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The importance of agitation and fill volume in small scale scientific microwave reactors

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Abstract—The effect of agitation and fill volume in a microwave tube on the rate of homogenous reaction solutions under both stirred and unstirred conditions is reported. Significant increases in rate are found in two different microwave instruments when the homogenous reaction mixture is unstirred. These results have significant implications for the continuing use of domestic or kitchen type microwaves in synthetic applications; and in scientific microwaves where stirring may be compromised, for example in the presence of heavy slurries or viscous liquids.

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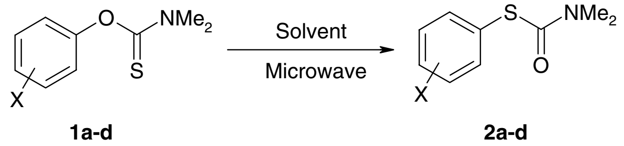
Since the advent of microwave technology in 1986 for use in organic synthetic chemistry applications,[1] microwave synthesis has been plagued by claims and counter-claims of reaction rate enhancements and other thermal and non-thermal effects. This issue has been covered in some measure in recent books[2] and reviews[3] on the subject, and more specifically in the review by de la Hoz.[4] Many of the initial claims were made when using domestic or kitchen type microwave instruments modified for synthesis. In these early cases, little attempt was made to measure the temperature or pressure either accurately or even at all, often because it was in fact not very easy.[5] Agitation was also often optional in these early examples. As the claims for reaction rate enhancements became more widely known, there was increasing interest in microwave assisted organic synthesis. Strauss, an early pioneer of microwave synthesis, was one of the first to argue that careful kinetic experiments were required to support such claims.[6] This necessitated accurate measurement of the physical parameters, particularly the temperature, for valid comparisons to be made with conventionally heated reaction mixtures. The use of the more accurate scientific microwaves[7] has disproved many previously claimed examples of non-thermal heating effects.[8] However, this is still a contentious area, and a small residue of genuinely unusual results, largely in the areas of metal-catalyzed organic reactions, peptide and polymer chemistry, and solid supported reactions, remain unexplained.[9]

We have previously reported our re-evaluation of the Newman–Kwart rearrangement[10] (NKR) under microwave and conventional heating (Scheme 1).[11] In that study, we found there to be no difference between the modes of heating under appropriately controlled and comparable conditions. We also confirmed reaction parameters previously known from conventional thermal studies, namely, that this reaction is a simple unimolecular first order rearrangement under dilute to moderately concentrated conditions (up to 0.5 M), and which is promoted purely by thermal energy, irrespective of heating source. From this and further studies,[12] we have found this to be an exceptionally reliable and robust reaction under a range of conditions. The NKR is therefore an excellent probe reaction, not least because it is homogenous; there are no phase equilibria, or phase boundaries for reacting centres to cross. However, we had observed from early studies on unstirred homogenous reaction mixtures that the reaction rates were much higher than they should have been. We attributed this to superheating in the reaction tube above where the IR pyrometer was measuring the internal temperature. Concerned with the continuing appearance in the literature



Scheme 1. Reagents: **a**, 2-nitrophenyl; **b**, 4-cyanophenyl; **c**, 2-naphthyl; **d**, 4-methoxyphenyl.

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of reports on synthesis conducted in kitchen type microwaves, often clearly without active stirring,[13] and in our own and others work regarding the efficiency of agitation in the presence of heavy slurries or viscous liquids, we determined to investigate this phenomena more thoroughly using this reliable homogenous reaction.

Two small scale synthetic mono-mode microwave reactors were used, the CEM Discover[7c] and the Biotage Initiator.[7b] Both of these instruments use an IR pyrometer on the outside of the reaction vial to determine the temperature. Although these pyrometers can give misleading temperature readings due to measuring the external rather than internal temperature of the vial contents,[14] we have found them to be generally reliable[11] when used appropriately. For strictly accurate comparisons, a fibre optic probe or other pyrometer should be used, as recommended by other groups (Kappe[2a] pp #16–28; Leadbeater;[8c] Ondruschka[14]). However, the point of this exercise was to demonstrate aspects of agitation and fill volume when relying on the IR pyrometer in normal usage, not to demonstrate that the fibre optic probe is inherently more accurate, as has already been demonstrated.

The IR pyrometers in the two instruments are aligned in different positions (Fig. 1), the one on the Discover being in the base, and on the Initiator, at the side, ~3 cm above the base of the vial. There are advantages and disadvantages to both configurations. The Discover will accommodate very small volumes in one standard size tube (10 mL), even down to 50 μL, as used by Cavaleiro and Kappe, for example.[15] In the Initiator, a minimum fill is required in the tube to ensure that the solvent is above the level of the IR pyrometer. To accommodate both smaller and larger volumes, a range of tube sizes and geometries is available for use with the Initiator, from 20 mL down to a minimum of 200 μL. We used exclusively the 2–5 mL round-bottomed tubes, which are very similar in size and shape to Discover 10 mL tubes. In addition, brief consideration of Figure 1 will show that for a two-phase liquid–liquid mixture, different temperatures will be read, dependent on the microwave-absorbing characteristics of each solvent, due to the placement of the IR pyrometer. This is particularly marked in the case of ionic liquids immiscible with non-polar solvents, as noted by Kappe.[16]

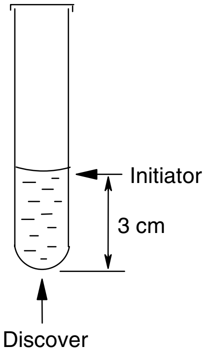

Figure 1. Position of IR pyrometers in different microwave instruments.

