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# The Molecularity of the Newman−Kwart Rearrangement

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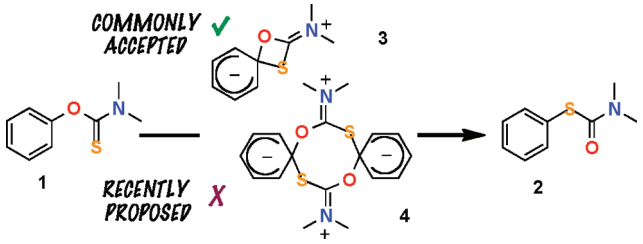


It was recently reported that the venerable Newman−Kwart rearrangement (**1**→**2**) proceeds via mixed first- and second-order kinetics. Prior to this, the rearrangement had been considered to proceed exclusively via an *intramolecular* $O_{Ar}$→$S_{Ar}$ migration. A new bimolecular pathway, possibly involving an 8-membered cyclic transition state, was proposed to account for reaction rates that increased disproportionately with substrate concentration under microwave heating conditions. We report a reanalysis of the kinetics and molecularity of the rearrangement of *N*,*N*-dimethyl *O*-(*p*-nitrophenyl)thiocarbamate **1a** in *N*,*N*-dimethylacetamide solvent. Using HPLC, isotopic labeling ($^{2}$H, $^{18}$O, $^{34}$S), and ESI-ICRMS methods, we show that there is no evidence for a bimolecular pathway en route to **2a**, with near-perfect exponential decay in **1a** at concentrations ranging from 0.11 to 4.70 M. Instead, it is demonstrated that under the microwave heating conditions, a delayed negative feedback signal to the microwave power balancing loop results in oscillatory reaction overheating. Due to higher tan $\delta$ in the solute, the amplitude of this oscillation increases with the concentration of **1a**, and this phenomenon best accounts for the kinetic behavior previously misinterpreted as being mixed first- and second-order in nature.

## Introduction

The thermally induced rearrangement of *O*-arylthiocarbamates (**1**) was discovered in the 1960s[1] and is commonly referred to as the Newman−Kwart rearrangement[2] (NKR). The ready preparation of *N*,*N*-dimethyl *O*-arylthiocarbamates from the corresponding phenol,[3] and the facile cleavage of the *S*-arylthiocarbamate rearrangement products (**2**), has resulted in the NKR becoming one of the prime routes to thiophenols, Scheme 1, with applications as diverse as chiral ligands, agrochemicals, dyestuffs, pharmaceutical intermediates, copper−protein mimics, and precursors to supramolecular assemblies.[4]

In addition to synthetic utility, the mechanism of the NKR has also attracted considerable attention.[4] Soon after its discovery,[1] independent investigation by Relles et al.[5] and by Miyazaki[6] led to the proposal of unimolecular rearrangement ($k_1$) proceeding via a four-membered 1,3-oxathietane transition state (**3**, Figure 1); this is fully consistent with extensive kinetic data and a series of linear free energy relationship analyses.[5,6] Well over three decades later, high-level DFT studies[7] fully supported the proposed mechanism and

(1) (a) Edwards, J. D.; Pianka, M. *J. Chem. Soc.* **1965**, 7338. (b) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410. (c) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980.

(2) Zonta et al. (ref 4a) have suggested that the process be referred to as the Newman−Kwart−Miyazaki rearrangement to reflect the extensive mechanistic work conducted by Miyazaki (ref 6).

(3) Ponaras, A. A.; Zaim, O. Dimethylthiocarboamyl Chloride. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; John Wiley: New York, 1995; p 2174.

(4) Reviews on the NKR: (a) Zonta, C.; Lucchi, O. D.; Volpicelli, R. *Top. Curr. Chem.* **2007**, *275*, 131. (b) Lloyd-Jones, G. C.; Moseley, J. D.; Renny, J. S. *Synthesis* **2008**, 661.

(5) Relles, H. M.; Pizzolato, G. *J. Org. Chem.* **1968**, *33*, 2249.

(6) (a) Miyazaki, K. *Tetrahedron Lett.* **1968**, *23*, 2793. (b) Kaji, A.; Araki, Y.; Miyazaki, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1393.

(7) (a) Albrow, V.; Biswas, K.; Crane, A.; Chaplin, N.; Easun, T.; Gladiali, S.; Lygo, B.; Woodward, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2813. (b) Jacobsen, H.; Donahue, J. P. *Can. J. Chem.* **2006**, *84*, 1567.

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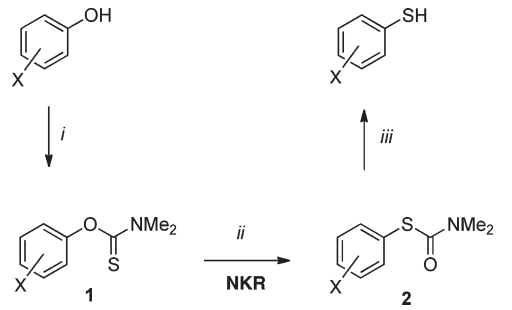
**SCHEME 1. NKR Route for the Preparation of Thiophenols from Phenols**[a]




[a]Reagents and conditions: (i) DABCO or NaH, $ClC(S)NMe_2$; NMP or DMF; (ii) NKR, $\Delta = 200-300$ °C; (iii) NaOH (aq) or KOMe, $\Delta$; or $LiAlH_4$; or Na, $NH_3$.

confirmed 1,3-oxathietane **3** as a transition state rather than an intermediate.

