direct interaction of MW energy with the ionic solute. *p*-Xylene was deemed an appropriate solvent, because it is nearly MW transparent yet suitable for Friedel–Crafts trapping of the thermally generated phenylcarbenium species. Nothing else was added to the reaction vessel except for the Teflon-coated stir bar, which is not a significant source of heat in these experiments. Importantly, the MW reaction vials were made of quartz, because borosilicate glass (Pyrex) absorbs MW energy and *does* contribute significantly to heat buildup in this system (Figure 6).[32]

Conversion over time for the reaction conducted in our MW reactor at full power (up to 300 W[33]) is shown in Figure 7. The reaction reached 86% conversion after 10 min and was essentially complete within 30 min. We monitored the temperature using a calibrated external IR pyrometric sensor, which correlates the surface temperature of the reaction vial with the solution temperature, as measured by an internal fiber-optic probe (vide infra). The recorded temperature was 35 °C at the start of the experiment, because of the prior warming needed to achieve a homogeneous solution of BnOPB in *p*-xylene-d_{10}. The maximum recorded temperature was 97 °C, and the average

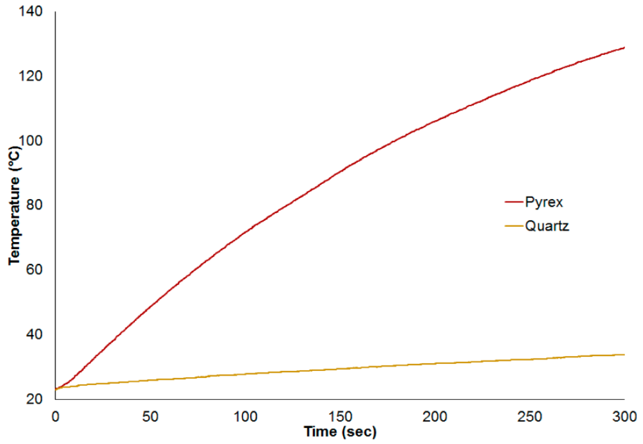


Figure 6. Heating curves for neat *p*-xylene in borosilicate (Pyrex, garnet line) and quartz (gold line), showing that Pyrex can contribute significantly to MW heating. Vials were kept open to the atmosphere (open vessel) while the sample was stirred and heated using 300 W of applied MW power.

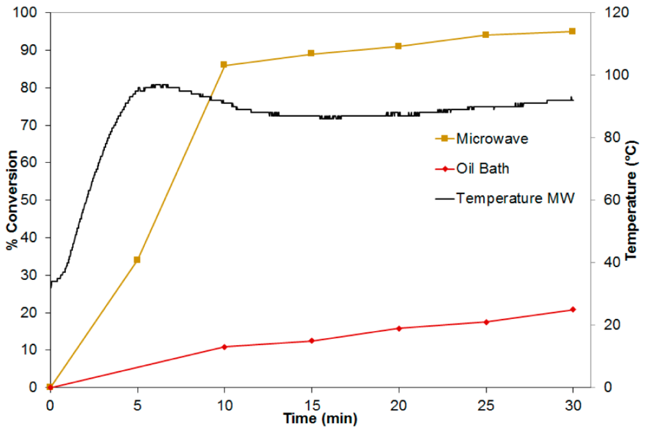


Figure 7. Reaction conversion over time for experiments heated in the MW at full power (300 W, gold squares) and in a 100 °C preheated oil bath (red diamonds). The recorded MW temperature profile is also plotted (black line).

over the course of the 30 min reaction was 86 °C. Temperature changes occurred gradually and predictably,[34] without the fluctuations or spikes that were observed using variable MW power.

It is practically impossible to replicate this temperature profile using convective heating. Therefore, for comparative purposes, we elected to conduct an analogous experiment at a *constant but higher temperature* under convective heating. We reasoned that if we observe lower conversion at higher temperature under convective heating, then we could qualitatively attribute the higher conversion in the MW experiment to MW-specific effects.

For this qualitative comparison, an otherwise-identical reaction system was immersed in an oil bath that had been preheated to 102 °C. (We separately examined the heating profile of this reaction system, including the same vial and oil bath, and found that the internal solution temperature reached 100 °C within 3 min.) Conversion over time for this reaction is also plotted in Figure 7. In contrast to the MW experiment, we observed a reaction conversion in the oil bath of only 12% after 10 min and 25% after 30 min. Considering that the measured temperature of the oil bath experiment was higher than the measured temperature in the MW experiment, and that MW energy was the only other variable, we concluded that MW energy played a role in promoting thermal reactivity beyond what would be expected on the basis of the system temperature; this reaction system is MW-actuated.[26,35] The distinction between thermal energy (heat) of individual solute molecules and recorded temperature of the bulk solution is a critical aspect of this conclusion.

Control Experiment 1. Indirect MW heating through a MW-absorbing jacket suppressed the observed effects. We suspended our quartz reaction vial in a larger quartz flask and immersed the vial in a bath of propylene glycol (ca. 80 mL). We then heated this "shielded" system at 100 °C using either a preheated oil bath or our CEM Discover MW reactor (constant-temperature mode), again using a calibrated external IR sensor to monitor internal solution temperature. The use of the highly MW absorbing propylene glycol bath resulted in efficient bulk heating using low and variable MW power,[36] and this control experiment also produced reaction conversions that tracked well with oil bath heating (Figure 8). The MW-specific rate enhancement is thus effectively suppressed by the propylene glycol bath.

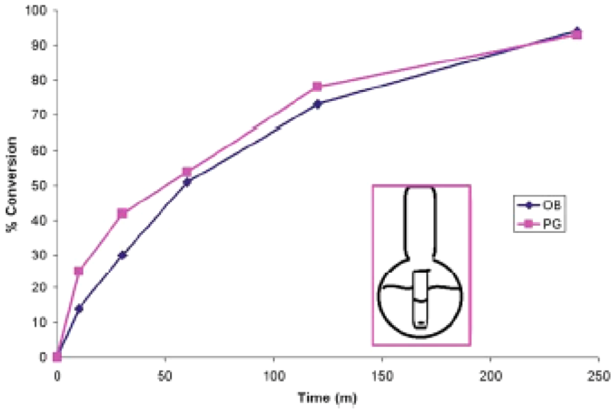


Figure 8. Reaction conversion over time for experiments heated at 100 °C in the MW in constant-temperature mode (pink squares) and a preheated oil bath (navy blue diamonds) through a bath of propylene glycol (cf. inset cartoon), reproduced from ref 26.

