Microwaves in Synthesis

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Reply to the Correspondence on Microwave Effects in Organic Synthesis**

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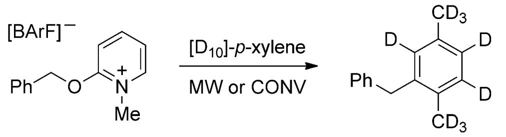
Friedel–Crafts alkylation · microwave chemistry · microwave effects · organic synthesis · temperature monitoring

Earlier this year our Essay on the subject of microwave effects in organic synthesis appeared in *Angewandte Chemie*.[1] The aim of this Essay was to provide a critical overview on the current state-of-affairs on this subject ten years after a similar report was published in *Angewandte Chemie* by Kuhnert.[2] In the introductory paragraphs we outlined the currently accepted definitions for so-called thermal, specific, and nonthermal microwave effects in organic chemistry. Importantly, we made it clear right from the beginning that these definitions are somewhat vague and that in particular „a clear differentiation between specific and nonthermal microwave effects following the definitions stated herein is not always expressed in the literature“.[1] What we were particularly interested in was emphasizing the importance of applying proper temperature measurement technology in microwave chemistry, and highlighting the consequences of inaccurate temperature measurement in the context of studying microwave effects. As we pointed out in our Essay, the literature is full of reports claiming the existence of specific or nonthermal microwave effects that could not be independently verified.[1,3] More than half of the body of the Essay deals with these general issues pertaining to microwave chemistry, and these sections (both in the introduction and conclusion segments) are heavily referenced with case studies from the recent literature.[1]

To make the reader appreciate the difficulties and many pitfalls in investigating microwave effects we incorporated two experimental case studies into the Essay, where we describe and discuss our attempts to verify two recently published reports where microwave irradiation was claimed to lead to significant enhancements in reaction rate or product yield that could not be duplicated by conventional conductive heating *at the same temperature*.[1] One of these studies involves a publication by Dudley and co-workers[4] in which the thermal Friedel–Crafts benzylation of $[D_{10}]$*p*-xylene using a 2-benzyloxy-1-methylpyridinium salt as the precursor is described (Scheme 1). Applying a variety of different microwave processing techniques the authors generally found that under microwave conditions conversions were significantly higher than with classical oil-bath heating at similar reaction temperatures.[4] The central design hypothesis in the original manuscript published in 2012 is that the reactivity of a highly polar ionic solute (i.e., a reactant) in a nearly microwave-transparent solvent can be influenced by steady-state microwave irradiation in a way that cannot be achieved by conventional heating at the same temperature.[4] As a rationalization the authors proposed a microwave-initiated increase of the pre-exponential factor A in the Arrhenius law, whereby „increased molecular motion results in more solute collisions and thus enhanced solute reactivity“ (see below).[4] It is interesting to note that in their current Correspondence these arguments are not repeated.[5] Instead, a different theory is presented that is based on the concept of selective heat storage in the domains that exist around microwave-absorbing solutes in nonabsorbing media when microwave irradiation is applied. These arguments are apparently derived from dielectric relaxation studies performed by Richert and Huang[6] which were not cited in the original manuscript.



Scheme 1. Friedel–Crafts benzylation of $[D_{10}]$-*p*-xylene using 2-benzyloxy-1-methylpyridinium BArF as precursor. BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

While the new arguments, additional thoughts, and experiments presented by Dudley and co-workers in their Correspondence are certainly of general relevance and worth considering, the experiments performed in our laboratories suggest a different explanation for this particular case, namely, that the enhanced conversions in the above-mentioned Friedel–Crafts alkylations are due to microwave-assisted superheating under atmospheric conditions, and thus ultimately are the consequence of an increased bulk temper-

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ature of the reaction mixture (see below). The arguments that support this premise were extensively documented in our Essay and for the sake of brevity are not be repeated in full here. The interested reader is advised to consult our Essay for a complete documentation.[1]

In this Reply, we will focus on the three specific concerns raised by Dudley and co-workers in their Correspondence.