Thermal NKR typically requires[4] temperatures of 200−300 °C to facilitate access to the high energy 1,3-oxathietane transition state **3**. This means that fragile substrates, e.g. those that decompose, racemize, or undergo other undesired reactions at these temperatures, cannot readily be used for NKR.[4] A recently developed Pd-catalyzed NKR offers a partial solution to this problem, allowing rearrangement at 100 °C; however, substrate scope for this process is currently limited.[8]

Even for substrates and products that are nominally stable at the temperatures required for the thermal NKR, the temperature gradient induced by the external heating source (oil bath, mantle etc.) can result in extensive "charring" on the inner surface of the reaction vessel.[9] Short exposure to much higher temperatures (400−700 °C) can provide a highly effective solution to these problems but requires specialized equipment.[10] However, the most readily applicable method for inducing efficient NKR is the microwave heating approach, first reported by Villemin in 1996 for reactions conducted on a graphite support[11] and then extensively developed by Moseley and co-workers in 2006 for solution-phase reactions.[12]

In 2008, Gilday et al. published a study on the kinetics of the NKR under microwave heating,[13] the principal aim of which was to demonstrate the utility of the method for the rapid generation of kinetic data from single time point experiments. For control experiments employing 0.44 M solutions in xylene, it was found that identical rates were obtained under conventional convective heating as compared to microwave heating; a large data set was then gathered under microwave heating conditions and analyzed to determine the effects of substituent, solvent, and concentration on the reaction order.[13] In accord with previous studies,[5,6] a strong dependence of reaction rate on the nature of aryl ring substituent was observed, with only a modest effect of solvent.[12b,c,e] However, *in contrast to all prior studies* on NKR,[4−6] it was reported that as the initial concentration of **1** was raised, disproportionately higher rates of rearrangement occurred. The kinetics were analyzed by application of a mixed first-order/second-order model ($k_1$ and $k_2$, Figure 1), with a cyclic 8-membered transition state (**4**) tentatively suggested for the second-order process ($k_2$). The second-order process was proposed to be kinetically significant above concentrations of ca. 2.0 M, and it is pertinent to note that all previous studies on the kinetics of the solution-phase NKR were conducted on relatively dilute solutions of **1** (0.05−0.3 M).[1c,5]

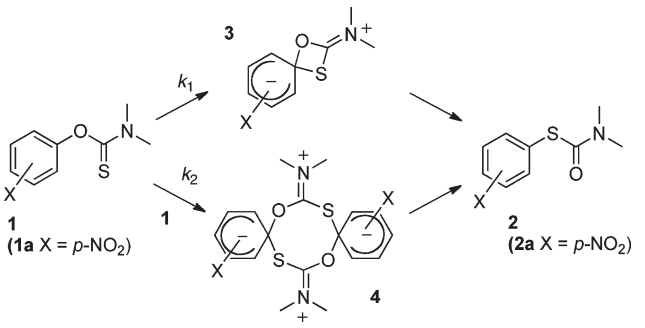



**FIGURE 1.** Unimolecular ($k_1$; via **3**[5−7]) and bimolecular mechanisms ($k_2$; via **4**[13]) for NKR.

In light of the fact that the unimolecular nature of the NKR has become so well-accepted that the reaction has been used as a "benchmark" first-order process,[14] we felt that a more detailed search for evidence for a bimolecular pathway is essential. Herein we report on an investigation into the molecularity of the NKR of *N*,*N*-dimethyl *O*-*p*-nitrophenylthiocarbamate **1a** (X = *p*-$NO_2$) in *N*,*N*-dimethylacetamide (DMA) under the reaction conditions for which mixed first-order/second-order rate analyses had been reported.[13]

## Results and Discussion

All of the substrates studied by Gilday et al.[13] were reported to display disproportionately higher rates of rearrangement at higher concentrations; we thus chose to focus on one example in detail. The 4-nitro substrate **1a**, a crystalline solid with well-established procedures for purification, was selected for its relatively low rearrangement temperature, meaning that in addition to microwave heating, conventional heating by immersion in a silicone oil bath at 160 °C could also be conveniently applied; DMA was selected as the solvent.

**Reaction Kinetics: Convective Heating.** The instantaneous partitioning between the proposed first- and second-order processes, Figure 1, is given by $k_1/k_2$[**1a**], this being the

(8) Harvey, J. N.; Jover, J.; Lloyd-Jones, G. C.; Moseley, J. D.; Murray, P. M.; Renny, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7612.

(9) In addition, the negative effect of trace impurities in the substrate on the efficacy of the NKR (see ref 4b for a more detailed discussion) may well arise from catalytic or autocatalytic charring/decomposition processes.

(10) See, for example, the technique of "direct insertion vapor phase flash vacuum pyrolysis" (DIVPFVP): Higgs, T. C.; Carrano, C. J. *Eur. J. Org. Chem.* **2002**, 3632.

(11) Villemin, D.; Hachemi, M.; Lalaoui, M. *Synth. Commun.* **1996**, *26*, 2461.

(12) (a) Moseley, J. D.; Lenden, P.; Lockwood, M.; Ruda, K.; Sherlock, J.-P.; Thomson, A. D.; Gilday, J. P. *Org. Process Res. Dev.* **2008**, *12*, 30. (b) Moseley, J. D.; Lenden, P.; Thomson, A. D.; Gilday, J. P. *Tetrahedron Lett.* **2007**, *48*, 6084. (c) Moseley, J. D.; Lenden, P. *Tetrahedron* **2007**, *63*, 4120. (d) Moseley, J. D.; Lawton, S. J. *Chem. Today* **2007**, *27* (2), 16. (e) Moseley, J. D.; Sankey, R. F.; Tang, O. N.; Gilday, J. P. *Tetrahedron* **2006**, *62*, 4685.

(13) Gilday, J. P.; Lenden, P.; Moseley, J. D.; Cox, B. G. *J. Org. Chem.* **2008**, *73*, 3130.

(14) Obermayer, D.; Gutmann, B.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321.

