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The Newman−Kwart Rearrangement: A Microwave Kinetic Study

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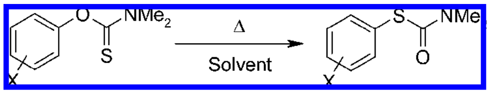
Received December 11, 2007



The kinetic profile of the Newman−Kwart rearrangement has been evaluated using microwave heating. After first demonstrating equivalence between conventional convective heating and microwave heating, data was gathered and analyzed to determine the effects of substituent, solvent, and concentration on the reaction order. Reaction rate constants, Arrhenius constants, and activation energies have been determined. The reaction rate shows strong sensitivity to the substituent and modest sensitivity to the solvent. At high concentrations, the reaction order increases from the previously reported first-order to a mixed first/second-order reaction. Overall, this re-evaluation of the Newman−Kwart rearrangement has shown the reaction rate order to be more complex than previously thought. In addition, microwave heating has proven ideal for the rapid collection of data to facilitate this type of kinetic study.

Introduction

Microwave-assisted organic synthesis (MAOS) was first reported in 1986 and has grown exponentially since then, as demonstrated by the number of recent reviews[1] and books[2] on the subject. MAOS is now widely used within pharmaceutical research departments since the features of small scale, fast reaction time, and ready automation marry well with combinatorial and library synthesis techniques, which has provided a step change in drug discovery programmes.[2a] Furthermore, in addition to its now well-established use in post-graduate research laboratories, microwave heating is a potential boon in undergraduate teaching laboratories where automation and fast reaction times can allow students to progress reactions to useful outcomes within the time constraints of laboratory teaching sessions.[3] The other advantages of microwave heating such as instantaneous volumetric heating, lack of wall heating effects, improved purity profile, reduced catalyst loading requirements, and possible energy savings have been presented previously elsewhere.[1,2]

Early in our own investigations on microwave heating, we realized that rapid heating and the consequent increased reaction rates made microwave heating potentially ideal for kinetic studies. As Strauss has pointed out, multiple data points are needed for reliable kinetic studies, whether they be derived from conventional or microwave heating.[4] Microwave heating can provide this data very quickly, and, in addition, can readily access temperatures above the solvent bp under autoclave conditions to provide a wider operating envelope for kinetic analysis. However, in order to validate the microwave kinetic studies, it was important to establish that conventional and microwave heating were equivalent.

Results and Discussion

Because of the ongoing debate over nonthermal microwave effects,[5] we decided to concentrate our studies on a completely reliable reaction for which there were no claims of any

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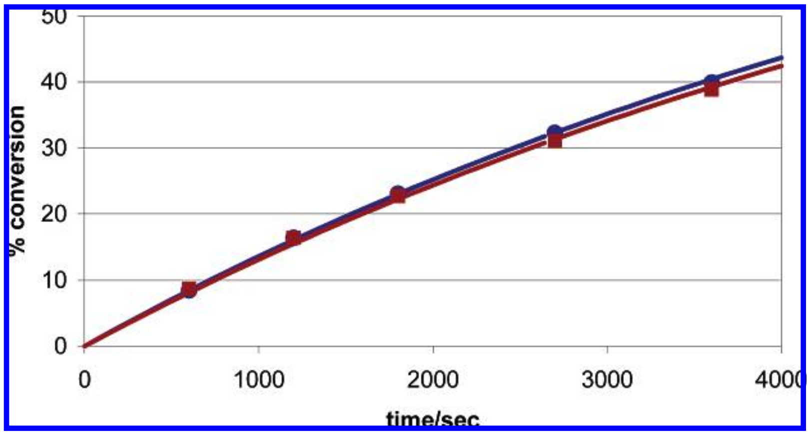
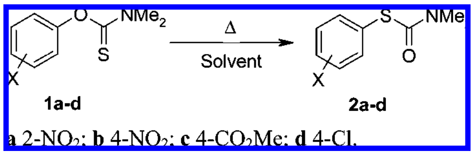


FIGURE 1. Comparison of extent of reaction with time for conventional (red) and microwave (blue) heating in the rearrangement of **1a** (0.25 M) in NMP at 140 °C.

