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The effect of leaving radical on the formation of tetrahydroselenophene by SHi ring closure: an experimental and computational study

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The effect of leaving radical on the formation of tetrahydroselenophene by S_Hi ring closure: an experimental and computational study.

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Competition kinetic studies augmented with laser-flash photolysis and high-level computational techniques (G3(MP2)-RAD), with (COSMO-RS, SMD) and without solvent correction, provide kinetic parameters for the ring closures of a series of 4-(alkylseleno)butyl radicals **1**. At 22°C rate constants (k_c) that lie between $10^4 – 10^7$ s^{-1} were determined experimentally and correlate with expectations based on leaving group ability. Activation energies (E_{act}) were determined to lie between 10.6 (R = Ph$_2$CH) and 28.0 (R = n-Bu) kJ mol^{-1}, while log (A/s^{-1}) values were generally between 9 and 10 in benzene. Computationally determined rate constants were in good-to-excellent agreement with those determined experimentally, with the COSMO-RS solvation model providing values that more closely resemble those from experiment than SMD.

Introduction

Just over two decades ago we reported the first example of the use of intramolecular homolytic substitution (S_Hi) chemistry at selenium when we demonstrated that the 4-(benzylseleno)butyl radical (**1**, R = Bn) cyclizes to form tetrahydroselenophene (Scheme 1).[1,2] At the time there were no kinetic data for these types of reactions and we relied on inspired guesswork to arrive at an approximate rate constant for this reaction ($10^5 – 10^6$ s^{-1} at 80°).[3]

Following on from this pioneering work, we, and others, have reported the preparation of numerous selenium-containing heterocycles (eg. **2 – 10**) using this chemistry.[2,4–11] Some of these compounds (eg. **6 – 10**) are of biological significance,[6–10] while a subset of these (eg. **9**, **10**) have undergone pre-clinical studies as potential new pharmaceuticals for the treatment of conditions such as hypertension and related cardiovascular disorders.[9,10]

The vast majority of the homolytic substitution chemistry used for the construction of these interesting heterocycles has employed the benzyl radical as the leaving group, as it is a well-
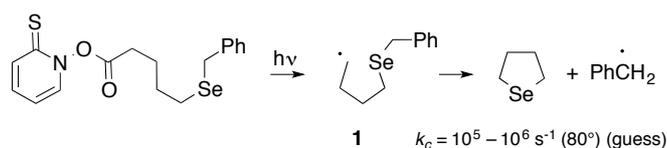
2   **3**   **4**   **5**

6
ebselen

7
a selenopenam

8 (R = Phytyl)
α-selenotocopherol

9
selenoeprosartan

10
selenomilfasartan

1 $k_c = 10^5 – 10^6$ s^{-1} (80°) (guess)

Scheme 1.
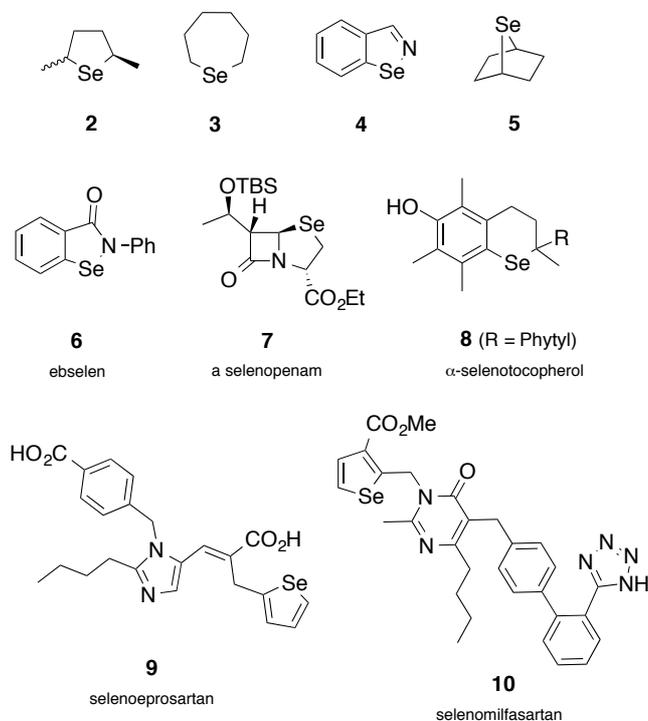
established stable radical that should be effective in radical substitution chemistry.[12–14]

Most free radical reactions of synthetic significance are under kinetic control.[15] Recognising this, we have spent considerable effort over the past decade or so to create a kinetic scale for intramolecular homolytic substitution in much the same way as exists for more traditional radical cyclizations and rearrangements.[16] Some of this work has been experimentally driven and has employed competition kinetics as well as laser-flash photolysis (LFP) techniques,[3,17–19] however, when precursors have been difficult to prepare or handle, or the chemistry has been difficult, we have also resorted to high-level computational techniques to provide kinetic information.[5,13,20]
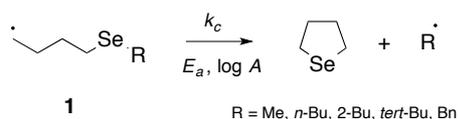
Scheme 2.