The propylene glycol bath absorbs MW radiation and in turn heats the solution convectively. Similar control experiments have been reported using silicon carbide (SiC) vials,[37] although technically SiC vials neither exclude MW radiation nor prevent MW dielectric heating (cf. Figure 9), particularly in systems involving ionic MW-absorbing species: "the SiC tube—at comparatively low temperatures—does not completely shield the contained solvents from the electric field."[38] Our propylene glycol design may be superior to SiC for this type of control experiment.[39]

This control experiment supported our conclusion that MW power is an important variable in promoting Friedel−Crafts benzylation of xylene using BnOPB, because shielding the reaction medium from MW radiation with the propylene glycol bath resulted in regression of reactivity back to what is seen with conventional convective heating in an oil bath. As noted previously, heating these reaction mixtures in constant-temperature mode using relatively low applied MW power produced no discernible MW-specific effects, in contrast to experiments designed and conducted in accord with our central hypothesis.

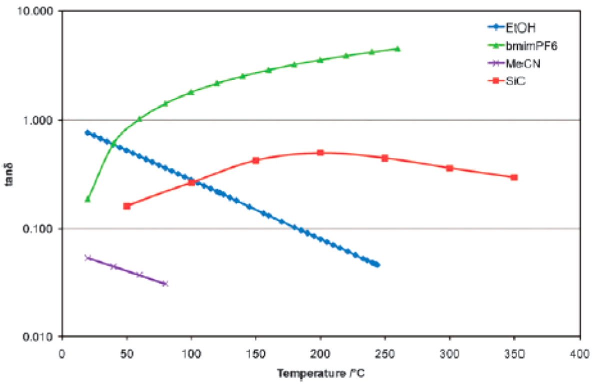


Figure 9. tan δ as a function of temperature for acetonitrile (purple), silicon carbide (red), ethanol (blue), and an ionic liquid (bmimPF$_6$, green); reproduced from ref 38. The dielectric loss tangent (tan δ) quantifies the ability of a substance to convert MW energy into heat. In the temperature range relevant to our studies (≤100 °C), silicon carbide reportedly absorbs MW energy and generates heat more efficiently than most common organic solvents but less efficiently than ethanol or a representative ionic liquid. *p*-Xylene (not shown) has a tan δ value of close to 0 at room temperature, and this should not change at higher temperatures. Reproduced with permission from the Royal Society of Chemistry.

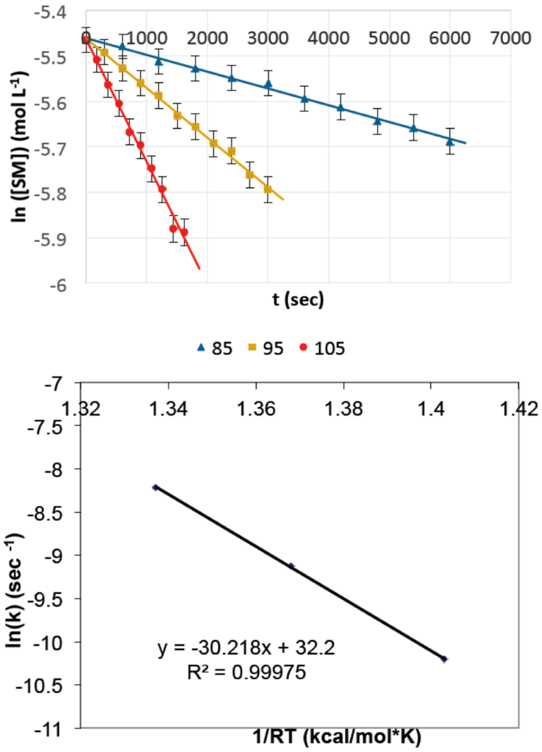


Figure 10. (top) First-order kinetic plots for the thermal benzylation of *p*-xylene at 103.4, 94.9, and 85.7 °C. (bottom) Arrhenius plot of the rate and temperature data. See the Supporting Information for larger images and tabular data.

Kinetics and Magnitude of the Effect. The next phase of our study was to characterize MW-specific thermal effects in terms of deviation from the Arrhenius-based link between measured temperature and kinetic reactivity. The Arrhenius equation—$k = Ae^{-E_a/RT}$—uses solution temperature as a measure of kinetic molecular energy of the reactive species; selective MW heating that perturbs thermal equilibrium would result in reactivity that is inconsistent with temperature-based Arrhenius predictions. It is important to note that any such deviations would be attributable to molecular-level thermal effects that cannot be captured by bulk temperature measurements (vide infra for additional discussion and alternative treatments of our experimental data).

We measured first-order rate constants for reactions in *p*-xylene at three different temperatures—$k = 0.369 \times 10^{-4}\ \mathrm{s}^{-1}$ at 85.7 °C, $1.09 \times 10^{-4}\ \mathrm{s}^{-1}$ at 94.9 °C, and $2.70 \times 10^{-4}\ \mathrm{s}^{-1}$ at 103.4 °C (Figure 10, left)—and plotted the natural log of these values—ln k—against $1/RT$ to determine the Arrhenius parameters (Figure 10, right). Reaction mixtures were heated in an insulated oil bath, and reaction temperatures were monitored using an internal thermometer. The activation energy E_a = 30.2 kcal/mol and the pre-exponential term $A = 9.64 \times 10^{13}\ \mathrm{s}^{-1}$ for first-order thermal benzylation of *p*-xylene (solvent) using BnOPB were thus determined.

Returning to the data presented in Figure 7,[40] we can crudely quantify the observed MW-specific effects. These calculations roughly illustrate the magnitude of the impact of MW heating beyond raising the bulk solution temperature. The MW-heated reaction reached 86% conversion within 10 min, during which time the recorded temperature had increased from 35 to 97 °C (80 °C average). In contrast, the reaction in a preheated oil bath (102 °C) had only reached 12% conversion.

On the basis of the Arrhenius parameters measured for *p*-xylene, heating this reaction mixture at 100 °C for 10 min should produce 11% conversion with a rate constant $k = 1.89 \times 10^{-4}$ s^{-1}, which is in line with the 12% conversion observed in the oil bath experiment. The 86% conversion observed in the MW experiment corresponds to a rate constant $k = 33 \times 10^{-4}\ \mathrm{s}^{-1}$, roughly 17x higher than in the oil bath experiment. This MW reaction rate constant corresponds to a temperature of 128 °C (401 K), 48 °C higher than the average recorded temperature and 31 °C higher than the *maximum* recorded temperature.

