Microwave-specific acceleration of a retro-Diels-Alder reaction

Journal:	*ChemComm*
Manuscript ID	CC-COM-07-2020-004584.R1
Article Type:	Communication

COMMUNICATION

Microwave-specific acceleration of a retro-Diels-Alder reaction

Michael A. Frasso,[a] Albert E. Stiegman[b] and Gregory B. Dudley*,[a]

Received 00th January 20xx,
Accepted 00th January 20xx

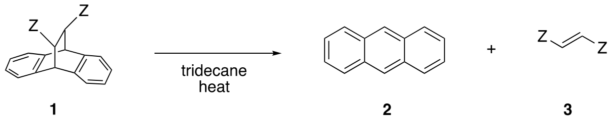
DOI: 10.1039/x0xx00000x

A high-temperature retro-Diels–Alder reaction is accelerated by microwave (MW) heating to rates higher than expected based on Arrhenius kinetics and the measured temperature of the reaction mixture. Observations are consistent with selective MW heating of the polar reactant relative to other, less polar components of the reaction mixture.

Microwave (MW) reactors have become a common heat source for organic chemistry laboratories. They provide rapid, uniform heating of reaction mixtures and make it easy to conduct reactions in pressure tubes above the boiling point of a solvent. Early observations of unique effects of MW heating compared to conventional heating (CH) methods were compromised by inaccurate temperature measurements,[1] but many examples remain showing discrepancies between MW and CH even under carefully controlled and well defined temperatures.[2-5]

Our lab has provided several examples of increased reaction rates under MW heating in carefully engineered (albeit not synthetically practical) reaction systems.[6-10] More recently, we reported significant and synthetically relevant increases in reaction yield in a key oxidative cycloisomerization step in the synthesis of the natural product illudinine.[11] Specifically, we observed higher yields under MW heating compared to CH (e.g., 39% vs. 62%), perhaps associated with differences in thermal decomposition of the product, which was less subject to MW heating in solution.

The hypothesis for this observation is a central theme in our work, namely that some reaction components can be selectively heated over others using MW heating and careful reaction system design. MW irradiation generates heat by a fundamentally different mechanism than CH.[12] MW heating relies on the interaction of the electric field component with molecular dipoles, whereas CH relies on convective heat transfer from the walls of the reaction vessel. Solutes having larger dipole moments tend to heat more efficiently than others in solution under MW irradiation.[13,14] The question that remains is whether these differences can be exploited in a useful manner.



Scheme 1. General retro-DA reaction. Z = carboxylic acid, amide, ester, etc.

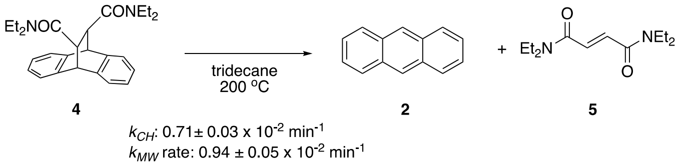
Continuing to probe our central hypothesis that polar solute microdomains can be heating selectively in nonpolar solvents,[15] and to explore the potential for enhanced utility of MW heating, we examined retro-Diels–Alder (DA) reaction processes of anthracene adducts bearing polar functional groups on the bridged bicycle. DA adducts of anthracene and fumaric acid derivatives (**1**, Scheme 1) should have substantially larger dipole moments than either of the retro-DA products. This should allow for MW radiation to heat **1** selectively over **2** and **3**. We chose a nearly MW-transparent hydrocarbon solvent, tridecane ($C_{13}H_{28}$,), such that heat generated within the reaction system is primarily a function of MW radiation interacting with substrate **1**. This weak, nonpolar solvent may also promote aggregation of polar solutes in solution, which could lead to stronger MW absorption in microdomains as discussed herein.

We focused on fumaric acid amide derivatives in this study because of ease of synthetic modification and tunable solubility in nonpolar solvents, expecting also that they would interact with MW energy, heat effectively, and provide opportunities for rate enhancements under MW heating. Indeed, thermal first-order retro-DA reactions of tetraethyl-amide **4** showed an approximately 32% increase in reaction rate constant (0.94×10^{-2} vs. 0.71×10^{-2} min^{-1}) over the conventional heating control experiment at 200 °C in tridecane solvent (Scheme 2 and Figure 1). Temperatures were monitored using internal fiber optic probes and were essentially identical in the two sets of experiments: 199.9 ± 0.3 °C (CH) vs 200 ± 1 °C (MW).‡

---

[a] *C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506 USA.*
[b] *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306 USA.*

Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data, NMR spectra, kinetic data from individual experiments, and microwave reactor output data. See DOI: 10.1039/x0xx00000x



Scheme 2. The rate of retro-DA reaction of **4** can be accelerated by MW heating.