We determined to study substrates of the NKR at several temperatures to prove the generality of the effect over a wide temperature range, and as far as possible in both instruments. We chose the following dimethyl-*O*-thiocarbamates and temperatures:- 2-nitrophenyl (**1a**) at 160 °C; 4-cyanophenyl (**1b**) at 200 °C; 2-naphthyl (**1c**) at 240 °C; and 4-methoxyphenyl (**1d**) at 280 °C. The temperatures were chosen to give partial rather than full conversions to the *S*-thiocarbamates **2a**–**d** after 20 min of microwave heating (Scheme 1).[17] Conversions plateau towards the end of the reaction, as shown in the generic first order rate plot typical for these rearrangements (Fig. 2), which reduces the discrimination between individual data points at high conversions. Target conversions of ~50% were chosen for the stirred cases, although this proved to be too much in some of the unstirred cases. Samples were heated in both microwave instruments with and without stirring to nominally the same temperature as determined by their respective IR pyrometers. The relatively long 20 min hold time was chosen to minimize the effect of the heating and cooling times on both instruments. To reduce errors further, a mean average was taken from three identical microwave runs prepared from the same bulk (liquid) sample and run under identical conditions in close succession. Two standard deviations were generally less than 2.5% in the majority of cases. The results are collated in Table 1 (Discover results), Table 2 (Initiator results) and Table 3 (solvent effects in Initiator).

Before addressing the primary purpose of this study, it is worth noting other aspects of the data. It will be seen that the reproducibility of the stirred experiment results for both instruments is very good for each given substrate and temperature, across the range of tube fill volumes (Tables 1 and 2). The reproducibility between the two instruments is also high, which given the different software protocols used between them, is pleasing. Furthermore, given that most users of these instruments are in the medicinal chemistry area, where high conversions are desired, they would not notice these differences for partial conversions due to operating on the plateau section of the rate plot (Fig. 2). In practical terms therefore, there is no difference between the two instruments if regularly calibrated and in the hands of a competent user.

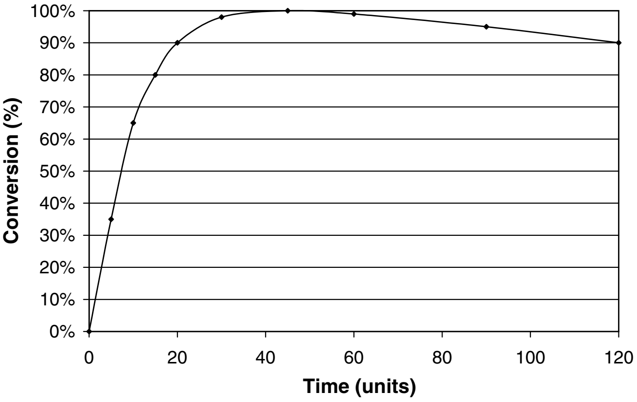

Figure 2. First order rate plot typical of the Newman–Kwart rearrangement.

Table 1. Discover results—conversions for compounds **1a–d** to **2a–d**, respectively, after 20 min at set temperature, stirred and unstirred, at different tube fills in NMP

Temp./compound	Tube fill (mL)	Stirred conversion (%)	Unstirred conversion (%)
160 °C/**1a**	0.2	65	100
	2.0	65	100
	3.0	66	100
	4.0	66	100
	5.0	65	100
200 °C/**1b**	2.0	59	100
	3.0	n/d	n/d
	4.0	n/d	n/d
	5.0	60	100
240 °C/**1c**	2.0	19	99
	3.0	25	98
	4.0	22	98
	5.0	24	95
280 °C/**1d**	2.0	72	95
	5.0	71	97

Table 2. Initiator results—conversions for compounds **1a–c** to **2a–c**, respectively, after 20 min at set temperature, stirred and unstirred, at different tube fills in NMP

Temp./compound	Tube fill (mL)	Stirred conversion (%)	Unstirred conversion (%)
160 °C/**1a**	2.0	58	48
	3.0	60	65
	4.0	58	73
	5.0	58	80
200 °C/**1b**	2.0	43	36
	3.0	44	49
	4.0	45	60
	5.0	46	69
240 °C/**1c**	2.0	17	12
	3.0	18	22
	4.0	19	31
	5.0	19	36

Table 3. Initiator solvent effects—conversions for compound **1c** to **2c** after 20 min at 240 °C, stirred and unstirred, at different tube fills in different solvents