SCHEME 1



a 2-NO_2; **b** 4-NO_2; **c** 4-CO_2Me; **d** 4-Cl.

microwave effect, and which was reliable under a wide range of known parameters (temperature, pressure, solvent, etc.). We have already reported our findings on re-evaluating the Newman−Kwart rearrangement (NKR)[6] under both microwave and conventional thermal heating, and have shown that there is no difference between the two under easily achieved and well-controlled conditions.[7] The NKR has previously been shown to be a first-order, unimolecular rearrangement converting an *O*- to *S*-thiocarbamate (Scheme 1; **1** to **2**).[8] The rate of reaction is also well-known to be strongly dependent on the aromatic substituent,[6a,8,9] and we have more recently shown a modest solvent effect also.[7,10]

It is important to note that the reaction mixture must be a well-stirred homogeneous solution to avoid the potential problem of localized superheating due to inefficient agitation.[10] It is equally important to measure the temperature that accurately reflects the contents of the reaction vessel. Although others have rightly pointed out the potential concerns with relying on the use of external IR pyrometers,[11] compared to the more reliable fiber optic probes or shielded thermocouples inserted in the reaction mixture for example, we have found external IR pyrometers to be reliable for this reaction when regularly calibrated and in the hands of a competent user.[7]

TABLE 1. Rate Constants (140 °C) and Activation Parameters for 1a in DCB at 0.25 M

heating method	k/s^{-1} at 140 °C	A/s^{-1}	E_a/(kJ mol^{-1})
microwave	1.35×10^{-4}	5.1×10^{10}	116.2
thermal	1.13×10^{-4}	7.8×10^{10}	118.7

Comparison Between Conventional Thermal and Microwave Temperature Control/Heating. Although we were confident that the NKR gave equivalent reaction rates under both conventional and microwave heating in general synthetic applications,[7] we decided to establish a higher level of accuracy before beginning this study. Therefore, experiments were performed to confirm that reactions carried out under microwave heating showed similar kinetic behavior to those carried out under conventional convective heating (i.e., in a thermostatically controlled silicon oil heating bath). The initial comparison was performed on identical scale in microwave reaction tubes with stirring bars. The oil bath reaction tube was sampled at multiple time points, while each microwave data point was taken from a single reaction tube. This avoids a possible cumulative error in the microwave case for heating up the microwave tubes, since they must be cooled each time before sampling (although control studies show these effects to be negligible for reaction times of >10 min, even at low conversions). Figure 1 shows the comparison for the reaction of 2-nitrophenyl-*O*-thiocarbamate (**1a**) at 0.25 M in NMP at 140 °C under conventional and microwave heating. The solid lines are best-fit lines and show that the rate constants for the reactions agree within 4%.

Reaction of the 2-nitro substrate **1a** in dichlorobenzene (DCB) over the temperature range of 120−180 °C at the same concentration showed very similar rates and activation parameters using the two methods of heating (Table 1).

The difference in rate constants at 140 °C corresponds to an effective temperature for microwave control of 3.5 °C above that for thermal control. In other cases, apparent small increases in effective temperature of between 2 °C and 4 °C at around 150 °C were observed for reactions in which microwave heating was used to achieve and control reaction temperature; the effects were smaller at higher temperatures. This difference, if real, suggests a small extent of superheating associated with the microwaves, depending upon the efficiency of the reaction stirring, or possibly a slight systematic error in the temperature measurement.