The calculated temperature value of 128 °C in this crude analysis represents the "effective temperature" (T_{eff}) of the MW-absorbing solute as it plays the role of both molecular radiator and reactant. That is, the average thermal molecular energy of the solute corresponds to it being heated at 128 °C. The discrepancy between the bulk solution temperature and the observed chemical reactivity can be explained by selective MW heating of the polar solute, with subsequent chemical transformations that occur faster than thermal equilibration of the solute with the bulk solution (e.g., selective heating and thermal reactivity occurring according to the "transient solvent cage domain model" as described in the Introduction).[41]

The external IR temperature sensor does a reasonable job of capturing the internal solution temperature in this system (Figure 11). Subsequent to the experiments just described, we acquired a Neoptix Reflex internal FO probe, calibrated it between 150 °C and room temperature with a NIST-traceable thermocouple, and used it to monitor solution temperature directly in conjunction with the IR sensor. We heated our reaction mixture at 300W while recording the solution temperature simultaneously with the external IR sensor and the internal FO probe. As can be seen in Figure 11, the IR sensor data tracked closely with the FO probe data while the MW power was on and before the solution started to boil. Close examination of the tabular data (see Supporting Information) reveals a 5−10 s delay between the internal FO probe and the external IR sensor as the solution is heating up to around 100 °C. Once the solvent starts to evaporate and boil, the differences

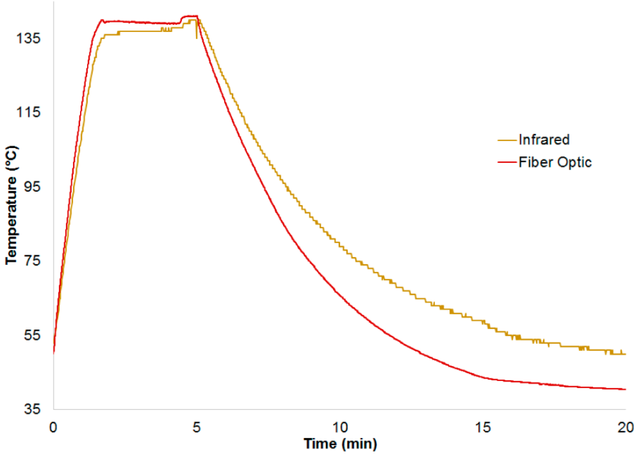


Figure 11. Temperature profile for a reaction mixture heated in the MW at 300W as recorded by an external IR sensor (gold trace) and an internal FO probe (garnet trace). The IR sensor tracks reasonably well with the FO probe while the solution is heating, indicating that our IR temperature data is reliable. Interestingly, the IR sensor then underestimates the solution temperature as it boils and markedly overestimates the temperature as it cools. These discrepancies likely reflect dynamic heat-transfer events for which the IR sensor was not calibrated, but they are not relevant to the studies here.

become more pronounced. However, these deviations are not relevant to the studies at hand. They probably reflect heat-transfer events that occur during solvent reflux and cooling for which the IR sensor was not calibrated. Also evident in Figure 11 is that our *p*-xylene system heated faster than we had observed previously in *p*-xylene-d_{10}.[26,40] Therefore, we reoptimized the system for documenting MW-specific thermal effects on BnOPB in using an internal probe.

We heated solutions of BnOPB in *p*-xylene with constant MW power (300W) and recorded solution temperature continuously using the FO probe. Bulk heating here was partially offset by cooling the outside of the reaction vessel using a stream of cold air.[42] Thus, the internal solution temperature could be moderated while applying high constant MW power of 300W. To reduce the amount of bulk heat being produced, we also reduced the amount of MW-absorbing substrate in each experiment. A reaction mixture comprising 7.5 mg of BnOPB in 2 mL of *p*-xylene in an open quartz vial was heated using 300W of applied MW power for 5 min while the outside of the vial was actively cooled by a stream of cold compressed air. The internal bulk solution temperature was recorded using the internal FO probe and plotted as a function of time in Figure 12. The highest recorded solution temperature was 105 °C, and the average was 94.9 °C. As before, the maximum temperature was recorded early in the experiment, and temperature decreased as the reaction progressed. Reaction conversion as determined by ^{1}H NMR spectroscopy was 35% at t = 5 min.

The expected reaction conversion based on the bulk solution temperature profile can be predicted using our Arrhenius parameters. We manually integrated the Arrhenius parameters over the course of the reaction. We calculated the instantaneous rate for each time the temperature was recorded (at 1.0 s intervals), calculated the expected reaction conversion during the time that elapsed before the next temperature reading, and then summed these conversions over the 5 min reaction window. On the basis of the Arrhenius parameters and the temperature profile, this time captured by an internal FO probe, the expected reaction conversion after 5 min was 5.2%. This expected level of conversion would be also achieved by heating at a temperature of 99.8 °C to achieve the rate constant $k = 1.8 \times 10^{-4}\ \mathrm{s}^{-1}$. We refer to the constant temperature (99.8 °C) needed to produce the same expected conversion as what we get by manually integrating the Arrhenius equation the variable-temperature profile as the “integrated average temperature”. It is generally slightly higher than the time-averaged temperature (in this case, 99.8 vs 94.9 °C).

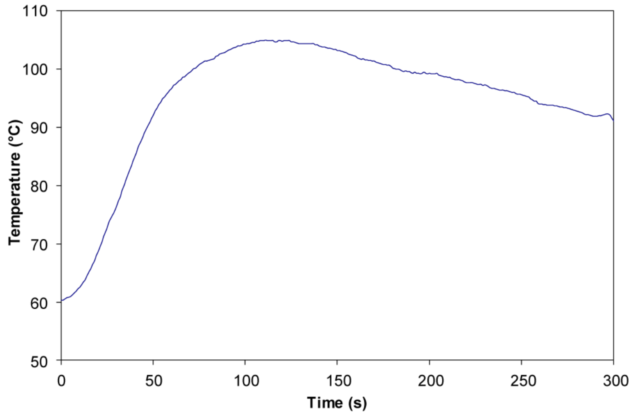


Figure 12. Temperature profile for heating 7.5 mg of BnOPB in the MW at 300W power with external cooling, as recorded by the internal FO probe. A 35% conversion was observed at the end of this 5 min experiment, whereas 5.2% conversion is expected based on integrated Arrhenius calculations.

The 6.7-fold difference in observed (35%) vs calculated (5.2%) reaction conversion is again attributed to selective MW heating of the strongly absorbing reactant in an otherwise nonabsorbing system. We assume that the magnitude of selective MW heating is not constant during this 5 min window as the bulk temperature increases, but we can quantify the *time-averaged* MW effect over the 5 min course of the reaction. In this case, to achieve a 35% conversion over 5 min requires substrate thermal molecular energy that corresponds to an effective temperature of 120 °C. This effective temperature is 15 °C higher than the maximum recorded internal temperature and 20 °C higher than the integrated average solution temperature.