Our Conclusions Are Misstated in the Essay and Their Conclusions Are Inconsistent—Reply

In their Correspondence,[5] Dudley and co-workers have suggested that we attempt to impugn their credibility by associating their rationalization for the observed effect with the concept of nonthermal microwave effects. This is clearly not the case. On the contrary, we specifically state in the Essay that „The proposed effect perhaps can best be classified as a specific microwave effect involving selective heating of a strongly microwave-absorbing species in a homogeneous reaction mixture (“molecular radiators).„[1,7] As we have already pointed out, our Essay was mainly intended to provide an overview on the current state-of-affairs regarding microwave chemistry and microwave effects research. Not surprisingly, therefore, out of the incriminated 22 uses of the word “nonthermal„ in our Essay, this word was used only twice in reference to the Dudley chemistry, and in both of these instances in conjunction with the term “specific microwave effect„.

The confusion perhaps arises since in the original publication by Dudley, the authors provide no clear-cut classification (thermal, specific, nonthermal) of the microwave effect that they have observed.[4] In fact, they do not unequivocally state that they believe the effect is connected to a purely thermal phenomenon, but rather invoke arguments about molecular collisions and the pre-exponential factor A in the Arrhenius equation (for example: „Chemical reactions arise from specific molecular collisions, which typically increase as a function of temperature but also result from incident microwave irradiation“).[4,8] Statements like this that appear to separate a thermal phenomenon from a microwave irradiation event clearly invite speculation by non-experts about the involvement of microwave effects that are not purely thermal in nature. This is very apparent by the news feature in *Chemistry World* following the publication of the Dudley article entitled: „Magical microwave effects revived. Microwaves can accelerate reactions without heating“.[9]

Again, we wish to stress that this is not our opinion and we do not intend to advance claims that the Dudley group is in support of such arguments involving nonthermal microwave effects. We maintain, however, based on our extensive experimental investigations on the Friedel–Crafts system introduced by Dudley (see below),[1] that what we are dealing here most likely is the result of solvent superheating under atmospheric conditions. This is in contrast to the theory advanced by Dudley which essentially proposes selective heating of the strongly microwave-absorbing reactant in a microwave-transparent solvent.[4,5] Both hypotheses may be classified under the category of specific microwave effects.[10] As we already emphasized in our Essay and in the introductory paragraph of this Correspondence, those definitions are somewhat vague, and it is not always entirely clear in the literature what constitutes a specific or nonthermal microwave effect.[1] In this context we wish to acknowledge that in their Correspondence[5] Dudley and co-workers point out correctly that the wording chosen for the text accompanying the Table of Contents graphic is not consistent with the conclusions we advance in the Essay („…the existence of so-called nonthermal or specific microwave is highly doubtful“).[1] What we meant to say—as stated several times in the body of the Essay—is that while nonthermal microwave effects probably do not exist at all, the occurrence of specific microwave effects is relatively rare and of little practical relevance to synthetic organic chemists.[1]

Our Experimental Conditions Were Not Appropriately Replicated—Reply

A key argument by Dudley and co-workers to rationalize the observed effect is that the microwave power itself is of crucial importance for the reaction enhancement (and not the bulk reaction temperature).[4] In their Correspondence, Dudley and co-workers argue that we did not replicate their experimental design properly since we did not use the same high microwave powers (e.g., 200–300 W) that they had used in their experiments.[5] At this point it must be stressed that the magnetron power readings obtained from a particular commercial microwave instrument have very little physical relevance. These values can be described at best as „nominal magnetron power outputs“ which are instrument specific and cannot be directly translated to other microwave instruments. As the design of the microwave cavity of the various commercially available single-mode microwave reactors varies significantly, the nominal magnetron output power readings are more or less irrelevant as they do not reflect how much microwave power is actually absorbed by the sample, apart from the fact that magnetron age, temperature, and a variety of other factors can influence the performance of these devices. Therefore, it is important to emphasize that even a comparison of microwave power values obtained from the same type of microwave reactor is troublesome. For the very same reason that the attempt by Dudley and co-workers to duplicate the results obtained in constant power mode with one particular instrument (CEM Discover) on a different reactor (Anton Paar Monowave 300) using the same nominal power settings had to fail,[4] it cannot be expected that in our laboratories the same nominal microwave powers will lead results similar to those obtained in the Dudley laboratories, even using the same type of instrument (CEM Discover). Attempts to exactly duplicate experimental microwave conditions that are based solely on microwave power values thus are flawed from the outset, one of the reasons why we have argued for many years that microwave chemistry should be performed exclusively in temperature-control mode.[11,12]

