Accounting for clean, fast and high yielding reactions under microwave conditions†

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Thermal reactions proceed optimally when they are rapidly heated to the highest tolerable temperature, held there for the shortest possible time and then quenched. This is explained through assessments of reaction kinetics in literature examples and models. Although presently available microwave equipment is better suited to rapid heating than resistance-heated systems, the findings do not depend upon the method of heating. Claims that microwave heated reactions proceed faster and more cleanly than their conventionally heated counterparts are valid only when comparably rapid heating and cooling cannot be obtained by conventional heating. These findings suggest that rigid adherence to the sixth principle of green chemistry, relating to the use of ambient temperature and pressure, may not always afford optimal results.

Introduction

Clean, fast and high yielding reactions are efficient and they avoid waste. Such properties are sought by synthetic chemists for green and sustainable chemistry. Microwave heating[1] particularly with dedicated reactors,[2] has proven advantageous in that regard.[3] Many reports that microwave-heated reactions typically proceed more cleanly, in higher yields and in less time than their conventionally heated counterparts have appeared.[4] Although the reason behind such findings has been a subject of speculation, no explanation supported by compelling evidence has been offered.[5]

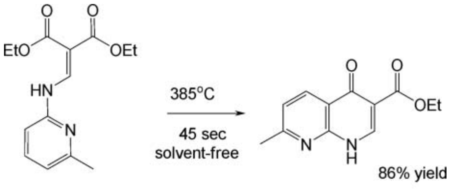
Some workers had invoked specific non-thermal "effects" to account, among other things, for faster, cleaner and higher yielding microwave reactions.[6] Now, however, a body of accumulated results has shown that under microwave conditions the vast majority of reactions proceed thermally.[7,8] Thus, as reported in 1996, before microwave reactors became available commercially, reactions conducted under microwave conditions or by conventional heating should afford identical outcomes if their thermal profiles are identical.[9]

This indicates that the question as to why microwave-heated reactions go faster, more cleanly and in higher yields than their conventionally heated counterparts, should be superseded by one that asks if and/or why rapidly heated organic reactions go faster, more cleanly and in higher yields than their more slowly heated counterparts, regardless of the method of energy input. The present report addresses those aspects and offers an explanation.

Discussion

We begin by consideration of the optimal thermal conditions required to obtain products from highly competitive reactions. Unless optimised, such processes do not go cleanly or afford high yields. When more than one potential product could be formed, the outcome would be influenced by the thermal history of the reaction. Other variables including catalysis, concentration and solvent effects could also affect the result, but for the present purposes only heating is considered. In that regard, yields may be affected by equilibria, the appearance and disappearance of kinetic products, the formation of thermodynamic products and decomposition. Even in apparently simple competitive processes that employ single starting materials, reactions can follow diverse pathways. Intermediates and products can react with starting materials, with themselves or with each other. Consequently, unreacted starting material, alternative products and by-products often co-occur in mixtures containing the desired product, with adverse effects on isolation processes and yields.

Examples necessary for this discussion involve competitive reactions which have accurate and precise thermal histories, supported by quantitative analytical results for all significant components. A thermal, intramolecular cyclisation of the methylpyridyl diester **1** to quinolone derivative **2** with loss of EtOH (Scheme 1) met the criteria.[10]



1 **2**

Scheme 1 Thermal cyclisation of **1** to quinolone derivative **2** in the absence of solvent.[10]

The industrial reaction affording **2** from **1** was conducted at temperatures around 250 °C with heat transfer oil as a

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diluent and thermal medium. Seemingly incongruously, the alternative optimised process employed solvent-free conditions at 385 °C.[10] The lowest temperature investigated under solvent-free conditions was only 10 °C higher than that for the industrial process in heat-transfer media. It afforded the poorest yield owing to comparable rates of formation and decomposition of the product. Increasing the reaction temperature and commensurately lowering the time gave trends toward cleaner processes and higher yields, if and only if, the heating and subsequent cooling steps were rapid. If heating were continued for even seconds beyond the ideal reaction time, the product fully decomposed. The optimal yield of **2** was 86% after 45 s at 385 °C and the developed solvent-free reaction was performed as a flow-through process for more than an hour. For all reaction times at all temperatures below 300 °C it was barely possible to obtain half the optimal yield under solvent-free conditions.[10]

High dilution is a long established means of minimising competition from intermolecular processes while conducting intramolecular reactions. Findings that an intramolecular cyclisation could proceed in higher yield from neat starting material and at a temperature 135 °C above that used for an established industrial process requiring dilution appear to contradict conventional thought and practice. Hence for this competitive process, the results strikingly demonstrated the efficacy of rapid heating and cooling for the isolation of a clean product in high yield within a short period of time.