Solvent	Tube fill (mL)	Stirred conversion (%)	Unstirred conversion (%)
NMP	2.0	17	12
	5.0	19	36
DCB	2.0	51	45
	5.0	55	67
DPE	2.0	14	7
	5.0	21	34

Having shown good general reproducibility for the stirred experiments, the effects on the unstirred homogenous reaction mixtures can now be considered. Predictably, the results for the Discover, which has its temperature probe in the base, show that it is very susceptible to over-heating the reaction mixture in the unstirred cases. Stirred reactions with conversions in the range 59–72% were all effectively complete when unstirred comparisons were run, and no useful comparison between the fill volumes could be made in these cases (Table 1). Even when the conversion was relatively low, around 20% for the conversion of **1c** to **2c** at 240 °C, the unstirred reactions were again effectively complete, showing conversions of 95–98%. This equates to an effective temperature increase of ~40 °C above the notional set temperature that the IR pyrometer reads, higher than is normally attributed to super-heating alone or errors in external pyrometer readings.[14]

The Initiator with its temperature probe on the side of the vessel, at the minimum fill solvent line, has a much smaller error in the unstirred cases, although it is still significant (Table 2). Interestingly, it also manifests a distinctive pattern for the different fill volumes. So, for the minimum 2.0 mL fill, the result is slightly low; for the 3.0 mL result, it is in fairly good agreement with the correct (i.e., stirred) result; for 4.0 and 5.0 mL fills, the unstirred results are increasingly high (NB. differences look more significant for low conversions, less so for higher conversions—cf. Fig. 2). Presumably the higher fill volumes in the Biotage tubes suffer the same type of effect as in the Discover when unstirred, in that up to 3 mL of solution volume is unmixed above the side mounted temperature probe, and tends to over-absorb microwaves without the pyrometer measuring this heating. The consistent slightly low reading for the low fill (2.0 mL) results is more difficult to rationalize, although we believe this to be a significant difference.

The very high temperature comparison at 280 °C with the 4-methoxy substrate (**1d/2d**) could only be performed in the Discover. Other tube sizes for the Initiator were also not investigated (although the pyrometer is mounted in the same place for all) because the tubes have a distinctly different geometry, which we know can affect some results; and additionally, comparisons with the Discover would not be possible. However, a small survey of different reaction solvents was conveniently performed in the Initiator, to ensure these effects were not specific to highly polar NMP. Therefore, reactions at 2.0 and 5.0 mL fill volumes were run for substrate **1c/2c** at 240 °C in solvents of high (NMP), medium (*o*-dichlorobenzene, DCB) and low (diphenyl ether, DPE) polarity. The results are shown in Table 3.

The reproducibility within the stirred tubes at high and low volume was fairly good for NMP and DCB, but somewhat poor for DPE. This may have been because the Initiator was working near its limit of 250 °C, and solutions of the very non-polar DPE can be difficult to heat. Most notably however, NMP and DPE gave similar conversions, whilst DCB gave much higher values. The reaction is known to be aided by polar solvents from our previous results.[11] This may suggest that NMP has reduced polarity at this temperature, which agrees with other observations we have made,[12a,18] particularly regarding the ease of heating NMP by microwaves above ~200 °C. However, without direct measurement of the dielectric constant (and other parameters), this is speculation drawn from empirical data.

The unstirred NMP results were the same as before, and showed the same pattern discussed above for all Initiator results, that is, slightly low conversion for low fill, double conversion for high fill. The trend was similar for the unstirred DPE results. The unstirred DCB results were actually in moderate agreement with their stirred results, and the standard deviations show the results are just about significant, slightly low at low fill, slightly high at high fill. A higher polarity solvent could be expected to conductively diffuse heat more readily within the tube than a low polarity one like DPE, but again, without direct measurement of the dielectric constant of DCB, no firm conclusions can be made about its polarity at this temperature.

In summary, we have used a highly reliable and robust, homogenous reaction mixture to determine the reproducibility of results from stirred and unstirred reaction solutions of different volumes in two small-scale scientific microwave instruments. We find the reproducibility of the stirred reaction mixtures in both instruments to be very good between reaction tubes for the same experiment, and between the two instruments themselves.

For the unstirred reaction mixtures, the results are seriously compromised in both instruments. Of course, one is unlikely to deliberately perform a reaction without effective agitation, and this study is not intended to assess these instruments when they are used sub-optimally. In fact it is their very reliability that has allowed us to access the data needed for the main aim of this study, which is to show that where agitation is non-existent or ineffective, even with apparently accurate temperature measurement, the results will be seriously compromised. Significantly, the results may also vary with the depth of reaction solution within a reaction vessel under these circumstances.[19]

These results should therefore serve as a warning to the interpretation of data from domestic or kitchen microwaves, which still appear in the literature. They are also of relevance to the use of scientific microwave instruments where agitation *may* be compromised,[20] for example in the case of reactions involving heavy slurries (perhaps particularly with K_2CO_3 or Cs_2CO_3), viscous liquids and solvent-less microwave chemistry.[21]

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