In this context it is of importance to emphasize that irradiating a sample in a microwave reactor with, for example, 100 W nominal magnetron output power does not mean that

100 W of microwave power is actually absorbed by the sample. One of the pitfalls of most laboratory-scale microwave instruments is that the reflected microwave power is not measured.[13] Simulations for the CEM Discover instrument have shown that in the case of low-absorbing solvents (3 mL solvent in quartz vessels) most of the microwave power is in fact reflected from the sample (99.86 % for hexane, 95.56 % for acetonitrile).[14] This further supports the notion that the use and interpretation of magnetron output data available from commercially microwave instruments is highly problematic. The criticism made by Dudley and co-workers in their Correspondence that we applied a lower magnetron power than that used in the experiments performed in their laboratory[5] is therefore meaningless and irrelevant as these power values are instrument dependent and how much power was actually absorbed by the sample (the only relevant physical parameter in this context) was not determined in either of the two laboratories.

Apart from the original optimization studies using standard cylindrical microwave vials, the key experiments in the Dudley paper are Friedel–Crafts alkylations performed under open-vessel reflux conditions in constant power mode using toluene as the solvent.[4] Open-vessel microwave processing has the advantage that the reaction can be performed with a constant level of microwave power and that the reaction temperature—in principle—should always correspond to the boiling point of the solvent and should therefore be easier to control, although this is not the case as will be discussed in detail below. In this particular series of experiments we were able to use the same nominal magnetron output setting as that reported by Dudley and co-workers (i.e., 300 W)[4] and although based on the discussion above this clearly does not mean that the same amount of microwave power was absorbed by the reaction mixture, this is the closest direct comparison to the Dudley experiments that could be achieved. The results from these experiments will be discussed in the following sections.

The Text of the Essay Does Not Match the Supporting Information—Reply

In their Correspondence, Dudley and co-workers attempt to portray the results obtained in our laboratory using the open-vessel reflux set-up as being somehow inconsistent and suggest some sort of discrepancy between the data presented in the main body of the Essay and in the Supporting Information.[5] We wish to state that this is clearly not the case if one considers that for such a complex subject matter not all information can be given in the main body of an Essay.[15] The main criticism of Dudley is connected to the data we present in Table S3 of the Supporting Information (see Figure 2 in Ref. [5]) highlighting kinetic experiments under reflux conditions in toluene using conventional heating and microwave irradiation at 300 W constant power applying magnetic stirring with or without boiling chips.[5] What the authors fail to mention in their Correspondence,[5] and of critical importance in this context, is that while the reaction temperature for the oil-bath experiment (CONV) and for the microwave experiment carried out in the presence of boiling chips corresponded to the standard atmospheric boiling point of toluene (roughly 111 °C), the bulk reaction temperature for the microwave experiment performed in the absence of boiling chips was in the range of 120 °C.[1] The temperature measurements were performed with accurate fiber-optic probes directly inserted into the reaction mixture and were shown in Figure S7 in the Supporting Information of our Essay (see Figure 1).[1] It is therefore not surprising at all, and fully consistent with our hypothesis of microwave superheating (see below),[14] that the conversions in the latter case were higher than those of reactions carried out at 111 °C using either microwave heating with boiling chips (suppressing superheating)[16] or under oil-bath reflux conditions.