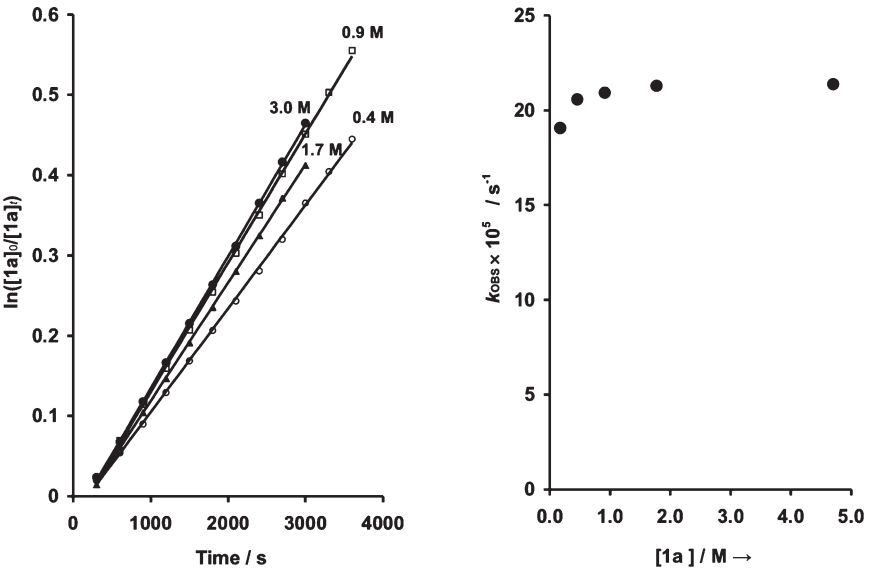



**FIGURE 2.** Left-hand graph: plots of $\ln[\mathbf{1a}]_0/[\mathbf{1a}]_t = k_{obs}t$; for NKR of **1a** at initial concentrations of 0.4, 0.9, 1.7, and 3.0 M; heating by partial immersion in an oil-bath at 160 °C. Right-hand graph: the effect of initial concentration of **1a** on $k_{obs}$ in DMA; heating in sealed capillary tubes in a GC oven at 160 °C.

nominal ratio of **2a** generated via **3a** versus **4a**. Using the rate constants reported by Gilday et al. for the microwave-induced NKR of **1a** in DMA at 160 °C[13] ($k_1 = 16.6 \times 10^{-5}$ s$^{-1}$; $k_2 = 5.41 \times 10^{-5}$ M$^{-1}$ s$^{-1}$), the concentration of **1a** required for equal partitioning is 3.0 M, and a substantial deviation from a simple exponential decay in **1a** should be evident as this concentration is approached. We thus conducted NKR on **1a** at initial concentrations of 0.11, 0.40, 0.90, 1.71, and 3.0 M in DMA, as well as neat (4.70 M) in thick-walled boiling tubes, under a nitrogen atmosphere, using a silicone oil-bath set at 160 °C. Small samples were removed, via a glass capillary, and rapidly cooled, and then the conversion (**1a**→**2a**) was analyzed by HPLC using predetermined response factors. In all cases, analysis according to an integrated second-order rate-law ($1/[\mathbf{1a}]_t - 1/[\mathbf{1a}]_0$ vs $t$) gave plots that displayed distinct upward curvature (see the Supporting Information), whereas very good linear correlations ($R^2 = 0.9960-0.9999$) were obtained by applying a standard integrated first-order rate-law ($\ln [\mathbf{1a}]_0/[\mathbf{1a}]_t = k_{obs}t$), affording an average $k_{obs}$ value of $16.8 \times 10^{-5}$ s$^{-1}$.[15] Although this value corresponds well with the unimolecular rate constant ($k_1 = 16.6 \times 10^{-5}$ s$^{-1}$) reported by Gilday et al.,[13] there was substantial variation between repeated runs.[16]

Using the published thermodynamic parameters for the NKR of **1a**,[13,15] a 2.0 °C change in the reaction temperature is predicted to result in a change in rate of ca. 20%, and we suspected that the temperature control under the oil-bath heating conditions was insufficiently accurate. We thus conducted a series of NKR in parallel, sealing the solutions in capillary tubes and then simultanously heating them in a GC oven that had been precalibrated to 160 °C. This technique ensured homogeneous heating of all the samples, and analysis of the data gave a unimolecular rate constant of $k_{obs} = 20.7(\pm 1.5) \times 10^{-5}$ s$^{-1}$ at initial concentrations of **1a** ranging from 0.173 to 4.70 M, Figure 2. We therefore find no evidence for any *significant* effect of concentration on the rate of NKR of **1a** other than that expected for a standard first-order relationship: $d[\mathbf{1a}]/dt = k_1[\mathbf{1a}]$, possibly augmented by a very small increase in $k_{obs}$ arising from the change in the medium[12b,c,e] from predominantly DMA to exclusively **1a**/**2a**.

**Reaction Kinetics: Microwave Heating.** Having found no evidence for higher molecularity in the NKR of **1a** under convective heating conditions, we then examined whether the situation was different under microwave heating conditions. Using the unimolecular and bimolecular rate constants $k_1$ and $k_2$ published by Gilday et al.,[13] for NKR at 160 °C, the concentration-normalized relative initial rates ($r_{norm}$) for 0.5, 0.8 and 1.5 M samples of **1a** are calculated to be 1.00, 1.09, and 1.28, respectively.[17] In other words, over a standard time interval in the initial phase of reaction, the fractional conversion of **1a** (%) is predicted to be about 9% and 28% higher in 0.8 and 1.5 M samples, respectively, as compared to the 0.5 M sample, by way of the bimolecular process ($k_2$).

When we conducted the NKR of **1a** under the reported microwave conditions,[18] the appearance of plots of fractional

(15) Miyazaki reported a value for $k_1$ at 170 °C of $74.0 \times 10^{-5}$ s$^{-1}$ (ref 6a); Newman conducted rearrangements at 0.0477 and 0.221 M in Carbowax 400 at 180 °C and found no difference in conversion (<10%) by UV analysis (ref 1c). Relles conducted rearrangement of the *o-tert*-butyl analogue of *p*-nitro substrate **1a** at 0.3 and 1.2 M and found no change in $k_1$ (ref 5).

(16) The major cause of this was probably variation in the degree of cooling of the nonsubmerged section of the thick-walled reaction vessel by the air current passing through the fume hood. The cooling caused by this process was constant within a run, as evidenced by the excellent correlation of $(\ln([\mathbf{1a}]_0/[\mathbf{1a}]_t) = k_{obs}t$ but varied between runs due to different positions in the oil bath and different extent of fume hood sash opening, etc. Also of note was that when NKR was conducted on neat samples of **1a** (4.70 M) the volume of fused **1a** was considerably smaller than that of the DMA solutions used for runs at lower concentrations, meaning that the bulk of the reaction mixture was well below the surface of the silicone oil bath, leading to noticeably greater $k_{obs}$ values. See the Supporting Information for further details.

