The cyclization of *N*-butylpent-4-enylaminyl revisited: a combined theoretical and experimental study †

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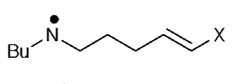
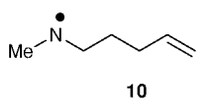
The cyclization reactions of *N*-methylpent-4-enylaminyl (**10**), hex-5-enyl (**11**) and pent-4-en-1-oxyl (**12**) radicals were investigated theoretically at the CBS-RAD(B3LYP, B3LYP) level of theory. In all three cases the correspondence between calculated and experimental data was excellent. *N*-Methylpent-4-enylaminyl (**10**) is predicted to undergo irreversible ($\Delta G = -5.4$ kcal mol^{-1}; $\Delta G^{\ddagger} = 12.1$ kcal mol^{-1}) cyclization through the 5-*exo* manifold. The role of $(Bu_3Sn)_2O$ in the reactions of arenesulfenamides **6**–**9** and *N*-butyl-2-[(phenylselenyl)methyl]-pyrrolidine (**15**) with Bu_3SnH in benzene at 80 °C has been reassessed. The purpose of $(Bu_3Sn)_2O$ in these reactions is to scavenge 2-mercaptobenzothiazole and PhSeH, respectively, which are produced *in situ* from the reaction of adventitious bis(benzothiazol-2-yl) disulfide and PhSeSePh, respectively, and Bu_3SnH. The reaction of *N*-butyl-2-[(phenylselenyl)methyl]pyrrolidine (**15**) with Bu_3SnH was reinvestigated and found to produce only *N*-butyl-2-methylpyrrolidine (**16**) thus confirming the irreversible nature of the cyclization of *N*-methylpent-4-enylaminyl (**10**) under the conditions employed in this study.

Introduction

We have previously reported on the preparation of arenesulfenamides and their utility as precursors to dialkylaminyl radicals in the presence of Bu_3SnH.[1c] Moreover, we have investigated the cyclization reactions of the *N*-butylpent-4-enylaminyls (**1**–**4**) through a detailed *pseudo*-first order kinetic rate study.[1a,b] The critical outcomes from these studies were that (i) the *N*-butylpent-4-enylaminyl (**1**) undergoes slow, irreversible cyclization to the pyrrolidinylmethyl radical (**5**) under the prevailing reaction conditions and (ii) that $(Bu_3Sn)_2O$ appeared to accelerate the rate of cyclization of aminyls **1**–**4**. These results were at odds with the literature, which suggested that the cyclization of **1** was a reversible process.[2] Indeed, our disclosure evoked a critical response[3] which defended the *status quo* and described our results as "spurious". We now wish to respond to the criticisms (i) by reassessing the role of $(Bu_3Sn)_2O$ in the Bu_3SnH mediated cyclization of the arenesulfenamides **6**–**9**, (ii) by providing additional experimental evidence relevant to the ring opening of the pyrrolidinylmethyl radical (**5**) and (iii) by reporting the results of a high level molecular orbital study of the cyclization of *N*-methylpent-4-enylaminyl (**10**), hex-5-enyl (**11**) and pent-4-en-1-oxyl (**12**).



1 X = H
2 X = $SiEt_3$
3 X = Me
4 X = Ph



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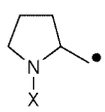
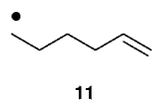


5 X = Bu
23 X = Me



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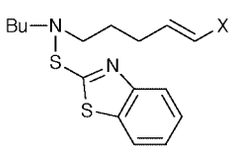
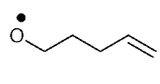


6 X = H
7 X = $SiEt_3$
8 X = Me
9 X = Ph



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Role of $(Bu_3Sn)_2O$ in the Bu_3SnH mediated cyclization reactions of arenesulfenamides 6–9

As reported previously,[1a,b] the presence of added $(Bu_3Sn)_2O$ in the reactions of the arenesulfenamides **6**–**9** with Bu_3SnH in benzene at 80 °C under *pseudo*-first order conditions was essential to ensure reproducible kinetic data. This puzzling and unexpected result led us to suggest that the influence of $(Bu_3Sn)_2O$ in these reactions may have been due to a Lewis acid-type interaction between $(Bu_3Sn)_2O$ and aminyls **1**–**4**, and that this putative interaction was responsible for accelerating their rates of cyclization. Since the completion of that study, however, additional information from other laboratories became available which questioned our conclusions regarding the function of $(Bu_3Sn)_2O$ in these reactions. Most significantly, Newcomb and coworkers[3] investigated the cyclization of the closely related aminyl **13** in the presence of $(Bu_3Sn)_2O$ in both benzene and THF using laser flash photolysis (LFP) and found no evidence for catalysis. This observation, coupled with the findings of Crich and coworkers[4]—that PhSeSePh reacts