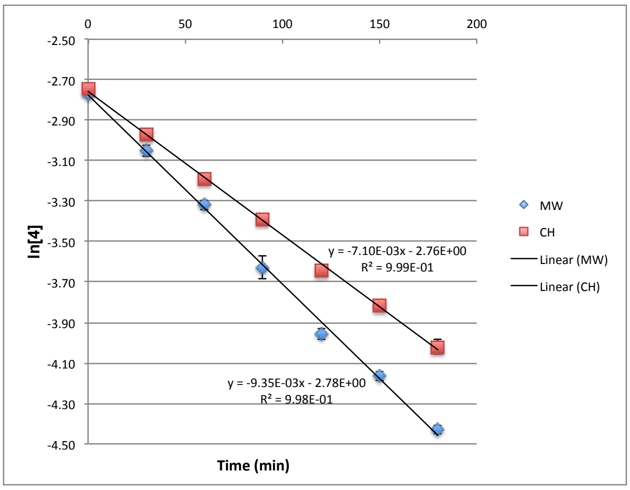


Figure 1. First order kinetic plot of the consumption of **4** under both CH and MW irradiation at 200 °C.

We attribute the difference in rate to selective microwave heating of polar solutes aggregated in the nonpolar reaction solvent. As we have discussed previously,[14,15] if polar solutes aggregate transiently into nano- or micro-scale phases in the bulk nonpolar solvent, then these polar nano- or microdomains create opportunities for selective microwave heating in a macroscopically homogeneous solution. Selective microwave heating of the microdomain creates a local temperature within in the domain that is hotter than the bulk solution, enhancing thermal reactivity of solutes within the domain relative to those outside of the domain and beyond what would be expected based on measured temperature of the bulk solution. In other words, the microwave-specific rate enhancement is purely thermal and linked to nonuniform heat distribution between polar and nonpolar components of the solution. The magnitude of selective heating can be quantified using the Arrhenius equation (Eq 1).

$$k = Ae^{-\frac{Ea}{RT}} \quad (1)$$

The thermal Arrhenius parameters for the retro-DA reaction under conventional heating were determined in order to quantify the acceleration under microwave heating (Figure 2). An Arrhenius plot was constructed using the average first-order thermal rate constants from three independent measurements at temperatures between 200-215 °C in 5 °C increments. Based on this plot, the activation energy (E_a) is 141 ± 2 kJ/mol, and the best fit for the pre-exponential term (A) is 2.30 x 10^{13}.

The rate of a thermal first-order reaction is a function of temperature, but the retro-DA reactions presented in Scheme 2 proceed at different rates for the same measured temperature. Our interpretation is that the measured temperature does not fully capture the thermal molecular energy of the polar solutes;selective microwave heating creates a disconnect between the measured temperature (T_{meas}) of the solution and the thermal energy of the polar solutes aggregated therein. The “effective temperature” (T_{eff})[6,7] is the temperature that corresponds to the observed thermal reaction rate. In the absence of selective MW heating, $T_{meas} = T_{eff}$.

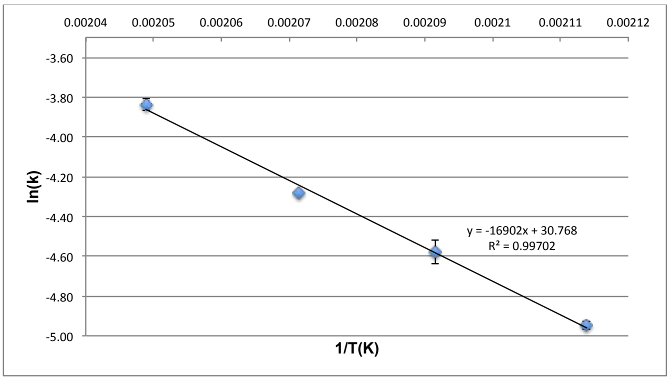


Figure 2. Arrhenius plot of rate constant data obtained at 200-215 °C in 5 °C intervals.

We can use the solute as a “molecular probe”[16] with the Arrhenius equation to determine the effective temperature of the reactive solutes in solution. For the reaction heated conventionally, the observed rate constant of 0.71 x 10^{-2} min^{-1} corresponds to an effective temperature of 200 °C, consistent with the measured temperature of 199.9 °C. For the analogous reaction under microwave heating, the observed rate constant of 0.94 x 10^{-2} min^{-1} corresponds to an effective temperature of 204 °C, or 4 °C higher than the measured solution temperature.