Plots of the yield of **2** (ordinate) against reaction time (abscissa) became taller (*i.e.* yields increased), narrower (the product formed and decomposed more readily) and moved closer to the *y*-axis with increasing reaction temperature (reaction times decreased with temperature increase). Three schematic plots highlighting such features are presented in Fig. 1 by way of illustration.

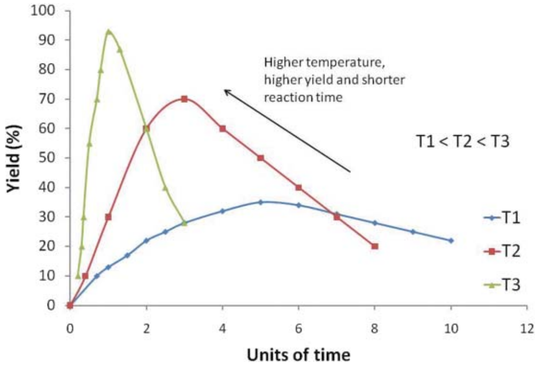


Fig. 1 Schematic plots depicting the influence of time and temperature upon the yield of a product for the same competitive thermal process conducted at temperatures of T1 (lowest), T2 and T3 (highest).

The peak for the shortest and widest plot (poorest yield in the longest time) was the most remote from the *y*-axis and it belonged to that for the lowest temperature investigated. An explanation for such results is that at higher temperatures, product formation and decomposition predominantly occurred in rapid succession, while at lower temperatures they overlapped to a significant extent. Consequently, the product could be isolated in high purity and yield only from reactions at higher temperatures, albeit through a narrow window of time.

To demonstrate with a hypothetical example, in Fig. 2 data have been plotted for a model reaction of the type A → B → C which is described by first order equations and where the activation energy for the second step (*i.e.* B → C) is lower than that of the first. In this model, the activation energy for the second step is half that of the first and the pre-exponential constants have been adjusted to give a rate constant of 1×10^{-3} s^{-1} at a temperature of 298 K. Inspection of the reaction surface presented in Fig. 2 indicates that under those circumstances, the highest yield of intermediate B (80%) would have been obtained at the highest temperature (400 K), within about 10 s. Lower temperatures and longer times would have afforded inferior yields.

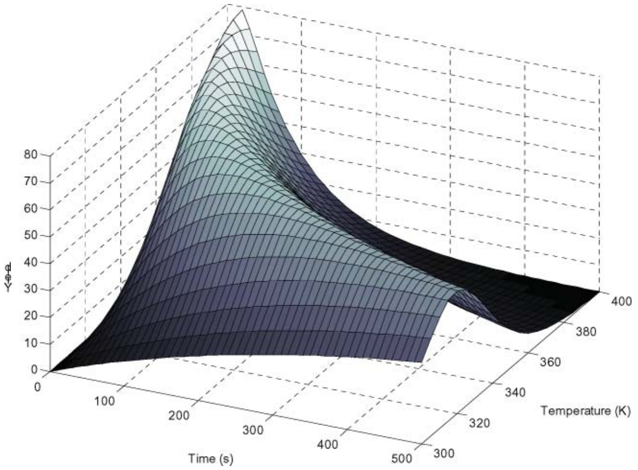
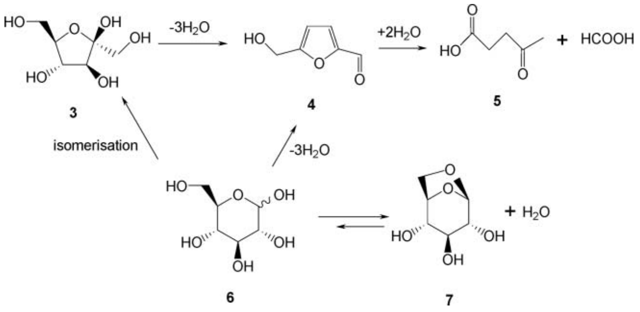