(17) The *initial* rate ratio ($r_i$ / $r_{ii}$) under conditions *i* and *ii* is given by $[\{k_1[\mathbf{1a}^i]_0 + k_2([\mathbf{1a}^i]_0)^2\}/\{k_1[\mathbf{1a}^{ii}]_0 + k_2([\mathbf{1a}^{ii}]_0)^2\}]$; this can then be concentration-normalized as $r_{norm} = ([\mathbf{1a}^{ii}]_0/[\mathbf{1a}^i]_0)(r_i/r_{ii})$ to reflect the relative rate acceleration attained by the second-order (bimolecular) process.

(18) See the Supporting Information in ref 13 for details.

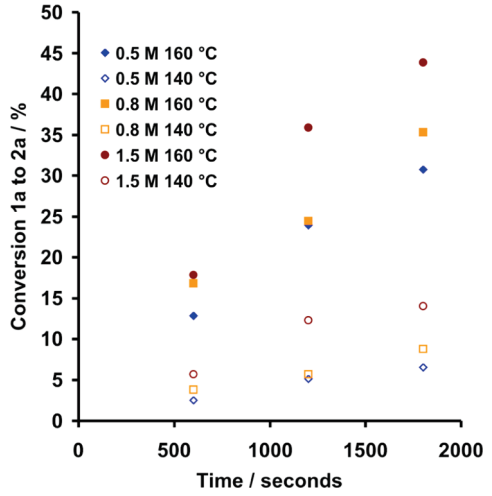


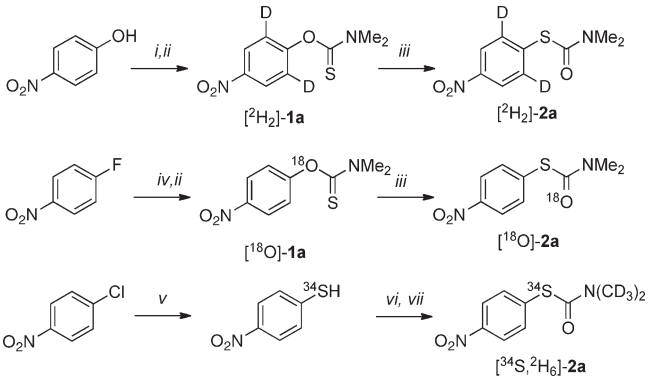

**FIGURE 3.** Apparent concentration dependence on the temporal fractional conversion for NKR **1a**→**2a** under microwave heating conditions,[13] 160 °C and 140 °C in DMA for 0.5 M (blue), 0.8 M (orange), and 1.5 M (red) initial concentrations of **1a**. Data points are single time-point experiments; i.e., they originate from separate reactions run to the time-point given on the *x*-axis, cooled, and then analyzed for conversion by HPLC.

conversion of **1a** (%) versus time were similar to those reported by Gilday et al.[13] in that the conversions of **1a** to **2a** at 0.8 M/1.5 M initial concentrations were indeed greater than that at 0.5 M, Figure 3. In fact, the conversions were significantly greater: an average of 26% and 44%, respectively, over the first 1800 s.[19]

**Preparation of Isotopically Labeled Substrates.** In contrast to unimolecular NKR proceeding via **3a**, conversion of **1a** into **2a** via the 8-membered ring in **4a**, irrespective of whether the latter is a transition state or intermediate, will result in 100% crossover between the aromatic moiety and the thiocarbamoyl moiety. The molecularity of the NKR was probed in the early studies of Miyazaki, who coreacted *O*-arylthiocarbamates and found no evidence for crossover in the rearrangement products.[6a] However, the results were not strictly definitive as the relative rates of the substrate pairs that were tested differed by ca. 1 order of magnitude. Moreover, the Miyazaki work involved conventional heating, under which the NKR was observed to proceed exclusively via first-order kinetics, as we have found with **1a**, vide supra. We thus designed an isotopic labeling-based probe for crossover, which will not suffer any significant difference in the relative rates of coreacting substrates, the primary kinetic isotope effects for C−$^{16/18}$O, C−$^{32/34}$S cleavage typically being less than 2% in magnitude. The aryl ring in **1a** was labeled with $^{2}$H, via the phenol, and the *O*-aryl thiocarbamate, [$^{2}H_2$]-**1a**, prepared via the standard procedure, Scheme 2. The thiocarbamoyl unit in **1a** was labeled with $^{18}$O, via generation of the $^{18}$O-phenol by aromatic nucleophilic substitution and, again preparation of the *O*-aryl thiocarbamate, [$^{18}$O]-**1a**, via the standard procedure, Scheme 2.

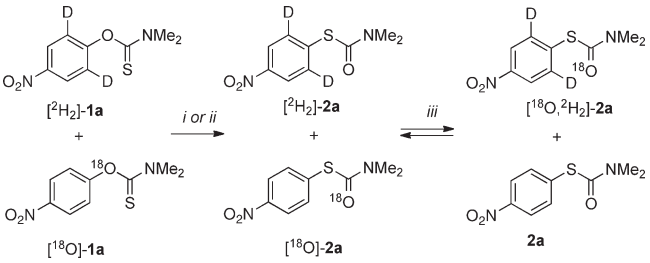
The labeled substrates [$^{2}H_2$]-**1a** and [$^{18}$O]-**1a** were rearranged independently (NKR at 180 °C) to obtain samples

**SCHEME 2. Preparation of Isotopically Labeled *O*-Aryl and *S*-Aryl Thiocarbamates**[a]




[a]Reagents and conditions: (i) DCl, $D_2O$, Δ, 82% yield (93% $D_2$, 7% $D_1$); (ii) DABCO, $ClC(S)NMe_2$, DMF; (iii) 180 °C, $N_2$, 60 min, quant; (iv) THF, $^{18}OH_2$, *t*-BuOK, 95 °C, 24 h, 98% yield (two samples: 88% $^{18}$O and 65% $^{18}$O); (v) $^{34}S_8$, $Na_2S{\cdot}9H_2O$, EtOH, reflux, then NaOH, then HCl, 43% yield (52% $^{34}$S); (vi) triphosgene, DCM, 0 °C, followed by $(CD_3)_2NH_2Cl$, $Et_3N$, THF; 20% yield (>99% atom % D).