Having established that microwave-specific rate enhancements are observable and reproducible in this system, efforts to increase the MW rate enhancement focused on altering aggregation and/or selective heating of diamide **4**. Two ideas that have not (yet) translated into substantial gains in MW rate enhancements are as follows. One idea is to increase selective heating by coordinating a metal cation selectively to the carbonyl oxygens on the bridged bicyclic adduct. The DA adduct should be able to coordinate more efficiently than the acyclic fumarate product **5** due to the proximity of the carbonyls in **4**, and the ionic complex should heat more efficiently than the polar solute alone. In practice, however, the systems and additives we explored (sodium dodecyl sulfate, $NaBF_4$, KBF_4, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl)]borate) did not reproducibly provide any further microwave enhancement.

A second approach we explored is the use of reverse micelles, in which the interior of the micelle is more polar and could promote solute aggregation and selective heating inside the inverse micelle. The Span series of reverse micelles, sorbitan derivatives that contain esters of fatty acid, have found use at elevated temperatures[17] (albeit not as high as the temperatures in this study). Span-60 had no observable effect on reaction rates under CH (Table 1, entries 1 and 3). Adding span-60 had a small positive impact under MW heating, although the rate increase was barely distinguishable statistically from the MW-specific in the absence of span-60 (entries 2 and 4).

Table 1. Effect of Span-60 on retro-DA reaction with both CH and MW.

Entry	Heat source	Span-60 (equiv)	*k* (x10^{-2} min^{-1})
1	CH	0	0.71 ± 0.03
2	MW	0	0.94 ± 0.05
3	CH	0.094	0.71 ± 0.05
4	MW	0.094	1.07 ± 0.07

Table 2. Effect of concentration on rate constant for retro-DA of **4**. Entries 1, 4, and 5 are based off of a single experiment.

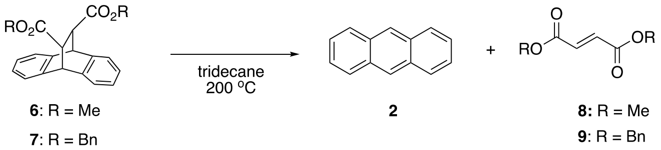
Entry	Heat source	Conc. [M]	*k* (x10^{-2} min^{-1})
1	MW	0.010	0.94
2	MW	0.020	1.0
3	MW	0.065	0.94
4	MW	0.10	0.92
5	CH	0.020	0.72

Table 3. Investigation of heptadecane solvent for retro DA reaction.

Entry	Heat source	Conc. [M]	*k* (x10^{-2} min^{-1})
1	CH	0.065	0.74 ± 0.04
2	MW	0.065	1.21 ± 0.09
3	CH	0.020	0.70 ± 0.07
4	MW	0.020	1.33 ± 0.06

Reaction concentration was also examined briefly (Table 2). A substrate concentration of 0.065 M was originally selected by analogy to concentrations used in some of our prior work.[8] In this case, decreasing the reaction concentration to 0.020 M resulted in an increase in rate (0.94→1.0 x10^{-2} min^{-1}, entries 3 and 2, respectively). The CH rate at 0.020 M (entry 5) was effectively the same as at 0.065 M (entry 5, cf. Scheme 2 or Table 1, entry 1). The observed rates from single experiments at 0.010 M and 0.10 M in the MW were lower than at 0.020 M (entries 1 and 4). These observations are potentially interesting because the rate constant of a first-order reaction, like its half-life,[6] does not depend on starting concentration. We see this MW-specific concentration dependence consistently in our work and have reported it previously.[6] Variations in rate as a function of concentration are consistent with selective heating of solute aggregates, which themselves vary with concentration.

Solvent viscosity plays a role in MW heat dissipation[14] and could be an important consideration for selective heating. We explored the possibility of using solvent viscosity as a means of increasing the MW rate enhancement, testing this hypothesis with preliminary experiments in a more viscous hydrocarbon solvent, heptadecane (Table 3). Heptadecane ($C_{17}H_{36}$) was selected due to its low cost and relative ease of handling compared to higher hydrocarbons. At a starting reaction concentration of 0.065 M, we observed a significant jump in reaction rate (0.74→1.21 x 10^{-2} min^{-1}) between MW heating at CH in heptadecane (entries 1 and 2), which represents a 66% rate enhancement for MW over CH. This is approximately double the MW-specific 32% rate enhancement observed in tridecane (cf. Scheme 2). If we assume similar Arrhenius parameters for reactions in heptadecane as in tridecane (Figure 2), then this rate constant under MW heating at 200 °C in heptadecane would correspond to an effective temperature of 207 °C. The observed rate enhancement was larger at 0.020 M (0.70→1.33 x10^{-2} min^{-1}, entries 3 and 4), although more measurements are needed to establish the statistical significance of these various observed differences.