† Calculated energies and Cartesian coordinates of optimized structures are available as supplementary data on-line. For direct electronic access see http://www.rsc.org/suppdata/p2/a9/a909747c. NMR spectra of compounds **20**, **21** and **15** are also available from BLDSC (SUPPL. NO. 57692, 11 pp.) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

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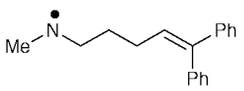
rapidly with Bu_3SnH to produce $PhSeSnBu_3$ and PhSeH—prompted Newcomb and coworkers[3] to speculate that the arenesulfenamides **6**–**9** used in our study may have been contaminated by "disulfide", and that the function of $(Bu_3Sn)_2O$ was to react with *in situ* produced "arylthiol". These suggestions motivated us to investigate the reactions of Bu_3SnH and $(Bu_3Sn)_2O$ with bis(benzothiazol-2-yl) disulfide ($(MBT)_2$) and 2-mercaptobenzothiazole (MBT) under the prevailing reaction conditions as a means of reassessing the role of $(Bu_3Sn)_2O$ in the Bu_3SnH mediated cyclization reactions of the arenesulfenamides **6**–**9**.

Reaction of a mixture of Bu_3SnH, $(MBT)_2$ and $(Bu_3Sn)_2O$ in benzene, in the presence of catalytic AIBN, at 80 °C for 1 h produced benzothiazol-2-yl tributylstannyl sulfide (**14**). There



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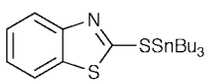

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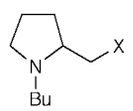
was no detectable $(MBT)_2$. Furthermore, the reaction of $(Bu_3Sn)_2O$ and MBT in benzene at 80 °C for 1 h produced only **14**.[5] These reactions demonstrate unequivocally the ability of the Bu_3SnH–$(Bu_3Sn)_2O$ reagent system to effectively consume both $(MBT)_2$ and MBT in benzene at 80 °C. On the basis of these findings it is now clear that the lack of reproducibility encountered with our kinetic studies in the absence of added $(Bu_3Sn)_2O$ was due to small amounts (undetectable by ^1H NMR, ≤1%) of either MBT and/or $(MBT)_2$ present in the arenesulfenamide **6**. Thus, the initial *pseudo*-first order kinetic experiments performed with the arenesulfenamide **6** (Fig. 1 of ref. 1a) were quite probably conducted in the presence of small, but varying, amounts of MBT,[4] which is likely to be a more effective H-transfer agent than Bu_3SnH.[6]

In the light of these new results the role of $(Bu_3Sn)_2O$ in the reactions of arenesulfenamides **6**–**9** with Bu_3SnH in benzene at 80 °C under *pseudo*-first order conditions is now clear. Specifically, the purpose of $(Bu_3Sn)_2O$ was to consume MBT, thus ensuring a *thiol-free* reaction medium. Thus, the kinetic data reported previously[1a] can now be interpreted unambiguously. In the reactions of **6** with Bu_3SnH (Fig. 1 of ref. 1a) the observed variability between each of the kinetic runs can be rationalized as a compromise between adventitious $(Bu_3Sn)_2O$ in the Bu_3SnH[1a] and the $(MBT)_2$/MBT impurities present in the arenesulfenamide **6** employed, whereas the same reactions in the presence of added $(Bu_3Sn)_2O$ (Fig. 4 of ref. 1a) give rise to reproducible kinetic data which conform to *psuedo* first-order kinetics.[7] Furthermore, the data depicted in Fig. 2 of reference 1a clearly demonstrate the ability of $(Bu_3Sn)_2O$ to effectively scavenge adventitious MBT present in low concentrations. Therefore, we now suggest that the kinetic data of ref. 1a (represented in Figs. 4 and 6 of ref. 1a) *should now be accepted as true representations of the reactions of the arenesulfenamides* **6**–**9** *with* Bu_3SnH *under neutral, thiol-free reaction conditions.* Accordingly, cyclization rate constants for the aminyls **1**–**4** at 80 °C can be extracted from these data (Table 1). The cyclization rate constant (k_c) for **1** of 2.5×10^4 s^{-1} differs from that suggested by Newcomb and coworkers[3] by a factor of ≈6 ($k_c = (14.6 \pm 0.6) \times 10^4$ s^{-1} at 80 °C).[3] Our determination for k_c for **4** (4.2×10^6 s^{-1} at 80 °C), however, is in reasonable agreement with that obtained by Newcomb and coworkers[3] (k_c (80 °C) = 1.1×10^6 s^{-1}) and that determined by Lusztyk and coworkers[9] (k_c (22 °C) ≤ 3.8×10^5 s^{-1}) for the *N*-methyl analogue of **4** using the more reliable LFP method.