**SCHEME 3. Lack of Crossover on NKR of 1a and Exchange between Isotopically Labeled *S*-Aryl Thiocarbamates under Thermal Aerobic Conditions**[a]




[a]Reagents and conditions: (i) 4.70 M (neat), 180 °C, $N_2$ or air, 30 min, quant; N.B. the initial sample of [$^{2}H_2$]-**1a** and [$^{18}$O]-**1a** contains unlabeled **1a** which is converted to **2a** via the non-crossover pathway (not shown); (ii) 1.50 M DMA solution microwave heating to 180 °C, 11 min, 61% conversion to **2a**; (iii) 4.70 M (neat), 180 °C, dry air, 120 min, ca. 10% equilibration.

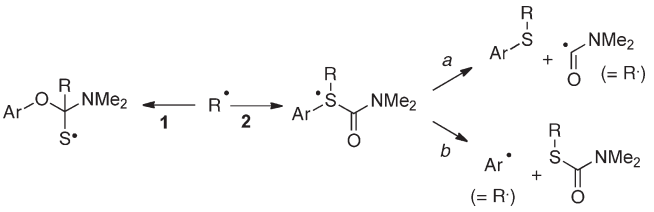
of [$^{2}H_2$]-**2a** and [$^{18}$O]-**2a** for the purposes of reference spectra for the mass spectrometric (MS) analysis. Unexpectedly, when [$^{2}H_2$]-**2a** and [$^{18}$O]-**2a** were mixed and heated to 180 °C under (dry) air, exchange occurred to generate ca. 10% [$^{18}$O, $^{2}H_2$]-**2a** and **2a** over a 2 h period, Scheme 3, as detected by MS (vide infra). The exchange process was found to be rather capricious and did not proceed at all under nitrogen or under air in the presence of **1a**.[20]

Refluxing [$^{18}$O]-**2a** in water, or heating it to 180 °C with water in a sealed tube, resulted in no loss of $^{18}$O, and thus, the exchange process (Scheme 3) does not proceed via traces of water acting catalytically to transfer the carbonyl oxygen between molecules of [$^{2}H_2$]-**2a** and [$^{18}$O]-**2a**. The requirement for air suggests a radical chain mechanism for transfer, and **1a** is presumably a powerful inhibitor for exchange because

(19) An identical analysis (ref 17) using the rate constants reported in ref 13 for 140 °C predicts ($r_{norm}$) = 1.00, 1.12, and 1.39; under similar conditions (see ref 23), we found a 75% and 126% average increase in fractional conversion of **1a** after 600, 1200, and 1800 s at 140 °C for 0.8 M/1.5 M initial concentrations of **1a**.

(20) The inhibitory effect of **1a** on exchange in **2a** was powerful: on NKR of labeled **1a** under a dry air atmosphere at 180 °C, no exchange in the product (**2a**) was detected until >99% conversion of **1a**, after which exchange-equilibration (as assayed by MS) increased approximately linearly with time.

**SCHEME 4. Possible Radical Chain Mechanism for Exchange between Isotopically Labeled *S*-Aryl Thiocarbamates (2) under Thermal Aerobic Conditions, Together with Inhibition by 1**



the thiocarbonyl moiety functions as an efficient radical trap.[21]

In an attempt to distinguish whether the exchange process proceeds via scission of the ArS−C(O) or the Ar−SC(O) bonds, processes *a* versus *b*, Scheme 4, we prepared [$^{34}$S,$^{2}$H$_6$]-**2a** (Scheme 2), generating the requisite $^{34}$S thiophenol by reaction of *p*-nitrochlorobenzene with Na$_2{}^{34}$S (52 atom %; prepared in situ from $^{34}$S$_8$, 90 atom %), and the thiocarbamate [$^{34}$S,$^{2}$H$_6$]-**2a**, via the thiochloroformate. Unfortunately, on mixing with [$^{2}$H$_2$]-**2a** and [$^{18}$O]-**2a**, the sample of [$^{34}$S,$^{2}$H$_6$]-**2a** (despite repeated purification) inhibited the exchange process, presumably because of the presence of trace impurit(ies) acting as radical trap.

**Probing the Molecularity of the NKR via Crossover Experiments.** As expected, MS analysis of the product mixture obtained after conducting the NKR of a 50/50 sample of [$^{2}$H$_2$]-**1a** and [$^{18}$O]-**1a**, under the standard thermal conditions (4.70 M, 180 °C, N$_2$, Scheme 2), confirmed that there was no detectable crossover product [$^{18}$O, $^{2}$H$_2$]-**2a** (unlabeled **2a** was present due to the incomplete isotopic substitution in the substrates), an outcome fully consistent with the reaction kinetics, vide supra, and with the experiments conducted by Miyazaki.[6a]

The experimental setup for the microwave-mediated NKR, as reported by Gilday et al.,[13] requires >1.5 mL volumes of reaction solution, thus placing some economic constraints on the molarity of the DMA solution of [$^{2}$H$_2$]/[$^{18}$O] isotopically labeled reactant **1a** that can be employed. Moreover, given the capricious exchange that had been observed between isotopically labeled samples of **2a**, Scheme 3, in the *absence* of **1a**, we wanted to ensure incomplete conversion of **1a** to **2a**. Using 2 mL of a 1.5 M solution of a 50/50 mixture of [$^{2}$H$_2$]-**1a** and [$^{18}$O]-**1a**, we conducted microwave-mediated NKR at 180 °C under the published conditions for 675 s. HPLC analysis indicated 61% conversion. According to the mixed first-order/second-order rate analysis,[13] 37% of the product should have arisen from the bimolecular pathway. Standard resolution HPLC−MS confirmed that there had been no scrambling in the remaining 39% substrate (**1a**). We then conducted a kinetic simulation of the crossover process, again using the published values of $k_1$ and $k_2$, including natural abundance $^{13}$C and $^{34}$S, along with the $^{2}$H and $^{18}$O incorporations, to predict the total array of isotopomers and isotopologues that would arise according to the mixed first-order/second-order rate analysis[13] (see the Supporting Information) at 1.5 M initial concentration and at 61% conversion. From this, we calculated the *predicted* ratio of the [MH]$^+$ ion that should arise from crossover product [$^{18}$O,$^{2}$H$_2$]-**2a** ([*m*/*z* = 231.0658) to the isobaric [MH]$^+$ ions arising from [$^{18}$O,$^{34}$S]-**2a** (*m*/*z* = 231.0491) and [$^{2}$H$_2$, $^{34}$S]-**2a** (*m*/*z* = 231.0574).