Fig. 2 Yield of intermediate B in the first order reaction $A \xrightarrow{k_1} B \xrightarrow{k_2} C$ as a function of temperature and time where $k_1 = 5.815 \cdot 10^5 \cdot e^{\left(\frac{-50\,kJ \cdot mol^{-1}}{R \cdot T}\right)} s^{-1}$, and $k_2 = 24.113 \cdot e^{\left(\frac{-25\,kJ \cdot mol^{-1}}{R \cdot T}\right)} s^{-1}$.

For the conversion of **1** to **2**, at lower temperatures, product formation and decomposition co-occurred to such an extent that they could not be distinguished regardless of heating time. Preparations under such conditions contained mixtures of (i) starting material mainly, with some kinetically formed by-product and some product (reaction times too short) (ii) starting material, kinetic by-product, product and thermodynamic by-products (result unsatisfactory, but the best attainable under the conditions) or (iii) product and mainly thermodynamic by-products (over-reaction).[10]

Several examples showing results consistent with those for conversion of **1** to **2** and displaying features and trends in common with those shown in Fig. 1 and 2 have been drawn from publications regarding the conversion of carbohydrates from biomass. Such processes have been well studied as they are important for the use of polysaccharides as renewable sources of fuel and synthetic building blocks. They have been carried out at various temperatures and several recent publications have contained comprehensive data regarding the interconversions investigated. Products of interest are fermentable sugars from polysaccharides *e.g.* fructose (**3**) and glucose (**6**) as well as 5-hydroxymethylfurfural (5-HMF, **4**), levulinic acid (**5**) and 1,6-anhydroglucose (**7**). The competitive nature of the reactions is well recognised and pathways for the conversion of **3** and **6** to various products have been described.[11] Processes involving interconversions of **3**, **4**, **5**, **6** and **7** as presented in Scheme 2 are now considered.



Scheme 2 Pathways for thermal degradation of fructose (**3**) and glucose (**6**) adapted from ref. 11.

Asghari and Yoshida explored the hydrolysis of fructose (**3**) to 5-HMF and subsequent degradation of 5-HMF to levulinic acid (**5**) and formic acid.[12] They employed dilute aqueous HCl at 210 °C, 240 °C and 270 °C under flow conditions and produced kinetic models. The time required for 99% decomposition of **3** decreased from 40 s at 210 °C to 10 s at 270 °C. Optimal conversion of **3** to **4** peaked between 25 s and 5 s depending on the temperature, with 210 °C affording the poorest result ($<30\%$ yield) in the longest time (25 s). The highest yield, about 70%, was obtained at 240 °C within 10 s. Such reaction temperatures lie within the operating range of modern microwave reactors, although it appears unlikely that they could be controllably attained in seconds with currently available systems. The results highlight the dramatic differences in selectivities and yields that can be obtained through what might otherwise be regarded as relatively small changes in time and temperature. Conversion of 5-HMF to levulinic acid (**5**) was explored under the same conditions as well.[12] After 150 s, degradation of 5-HMF was 50%, 80% and 100% at 210 °C, 240 °C and 270 °C respectively, with the corresponding yields of acid **5** being 28%, 38% and 42%. Consistent with those for the conversion of **1** to **2**, these results also reveal that optimal conditions to all products employed the highest temperatures and shortest times investigated.

The degradation of **3** to **4** was studied at temperatures of 180–220 °C and times of up to 100 min by Li and co-workers.[13] The rate of degradation of aldehyde **4** was significantly slower than that of formation, enabling reaction times of tens of minutes to be employed. As the product was not particularly labile in the absence of acid catalyst, the yields were comparable (about 50%) at all temperatures investigated. Addition of acetic or formic acid rendered **4** a little more reactive and afforded plots with salient features comparable with those discussed above and with those shown in Fig. 1. Higher yields of about 60% were obtained in an appreciably shorter reaction time across a range of temperatures.