Somewhat ironically, since our original publication in 1992,[1] we have still not determined kinetic parameters for the cyclization of the "parent" 5-(benzylseleno)pentyl radical (**1**, R = Bn). In this paper we rectify this long-overdue anomaly and report both experimentally and computationally determined rate constants and Arrhenius parameters for the ring-closure of **1**, and related systems that include a variety of leaving radicals, including benzyl.

Computational Methods

Ab initio and DFT calculations were carried out using Gaussian 09 Revision D.01[21] and ADF2013[22–24] on the NCI National Facility in Canberra, Australia. Systematic conformational searches were carried out to ensure global minima were located in all cases, as reported in our previous work.[20] Geometry optimizations and harmonic frequency calculations were performed at the B3LYP level of theory,[25,26] using the 6-31G* basis sets.[20,27,28] Optimized geometries and energies for all structures investigated in this study are available in the ESI.† Vibrational frequencies were inspected to ensure that all minimum and transition state structures were true stationary points. Partition functions and hence entropies and thermal corrections to the energies were calculated using standard textbook formulae for the statistical thermodynamics of an ideal gas under the harmonic oscillator rigid rotor approximation. Accurate gas-phase energies of reactants and transition states were calculated using the high-level composite G3(MP2)-RAD level of theory.[29] These energies were then combined with the entropic and thermal corrections to give Gibbs free energies. The effects of solvation in both benzene and acetonitrile were calculated for each species using COSMO-RS[30] at the BP[31,32]/TZVP[33] level (ADF) and using SMD[34] with M05-2X[35]/6-31G* (Gaussian).[36] Gas-phase Gibbs free energies were combined with these free energies of solvation via standard thermodynamic cycles to give Gibbs free energies in solution;

appropriate phase change corrections were included.[37] Kinetic parameters could then be determined using the Eyring equation.[38,39] We note that, although neither the reactants nor products for these reactions are chiral, the transition states are. This means that there are two possible reaction paths of equal energy for each reaction. Hence, calculated reaction rates have been multiplied by a factor of two in order to account for this degeneracy.[40]

Results and Discussion

4-(Benzylseleno)butyl radical

We began this work by examining the ring-closure of the "workhorse" 4-(benzylseleno)butyl radical (**1**). To that end, the required Barton ester (**11**, R = Bn) was prepared as described previously.[2] For the purpose of this study, radical **1** was produced by photochemically or thermally initiated cleavage of the N-O bond in **11** followed by a subsequent, rapid decarboxylation to afford the desired alkyl radical. The rate constant for cyclization of radical **1** was obtained by two independent routes: directly by LFP and indirectly using the PTOC-thiol method in competition experiments. The former experiments were fraught with complications (*vide infra*) and this led us to verify our results using an approach that is free from the limitations inherent to the LFP experiments.
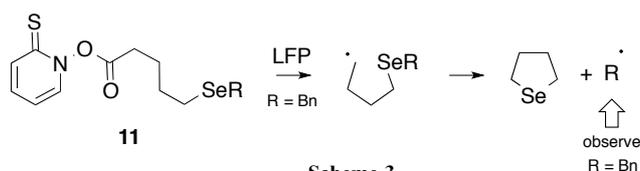
Scheme 3.