Scheme 3. Additional retro-DA reactions investigated.

Finally, we explored whether or not these observations translate to other anthracene/fumaric acid DA adducts. The two ester derivatives examined gave somewhat different and interesting results (Scheme 3). Under standard conditions in tridecane, dimethyl ester **6** showed similarly enhanced conversion at 3 h using MW heating over CH (60% vs. 51%) as compared to diamide **4** (81% vs. 72%). On the other hand, dibenzyl ester **7** showed a larger increase (48% vs. 31%) at this time point. It should be noted that the results using **6** and **7** are from a single experiment each; additional data would be required to confirm and expand upon these preliminary observations. Nonetheless, these results underscore the unexplored complexities that govern MW rate enhancements. In this case, higher order aggregates in solution, perhaps facilitated by π-stacking interactions of the benzyl groups, may be a potential explanation.

The MW-specific rate accelerations documented herein are significant, consistent, and reproducible, but they are not maximized. We designed our experiments here to prioritize consistency and reproducibility, including by applying constant temperature and pre-heating the microwave cavity.‡ We have shown previously that variable temperature (e.g., constant power) experiments can provide greater microwave accelerations but with dynamic temperature profiles that are difficult to reproduce with precision. Pre-heating the microwave cavity improves consistency but reduces the overall observed accelerations, presumably because it slows the release of heat from the system to the surroundings in the alternating microwave heating with intermittent cooling can maximize the impact of selective microwave heating.[15]

In summary, we have demonstrated and explored a retro-DA reaction of **4** that can be accelerated under MW irradiation. Solvent viscosity was identified as a new variable to consider in the design and implementation of selective MW heating effects. Cycloadduct **4** undergoes a thermal retro-Diels–Alder reaction in tridecane at 200 °C with a first-order rate constant $k = 0.0071$ min^{-1}, whereas the same reaction process under MW heating proceeds with a higher first-order rate constant early stages of the reaction while the cavity would otherwise be relatively cool. Maximizing MW-specific rate enhancements would follow alternative experimental design criteria. Previous work has shown that open quartz vials and constant power or $k = 0.0094$ min^{-1}. Changing the reactant concentration (0.065 M → 0.020 M) and/or solvent (to heptadecane) did not

Table 4. Comparison of conversion after 3 h of heating at 200 °C for compounds 4, 6, and 7. Entries 3-6 are based off of a single experiment.

Entry	Heat source	Substrate	Conversion at 3 h
1	CH	**4**	72%
2	MW	**4**	81%
3	CH	**6**	51%
4	MW	**6**	60%
5	CH	**7**	31%
6	MW	**7**	48%

have a significant effect on reaction rates under conventional heating (CH). Under MW heating, in contrast, these changes each had small to significant effects on rate. Changing the reactant concentration (0.065 M → 0.020 M) increased the first-order rate constant to $k = 0.010\ \text{min}^{-1}$. Changing the solvent to the more-viscous heptadecane increased the rate constant to $k = 0.0123\ \text{min}^{-1}$. Changing both concentration and solvent viscosity increased the rate constant to $k = 0.0133\ \text{min}^{-1}$. Adding a surfactant (span-60) also had a small positive impact on the rate of reaction under MW relative to CH. These observations are consistent with selective MW heating of the polar reactant relative to other, less polar components of the reaction mixture, and they suggest that perhaps solvent viscosity is an important variable to consider when strategically designing reaction systems to capitalize on the unique solution-phase heating properties of MW energy. Future work will focus on generalizing the effect of solvent viscosity and as well as structural features that contribute to larger rate enhancements.

Acknowledgments

Support from the National Science Foundation (NSF-CHE 1665029) is gratefully acknowledged. The NMR spectrometer used in this research was acquired through the NSF Major Research Instrumentation (MRI) program (CHE-1228336).

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ See Supplementary Information.