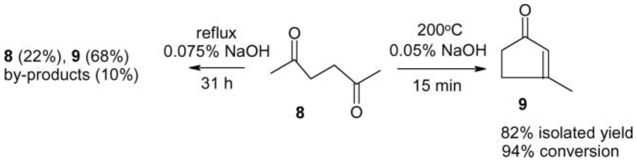
Jing and Lu studied the kinetics of decomposition of glucose (**6**) to **4** in water from 180–220 °C.[14] Here also, plots of the conversion of **6** and the formation and degradation of **4** displayed similar features and trends to those in Fig. 1 and 2 and discussed above, for the conversions of **1** to **2** and for **3** to **4** and **5**. At 180 °C, the conversion of glucose (**6**) was only 35% after 3 h, but at 220 °C it was 96% in half the time. The yield of **4** peaked at 32% at 220 °C after 30 min, but at all lower temperatures, regardless of the reaction time a comparably high return was unattainable.

At temperatures up to 400 °C, half-lives of the products from aqueous reactions of carbohydrates can be a matter of seconds. In such cases, processes have been performed under flow conditions with commensurately short space times. Thermal profiles were recently reported for the conversion of glucose (**6**) to 1,6-anhydro-β-D-glucose (**7**) in water at nine different temperatures between 200 °C and 400 °C.[15] The data also revealed trends that were consistent with those discussed above and with those depicted in Fig. 1. The highest concentration of product **7** (5.5 mmol L^{-1}) was obtained at the highest temperature within the shortest space time (about 0.25 s). The plot for concentration of product *versus* time also appeared to show the sharpest peak. At 250 °C, the maximum yield was only 4.2 mmol L^{-1}, about 23% less than that afforded at 400 °C. The space time was about 5 s (about 20 times longer).[15]

Finally, wheat straw was treated for various times with dilute aqueous sulfuric acid (1%, 3% or 5%) as catalyst, at temperatures of 190, 210 and 230 °C.[16] Its major potentially reactive components were cellulose (40%), hemicellulose (26%) and lignin (22%). The kinetics of the main intermediates, including "sugar" (*i.e.* monosaccharides) and 5-HMF were determined. Consistent with all of the plots discussed above and with those in Fig. 1, the highest concentration of recovered sugar (nearly 20 g L^{-1}) was obtained with the highest acid strength (5% H_2SO_4) in the shortest time (about 1 min) and at the highest temperature (230 °C). At all lower temperatures, regardless of the heating time the concentrations of sugar produced were lower. The gradients for formation and degradation were more equal though of opposite sense at the highest temperature investigated. Degradation of sugar became relatively slower than formation as the temperature decreased. Thus at lower temperatures the next kinetic product, **8** was contaminated by unreacted starting polysaccharides and unreacted sugar.

The above examples reinforce that for thermal reactions, to obtain clean products in short times and in high yields, a sound strategy involves rapid heating to high temperature followed by rapid cooling. The protocols facilitated high selectivity as well as respectable yields considering the complexity of the equilibria involved. For example, in dilute aqueous HCl at 240 °C, fructose (**3**) was converted to 5-HMF in 70% yield after 10 s.[12] After 300 s, the DMF had disappeared entirely, the products being levulinic acid (**5**) and formic acid.

Capabilities for rapid heating and cooling were regarded as essential features for the first dedicated microwave reactors constructed.[17] Examples of reactions performed with them include the intramolecular Claisen-Schmidt condensation of 2,5-hexanedione (**8**) to afford 3-methylcyclopent-2-enone (**9**) in dilute aqueous base (Scheme 3).[18] Rapid heating to 200 °C in 0.05% base and holding that temperature for 15 min afforded the desired product in 94% conversion and 82% isolated yield. The process was readily and comparably scalable under both microwave and conventional heating. At reflux in stronger base however, after 31 h the conversion to product was only 68%. Significant decomposition had occurred and yet 22% of the starting material remained. No matter how long or short the reaction time, under those conditions the desired product could



Scheme 3 Intramolecular cyclisation of hexanedione **8** to methylcyclopentenone **9**.[18]

never have been obtained in high yield owing to extensive contamination from the starting material and/or by-products.