In the flash photolysis study, irradiation of **11** at 355 nm yields a 480 nm transient generated within the timeframe of the laser pulse (Figure 1). This signal corresponds to the 2-pyridylthiyl radical; a hallmark of successful N-O bond cleavage and radical generation from a Barton ester.[41] The
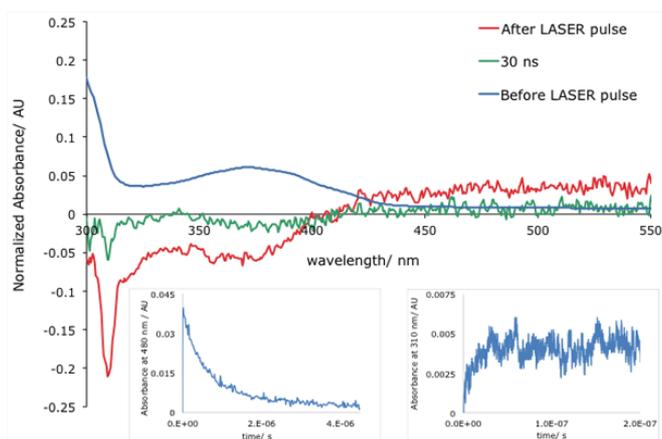
Figure 1. Spectra recorded for radical 1 in degassed benzene before laser flash excitation, immediately after excitation and 30 ns after excitation. (Left Inset: Transient decay curve for the 2-pyridylthiyl radical at 480 nm recorded after laser flash excitation, Right Inset: Transient growth curve for the benzyl radical at 310 nm recorded after laser flash excitation).

observation of the cyclization of radical **1** was confirmed by the formation of a UV signal growing in at 310 nm that is ascribable to the absorbance of the leaving benzyl radical. The benzyl radical forms concurrently with the cyclized product thus kinetic parameters were obtained by fitting to the growth curve for the benzyl radical.

In spite of our apparent ability to detect the desired chemistry, our studies were complicated by factors that limited our confidence in the elucidated kinetic parameters. With hindsight, the benzyl radical was an unfortunate choice of chromophore for LFP studies for these reasons: i) the benzyl radical has a low extinction coefficient,[42] and ii) there is notable and instantaneous bleaching of the ground state within the spectral window required to monitor the benzyl radical. In our system the use of benzene as a solvent limits our spectral window to > 300 nm forcing our rate constant measurements closer to the convoluted region of the spectrum where ground state bleaching also occurs hence limiting the practicality of this approach. Interestingly, in this system (**11**) we also observed a sharp narrow bleaching at the λ_{max} for the benzyl radical (310 nm) leading us to conclude that a further complication in this work is that the benzyl radical itself appears to be liberated by direct cleavage of the Se-CH$_2$Ph bond during the laser pulse. This observation is consistent with other photochemical studies conducted on benzylselenides.[43]

Despite the difficulties described above, an approximate rate constant (k_c) of 5.9 x 10^7 s^{-1} (log k_c = 7.77) was obtained from this LFP study at 22°. Given the concerns described above, we sought to provide confidence in this number by augmenting the LFP study with computational and competition studies.

In recent years, our team has employed high-level [G3(MP2)-RAD] computational techniques to provide rate data that are in good-to-excellent agreement with experimentally-derived rate constants (k_c).[13,14,17,44–46] It is useful, therefore, to compare our experimentally-determined value of k_c with that calculated previously (1.6 x 10^7 s^{-1} (21°)) using G3(MP2)-RAD [ONIOM].[20] Clearly, this previously reported (gas-phase) value for the cyclization of **1** is little lower than that obtained in our LFP study.

MeS—C(=S)—N(CH$_3$)—O—C(=O)—(CH$_2$)$_3$—Se—R

13
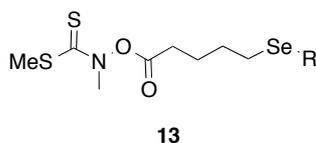
We chose to supplement these data with those from competition kinetic studies. In previous work, thiohydroximate (Kim) esters (**13**) were chosen as radical precursors.[3] Unfortunately, these proved to be unsuitable for studying the ring-closure of **1** because cleavage of the Se-Bn bond has been shown to compete with the formation of **1** upon photolysis with the low pressure (broad spectrum) mercury lamp used during competition kinetics experiments,[43] an observation consistent with the LFP studies in this work (*vide supra*). As a consequence, **11** was also employed for this competition study,
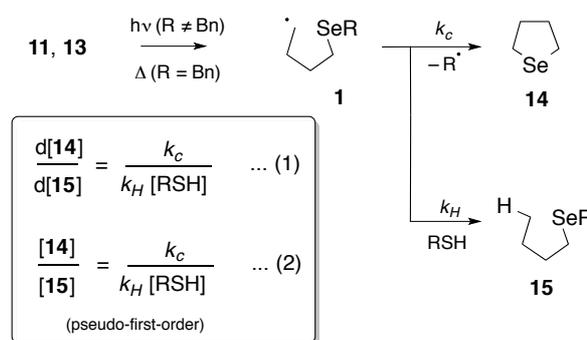
Scheme 4.

which was carried out using thermal initiation in the 70 – 100° temperature range.