To put this in terms of rates, the hypothetical rate constant that corresponds with this reaction reaching 35% conversion in 5 min is $k = 14 \times 10^{-4}\ \mathrm{s}^{-1}$, whereas only 5.2% conversion would be predicted on the basis of the measured temperature profile for $k = 1.8 \times 10^{-4}\ \mathrm{s}^{-1}$. The observed increase in conversion over the Arrhenius temperature based prediction for the first 5 min thus corresponds to a 7.8-fold increase in reaction rate.

Our discussion of expected conversion, hypothetical rate constants, and effective temperature is meant as a guide for understanding the relative magnitude of selective MW heating in this system. This reaction design is unusual and extreme: an ionic reagent in a nonpolar solvent at high dilution undergoing unimolecular rate-determining thermolysis. Moreover, our analysis focuses on the earliest stages of the reaction, during which time the net temperature change is sharply positive. It is unclear how easily these findings will translate to more synthetically relevant systems, and how advantageous such effects can be in organic synthesis. However, identifying these effects is the critical first step toward addressing those questions, and in this study we positively identify MW-specific thermal effects.

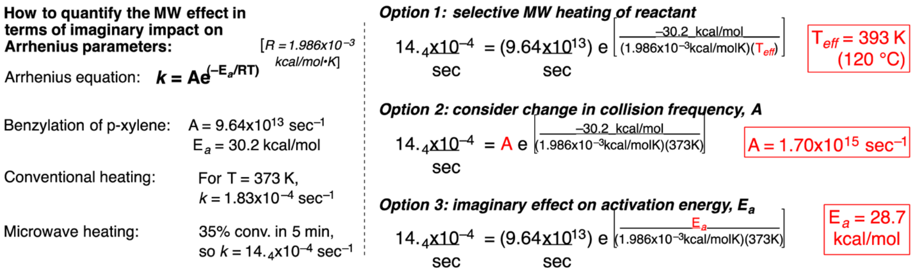


Figure 13. Mathematical treatments of the Arrhenius equation to put observed MW-specific thermal effects in terms of Arrhenius parameters. The MW reaction rate constant ($k = 14._4 \times 10^{-4}\ s^{-1}$) and integrated average temperature (T = 99.8 °C) do not equate for the Arrhenius parameters of this reaction ($A = 9.64 \times 10^{13}\ s^{-1}$ and E_a = 30.2 kcal/mol). Our interpretation is that MW-specific thermal effects perturb thermal equilibrium between solute and solvent, such that the measured solution temperature does not accurately reflect the solute kinetic molecular energy (option 1). The effective temperature of the reactant was thus calculated to be T_{eff} = 393 K (120 °C). However, one can alternatively quantify the observed MW rate enhancement in terms of impacts on the pre-exponential term (A, option 2) or the activation energy (E_a, option 3), as shown. They are all part of the same equation.

Control Experiment 2. We tested the effect of adding crushed borosilicate glass chips to the stirred reaction mixture. Our hypothesis was that heterogeneous additives can suppress MW-specific rate enhancements, and this turns out to be the case. The MW-specific rate enhancement that was observed in the homogeneous system was not reproduced in this heterogeneous system.

Perhaps surprisingly, the reaction system with added glass chips heated overall *less efficiently* than in the absence of this additive: qualitatively less external cooling was needed to moderate the internal temperature to an average of 100.3 °C (maximum recorded temperature of 105.0 °C). Reaction conversion after 10 min in the presence of glass chips was 16% in the MW experiment, which is not much above the reaction conversion expected (13%) on the basis of Arrhenius calculations integrated over the recorded temperature profile.[43] For comparison, an identical sample was heated in an oil bath at 100 °C for 10 min, which produced 12% conversion. This 12% conversion is also consistent with Arrhenius-based expectations; the calculated conversion after 10 min at 100 °C is 11%. Borosilicate glass absorbs MW energy and helps heat the system convectively (cf. Figure 6). These observations suggest that glass chips *also* scatter and/or reflect applied MW radiation. Additives that absorb and/or reflect MW energy are likely to disfavor selective MW heating of the solute, which explains why the glass chips attenuate the rate enhancements observed in the homogeneous system.

Our Interpretation. We have evolving ideas as to how to rationalize selective MW heating in homogeneous solution, while recognizing that ours is an empirical study aimed at validating selective MW heating. Drawing on ideas from the MW-assisted organic synthesis (MAOS) literature,[19] we first conceptualized our observations in terms of enhanced translational and rotational kinetic molecular energy of the solute leading to changes in the frequency and intensity of molecular collisions needed to achieve reactivity.[26] We later refined our working hypothesis to focus on collisions and other molecular events that occur within transient solvent cage domains.[35b]

We currently characterize the observed rate increase as a "MW-specific thermal effect" that arises from perturbing thermal equilibrium within a macroscopically homogeneous system. As such, the measured temperature (an Arrhenius parameter) does not adequately capture the thermal energy of the substrate of interest, again underscoring the nonequivalence of heat and temperature. Importantly for the larger discussion on MW effects, we do *not* interpret this to be an example of a "nonthermal effect", although it can be described as an extra-temperature effect: the measurable bulk solution temperature only captures a portion of the thermal energy available to the solute. Under the perturbation of MW energy, the average kinetic molecular energy of the absorbing solute is higher than that of the nonabsorbing solvent. Thus, the recorded temperature underrepresents the thermal energy of the ionic solute. In this example experiment, the effective temperature (average kinetic molecular energy) of the solute was T_{eff} = 120 °C and the integrated averaged temperature for the solution was T = 99.8 °C (cf. Figure 3).

One of the important next steps will be to examine systematically the role of variables, including solute concentration, solvent viscosity and heat capacity,[40] MW power, and perhaps frequency of the applied field (in consideration of the frequency dependence of tan δ); such efforts are underway.[10] Another may be to help develop theoretical models to account for the influence of MW energy on specific solutes. Any such future model would likely describe a difference in average kinetic molecular energy between the absorbing solute and nonabsorbing solvent. While the bulk temperature reflects the overall weighted average of kinetic molecular energies, solute-specific perturbations in thermal energy should correspond to solute-specific enhancements in chemical reactivity.

Alternative Explanations. Our discussion of effective temperature within the context of the Arrhenius equation is consistent with the transient solvent cage domain model of selective MW heating. However, the focus on effective temperature in the Arrhenius calculations is mathematically arbitrary, as one could just as easily use the bulk temperature values as measured and solve the Arrhenius equation for MW-specific impacts on other values such as activation energy. We do not favor the idea of there being any actual impact on the activation energy (E_a) of the reaction, although quantifying MW-specific thermal effects in terms of an imaginary impact on E_a may have some merit.