Finally, we further tested this point by studying the rearrangement of **1a** at a fixed bulk temperature (140 °C) using

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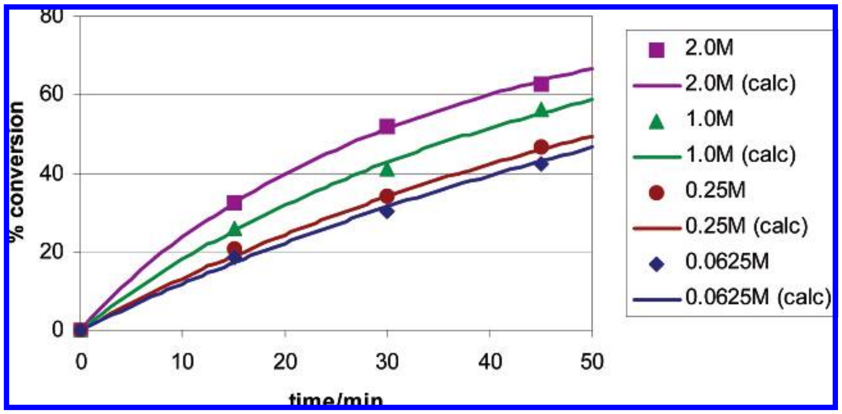

FIGURE 2. Rearrangement of 2-nitrophenyl-*O*-thiocarbonate (**1a**) in DCB at 150 °C. Experimental data are represented by the points, and the solid lines represent values calculated using the rate constants (eq 1): $k_1 = 2.02 \times 10^{-4}$ s^{-1}; $k_2 = 1.42 \times 10^{-4}$ M^{-1} s^{-1}.

TABLE 2. Comparison of Thermal and Microwave Reactions at Different Microwave Powers for 1a in Xylene at Solvent Reflux[a] **under Open Vessel Conditions**

heating method/ (microwave power supplied)	k/s^{-1}	temperature/°C
oil bath (0 W)	4.02×10^{-5}	140[b]
microwave (~25 W)	3.95×10^{-5}	138−142[c]
microwave (100 W)	7.9×10^{-5}	154−159[c]
microwave (300 W)	8.1×10^{-5}	160−165[c]

[a] Conversion of **1a** to **2a** at 140 °C and 0.44 M in *o*-xylene (bp 138−139 °C). [b] Measured by calibrated thermocouple. [c] Measured by calibrated IR pyrometer.

refluxing *m*-xylene as the solvent (bp 138−139 °C) at a concentration of 0.44 M. The microwave reactor can be used in open vessel mode with a conventional round-bottomed flask heated to the solvent's bp. The microwave supplies high power initially to achieve the set point temperature (140 °C) but then provides only enough power to maintain this temperature (typically ~25 W for a 10 mL sample in this case). Working with a larger sample (10 mL vs 2 mL) and at the solvent bp, where the latent heat of evaporation tends to stabilize the bulk temperature at the desired set point, made this experiment more robust. In addition, because it is in an open vessel, the microwave reaction vessel could be sampled while being heated, which required only one reaction mixture to be prepared and heated to temperature. The conventional convective heating reaction mixture was run under identical conditions of concentration, scale, vessel, etc. to achieve a similar level of reflux. Once data had been collected at normal reflux in the microwave case (using ~25 W), the power was increased to a fixed 100 W setting so that the reactor was now heated under power control, not temperature control. Further data points were taken, and then the power was ramped up to the maximum 300 W available. However, it was noticeable that, under both these sets of conditions, the IR pyrometer gradually recorded an increase in temperature, eventually up to 165 °C, indicating significant superheating of the solvent.[11,12] The apparent first-order rate constants under these conditions are shown in Table 2.

The results, while confirming the equivalence of the two heating methods at low power, show clear evidence of superheating at high microwave power, but there is no evidence of any fundamental difference between the reactions carried out under conventional thermal and microwave heating (~25 W) under temperature control. Once superheating has been achieved by high microwave power, the increase from 100 to 300 W makes no significant difference; more power cannot be forced into a system that is already superheated, even though the temperature probe gradually indicates a higher temperature.[12] For all systems, the same trends were observed, independent of the method of heating. For the remainder of this work, quantitative analysis refers to microwave reactions run under temperature control for which more comprehensive results were obtained.

Reaction Kinetics. Reactions were investigated at substrate concentrations varying from 0.0625 to 4 M. Initial data treatment was based on purely first-order kinetics, but, in all cases, there was a regular increase in apparent first-order rate constant as the concentration increased over this range. The effects were particularly significant at concentrations of 1 M and above, with the apparent rate constants being typically a factor of 2 higher at a reaction concentration of 2 M compared with low concentrations (0.25 M and below). It was also observed that, within individual reactions at higher concentrations, there were small but systematic deviations from exact first-order kinetics, with the apparent rate constant decreasing with increasing extent of reaction.