Gas chromatography (GC) analysis of the reaction mixture obtained when **11** was heated in the presence of 10 equivalents of *tert*-dodecanethiol (RSH, 0.05 – 0.3 M) in benzene revealed the presence of tetrahydroselenophene **14** and butyl benzyl selenide **15** (R = Bn) by comparison with authentic samples (Scheme 4). Integration of the appropriate rate equation [eqn 1, Scheme 4)] leads to eqn. 2 which is valid under "pseudo-first-order" conditions in RSH.

$$\frac{d[14]}{d[15]} = \frac{k_c}{k_H [RSH]} \quad \dots (1)$$

$$\frac{[14]}{[15]} = \frac{k_c}{k_H [RSH]} \quad \dots (2)$$

(pseudo-first-order)
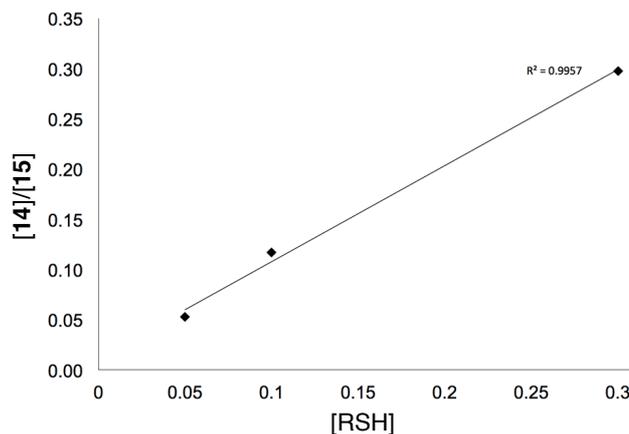
Figure 2. Dependence of [14]/[15] on RSH concentration at 80° for the cyclization of 1 (R = Bn) in benzene.

Initial experiments were carried out at 80° at three thiol concentrations in order to verify that the chemistry in question was indeed mechanistically consistent with free radical kinetics. The linearity observed (Figure 2) provides confidence in the adopted kinetic approach. The remaining data were obtained at

Table 1. Rate data for the ring closure of 5-(benzylseleno)butyl radical 1 (R = Bn).

Temp (°C)	[RSH] (M)	[14]/[15][a]	k_H (M^{-1} s^{-1})[b]	k_C (s^{-1})
70	0.10	7.54	1.34 x 10^7	1.01 x 10^7
80	0.10	8.56	1.45 x 10^7	1.24 x 10^7
90	0.10	9.08	1.57 x 10^7	1.43 x 10^7
100	0.10	10.43	1.69 x 10^7	1.76 x 10^7

[a]Average of three experiments. [b]Calculated from the reported Arrhenius expression for t-butylthiol (ref 32).

Table 2. Arrhenius parameters (E_{act}, log A) and rate constants (k_c) for the ring-closure of 4-(alkylseleno)butyl radicals 1 at 22°C.

Radical	Experimental[a]					G3(MP2)-RAD					
	log (A / s⁻¹)	E_{act} / kJ mol⁻¹	log (k_c / s⁻¹)[b]	k_c / s⁻¹[b]	ref	log (k_c / s⁻¹)　k_c / s⁻¹ (gas phase)		log (k_c / s⁻¹)　k_c / s⁻¹ (COSMO-RS)[c]		log (k_c / s⁻¹)　k_c / s⁻¹ (SMD)[d]	
R = Me	-	-	-	-	-	4.73	5.3 x 10⁴	4.35	2.2 x 10⁴	4.60	4.0 x 10⁴
n-Oct[e]	9.5 ± 0.6	28.0 ± 4.0	4.54 ± 1.31	3.4 x 10⁴[f]	t.w.[g]	5.57	3.7 x 10⁵	5.16	1.4 x 10⁵	5.70	5.0 x 10⁵
2-Oct[h]	9.2 ± 0.5	22.1 ± 3.2	5.28 ± 1.07	1.9 x 10⁵[i]	t.w.[g]	6.10	1.3 x 10⁶	5.75	5.6 x 10⁵	6.27	1.9 x 10⁶
tert-Bu	10.3 ± 0.5	24.1 ± 3.3	6.03 ± 1.08	1.1 x 10⁶[j]	t.w.[g]	6.40	2.5 x 10⁶	6.09	1.2 x 10⁶	6.66	4.5 x 10⁶
Bn	10.0 ± 0.2	19.3 ± 1.9	6.58 ± 0.53	3.8 x 10⁶[k]	t.w.[g]	6.61	4.1 x 10⁶	6.68	4.8 x 10⁶	6.97	9.4 x 10⁶
Ph₂CH[l]	8.9 ± 0.1	10.6 ± 0.6	7.02 ± 0.66	1.1 x 10⁷[m]	18	8.05	1.1 x 10⁸	7.85	7.1 x 10⁷	8.33	2.1 x 10⁸