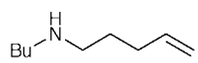
Table 1 Cyclization rate constants (k_c) for the *N*-butylpent-4-enylaminyls (**1**–**4**) in benzene at 80 °C

Aminyl	$(k_{NH}{}^a/k_c)/M^{-1}$	k_c/s^{-1}
1 (X = H)	68.3	2.5×10^4
2 (X = $SiEt_3$)	56.1	3.0×10^4
3 (X = Me)	32.3	5.3×10^4
4 (X = Ph)	0.4	4.2×10^6

[a] k_{NH} (80 °C) = 1.7×10^6 M^{-1} s^{-1} [derived from the Arrhenius parameters for the H-transfer reactions from Bu_3SnH to dialkylaminyl radicals ($\log k_{NH} = (9.11 \pm 0.21) - (4.66 \pm 0.28)/2.303RT$)].[8]



15 X = SePh
16 X = H



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The reaction of *N*-butyl-2-[(phenylselenyl)methyl]pyrrolidine (15) with Bu_3SnH

We have previously claimed that the reaction of the phenyl selenide **15** with Bu_3SnH at 80 °C resulted in the exclusive formation of *N*-butyl-2-methylpyrrolidine (**16**).[1a,b] However, Newcomb and coworkers, have reported that this same reaction at either 50 or 80 °C, produces both **16** and the ring opened product **17**, and have suggested a rate constant for the ring opening of radical **5** of $(5.1 \pm 0.2) \times 10^4$ s^{-1} at 80 °C.[3] In the light of the recent work of Crich and coworkers (*vide supra*) our claims[1a] were questioned, as it was argued that even small amounts of PhSeSePh in our sample of **15** would be capable of significantly influencing the reaction outcome, since PhSeH (from the reaction of PhSeSePh and Bu_3SnH) is a superior H-transfer agent than Bu_3SnH.[10]

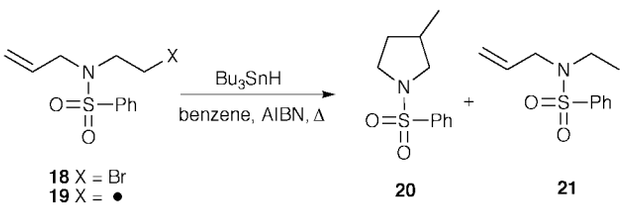
In order to address the issue of possible contamination of the phenyl selenide **15** initially employed[1a] with adventitious PhSeSePh, the reaction between Bu_3SnH and phenyl selenide **15** has been reinvestigated. The Bu_3SnH[1a] used in this work was distilled twice immediately before use, whereas the phenyl selenide **15** utilized was a colourless liquid acquired using Newcomb's procedure.[2] Gas chromatographic (GC) analysis of the reaction mixture produced from the reaction of **15** and Bu_3SnH (10 equivalents, 0.01 M, catalytic AIBN) in benzene (80 °C, 3 h) indicated the complete absence of the acyclic amine **17**; the pyrrolidine **16** was the only amine product identified. According to Newcomb's published results[3] ~8% of **17** should have been produced. This result clearly demonstrates that the ring opening of the pyrrolidinylmethyl radical **5** is not competitive with H-transfer from Bu_3SnH under the conditions employed in this study and certainly not consistent with a ring opening rate constant of $(5.1 \pm 0.2) \times 10^4$ s^{-1}.[3]

Is $(Bu_3Sn)_2O$ an effective scavenger for PhSeH?