It was thought possible that these effects are due to a change in reaction medium as the substrate concentration is increased, but this was not consistent with the relative insensitivity of the reaction to solvent (see below). Furthermore, the systematic deviations from first-order kinetics are difficult to reconcile with a medium effect. The data were therefore analyzed as a mixture of first and second-order kinetics, according to eq 1 for substrate S:

$$-\mathrm{d}[\mathrm{S}]/\mathrm{d}t = k_1[\mathrm{S}] + k_2[\mathrm{S}]^2 \qquad (1)$$

A typical result is shown in Figure 2 for the rearrangement of **1a** to **2a** in DCB at 150 °C. The results show an excellent quantitative fit to eq 1, with the calculated curves corresponding to

$$k_1 = 2.02 \times 10^{-4}\ \mathrm{s}^{-1};\ k_2 = 1.42 \times 10^{-4}\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$$

Similar behavior was found for all substrates, solvents, and temperatures, irrespective to the form of heating (microwave or thermal), and it was typically observed that

$$k_1/k_2 \approx 2\ \mathrm{M} \qquad (2)$$

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TABLE 3. Rate Constants for the Rearrangement of Aryl-*O*-thiocarbamates 1a−d in DCB at 140 °C

aryl substituent (X)	k_1 (s^{-1})[a]	k_1(X)/k_1(2-NO$_2$)
2-NO$_2$	9.6×10^{-5}	1
4-NO$_2$	5.7×10^{-5}	0.59
4-CO$_2$Me[b]	1.0×10^{-6}	0.010
4-Cl[c]	3.4×10^{-8}	0.00035

[a] Equation 1. [b] Extrapolated from measurements at 210−250 °C, using $k_1 = 9.54 \times 10^9 \exp(-126300/RT)$ s^{-1}. [c] Extrapolated from measurements at 210−250 °C using $k_1 = 1.19 \times 10^{10} \exp(-138800/RT)$ s^{-1}.

TABLE 4. Rearrangement of 2-Nitrophenyl-*O*-thiocarbamate (1a) at 140 °C in Solvents

solvent	$10^4\ k_1$/s^{-1} (eq 1)	A/s^{-1}[a]	E_a/(kJ mol^{-1})[a]
DCB	0.96	4.7×10^{10}	116.2
DMA	1.04	4.4×10^{10}	115.7
NMP	1.26	n/d	n/d
o-xylene	0.40	n/d	n/d

[a] Arrhenius parameters from $k_1 = Ae^{-E_a/RT}$; n/d = not determined; DCB = 1,2-dichlorobenzene; DMA = *N,N*-dimethylacetamide; NMP = *N*-methyl-2-pyrrolidinone.

TABLE 5. Activation Parameters for the Rearrangement of Aryl-*O*-thiocarbamates

system/solvent	$\Delta H_1^‡$/ J mol^{-1} [a]	$\Delta S_1^‡$/ J K^{-1} mol^{-1} [a]	$\Delta H_2^‡$/ kJ mol^{-1} [b]	$\Delta S_2^‡$/ J K^{-1} mol^{-1} [b]
2-NO$_2$/DCB	115.9 ± 1.6	−44.7 ± 3.9	100.8 ± 3.0	−83.7 ± 8.0
2-NO$_2$/DMA	111.8 ± 1.6	−51.4 ± 4.0	104.2 ± 3.0	−76.3 ± 7.0
4-NO$_2$/DMA	120.9 ± 1.8	−41.2 ± 3.9	100.8 ± 3.0	−96 ± 9
4-CO$_2$Me/DCB	122.2 ± 1.8	−66.5 ± 5.0		
4-Cl/DCB	134.6 ± 2.0	−64.7 ± 5.0	131.3 ± 4.0	−77.3 ± 8.0

[a] First-order process. [b] Second-order process.