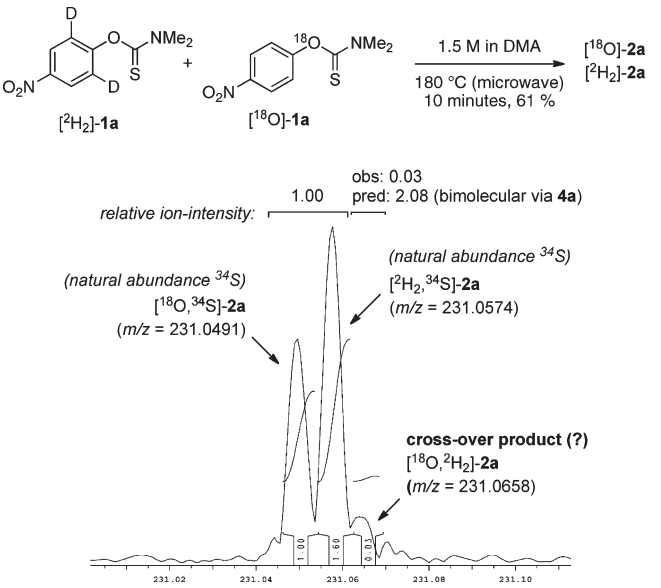



**FIGURE 4.** Integrated peak areas in the HR-ESI-ICRMS subspectrum of the 231 *m*/*z* region (3.6% of the total [**2a**H]$^+$ ion intensity) of **2a** isolated after NKR of a 50/50 mixture of [$^{2}$H$_2$]-**1a** and [$^{18}$O]-**1a** (65 atom %) in DMA under microwave heating[13] to 180 °C for 10 min. The relative ion intensities for the $^{34}$S natural-abundance isotopologues of the $^{18}$O- and $^{2}$H$_2$-labeled species ([$^{34}$S,$^{18}$O]-**2a** [$^{34}$S,$^{2}$H$_2$]-**2a**) versus the crossover product ([$^{18}$O,$^{2}$H$_2$]-**2a**) were calculated to be 1.00/2.08 by kinetic simulation using the reported values for $k_1$ and $k_2$;[13] see the Supporting Information.

Using HR-ESI-ICRMS to resolve and integrate the isobaric *m*/*z* = 231 ions (3.6% of the total [MH]$^+$ in the spectrum) in the purified labeled product **2a**, Figure 4, we established that there is no detectable crossover; the net peak intensity in the range *m*/*z* = 231.06 to 231.07, relative to the sum of the ions arising from [$^{18}$O,$^{34}$S]-**2a** and [$^{2}$H$_2$, $^{34}$S]-**2a**, corresponds to ≤1.5% of the intensity that is predicted for the crossover product [$^{18}$O,$^{2}$H$_2$]-**2a** arising via $k_2$ at an initial reactant concentration of 1.5 M.

We thus conclude that under both the standard thermal and the microwave heating conditions, there is no bimolecular pathway for NKR of **1a** involving **4a**, or if there is, its contribution to the net process is vanishingly small.

**Origin of "Concentration-Enhanced" NKR under Microwave Conditions.** It is hard to conceive of a bimolecular pathway for NKR of **1a** that does not cause crossover, and any direct intermolecular rate-enhancement arising from change in the reaction medium such as the dielectric or $\pi$-complexation effects should also be detected in the standard thermal reaction. We thus considered that there must be a concentration-dependent rate enhancement of the *unimolecular* NKR under the microwave conditions, which may then have been misinterpreted as mixed first order/second order due to the obtention of sparse data sets.[13]

The procedure reported for the microwave NKR[13] involves conducting the reaction in a thick-walled Pyrex microwave vessel containing a magnetic stirring bead and sealed with a crimp-top cap. This is then irradiated, with stirring, in a CEM Discover monomode 300 W microwave

(21) See, for example: Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 4727.

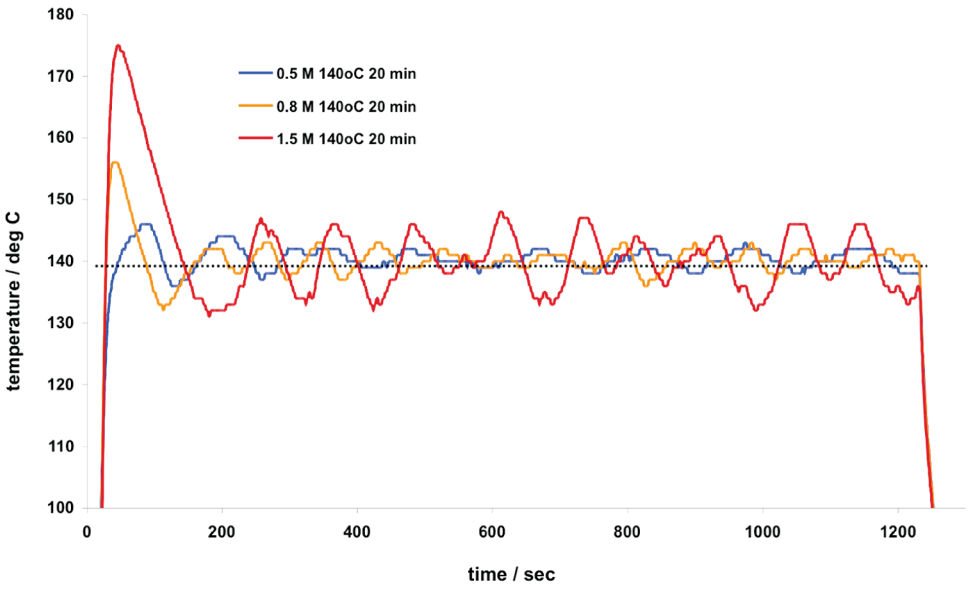



**FIGURE 5.** Temperature profile for NKR (**1a**→**2a**), as 0.5 M (blue) 0.8 M (orange), and 1.5 M (red) solutions in DMA, under conditions set up for reaction at 140 °C for 20 min.[13,23] Temperature is that recorded by an external IR pyrometer.[22,25] A sample with 0 M **1a** (i.e., pure DMA) gave a similar amplitude of oscillation to the 0.5 M sample.