If one takes the position that the measured solution temperature accurately reflects the thermal energy available to the substrate, then one can use the measured temperature and solve the Arrhenius equation for imaginary impacts of MW energy on either the effective activation energy or the pre-exponential term. Such treatments are exemplified here (Figure 13) using data from the MW heating experiment monitored with an internal FO probe, in which we observed 35% conversion after 5 min at an integrated average temperature of 99.8 °C.

The actual Arrhenius parameters for this reaction as given above are $E_a = 30.2$ kcal/mol and $A = 9.64 \times 10^{13}$ s^{-1}. However, one can take the observed reaction conversion of 35%—corresponding to a rate constant $k = 14._4 \times 10^{-4}$ s^{-1}—and the integrated average (measured) temperature of 99.8 °C and solve for "imaginary" or "effective" MW impacts on these parameters. Assuming that E_a is unchanged, the new pre-exponential under MW heating would be $A = 1.7_0 \times 10^{15}$ s^{-1}. Alternatively assuming an unaltered pre-exponential, the imaginary impact on activation energy would be $\Delta E_a = -1.5$ kcal/mol; the observed rate acceleration is as if the activation energy were lowered to $E_a = 28.7$ kcal/mol. One could also postulate partial impacts on both A and E_a simultaneously, or even spread across all three factors (A, E_a, and T), to rationalize the observed rate enhancement. Our current thinking is that the most reasonable explanation is selective MW heating of the solute to a higher effective temperature than the rest of the solution. However, these effects cannot be rigorously quantified in Arrhenius terms because the system is not thermally homogeneous, and Arrhenius calculations do not account for thermal gradients in the reaction mixture.

Temperature Measurements. One of the fundamental challenges of studying MW effects is that of accurately measuring the solution temperature. Internal fiber-optic (FO) temperature probes and external temperature measurement using IR sensors offer complementary approaches to monitoring system temperature, each with advantages and limitations. Fast-responding internal FO probes are critical for optimal temperature readings when highly MW absorbing systems are being heated using variable MW power. However, an external sensor can be appropriate when heating a poorly MW absorbing system at constant MW power, which produces only gradual and predictable changes in temperature, and a noninvasive external sensor may even be preferred in some cases.[44]

The experimental caveats of using external IR sensors have been thoroughly documented elsewhere.[6] Here we discuss two potential confounding issues with internal FO probes, and we discuss how they were addressed in this study. The first problem is that careless use of the probe can lead to erroneous temperature readings if the tip of the probe rests against the walls of the flask, which are not necessarily thermally equilibrated with the solution.[45] We took care to suspend and secure the tip of the fiber-optic probe close to the middle of the stirred solution but outside of the stirring vortex. The second problem is more of a fundamental disadvantage: it is impossible to probe a system without perturbing it. For example, fiber optic probe attachments can restrict or alter heat flow from the system to the surroundings depending on how the probe is secured in the solution. On the other hand, with the internal FO probe one can also use external cooling to accelerate release of bulk heat to the surroundings.[42] The external cooling mechanism would compromise external temperature readings, but external cooling does not confound internal solution temperature readings any more so than does external heating. We employed both external and internal sensors to collect our thermometric data, as there is value in validating observations using both types of temperature measurements. Both have a place in MW chemistry, although one can always argue that the limitations of one and/or the other may make it difficult to interpret the observed results.

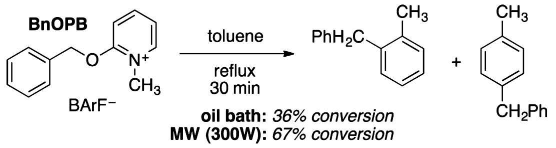
Reflux Experiments. As noted in the previous section, underlying complications inherent to MW heating experiments make it difficult to establish the validity of *any* thermometric data. We have used both accepted forms of MW temperature measurement—external IR sensors and internal FO probes—to record the temperature profile of experiments under MW heating, and we have benchmarked our observations in these systems against comparable experiments heated conventionally. Differences in reactivity have been attributed to MW-specific thermal effects: namely, selective MW heating of the absorbing solute. However, one cannot perfectly replicate the bulk temperature profiles for MW experiments using conventional heating, and we do not presume that thermometric data can capture all thermal events under MW heating. This is especially true in our experiments under constant and high MW power, in which we postulate that the thermal equilibrium is perturbed in a way that cannot be achieved with convective heating. Such thermal perturbations cannot possibly be captured thermometrically.

We therefore pursued a third avenue for comparing experiments under MW and convective oil bath heating in which solvent reflux at atmospheric pressure was used to moderate the thermal energy of the system. Thermometers are ultimately calibrated against physical properties of substances; for example, the melting and boiling points of water define the Celsius scale. Identical solutions in identical systems being heated at reflux under identical conditions must produce identical results. We conducted a series of parallel experiments in which identical solutions were heated at reflux under identical conditions, except that one was heated using MW energy and the other using a preheated oil bath. Using the boiling point of our specific solution obviates the need to record the temperature. In the absence of MW-specific effects, the reaction outcomes should be identical, and any differences in reactivity between the experiments would be attributed to MW-specific effects.

As described previously,[26] reflux experiments were conducted in toluene instead of xylene because the boiling point of toluene is more appropriate for monitoring these reactions over time. Toluene is not an ideal solvent for probing MW-specific thermal effects because it absorbs MW energy and produces heat more efficiently than xylene. However, toluene turned out to be good enough to support selective MW heating under certain circumstances. The MW-specific effects were attenuated in toluene in comparison to xylene, but they remained observable.

We reported parallel reflux experiments in which MW heating resulted in 67% conversion after 30 min and oil bath heating produced only 36% conversion after 30 min (Scheme 3).[26,46] The difference in conversion here is less than what we observed in the more MW transparent xylene solution, but it is significant nonetheless.