As demonstrated above $(Bu_3Sn)_2O$ functions as an effective scavenger for adventitious MBT in the reactions of the sulfenamides **6**–**9** and Bu_3SnH. Accordingly, we reasoned that $(Bu_3Sn)_2O$ may be capable of scavenging PhSeH with similar efficacy and thus may find a role as a protective agent in Bu_3SnH mediated radical reactions involving phenyl selenide precursors. For this to be the case the rate of consumption of *in situ* generated PhSeH, by $(Bu_3Sn)_2O$ must be sufficiently rapid so as to ensure complete consumption of *in situ* produced PhSeH prior to the commencement of the radical reaction in question. Thus, the first task was to show that PhSeH and $(Bu_3Sn)_2O$ react to generate radically inert products. To this end, addition of one equivalent of $(Bu_3Sn)_2O$ to *in situ* produced PhSeH (from one equivalent of PhSeSePh and one equivalent of Bu_3SnH[4]) in d_6-benzene at room temperature, resulted in the immediate formation (*i.e.* upon mixing) of a cloudy solution. Analysis of this solution by ^{77}Se and ^{119}Sn NMR indicated the absence of PhSeH; the only ^{77}Se signal in

the ^{77}Se NMR spectrum was that due to $PhSeSnBu_3$.[11] Although this data is of little quantitative value it demonstrates the ability of $(Bu_3Sn)_2O$ to consume PhSeH. A more quantitative assessment of this process was obtained through the reinvestigation of Bu_3SnH mediated cyclization reactions in the presence of PhSeSePh with and without added $(Bu_3Sn)_2O$.

Padwa and coworkers have previously shown that sulfonamide **18**, when exposed to Bu_3SnH in benzene in the presence of catalytic AIBN, undergoes reductive cyclization through the 5-*exo*-trig manifold to give the pyrrolidine **20** in excellent yield (Scheme 1).[12] Although these workers did not determine the

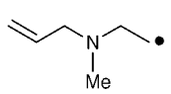


18 X = Br
19 X = •

20 **21**

Scheme 1

cyclization rate constant for this process they did speculate that it is about an order of magnitude greater than that of the hex-5-enyl radical (**11**). More recently, Della and Knill determined the Arrhenius parameters for the cyclization of the related radical, 3-methyl-3-azahex-5-enyl radical (**22**).[13] At 80 °C **22** undergoes



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cyclization with a rate constant of 6.8×10^7 s^{-1}. Reaction of **18** (0.12 M) with 1.4 equivalents of Bu_3SnH in benzene at 80 °C for 2 h produced a 98 : 2 mixture of **20** and **21** as determined by ^{1}H NMR integrations. As anticipated, and in keeping with Crich's observations,[4] the same experiment in the presence of 20 mol% PhSeSePh produced a mixture of **20** and **21** in a ratio of 91 : 9. When this latter experiment was repeated in the presence of one equivalent of $(Bu_3Sn)_2O$ the original ratio for **20** and **21** of 98 : 2 was reestablished, thereby demonstrating the ability of $(Bu_3Sn)_2O$ to effectively scavenge *in situ* produced PhSeH prior to the onset of the radical reaction. Superficially, this set of experiments provides good evidence that $(Bu_3Sn)_2O$ is capable of functioning as a protective agent for PhSeH compromised radical reactions. However, closer scrutiny of the data obtained reveals a more complicated situation.

An approximate cyclization rate constant of 3.7×10^7 s^{-1} for the 5-*exo*-trig cyclization of **19** at 80 °C is available from the reaction of **18** with Bu_3SnH alone, using an average concentration for Bu_3SnH (0.11 M).[10] This value compares favourably with that obtained for **22** (6.7×10^7 s^{-1}).[13] In the presence of 20 mol% PhSeSePh (*i.e.* 20 mol% PhSeH, 0.024 M), however, the anticipated ratio of **20** : **21** is 0.67. This value differs significantly from the experimentally derived value of 10 obtained from this study. Indeed, to get a ratio of 10 for **20** : **21** the concentration of PhSeSePh, thus PhSeH, required would be 0.0016 M, or just 6.6% of the actual amount of PhSeSePh added (38 mg). In other words, only ~2.5 mg out of the 38 mg added were involved in the reaction with **19**. The balance, ~35.5 mg was evidently involved in other reactions. This analysis suggests that the *in situ* generated PhSeH is being consumed either before and/or during the radical reaction. The most probable process likely to deliver this outcome is the reaction of PhSeH with Bu_3SnH. Indeed, Crich and coworkers have recently observed this process.[4] Thus in this particular case, 35.5 mg of PhSeSePh would require 66 mg of Bu_3SnH (2 equivalents, assuming a 1 : 1 stoichiometry for the reaction of PhSeH and Bu_3SnH) which would then leave sufficient Bu_3SnH (181 mg, 1.04 equivalents) to ensure the complete consumption of **18**. Indeed, this was observed. Finally, in the presence of an equivalent of $(Bu_3Sn)_2O$ the ratio of **20**/**21** was restored to its original value of 50, thus indicating that $(Bu_3Sn)_2O$ is more effective than Bu_3SnH at scavenging PhSeH.