reactor equipped with an IR pyrometer[22] and a noninvasive pressure transducer. Using the standard temperature profile programming on the instrument,[23] the microwave reactor is set to rapidly attain and hold the desired reaction temperature,[24] for a set period, followed by a rapid-cooling phase using an ambient temperature forced-air stream around the outer surface of the reaction vessel. The use of a "balancing loop"[25] to modulate the microwave irradiation power in response to reaction temperature inherently results in some oscillation, commonly termed "hunting",[25] about the temperature set-point. It is important to note that the IR pyrometer measures the temperature of the *outer surface* of the Pyrex microwave vessel, and the use of a thick-walled Pyrex microwave reaction vessel thus results in a significant lag-time between a change in temperature of the reacting contents and the external detection of this temperature. It is well-known that balancing loops with delayed negative feedback signals are prone to a greater amplitude of hunting[25] (this being the range between the maxima and minima in temperature about the set-point), and we thus studied the power−temperature−time files stored by the CEM Discover instrument after each run. It soon became evident that the amplitude of the hunting about the temperature set-point became larger as the concentration of **1a** was increased. This most likely arises from a change in the dielectric of the medium, and thus greater loss factor (tan $\delta$)[26] and more efficient conversion of the 2.45 GHz microwave energy into heat for **1a**. Thus, as the medium becomes richer in **1a** there will be a greater temporal discrepancy in negative feedback and a greater amplitude of oscillatory overheating.

The effect was even more pronounced when the reactions were run at "140 °C"[23] and under these conditions we found a 75% and 126% average increase in conversion after 600, 1200, and 1800 s, for 0.8 and 1.5 M initial concentrations of **1a**, as compared to 0.5 M, Figure 3. For the 1.5 M sample, the temperature profile, Figure 5, shows that the outer-surface of the reaction vessel, which being transparent to microwaves is convectively heated by its contents, reaches well over 170 °C for at least the first 30 s of reaction, during which period $k_1$ will increase by over an order of magnitude, whereas for the 0.5 M sample, the maximum overheating was just 6 °C. Moreover, the dependence of the amplitude of oscillatory overheating on the concentration of **1a**/**2a** is evident for the entire period of the subsequent 20 min of reaction, during which the microwave power, while limited in the temperature program to a maximum value of 30 W, does not exceed 11 W (see the Supporting Information for a full analysis of temporal power/temperature profiles).

(22) The monitoring of the reaction temperature in microwave reactors via the sole application of an infrared pyrometer reading from the external surface of the reactor vessel has been cautioned against, owing to concerns regarding their sensitivity and the accuracy with which they reflect the internal reaction temperature; see: (a) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417. (b) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36. (c) Obermayer, D.; Kappe, C. O. *Org. Biomol. Chem.* **2010**, *8*, 114. See also ref 25b.

(23) The specific program employed has two stages, with targets for the temperature, and set limits for the microwave device input power and reaction vessel pressure: Stage 1: 160 °C, power max = 180 W, ramp time 0 s, hold time 30 s, pressure max = 250 psi. Stage 2: 160 °C, power max = 30 W, ramp time 0 s, hold time 600−1800 s, pressure max = 250 psi. The magnitude of the set limit(s) for the microwave device input power will obviously impact on the amplitude of temperature oscillation that is attainable.

(24) Temperature control in equipment such as this is usually achieved by a proportional-integral derivative (PID) controller, a control loop feedback ("balancing loop") mechanism that calculates an "error" value as the difference between a measured process variable (in this case temperature) and a desired set point (the desired reaction temperature). The controller attempts to minimize the error by adjusting the process control inputs (in this case microwave power); if this power adjustment is not rapid or accurately related or timed to the desired reaction temperature, overheating will occur; see ref 25.

(25) (a) See: Control Systems, Robotics, and Automation. In *Encyclopedia of Life Support Systems* (*EOLSS*);Unbehauen, H., Ed.; Developed under the Auspices of the UNESCO, Eolss Publishers: Oxford, UK, 2004; [http://www.eolss.net]. See also: (b) Nüchter, M.; Ondruschka, B.; Weiβ, D.; Beckert, R.; Bonrath, W.; Gum, A. *Chem. Eng. Technol.* **2005**, *28*, 871.

(26) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213.

## Conclusions

In response to the recent report by Gilday et al. that the solution-phase Newman−Kwart rearrangement (NKR) proceeds via unimolecular (**3**) and bimolecular (**4**) pathways,[13] we have reinvestigated the kinetics and molecularity of the NKR of *N*,*N*-dimethyl *O*-*p*-nitrophenylthiocarbamate **1a**. Under standard thermal conditions, and as expected based on the extensive prior work of Newman,[1a] Relles,[5] Miyazaki,[6] Woodward,[7a] and Donahue,[7b] the kinetics of rearrangement at 160 °C are exclusively first order at concentrations ranging from 0.11 to 4.70 M. There is also no crossover between aromatic and thiocarbamoyl moieties during the reaction, although under aerobic thermal conditions exchange can occur in the product (**2a**, Schemes 3 and 4). Under microwave heating conditions, while there is no evidence for bimolecularity (a crossover experiment with a 1.5 M solution of a 50/50 mixture of [$^{2}H_2$]-**1a** and [$^{18}$O]-**1a** was negative: no [$^{18}O$,$^{2}H_2$]-**2a** could be detected above a baseline threshold of 1.5%), there is a disproportionate rise in conversion with increasing concentration of **1a**. This was identified as arising from a combination of two factors: (i) a delayed negative feedback signal of the reaction temperature to the microwave power-control balancing loop, resulting in oscillatory reaction-overheating, and (ii) a more efficient microwave to thermal energy conversion (greater loss-factor, tan $\delta$)[26] by **1a** as compared to DMA, resulting in a greater amplitude of oscillatory overheating as the initial concentration of **1a** is raised.