Scheme 3. MW-Specific Acceleration of Friedel–Crafts Benzylation of Refluxing Toluene



Having established a MW effect on this experiment, we then examined our reflux system for thermometric evidence of solvent superheating[47] and/or nucleation-limited boiling ("superboiling"),[48] in which MW heating produces a sustained but erratic reflux above the conventional boiling point of the solvent. Solvent superheating is well established under both

MW and conventional heating, whereas superboiling is MW-specific. Neither was observed in our stirred systems to any significant degree, although we <u>*can*</u> document both superheating and MW-specific superboiling in an *unstirred* system (Figure 14).[35b]

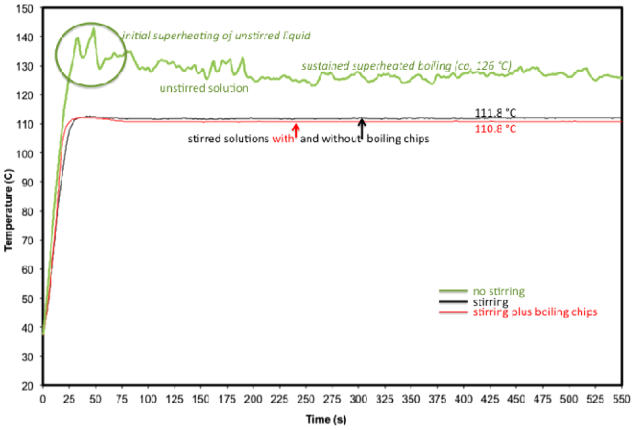


Figure 14. Plots of temperature over time for MW heating of our reaction system under three sets of conditions; reproduced from ref 35b. The top (green) line shows initial superheating followed by sustained superboiling, presumably due to the lack of proper nucleation sites *in the absence of stirring*. (This is the only experiment in which we did not vigorously stir the solution.) The lower two lines show the temperature profiles of a properly stirred system. The black line shows the temperature of the homogeneous system that is the focus of our study, and the red line shows the temperature of the system with boiling chips added.

In the absence of stirring, we measured solvent superheating to temperatures as high as 140 °C before nucleation began, followed by rapid and chaotic release of gas and heat.[47] Once the turbulence of the initial vaporization events subsided (within the first 2−5 min), the recorded temperatures fluctuated around 126 °C for the duration of the analysis. This is consistent with nucleation-limited superboiling, which is a consequence of the lack of nucleation sites in the bulk solution (where heat is being generated) limiting the rate at which phase change from liquid to gas can occur.[48] Superboiling does not occur under conventional heating because heat is introduced through the walls of the flask, where there are ample nucleation sites. It has been reported that boiling stones and/or proper stirring reduce or eliminate both types of superheating effects,[48c] and this is what we see as well. The recorded reflux temperature of our stirred solution was 111.8 °C, and a stirred solution with boiling chips boiled at 110.8 °C under our laboratory atmospheric conditions. In the latter case the heterogeneous boiling chips provide additional nucleation sites and may perturb the system in other ways as well (cf. Control Experiment 2). On the basis of these experiments, we rule out any significant contributions of bulk *solvent* superheating, in line with our conclusions of MW-specific effects related to selective heating of the *solute*.

■ CONCLUSION

The thermal Friedel−Crafts benzylation of toluene and xylene using BnOPB can be MW-actuated, in that MW energy can promote reactivity beyond temperature-based expectations. Central to understanding MW-specific thermal effects is the realization that heat and temperature are different. Thermal energy (heat, an extensive property) promotes chemical reactivity. Temperature (intensive property) measures the degree of thermal energy in a system at thermal equilibrium. MW heating can perturb thermal equilibrium between absorbing and nonabsorbing components of a system in such a way that the measured temperature cannot accurately capture the thermal energy of the absorbing components.

A graphical summary of representative experiments described over the course of these studies is provided in Figure 15. We conducted a series of thermal benzyl-transfer experiments in which macroscopically homogeneous and well-stirred reaction mixtures were subjected to either MW heating or convective (oil bath) heating to promote thermal reactivity. In cases where the ionic substrate (BnOPB) is uniquely capable of interacting with the applied MW field, clear differences in reaction rate were observed. The exact magnitude of the rate enhancement varied for different experimental setups, but *MW-specific rate enhancements were predictably observed under our prescribed conditions*. In cases where MW-absorbing and/or -reflecting species were introduced into the system, the MW-specific effects on BnOPB reactivity were effectively and reproducibly blocked. These observations support our central hypothesis that the chemical reactivity of a MW-absorbing solute in an otherwise-non-absorbing system can be **MW-actuated**: accelerated using MW energy to rates that cannot be duplicated by conventional heating to similar reaction temperatures.

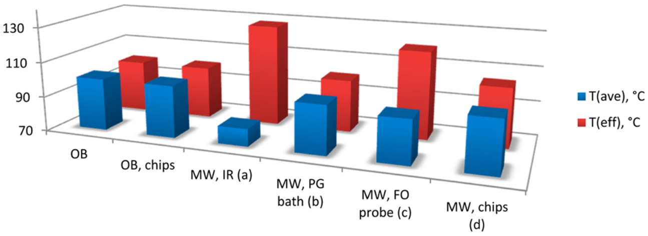


Figure 15. Graphical summary of temperature data and calculations (in °C) from representative experiments reported herein. The measured average temperature T(ave) is represented in the front row of blue columns, and the calculated effective temperature T(eff) is represented in the back row of red columns. T(ave) and T(eff) roughly coincided in the following experiments: oil bath, oil bath with boiling chips, MW with propylene glycol (PG) bath, and MW with boiling chips. Measured T(ave) and calculated T(eff) values were markedly different for MW heating of homogeneous solutions at high power, whether the temperature was monitored with an external IR sensor or an internal FO probe. The maximum recorded temperature T(max) in specific MW experiments was as follows: (a) T(max) = 97 °C (in p-xylene-d_{10}); (b) T(max) = 111 °C; (c) T(max) = 105 °C; (d) T(max) = 105 °C.

We interpret and rationalize these observations in terms of selective MW heating of the solute within transient solvent cage domains. Thermal activation of the absorbing solute occurs in solution within transient solvent cages. In contrast, the nonabsorbing solvent can only be heated indirectly by collisions with the solute. The solute must be hotter (i.e., at a higher effective temperature) than the solvent in order to transfer heat to the solvent.

The focus of this work was to establish the possibility of selective MW heating in macroscopically homogeneous solutions. The current reaction system is unusual in that it involves an ionic substrate dissolved at ultrahigh dilution in a nonpolar solvent, which doubles as the cation scavenger to track reactivity of the salt. The practical synthetic applications of this particular reaction are limited. The value of this work stems from the fact that it establishes parameters under which selective MW heating is possible in homogeneous solution. Practically every conceivable condensed-phase chemical reaction system is heterogeneous at the molecular level; thus, the potential implications here cover a wide range of reaction systems. Experiments described in this paper support the conclusion that the conversion of MW energy into heat within transient solvent cage domains can be faster than propagation of thermal energy through the bulk solution by convective heat transfer mechanisms. Thus, the thermal equilibrium is perturbed, resulting in observably enhanced reactivity of the absorbing solute. Our results can support a better understanding of previous reports of unusual MW effects in organic synthesis, and they provide a blueprint for future examination of other systems in which selective MW heating may be possible.

■ EXPERIMENTAL SECTION

General Experimental Methods. Commercially available starting materials, reagents, and solvents were used without further purification unless otherwise noted. NMR spectra were obtained using one of several solvents including DMSO-d_6, acetone-d_6, benzene-d_6, and toluene-d_8. All collected aliquots were stored in small vials with phenolic or Teflon-lined caps until prepared for and analyzed by NMR spectroscopy.