It follows that, at substrate concentrations of around 0.2 M and below, the first-order process dominates, with the second-order process contributing <10% to the initial rate and a decreasing proportion as the reaction proceeds. At these concentrations, the difference between k_1, determined via eq 1, and via a simple first-order rate law (neglecting any second-order contribution) is within experimental error (±5%). At reaction concentrations of 2 M, however, approximately 50% of the initial rate is due to the second-order process.

Substituent Effects on Reaction Rates. Rate constants were measured in DCB at 140 °C for several *O*-aryl thiocarbamates with differing electron-withdrawing aryl-substituents, and the first-order rate constants, k_1 (eq 1), are listed in Table 3. The results agree with those from earlier studies, which show a strong substituent effect on the reaction.[6a,8,9]

Solvent Effects on Reaction Rates. The reaction rates were found to show little sensitivity to solvent in the (aprotic) solvents investigated. Table 4 shows rate constants, k_1, obtained for the first-order rearrangement of 2-nitrophenyl-*O*-thiocarbamate (**1a**) at 140 °C in various solvents. Only in the very low-polarity solvent *o*-xylene was there a noticeable decrease in reaction rate constants relative to those observed for solvents varying from dichlorobenzene to the very highly polar solvents *N,N′*-dimethylacetamide (DMA) and *N*-methyl 2-pyrrolidinone (NMP). Earlier studies have also shown relatively little variation among aprotic solvents of moderate to high polarity, but a significant rate increase when the reactions are carried out in formic acid as solvent.[7]

Activation Parameters. Enthalpies ($\Delta H^‡$) and entropies ($\Delta S^‡$) of activation for several systems were determined using eqs 3 and 4:

$$k = (k_B T/h) \exp(\Delta S^‡ R) \exp(-\Delta H^‡ RT) \qquad (3)$$

or

$$\ln k/T = \ln(k_B/h) + \Delta S^‡ R - \Delta H^‡ RT \qquad (4)$$

Figure 3 shows k_1 values for 2-nitrophenyl-*O*-thiocarbamate (**1a**) in DCB over the temperature range of 120−170 °C plotted according to eq 4.

Results for the various systems are listed in Table 5.

The entropies of activation of the bimolecular process are strongly negative and are comparable to typical values observed for the coming together of two molecules to form the transition state, namely, −50 to −160 J K^{-1} mol^{-1} in the gas phase and frequently somewhat smaller in solution.[13] The activation enthalpies are also generally lower than those of the corresponding first-order process.

The first-order reactions also show quite strongly negative entropies of activation, reflecting the loss in conformational freedom resulting from the formation of the proposed four-membered transition state (Figure 4). Earlier work suggested that entropy losses upon forming the transition state are lower

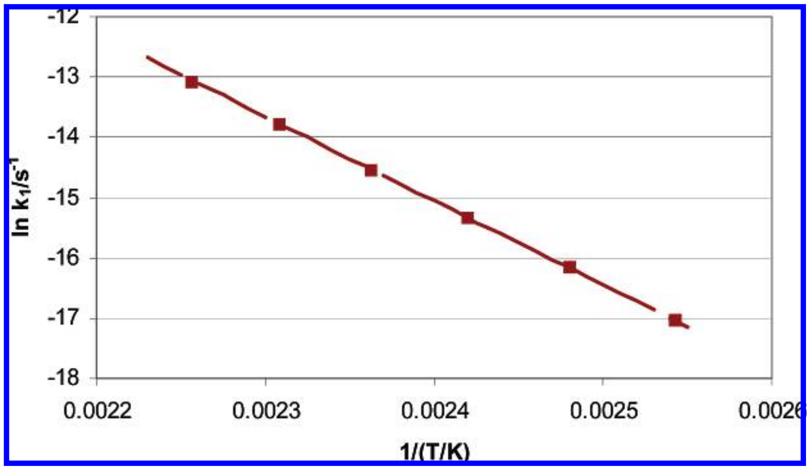

FIGURE 3. Activation plot (eq 4) 2-nitrophenyl-*O*-thiocarbamate (**1a**) in DCB. Points correspond to experimental values; solid line calculated according to eq 4 with $\Delta H^‡$= 115.9 kJ mol^{-1}, $\Delta S^‡$= −44.7 J K^{-1} mol^{-1}.