It is instructive to consider the circumstances that gave rise to the misinterpretation by Gilday et al. that the data is indicative of simultaneous unimolecular and bimolecular pathways.[13] The major issue arises from the setup of the microwave experiment. For reasons of safety, the reactions are conducted in crimp-cap sealed thick-walled Pyrex microwave vessels, which are firmly held in place in the microwave cavity. This means that it is not convenient to continuously sample the reaction; instead a series of reactions are conducted, leading to rather sparse temporal-conversion data sets, a situation that can readily lead to overinterpretation of data. The use of an IR pyrometer temperature probe, which measures the *external* surface of a thick walled reaction vessel, inherently results in a delayed, and fairly inaccurate,[22] negative feedback signal and thus substantial hunting about the desired temperature set-point, a situation that will be sensitive to changes in the loss-factor, tan $\delta$,[26] as the proportion of solvent/solute is varied.

We thus conclude that microwave reactors can be conveniently used to rapidly generate a series of single time point kinetic data for reactions that require relatively high temperatures; however, as with any kinetic determination, accurate control of temperature is crucial. In this regard, the current method of choice is probably the elegant approach developed by Kappe,[14] whereby semiconducting silicon-carbide reaction vessels are heated via ohmic resistance to microwave-induced electron flow, in turn heating the vessel contents via a standard convective mechanism, with a fiber-optic based temperature-power balancing loop.

## Experimental Section

**General Methods.** For each series of experiments, homogeneous solutions of **1a** were prepared at the required concentrations (0.11−4.70 M) in *N*,*N*-dimethylacetamide (DMA). Equal volumes (2.0 or 4.0 mL) were heated under nitrogen, with stirring, in thick-walled boiling tubes heated by partial immersion in a silicone oil bath, in sealed glass capillary tubes placed in the center of a precalibrated GC oven, or in glass sealed pressure tubes in a CEM Discover monomode 300 W microwave reactor with IR temperature monitoring and noninvasive pressure transducer. Conversions were determined by HPLC or LCMS analysis of acetonitrile-diluted samples and are corrected for relative response factors (RRFs). The *S*-arylthiocarbamate **2a** was prepared and purified to provide reference markers for the HPLC or LCMS method and RRF values.[8,12e]

**NKR Crossover Study Performed under Convective Heating Conditions.** [$^{18}O_{0.88}$]-**1a** (0.05 g, 0.22 mmol) and [$^{2}H_{0.97}$; $^{1}H_{0.03}$]-**1a** (0.05 g, 0.22 mmol) were fused at 180 °C in a Schlenk tube under nitrogen for 30 min. A sample was removed from the reaction mixture via glass capillary, diluted with acetonitrile, and analyzed by HPLC which indicated that >99% conversion of **1a** to **2a** had occurred. This sample was then analyzed by high-resolution ESI ICRMS ($m/z$ of $[MH]^+$ ion) and found to contain **2a**, [$^{1}H_1$]-**2a**, [$^{18}O_1$]-**2a**, and [$^{2}H_2$]-**2a** but no detectable crossover product [$^{18}O_1$,$^{2}H_2$]-**2a** ($m/z$ = 231).

**NKR Crossover Study Performed in a CEM Discover Microwave Reactor.** [$^{18}O_{0.65}$]-**1a** (0.34 g, 1.50 mmol) and [$^{2}H_{0.97}$; $^{1}H_{0.03}$]-**1a** (0.34 g, 1.50 mmol) were dissolved in DMA (2 mL) to give a solution of 1.50 M total concentration in **1a**. A thick-walled Pyrex microwave vessel equipped with a magnetic stirring bead was charged with the solution. The vessel was sealed with a crimp-top cap and irradiated with stirring in a CEM Discover monomode 300 W microwave reactor with IR temperature monitoring and noninvasive pressure transducer at 180 °C for 11 min (stage 1: 180 °C, 180 W, ramp time 0 s, hold time 75 s, pressure 250 psi; stage 2: 180 °C, 30 W, ramp time 0 s, hold time 600 s, pressure 250 psi). Once irradiation had ceased and the sample cooled, the glass microwave reaction vessel was opened, and a reaction sample removed via glass capillary, diluted with acetonitrile, and analyzed by HPLC which indicated that 61% conversion of **1a** to **2a** had occurred. The remaining reaction mixture was then diluted with a mixture of ethyl acetate (10 mL) and saturated brine (10 mL). The organic fraction was separated, washed with brine (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude material was purified by column chromatography on silica gel, eluting with a 5:1 mixture of toluene/ethyl acetate, to afford **1a** (240 mg, 35%) as an off-white solid and **2a** (376 mg, 55%) as a pale yellow solid. The purified sample of **2a** was then analyzed by high-resolution ESI ICRMS ($m/z$ of $[MH]^+$ ion) and found to contain **2a** ($m/z$ = 227), [$^{1}H_1$]-**2a** ($m/z$ = 228), [$^{18}O_1$]-**2a** ($m/z$ = 229), and [$^{2}H_2$]-**2a** ($m/z$ = 229) but no detectable crossover product [$^{18}O_1$,$^{2}H_2$]-**2a** ($m/z$ = 231). For full details of the mass spectrometric data, see the Supporting Information.

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**Supporting Information Available:** Full experimental details for kinetic analyses, the preparation of labeled forms of **1a**, HPLC and MS analysis/simulation of isotopomers and isotopologues in product mixture **2a**, and the analysis of power−temperature profiles for microwave heating of solutions of **1a** in DMA. This material is available free of charge via the Internet at http://pubs.acs.org.