Highly selective transformations of allylphenyl ether and its degradation products in water,[9] the isoaromatisation of carvone to carvacrol *via* the kinetic intermediate 8-hydroxy-*p*-6-menthen-2-one[19] and the isolation of methyl-*O*-glucofuranoside isomers as kinetic products from Fischer-Helferich glycosidation of glucose (**6**) with MeOH[20] all required rapid heating to an optimal temperature followed by quenching.

Several of the above examples have features in common. Many of the starting materials were relatively stable and vigorous conditions were required to activate them. They degraded by competitive processes to afford intermediates and products that also were labile under the conditions. At relatively low temperatures, the rates of formation and subsequent degradation of desired products were often comparable. Consequently, relatively low yields and complex mixtures tended to result, regardless of the reaction time. At higher temperatures, the rates of both formation and decomposition of the products increased.

Significantly, the highest temperature regularly afforded the highest yield of product, in the shortest time and often fleetingly. When the product could be isolated after the optimal time, the yield was the highest possible under the conditions regardless of the nature and concentrations of other components in the mixture. Because the concentration of contaminants was often significantly lower than that of the product, the reaction was clean as well as fast. The data demonstrate that in competitive thermal reactions such circumstances tend not to exist when heating is conducted at an appreciably lower rate and temperature. Collectively and individually they establish the critical role of rapid, precise heating as a tool for producing high yields of product in short times, depending of course, on the kinetics of the individual reactions and the thermal stability of the product under the conditions. In many cases, to avoid over-reaction it may be necessary to complement rapid heating with rapid post-reaction cooling.

Obviously, the challenge of meeting these preconditions does not lie exclusively within the realm of microwave heating. Presently available generic microwave equipment though, is more readily suited to that task than is conventional heating.[8] Resistance-heated autoclaves typically comprise thick-walled metal vessels, electrically heated by insulated bands or elements attached to the external walls. Response time is slow: heating to high temperatures and subsequent cooling usually require much longer times than they do with microwave systems where such operations may be completed within a few minutes.[9] With temperature gradients difficult to avoid, pyrolytic degradation of components on or near the inner walls is common.

In contrast, vessels for microwave chemistry are made from microwave-transparent insulating materials.[2,8] Direct bulk heating, combined with efficient mechanical stirring or mixing of the sample helps to minimise temperature gradients. The energy can be absorbed directly by the reaction mixture instead of the container. Thus, the response time will be short and the vessel usually no hotter than its contents, considerably reducing pyrolytic wall effects.

Rapid heating and cooling have also been applied to chemistry in micro-structured reactors, a field that has grown significantly over the past decade or so.[21] Such devices, which include micro-reactors, micro-mixers, and micro-heat exchangers, enable improved mixing and heat transfer, which in turn can allow higher yields and selectivities. Low overall energy costs and low hold-up of potentially dangerous intermediates increase their attractiveness for a variety of process chemistries.

Conclusion

Observations that microwave reactions proceed more quickly, cleanly and in higher yields than their conventionally heated counterparts have a rational as well as an empirical basis. Perusal of literature examples involving competitive thermal processes indicated that in nearly all cases, rapid heating often to the highest temperature investigated gave the highest yield of product in the shortest time. When the product was isolated after the optimal time, the yield was the highest attainable under the conditions and as a result, the process was the cleanest attainable.

Owing to lower thermal inertia and faster response, microwave systems are more readily suited to performing such tasks than are conventionally heated oil baths, heating mantles or autoclaves. Notwithstanding that, in many cases rapidly heated reactions proceed more cleanly, in higher yields and shorter times than their more slowly heated counterparts irrespective of the heating method. This work also demonstrates that application of the 6th principle of green chemistry *i.e.* that "synthetic methods should be conducted at ambient temperature and pressure"[22] will not always provide an optimal result. Conversely, we suggest a new rule of thumb stating that *thermal reactions proceed optimally when they are rapidly heated to the highest tolerable temperature, held there for the shortest possible time and then quenched.*

Although this discussion has focussed upon organic reactions, the interpretation appears to be relevant to some other thermal processes involving organometallics, inorganic compounds and materials such as ceramics and polymers. Our studies into the comparison of microwave and conventional heating are ongoing and reports involving the use of computer simulations in that regard will appear elsewhere.

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