General Procedure for Benzylation of *p*-Xylene in an Oil Bath. 2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BnOPB; 10.0 mg, 0.0094 mmol or 7.5 mg, 0.0071 mmol) was placed in a clean, dry ~6 mL lime glass test tube equipped with a triangular-shaped or small cylindrical stir bar. Any additives (glass boiling chips etc.) were added at this time, prior to addition of the solvent. To the salt was added 2.0 mL of *p*-xylene via syringe (2 × 1.0 mL aliquots). The tube was then gently heated with a heat gun with stirring until the solution became homogeneous. Once the solid was dissolved, a three-drop aliquot was removed (using a 9 in. disposable borosilicate glass Pasteur pipet) to ensure no reactivity prior to subjection to the reaction conditions. The test tube was then submerged in an oil bath preheated to 2 °C above the desired reaction temperature—the time of reaction began at this point. Three-drop aliquots were removed at the desired intervals according to the prescribed conditions, returning any excess solution to the reaction test tube.[49]

General Procedure for the Benzylation of *p*-Xylene in a Microwave Reactor. 2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BnOPB; 10.0 mg, 0.0094 mmol or 7.5 mg, 0.0071 mmol) was placed in a clean, dry, quartz 10 mL microwave reaction tube equipped with a triangular-shaped or small cylindrical stir bar. To the salt was added 2.0 mL of *p*-xylene via syringe (2 × 1.0 mL aliquots). The tube was then gently heated with a heat gun with stirring until the solution became homogeneous. Once the solid was dissolved, a three-drop aliquot was removed (using a 9 in. disposable borosilicate glass Pasteur pipet) to ensure no reactivity prior to subjection to the reaction conditions. The reaction tube was then placed into a CEM Discover Benchmate microwave reactor. The prescribed reaction conditions were programmed into the instrument using Synergy software as an open-vessel reaction, allowing for timed aliquots to be removed without interruption of the experiment. If external cooling was used, then the pressure of compressed air blown on the outside of the reaction vial was controlled by hand. The reaction was started, and aliquots were removed at desired intervals by inserting a glass pipet momentarily to remove the correct approximate amount needed. Excess solution was quickly transferred back into the reaction vessel.

General Procedure for the Benzylation of Toluene in Refluxing Toluene in an Oil Bath. 2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BnOPB, ;150.0 mg, 0.1410 mmol) was placed in a clean, dry, quartz round-bottom flask with an elongated neck equipped with a stir bar. To the salt was added 30 mL of dry toluene via a graduated 60 mL syringe. The flask was fitted with a condenser and submerged in a preheated oil bath (125 or 145 °C). Timing of the experiment began when the solvent began to reflux. The round-bottomed flask was removed from the oil bath after the prescribed reaction time, and a three-drop aliquot was removed (using a 9 in. disposable borosilicate glass Pasteur pipet) as soon as the reflux line fell below the reflux condenser joint.

General Procedure for the Benzylation of Toluene in Refluxing Toluene in a Microwave Reactor. 2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BnOPB; 150.0 mg, 0.1410 mmol) was placed in a clean, dry, quartz round-bottom flask with an elongated neck equipped with a stir bar. To the salt was added 30 mL of dry toluene via a graduated 60 mL syringe. The flask was then gently heated with a heat gun with stirring until the solution became homogeneous. Once the solid was dissolved, a three-drop aliquot was removed (using a 9 in. disposable borosilicate glass Pasteur pipet) to ensure no reactivity prior to subjection to the reaction conditions. The quartz round-bottom flask was then placed in the microwave reactor, followed by placement of the open vessel microwave attenuator. The flask was fitted with a condenser, followed by subjection to microwave irradiation (300 W). Timing of the experiment began when the solvent began to reflux (visible from the top of the instrument though the open-vessel attenuator). After reaction for the prescribed interval, the microwave irradiation was ceased. A three-drop aliquot was removed (using a 9 in. disposable borosilicate glass Pasteur pipet) as soon as the reflux line fell below the reflux condenser joint.

General Procedure for the Benzylation of *p*-Xylene in a Propylene Glycol Bath within a Microwave Reactor. 2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BnOPB; 10.0 mg, 0.0094 mmol) was placed in a clean, dry, quartz microwave reaction tube equipped with an oval-shaped stir bar. To the salt was added 2.0 mL of *p*-xylene via syringe (2 × 1.0 mL aliquots). The vial was then gently heated with a heat gun with stirring until the solution became homogeneous. Once the solid was dissolved, a three-drop aliquot was removed (using a 9 in. disposable borosilicate glass Pasteur pipet) to ensure no reactivity prior to subjection to the reaction conditions. The tube was suspended in a custom-made quartz round-bottom flask filled with propylene glycol and equipped with a stir bar using copper wire (see the Supporting Information for photographs of this experimental setup). The round-bottom flask was then placed into a CEM Discover Benchmate microwave reactor. The prescribed reaction conditions were programmed into the instrument using Synergy software as an open-vessel reaction, allowing for timed aliquots to be removed without interruption of the experiment. The reaction was started, and aliquots were removed at desired intervals by inserting a glass pipet momentarily to remove the correct approximate amount needed. Excess solution was quickly transferred back into the reaction vessel.

General Procedure for the Benzylation of *p*-Xylene in a Large Oil Bath for Collection of Data for Kinetic Plotting. 2-Benzyloxy-1-methylpyridinium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BnOPB; 13.5 mg, 0.0127 mmol) was placed in a small, clean, dry borosilicate vial equipped with a small cylindrical stir bar. To the salt was added 3.0 mL of *p*-xylene via syringe (3 × 1.0 mL aliquots). A heat gun was used to heat the sample as quickly as possible to the approximate oil bath temperature, as monitored by an internal fiber optic probe, and then the vial was submerged in a large, insulated, and preheated oil bath. Three-drop aliquots were removed at prescribed intervals. The temperature was noted by a fiber optic probe at each collection interval, with the average taken for use in kinetic calculations.