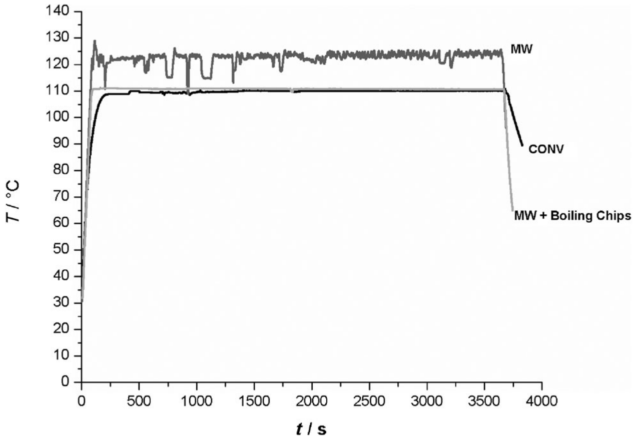

Figure 1. Heating profiles corresponding to the Friedel–Crafts alkylation (Scheme 1) using toluene as solvent under open-vessel reflux conditions applying conventional heating (CONV), microwave irradiation at 300 W constant power without boiling chips (MW) resulting in permanent superheating, and microwave irradiation at 300 W constant power with boiling chips (MW + Boiling chips). All experiments were performed with magnetic stirring of the reaction mixture (adapted from Ref. [1]).

In contrast, for the data presented by Dudley in their original publication (Figure 2 in Ref. [5]) no internal temperature measurement was carried out and the authors presume that in both cases (oil bath and microwave reflux) the reaction temperature is close to the boiling point of toluene (110–110 °C).[4] In order to explain the higher conversions in their microwave reflux experiment, despite the fact that the reaction temperature is (supposedly) the same as in the oil-bath experiment, the authors have suggested the theory of selective heating and molecular radiators.[4]

So while both sets of microwave reflux experiments (in the Dudley lab and in ours) under certain conditions indeed result in higher conversions than those under oil-bath conditions (Figure 2 in Ref. [5]), in our case these findings can be easily rationalized by the increased bulk reaction temperature, which in fact we were able to confirm experimentally using internal fiber-optic temperature probes.[1] In their Correspondence, Dudley and co-workers construe the fact that in some of the experiments we added boiling chips to suppress the microwave superheating effect (a known method),[16] as deliberately „altering our experimental design“.[5] The addition of boiling chips was of course done to support our hypothesis and to provide further evidence that the microwave effect that is experienced herein is connected to known atmospheric solvent/reaction mixture superheating.[16] Microwave superheating effects at atmospheric conditions were previously classified in the literature as a specific microwave effect,[10] but are clearly connected to a rather trivial bulk temperature phenomenon. What we meant by stating that „no evidence for any type of specific or nonthermal microwave effect could be obtained“,[1] was of course related to the theory proposed by Dudley and co-workers for which there is no precedent in the literature on microwaves in organic synthesis.

A Closer Look at the Question of Sustained Superheating Boiling—Reply

In this section of their Correspondence, Dudley and co-workers discuss the concept of superheating at atmospheric conditions and present new experimental data now involving internal fiber-optic temperature probes (Figure 3 in Ref. [5]) in which they demonstrate that under their experimental conditions the stirred reaction mixture does not show any appreciable superheating.[5] This of course is in stark contrast to the more or less identical experiment using similar fiber-optic probes carried out in our labs where we do find that significant superheating is indeed observed also for stirred reaction mixtures (see the discussion above and Figures S7 and S9 in Ref. [1]).[1] The reason for this discrepancy remains unclear, but considering the discussion above on the many pitfalls in comparing instrument magnetron power ratings it is not too hard to imagine that a 300 W power setting on one microwave instrument may lead to different results than those from an experiment in which the same nominal power setting is used on a different instrument in another laboratory.