1 M. A. Herrero, J. M. Kremsner and C. O. Kappe, Nonthermal microwave effects revisited: on the importance of internal temperature monitoring and agitation in microwave chemistry. *J. Org. Chem.* **2008,** *73*, 36-47.
2 S. Tashima, T. Sawada, K. Saito and T. Yamada, Microwave Specific Effect on Catalytic Enantioselective Conia-Ene Reaction. *Chem. Lett.* **2016,** *45*, 649-651.
3 T. Sawada, S. Tashima, K. Saito and T. Yamada, Microwave Enhancement on Ring-closing Metathesis of Macrocyclic Bisazole. *Chem. Lett.* **2017,** *46*, 274-276.
4 E. Altman, G. D. Stefanidis, T. van Gerven and A. Stankiewicz, Microwave-Promoted Synthesis of n-Propyl Propionate using Homogeneous Zinc Triflate Catalyst. *Ind. Eng. Chem. Res.* **2012,** *51*, 1612-1619.
5 M. De Bruyn, V. L. Budarin, G. S. J. Sturm, G. D. Stefanidis, M. Radoiu, A. Stankiewicz and D. J. Macquarrie, Subtle Microwave-Induced Overheating Effects in an Industrial Demethylation Reaction and Their Direct Use in the Development of an Innovative Microwave Reactor. *J Am Chem Soc* **2017,** *139*, 5431-5436.
6 P. K. Chen, M. R. Rosana, G. B. Dudley and A. E. Stiegman, Parameters Affecting the Microwave-Specific Acceleration of a Chemical Reaction. *J. Org. Chem.* **2014,** *79*, 7425-7436.
7 M. R. Rosana, J. Hunt, A. Ferrari, T. A. Southworth, Y. C. Tao, A. E. Stiegman and G. B. Dudley, Microwave-Specific Acceleration of a Friedel-Crafts Reaction: Evidence for Selective Heating in Homogeneous Solution. *J. Org. Chem.* **2014,** *79*, 7437-7450.
8 Y. Wu, J. Gagnier, G. B. Dudley and A. E. Stiegman, The "chaperone'' effect in microwave-driven reactions. *Chem Commun* **2016,** *52*, 11281-11283.
9 M. A. Frasso, A.E. Stiegman and G. B. Dudley, International perspectives on microwave heating in organic synthesis. *Chem. and Chem. Ind.* **2020,** *73*, 244-245.
10 H. F. Fulo, M. A. Vincent, A. E. Stiegman and G. B. Dudley, Cooperative application of conventional and microwave heating. *Asian J. Org. Chem.* **2020,** *9*, 961-966.
11 C. Duangkamol, P. Batsomboon, A. E. Stiegman and G. B. Dudley, Microwave Heating Outperforms Conventional Heating for a Thermal Reaction that Produces a Thermally Labile Product: Observations Consistent with Selective Microwave Heating. *Chem-Asian J.* **2019,** *14*, 2594-2597.
12 D. M. P. Mingos and D. R. Baghurst, Applications of Microwave Dielectric Heating Effects to Synthetic Problems in Chemistry. *Chem. Soc. Rev.* **1991,** *20*, 1-47.
13 E. Van Der Eycken, P. Appukkuttan, W. De Borggraeve, W. Dehaen, D. Dallinger and C. O. Kappe, High-speed microwave-promoted hetero-Diels-Alder reactions of 2(1H)-pyrazinones in ionic liquid doped solvents. *J. Org. Chem.* **2002,** *67*, 7904-7.
14 G. B. Dudley, R. Richert and A. E. Stiegman, On the existence of and mechanism for microwave-specific reaction rate enhancement. *Chem Sci* **2015,** *6*, 2144-2152.
15 G. B. Dudley and Stiegman, A. E., Changing Perspectives on the Strategic Use of Microwave Heating in Organic Synthesis. *Chem Rec* **2018,** *18*, 381-389.
16 (a) L. Hu, Y. Wang, B. Li, D. M. Du and J. Xu, Diastereoselectivity in the Staudinger reaction: a useful probe for investigation of nonthermal microwave effects. *Tetrahedron* **2007**, *63*, 9387-9392. (b) X. Li and J. Xu, Determination on temperature gradient of different polar reactants in reaction mixture under microwave irradiation with molecular probe. *Tetrahedron* **2016**, *72*, 5515-5520. (c) X. Li and J. Xu, Identification of microwave selective heating effort in an intermolecular reaction with Hammett linear relationship as a molecular level probe. *Curr. Microw. Chem.* **2017**, *4*, 339-346. (d) S. Sun, C. Teng and J. Xu, Sun, S., Teng, C. and Xu, J., 2020. Microwave Thermal Effect on Diels-Alder Reaction of Furan and Maleimide. *Curr. Microw. Chem.* **2020**, *7*, 67-73.
17 E. L. Michor and J. C. Berg, Temperature Effects on Micelle Formation and Particle Charging with Span Surfactants in Apolar Media. *Langmuir* **2015,** *31*, 9602-7.