[a]In benzene unless otherwise stated. [b]Calculated from the Arrhenius expression. [c]COSMO-RS (benzene). [d]SMD (benzene). [e]Calculated for R = 1-butyl. [f]$0.2 \times 10^4 < k_c < 5.8 \times 10^5$ s⁻¹. [g]This work. [h]Calculated for R = 2-butyl. [i]$1.6 \times 10^4 < k_c < 2.2 \times 10^6$ s⁻¹. [j]$8.9 \times 10^4 < k_c < 1.3 \times 10^7$ s⁻¹. [k]$1.1 \times 10^6 < k_c < 1.3 \times 10^7$ s⁻¹. [l]Determined by laser flash experiments in tert-butylbenzene. [m]$2.3 \times 10^6 < k_c < 4.8 \times 10^7$ s⁻¹.

a single thiol concentration (0.1M), in triplicate. Application of eqn 3 provided the rate constant data listed in Table 1.

Linear regressional analysis of the data provided in Table 1 provides the following relative Arrhenius expression for the cyclization of **1** (errors are expressed to 90% confidence and include random but not systematic errors):

$$\log(k_c / k_H) = (1.58 \pm 0.15) - (10.97 \pm 1.63) / \theta \qquad (3).$$

Combing this equation (eqn. 3) with that for hydrogen atom transfer from a tertiary thiol (RSH) to a primary alkyl radical,[47] namely:

$$\log k_H = (8.37 \pm 0.07) - (8.37 \pm 0.31) / \theta \qquad (4)$$

provides the following Arrhenius expression (Figure 2) for the ring-closure of the 4-(benzylseleno)butyl radical (**1**) in benzene:

$$\log k_c = (9.95 \pm 0.22) - (19.34 \pm 1.94) / \theta \qquad (5).$$

Application of equation 5 leads to a value for log k_c of 6.52 ± 0.56 at 22°, somewhat lower than the value of 7.77 obtained in our LFP study (*vide supra*). Interestingly, the value of k_c determined at 80° for **1** in this study, namely 1.4 x 10⁷ s⁻¹ is about two orders of magnitude higher than our initial guess back in 1992.[1] With hindsight, this initial underestimation probably contributed to the success of the chemistry being developed at the time.

Other 4-(alkylseleno)butyl radicals (R ≠ Bn)

With kinetic data for **1** (R = Bn) now (finally) available, we next chose complete the series that examines the effect of leaving radical (R) on rate of cyclization of radicals **1**. For this study, we chose to use the more robust Kim ester radical precursors (**13**), and these were prepared from ethyl 5-bromopentanoate as shown in Scheme 5. Accordingly, the required diselenide[48] was reacted with sodium borohydride in ethanol; the selenoate generated in this manner was further reacted with ethyl 5-bromopentanoate **16** to give the ethyl 5-(alkylseleno)pentanoate **17** in 50 − 84 % yield. Subsequent
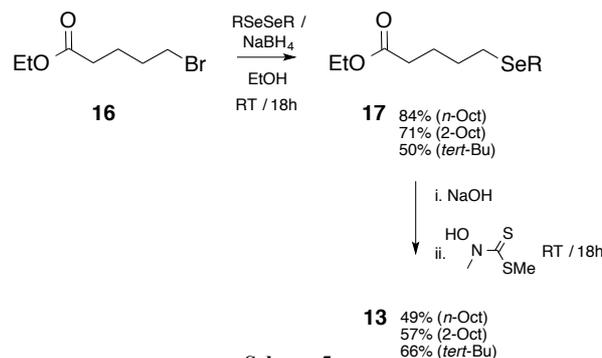
Scheme 5.

hydrolysis and coupling with *N*-methylhydroxydithiocarbamate afforded the required Kim ester **13**.

Photolysis of a benzene solution of **13**, at the required temperature, by a low pressure (broad spectrum) mercury lamp afforded reaction mixtures containing **14** and **15** as evidenced by GC analysis and by comparison with authentic samples. Because **13** is a more robust radical precursor than **11**, and because of the limitations described above for **1** (R = Bn), we were able to determine kinetic data for the remaining radicals **1** over a greater temperature range than was possible for the benzyl-substituted system; these data are displayed in Table 2.