In our Essay we pointed out that it is well known—and this is also our experience—that the microwave superheating effect under atmospheric conditions is notoriously difficult to reproduce and depends on many factors, including—apart from the applied microwave power—the geometry of the reaction vessel, stirring or nonstirring (and the type and size of the stirring device), the presence and type of boiling chips and other potential nucleation points in the mixture, and several other parameters as well.[1,16]

Our experience since the year 2000, in reinvestigations of dozens of similar cases of proposed microwave effects, has taught us that in these critical instances we can rely only on results obtained in our own laboratories using state-of-the-art microwave reactors in combination with accurate temperature monitoring devices.[3,17] As we have pointed out in a recent review article,[18] accurately monitoring reaction temperature during a microwave-heated experiment is far from trivial and requires both a basic understanding of microwave dielectric heating effects and use of appropriate temperature monitoring devices. Our own microwave experiments on the Friedel–Crafts alkylation system introduced by Dudley in 2012[4] do not support the hypothesis of selective reactant heating.[1] Neither the results performed in cylindrical microwave vials below the solvent boiling point, nor the results performed under open-vessel reflux conditions provided kinetic data that lead in this direction. Rather, all the evidence obtained in our laboratories points to the occurrence of atmospheric superheating when the reaction mixture is heated under open-vessel reflux conditions using high levels of microwave power.[1] As in this Correspondence we were limited to replying to the criticism in the Dudley Correspondence, we urge the reader to consult our Essay where many of our arguments are described in more detail.[19]

As a final thought we would like to point out that regardless whether the observed microwave effect in this controversial Friedel–Crafts alkylation discussed herein is due to selective reactant heating or bulk solvent superheating, both types of specific microwave effects are of little practical relevance to synthetic organic chemists. Microwave-induced atmospheric superheating under open-vessel conditions is difficult to control and maintain, not applicable to larger volumes for safety reasons, and requires a significant amount of microwave power. The comparatively small increase in the reflux temperature of a solvent above its normal boiling point can be realized more easily utilizing sealed-vessel microwave processing. In the case of the putative selective reactant heating as proposed by Dudley and co-workers,[4,5] it is hard to imagine that the strict design requirements (microwave-transparent solvent, soluble but highly microwave-absorbing reactant, no other microwave-absorbing substrates, etc.) will allow a lot of flexibility or provide some unique selectivity in synthetic transformations that could not be achieved in a different way, for example by simply running the experiment at a higher bulk reaction temperature.

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[1] C. O. Kappe, B. Pieber, D. Dallinger, *Angew. Chem.* **2013**, *125*, 1124; *Angew. Chem. Int. Ed.* **2013**, *52*, 1088.

[2] a) N. Kuhnert, *Angew. Chem.* **2002**, *114*, 1943; *Angew. Chem. Int. Ed.* **2002**, *41*, 1863; b) C. R. Strauss, *Angew. Chem.* **2002**, *114*, 3741; *Angew. Chem. Int. Ed.* **2002**, *41*, 3589.

[3] For additional reading on this topic published after the appearance of our Essay, see: C. O. Kappe, *Acc. Chem. Res.* **2013**, DOI: 10.1021/ar300318c.

[4] M. R. Rosana, Y. Tao, A. E. Stiegman, G. B. Dudley, *Chem. Sci.* **2012**, *3*, 1240.

[5] G. B. Dudley, A. E. Stiegman, M. R. Rosana, *Angew. Chem.* **2013**, DOI: 10.1002/ange.201301539; *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201301539.

[6] a) W. Huang, R. Richert, *J. Phys. Chem. B* **2008**, *112*, 9909; W. Huang, R. Richert, *J. Chem. Phys.* **2009**, *130*, 194509.

[7] Since there is no precedent in the literature on microwaves in organic chemistry for this type of effect, the classification is not as straightforward as it appears. Even though several previous reports mention the term „molecular radiator“ (see Ref. [6] in the Dudley Correspondence) the concept is not discussed in any further detail in these publications. We received conflicting opinions from the referees on how to best classify the effect demonstrated by Dudley and co-workers, but ultimately considered this to be a specific microwave effect in our Essay.