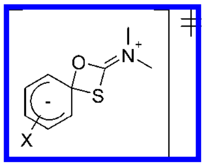

FIGURE 4. Proposed four-center transition state.

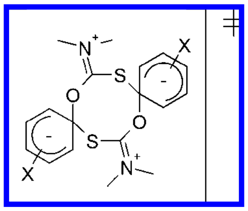

FIGURE 5. Possible bimolecular transition state structure.

in systems with sterically bulky substituents in the 2-position, because of hindered motion in the ground state,[9] but this does not appear to be a significant factor for the substrates investigated here.

A recent computational study concluded that the unimolecular rearrangement is reasonable (concentration would not be considered in gas-phase calculations) and proceeds in synchronous fashion through the four-membered cyclic transition state proposed (Figure 4) not involving an intermediate.[14] Given the conclusions of this computational study, one might propose that the bimolecular reaction could proceed through a synchronous mechanism via an analogous eight-membered transition state as postulated in Figure 5. This might be expected to exhibit a lower strain energy, but the entropy losses associated with the bringing together of two reactant molecules would mean that this process would be relatively disfavored at lower concentrations. As noted above, quite high concentrations (~2 M) are required before the second-order process makes a similar contribution to the overall reaction rate to that of the first-order process.

Conclusions

In summary, we have reported a microwave-facilitated kinetic study of the Newman−Kwart rearrangement. This has confirmed that the aromatic substituent has the greatest effect on the reaction rate, with somewhat smaller variations arising from change in solvent. The reaction rate (percentage conversion at a given time) has been shown to increase steadily with increasing reactant concentration. Quantitative analysis of the data over a range of reactions and concentrations strongly suggests that this is due to a change in reaction order at higher (>1 M) concentrations. Overall, the reaction order of the Newman−Kwart rearrangement is more complex than previously thought, especially at the high concentrations typically used in preparative and synthetic procedures. Finally, microwave heating has proven to be an ideal method for the rapid acquisition of data for a kinetic study of this kind.

Experimental Section

For each series of experiments, homogeneous solutions of the appropriate aryl-*O*-thiocarbamate **1a−d** were made up at the required concentrations (0.0625−4.0 M) in the appropriate solvent (NMP, DMA, DCB, or *o*-xylene). Equal volumes (typically 2.0 mL) were heated with stirring in thick-walled glass sealed tubes in a CEM Discover monomode 300 W microwave reactor with IR temperature monitoring and noninvasive pressure transducer. The heating time to reach the set temperature was typically 30−90 s, depending on the scale, the maximum wattage supplied (100−300 W), and the temperature required (100−250 °C). The heating time is not included in the quoted hold time for any given procedure, but control studies show that the heating time has a negligible effect on overall conversion.

Conventional (oil bath) and microwave open vessel experiments were performed at the same bulk temperature in *o*-xylene at reflux (~140 °C) and sampled at regular time points (typically every 10 min). Open vessel reflux in the microwave reactor required ~25 W to maintain a 10 mL sample once at 140 °C. Later microwave experiments were performed under fixed wattage control (100 or 300 W), whereupon the IR pyrometer gradually registered higher temperatures (as the microwave reactor retained more heat), while the bulk sample was notionally still at reflux.

Conversions were determined by HPLC analysis of diluted samples and are corrected for relative response factors (RRFs). The aryl-*S*-thiocarbamate products (**2a−d**) had been isolated previously to provide reference markers for the HPLC method and RRF values.[7]

Supporting Information Available: HPLC method; general experimental conditions; preparation and data on aryl-*O*-thiocarbamates **1a−d**; physical and spectroscopic data on aryl-*S*-thiocarbamates **2a−d**; general notes on the use of microwave reactors in obtaining kinetic data points; primary kinetic data for activation parameters (Tables S1−S5); additional references for Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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