Once again, single temperature concentration studies show excellent linearity for each system, providing confidence that we are observing radical chemistry (Figs. S1 − S3, see ESI).† Application of eqn 2 to these data, together with eqn 4, leads to the Arrhenius expressions (Figure 3) for the cyclization of **1** listed in Table 2.

Inspection of Table 2 reveals clear trends in rate constant for cyclization (k_c) at 22° that range from 10⁴ (*n*-Oct) – 10⁷ s⁻¹ (Ph₂CH) and correlate with expectations based on leaving group ability. Decreases in activation energy (E_{act}) in moving from n-Oct to Ph₂CH appear to be the main driver for the observed increases in k_c, with log A (activation entropy) being approximately the same, to within experimental error, for the majorty of systems in this study.

Computationally-determined rate data

In order to provide confidence in the data displayed in Table 2, we chose to provide computationally-determined values for k_c that augment these experiments, especially in light of the

discrepancy between the original LFP determined rate constant for R = Bn and that determined by competition kinetics.

In previous work, we had determined rate data for radicals **1** in the gas phase using G3(MP2)-RAD for R ≠ Bn, Ph_2CH; and G3(MP2)-RAD[ONIOM] for the remaining systems.[20] We now augment this work and include solvent correction (benzene) using the COSMO-RS and SMD methods.[30,34] For computational expediency, calculations for the cyclization of the primary (*n*-Oct) and secondary (*2*-Oct) containing systems were performed using smaller primary and secondary leaving groups, namely *n*-butyl and 2-butyl. All structures were reoptimised using at B3LYP/6-31G* using the improved 6-31G* basis set for selenium reported by Rassolov.[28] Rate constants were calculated in the gas-phase and in solution using the harmonic oscillator approach, which performed to within experimental accuracy for the systems in this study (Table 2). Included in this computational study is the cyclization of **10** (R = Me), a system that we were unable to study experimentally. Optimized geometries for all transition states **18** involved in the ring-closures of radicals **1** are provided in the ESI;† the B3LYP/6-31G* optimised geometry of **18** (R = Bn) is depicted in Figure 4.
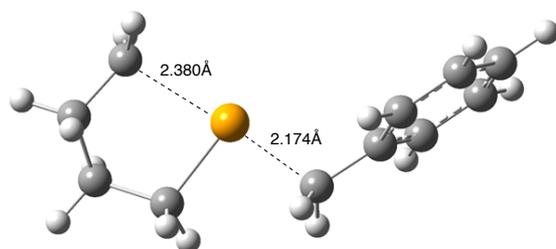
Figure 4. B3LYP/6-31G(d) calculated transition state 18 for the cyclization of radical 1 (R = Bn).

Inspection of Table 2 reveals that the calculated data at 22° are in good-to-excellent agreement with those determined experimentally, with calculated values of log k_c that are generally within experimental error, especially when solvent correction is included. For the chemistry in this study, it appears that the COSMO-RS solvation model provides data that are in closer agreement with experiment than those determined using the SMD model. It is interesting to note that the
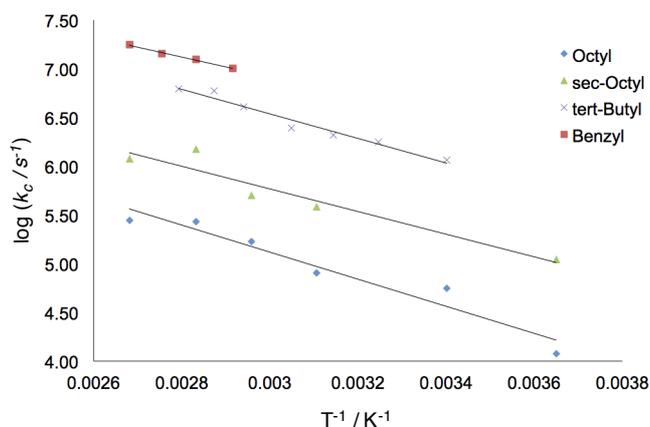
Figure 3. Overlay of experimentally-determined Arrhenius expressions for the cyclization of radicals 1.
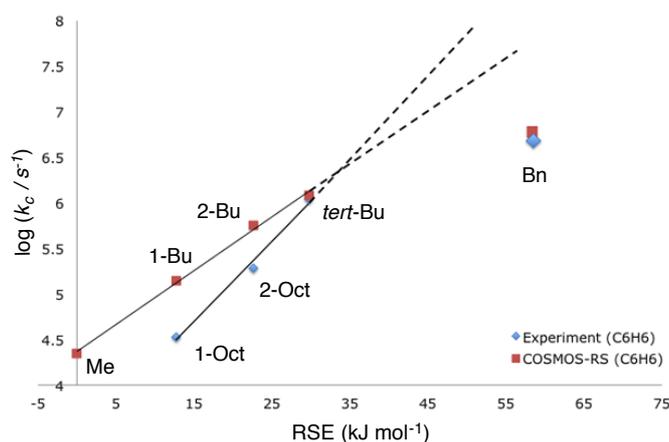
Figure 5. Correlation between experimentally and computationally determined log (k_c/s^{-1}) (22°) and radical stabilisation energy (RSE) of the leaving radical, R, Scheme 4.