Procedure for the Synthesis of 2-Benzyloxy-1-methylpyridinium Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BnOPB). Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF; 2.29 g, 2.58 mmol) was placed in a clean, dry 100 mL round-bottom flask equipped with a stir bar and flushed with nitrogen. Separately, 2-benzyloxy-1-methylpyridinium triflate (BnOPT; 0.900 g, 2.58 mmol) was placed in a clean, dry 250 mL round-bottom flask equipped with a stir bar and flushed with nitrogen. Tetrahydrofuran was added via syringe to each flask (~50 mL per flask). Each flask was heated in an oil bath set at 40 °C and stirred. THF was gradually added via syringe until no solid particles remained in either flask. Once the reagents were dissolved, both flasks were opened, and the NaBArF−THF solution was quickly poured into the BnOPT−THF solution, using a magnet to prevent transfer of the stir bar. The solution was again capped and stirred under nitrogen overnight, after which time the THF was removed under reduced pressure to yield a clear yellow oil. α,α,α-Trifluorotoluene (PhCF$_3$) was added to make a clear, yellow solution with a precipitate. The precipitate (presumably NaOTf) was removed by filtration. BnOPB was crystallized from the PhCF$_3$ solution by adding hexane. Once the solution became cloudy, it was placed on ice. The resulting precipitate was filtered off as a yellow solid. A second recrystallization from PhCF$_3$/hexanes yielded a fine, shiny white solid in 63% yield (~1.7 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.04 (s, 3H), 5.66 (s, 2H), 7.47−7.53 (m, 3H), 7.60−7.62 (m, 4H), 7.65 (broad s, 8H), 7.76 (broad s, 4H), 7.85−7.87 (d, 1H), 8.53−8.58 (dt, 1H), 8.72−8.74 (dd, 1H) ppm. ^{19}F NMR (400 MHz, DMSO-d_6): δ −64.18 (s, 24F) ppm.

ASSOCIATED CONTENT

Supporting Information

Figures giving NMR spectra of various crude reaction mixtures, expanded kinetic plots and data, and plots of temperature vs time in MW experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail for G.B.D.: gdudley@chem.fsu.edu.

Notes

The authors declare no competing financial interest.

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(32) As a side note, it is clear to us from our experiments that quartz vials (as opposed to Pyrex) should be employed in any studies aimed at probing MW-specific thermal effects.

(33) The instrument ramped up to full power (nominally 300 W) within the first 60 s and maintained full power for the duration of the experiment. However, at that time (cf. ref 26) we were relying solely on instrument power readings; thus, we cannot confirm that "full power"

equated to 300 W. We now measure the power output periodically to confirm that the magnetron delivers 300 W of applied MW power into the sample cavity. Also, we erroneously reported the average recorded temperature as 92 °C, which included extended heating time after reaction was complete; the average over the 30 min reaction time was actually only 86 °C. We apologize for these oversights, which may have caused us to underestimate the impact of MW heating on our reaction system.

(34) It was interesting to us that the maximum temperature was recorded early in the process, prior to full consumption of the starting material. The solute composition changes over time (from substrate to product) as the reaction progresses, and from this early temperature maximum we infer that the starting materials are more absorbing (and consequently produce more heat) than the products of this reaction.

(35) Kappe and co-workers later reported that heating similar reaction systems in constant-temperature mode using relatively low MW power did not produce any rate enhancement. However, their use of low and variable MW power was inconsistent with our design parameters, which called for high and constant MW power (cf. our control experiments using low and variable MW power). Prof. Kappe declined our offers to work with his laboratory to resolve any experimental discrepancies. For more information, see: (a) Kappe, C. O.; Pieber, B.; Dallinger, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 1088−1094. (b) Dudley, G. B.; Stiegman, A. E.; Rosana, M. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 7918−7923.

(36) This type of experimental design—variable MW power, highly absorbing system, external temperature readings—is prone to "false positive" identification of MW effects, which perhaps accounts for the slightly elevated conversions observed in the early stages of this experiment. This minor discrepancy notwithstanding, our interpretation is that there is *not* a significant difference in conversion between MW and oil bath heating through a propylene glycol bath.

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(39) Assuming that propylene glycol absorbs at a level comparable to that ethylene glycol (i.e., better than ethanol), our 80 mL bath of propylene glycol likely blocked MW radiation more effectively than would a 2−3 mm thick wall of silicon carbide. Further experiments aimed at validating this assumption are in progress and will be reported separately.

(40) We switched from *p*-xylene-d_{10} to *p*-xylene for cost reasons, once it became apparent that we could monitor the reactions by ^{1}H NMR in either case. No solvent kinetic isotope effect is expected (or observed) for rate-determining first-order thermolysis of the substrate. However, we have observed different heating profiles (perhaps due to different heat capacities) for deuterated vs nondeuterated solvents in MW experiments, which can affect the magnitude of observed MW effects. Relationships among isotope effects, solvent heat capacity, and MW effects are beyond the scope of the present study and will be investigated in future work.

(41) An alternative explanation—that the solution temperature "must have been significantly higher than the values recorded using external IR sensor technology" in this experiment—has been advanced in the literature.[35] We rule this out because: (1) our sensor was calibrated repeatedly against an internal thermocouple probe to correlate the external surface temperature with the internal solution temperature for a range of relevant temperatures and for each reaction vial (cf. Figure 11); (2) there is no physical reason to suspect erroneous temperature readings in this particular experiment under constant MW power, in contrast to strongly absorbing systems heated under variable MW power (cf. the propylene glycol control experiment and reference 36); and (3) a faulty IR sensor (i.e., that is off by an average of ca 48 °C here) would produce inaccurate readings systematically, as opposed to impacting specifically this experiment. Our IR sensor has proven reliable for measuring temperature in diverse MW experiments and not just in those experiments designed to probe MW-specific effects. Wang, T.; Intaranukulkit, T.; Rosana, M. R.; Slegeris, R.; Simon, J.; Dudley, G. B. *Org. Biomol. Chem.* **2012**, *10*, 248−250.

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(43) The integrated average temperature was 102 °C, and the effective temperature was 104 °C. As discussed above, the integrated average temperature is the temperature that would produce the same conversion as the measured variable temperature profile according to Arrhenius predictions (i.e., 13% over 10 min), and the effective temperature is the temperature that would produce the same conversion as was observed in the experiment: 16% over 10 min.

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(45) The external IR sensor, in contrast, is calibrated to correlate vial temperature with solution temperature.

(46) The Kappe laboratory repeated these experiments and observed a similar MW-specific rate enhancement; they reported 75% conversion under MW heating and 41% conversion using oil bath heating after 30 min (see the Supporting Information for ref 35a). They went on to show that adding heterogeneous "boiling chips" (made by crushing various materials, including borosilicate glass) negated the MW-specific rate accelerations. As discussed above in the control experiment 2, heterogeneous additives can suppress MW-specific thermal effects in our homogeneous system.

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(49) Reactions run in *p*-xylene show a solvent impurity peak present at ∼4.65 ppm. Additionally, a triplet near 5.3−5.4 ppm appears as a result of minor degradation of BnOPB in some NMR solvents. Efforts were made to minimize the exposure of our samples to NMR solvents prior to spectrum acquisition.