[8] Arguments pertaining to the pre-exponential factor A and the Arrhenius law in the context of microwave effects are typically discussed in the context of nonthermal microwave effects. See for example: L. Perreux, A. Loupy, A. Petit in *Microwaves in Organic Synthesis*, 3rd ed. (Eds.: A. De La Hoz, A. Loupy), Wiley-VCH, Weinheim, **2013**, chap. 4, pp. 127–208.
[9] E. Richards, *Chem. World* **2012**, March issue, p. 25.
[10] For definitions and examples for thermal, specific, and nonthermal microwave effects in organic chemistry, see: a) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; b) C. O. Kappe, A. Stadler, D. Dallinger, *Microwaves in Organic and Medicinal Chemistry*, 2nd ed., Wiley-VCH, Weinheim, **2012**, chap. 2, pp. 9–39.
[11] a) C. O. Kappe, *Chem. Soc. Rev.* **2008**, *37*, 1127; b) C. O. Kappe, D. Dallinger, S. S. Murphree, *Practical Microwave Synthesis for Organic Chemists—Strategies, Instruments, and Protocols*, Wiley-VCH, Weinheim, **2009**; c) C. O. Kappe, A. Stadler, D. Dallinger, *Microwaves in Organic and Medicinal Chemistry*, 2nd ed., Wiley-VCH, Weinheim, **2012**.
[12] In rare instances we have performed microwave irradiation experiments in power-control mode, mainly to investigate the arcing behavior of metals under different electric field strengths. For details, see: a) B. Gutmann, A. M. Schwan, B. Reichart, C. Gspan, F. Hofer, C. O. Kappe, *Angew. Chem.* **2011**, *123*, 7778; *Angew. Chem. Int. Ed.* **2011**, *50*, 7636; b) W. Chen, B. Gutmann, C. O. Kappe, *ChemistryOpen* **2012**, *1*, 39.
[13] The measurement of forward and reflected microwave power is typically only implemented in industrial-scale microwave devices, which also allows the determination of an energy balance. See for example: R. Morschhäuser, M. Krull, C. Kayser, C. Boberski, R. Bierbaum, P. A. Püschner, T. N. Glasnov, C. O. Kappe, *Green Process. Synth.* **2012**, *1*, 281.
[14] J. Robinson, S. Kingman, D. Irvine, P. Licence, A. Smith, G. Dimitrakis, D. Obermayer, C. O. Kappe, *Phys. Chem. Chem. Phys.* **2010**, *12*, 4750.
[15] References [23] and [24] in our Essay point the reader to the Supporting Information for full experimental details and an extended discussion. Therefore the discussion provided in the Supporting Information is an integral part of the Essay and cannot be considered separately from the main body of the Essay.
[16] For seminal references on microwave superheating effects at atmospheric conditions, see: a) D. R. Baghurst, D. M. P. Mingos, *J. Chem. Soc. Chem. Commun.* **1992**, 675; b) R. Saillard, M. Poux, J. Berlan, M. Audhuy-Peaudecerf, *Tetrahedron* **1995**, *51*, 4033; c) F. Chemat, E. Esveld, *Chem. Eng. Technol.* **2001**, *24*, 735.
[17] For selected references from our laboratory on reinvestigating microwave effects, see Refs. [10–13], and [17–19] in our Essay (Ref. [1]).
[18] C. O. Kappe, *Chem. Soc. Rev.* **2013**, *42*, 4977.
[19] We note that in their Correspondence, Dudley and co-workers did not respond to some of our general criticism of their experimental work, in particular the questionable NMR analysis, lack of statistical analysis of data, and some rather difficult to rationalize microwave hardware issues. For example, while the authors were able to heat a 2 mL reaction mixture to 80 °C using 88 W of average microwave power, they were unable to heat the same reaction mixture on the same instrument to 100 °C using 200 W or 300 W magnetron output power. This is rather difficult to comprehend.