COSMO-RS determined log k_c for the cyclization of **1** (R = Bn) of 6.68 (22°) is in excellent agreement with experimentally determined value (6.58 ± 0.53).

It is interesting to note that with the exception of the benzyl-substituted system, both calculated and experimentally-determined rate data (log k_c) correlate well with the stability of the leaving radical as measured by its radical stabilisation energy (RSE).[12,20] As observed in other cases,[13,14] the benzyl-substituted system **11** ring-closes more slowly than predicted by this thermochemical parameter (Figure 5) because the transition state **18** derives less resonance stabilisation than does the benzyl radical itself.

The trends displayed in Figure 5 and listed in Table 2 provide important information for the synthetic practitioner interested in the rational design of syntheses based on intramolecular homolytic substitution chemistry. Indeed, a similar approach has been adopted by Alabugin and coworkers who describe controlling cascade reactions through manipulation of the leaving group in β-scission chemistry.[49,50]

Conclusions

Competition kinetic studies augmented with high-level computational techniques (G3(MP2)-RAD) with (COSMO-RS, SMD) and without solvent correction, provide kinetic parameters for the ring closures of a series of 4-(alkylseleno)butyl radicals **1**. At 22°C rate constants (k_c) that lie between $10^4 – 10^7$ s^{-1} were determined experimentally and correlate with expectations based on leaving group ability. Activation energies (E_{act}) were determined to lie between 10.6 (R = Ph_2CH) and 28.0 (R = *n*-Bu) by competition kinetic experiments, while log (A/s^{-1}) values were generally between 9 and 10 in benzene. Computationally determined rate constants were in good-to-excellent agreement with those determined experimentally, with the COSMO-RS solvation model providing values that more closely resemble those from experiment than SMD.

Experimental

Ethyl 5-(benzylseleno)pentanoate **17** (R = Bn) and its PTOC (Barton) ester **11** were prepared as reported previously.[2] General procedures for the preparation of selenides **17** (R ≠ Bn), thiohydroxamate (Kim) esters **13** are provided in the ESI.† An authentic sample of tetrahydroselenophene and authentic products **15** were prepared as described previously.[48,51]

Ethyl 5-(1-octylseleno)pentanoate 17 (R = *n*-Oct) was isolated in 84% yield as a yellow oil. δH (500 MHz, CDCl$_3$) 4.13 (q, J = 7.2 Hz, 2H), 2.57 – 2.53 (m, 4H), 2.32 (t, J = 7.1 Hz, 2H), 1.61 – 1.75 (m, 6H), 1.36 – 1.23 (m, 13H), and 0.88 (t, J = 7.0 Hz, 3H); δC (125 MHz, CDCl$_3$) 173.4, 60.3, 33.8, 31.8, 30.6, 30.1, 30.0, 29.2, 29.1, 25.3, 24.1, 23.2, 22.7, 14.3 and 14.1; δ_{Se} (95 MHz, CDCl$_3$) 168; ν_{max} (neat) 2924, 2854, 1735 cm^{-1}; HRMS C$_{15}$H$_{30}$O$_2$SeNa requires 345.13032; found 345.13039.

Ethyl 5-(2-octylseleno)pentanoate 17 (R = 2-Oct) was isolated in 71% yield as a yellow oil. δH (500 MHz, CDCl$_3$) 4.13 (q, J = 7.2 Hz, 2H), 2.95 – 2.91 (m, 1H), 2.58 – 2.55 (m, 2H), 2.32 (t, J = 7.2 Hz, 2H), 1.75 – 1.50 (m, 6H), 1.42 – 1.36 (m, 5H), 1.32 – 1.24 (m, 9H), 0.90 – 0.86 (m, 3H); δC (125 MHz, CDCl$_3$) 173.4, 60.3, 38.1, 35.0, 33.9, 31.8, 30.3, 29.2, 27.8, 25.4, 22.6, 22.5, 22.0, 14.3 and 14.1; δ_{Se} (95 MHz, CDCl$_3$) 267; ν_{max} (neat) 2957, 2828, 1737 cm^{-1}; HRMS C$_{15}$H$_{30}$O$_2$SeNa requires 345.13032; found 345.13034.

Ethyl 5-(tert-butylseleno)pentanoate 17 (R = *tert*-Bu) was isolated in 50% yield as a yellow oil. δ_H (500 MHz, CDCl$_3$) 4.10 (q, *J* = 7.1 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.1 Hz, 2H), 1.76 – 1.63 (m, 4H), 1.42 (s, 9H) and 1.23 (t, *J* = 7.1 Hz, 3H) ppm; δ_C (125 MHz, CDCl$_3$) 173.36, 60.23, 38.54, 33.84, 32.51, 30.18, 25.55, 21.31 and 14.23 ppm; δ_{Se} (95 MHz, CDCl$_3$) 377.61 ppm; ν_{max} (neat) 2948, 2931, 2855, 1731, 1451, 1366, 1268, 1247, 1182, 1156, 1116 and 1030 cm^{-1}; HRMS C$_{11}$H$_{22}$O$_2$SeAg requires 372.98305; found 372.98301.

Kim ester 13 (R = *n*-Oct) was isolated in 49% yield as an oil. δH (500 MHz, CDCl$_3$) 3.79 (s, 3H, CH$_3$), 2.60 – 2.52 (m, 9H), 1.89 – 1.75 (m, 4H), 1.67 – 1.61 (m, 2H), 1.39 – 1.24 (10H, m), 0.88 (t, J = 6.8 Hz); δC (125 MHz, CDCl$_3$) 196.7, 169.6, 42.7, 31.8, 31.0, 30.6, 30.0, 29.8, 29.2, 29.1, 24.6, 24.2, 22.9, 22.6, 18.7 and 14.1 ppm; δSe (95 MHz, CDCl$_3$) 161; ν_{max} (neat) 2955, 1797, 1739 cm^{-1}; HRMS C$_{16}$H$_{31}$NO$_2$S$_2$SeNa requires 436.08536; found 436.08549.

Kim ester 13 (R = 2-Oct) was isolated in 57% yield as an oil. δH (500 MHz, CDCl$_3$) 3.79 (s, 3H, CH$_3$), 2.97 – 2.92 (m, 1H), 2.62 – 2.52 (m, 7H), 1.90 – 1.76 (m, 4H), 1.66 – 1.51 (m, 4H), 1.50 – 1.24 (7H, m), 0.89 (t, J = 6.7 Hz); δC (125 MHz, CDCl$_3$) 196.7, 169.6, 42.7, 38.8, 35.2, 31.8, 31.0, 30.0, 29.1, 27.8, 24.8, 22.6, 22.5, 21.6, 18.7 and 14.1 ppm; δSe (95 MHz, CDCl$_3$) 266; ν_{max} (neat) 2954, 1798, 1739 cm^{-1}; HRMS C$_{16}$H$_{31}$NO$_2$S$_2$SeNa requires 436.08536; found 436.08552.

Kim ester 13 (R = *tert*-Bu) was isolated in 66% yield as an oil. δ_H (500 MHz, CDCl$_3$) 3.79 (s, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.56 (s, 3H), 2.54 (t, *J* = 7.3 Hz, 2H), 1.91 – 1.73 (m, 5H), 1.45 (s, 9H) ppm; δ_C (125 MHz, CDCl$_3$) 196.77, 169.60, 42.67, 38.82, 32.52, 30.99, 29.96, 24.93, 21.00 and 18.66 ppm; δ_{Se} (95 MHz, CDCl$_3$) δ 376.36 ppm; ν_{max} (neat) 3449, 3015, 2970, 2940, 1737, 1434, 1366, 1228, 1217, 1203, 1092, 895 and 776 cm^{-1}; HRMS C$_{12}$H$_{23}$NO$_2$S$_2$SeAg requires 463.93809; found 463.93836.

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Notes and references

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† Electronic Supplementary Information (ESI) available: General procedures for the preparation of **13** and **17** (R ≠ Bn). Figures S1 – S3 depicting the dependance of [**14**]/[**15**] on thiol concentration for the cyclization of **10** (R = *n*-Oct, 2-Oct, *tert*-Bu) in benzene. Gaussian Archive Entries for all transitions states **18** and related structures calculated in this study. ^{1}H, ^{13}C and ^{77}Se spectra of **13**, **15** and **17** (R ≠ Bn). (49 pages). See DOI: 10.1039/b000000x/

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