Further evidence in support of the above observations was obtained from an analogous set of experiments involving 7-bromoheptene. Beckwith and Moad have shown that the hept-6-enyl radical undergoes predominantly 6-*exo*-trig cyclization with a rate constant of $\sim 2 \times 10^4$ at 65 °C.[14] Exposure of 7-bromoheptene to Bu_3SnH (10 equivalents, 0.0029 M, catalytic AIBN) in benzene at 65 °C produced a mixture of methylcyclohexane and hept-1-ene in a ratio of 46 : 54 (GC; uncorrected). Interestingly, the same reaction in the presence of 15 mol% PhSeSePh produced methylcyclohexane and hept-1-ene in the ratio of ~1 : 1 which represents an increase in the extent of cyclization. This result is in accord with the above observations and points to the sufficiently rapid consumption of *in situ* produced PhSeH by Bu_3SnH, this time present in considerable excess.[4]

Thus, the results from the above experiments with both **18** and 7-bromoheptene provide compelling evidence for the case that (i) both Bu_3SnH and $(Bu_3Sn)_2O$ are capable of consuming PhSeH under standard radical reaction conditions and (ii) that $(Bu_3Sn)_2O$ is a more effective scavenger for PhSeH than is Bu_3SnH. Consistent with these observations, even the reaction of "impure" **15**[3] with Bu_3SnH (10 equivalents, 0.018 M) in benzene at 80 °C, in the presence of 1 equivalent $(Bu_3Sn)_2O$, would be expected to produce the pyrrolidine **16**, exclusively. This was found to be the case, as the presence of excess Bu_3SnH is capable of consuming any *in situ* produced PhSeH.

Finally, in the light of the above findings it is appropriate to reflect on the recent work of Crich and coworkers.[4] These workers demonstrated unambiguously the practical utility of controlled quantities of PhSeH in Bu_3SnH mediated radical reactions. It must be understood, however, that in that work the addition of Bu_3SnH was always performed dropwise over several hours to a solution of the radical precursor and PhSeSePh, thereby maintaining a very low effective concentration of Bu_3SnH. Evidently, such a reaction regime overcomes the competing reaction of Bu_3SnH and PhSeH.

Molecular orbital study of the cyclizations of *N*-methylpent-4-enylaminyl (10), hex-5-enyl (11) and pent-4-en-1-oxyl (12) radicals

Computational methods. Molecular orbital calculations[15] were performed using the Gaussian 94 program.[16] Calculations were performed at the CBS-RAD(B3LYP,B3LYP) level.[17] This is a composite method aimed at obtaining highly accurate heats of formation for radical systems, based on the CBS-Q method of Petersson *et al.*[18] The CBS family of model chemistries combines an extrapolation to the complete basis set (CBS) limit with smaller basis set higher-order correlation energies to provide accurate energies. In the original CBS-Q method, energies are evaluated upon geometries optimized at the MP2/6-31G† level (using all electrons), while frequencies used in the evaluation of the zero-point energy are calculated at the HF/6-31G† level. In CBS-RAD(B3LYP,B3LYP) both geometries and frequencies are calculated at the B3LYP/6-31G(d) level. The zero-point vibrational energy (ZPE) and temperature correction scaling factors used are those appropriate for this level of theory, and have been taken from the recent study by Scott and Radom.[19] In addition, the coupled-cluster energy (CCSD(T)) is used in place of the quadratic configuration interaction energy (QCISD(T)) in single-point energy calculations.

The CBS-RAD(B3LYP,B3LYP) energies are derived from energies calculated at the HF/6-311++G(3d2f,2df,2p) level augmented by corrections from higher level calculations. These

include the following terms, (i) a correction for the truncation of the one-electron basis set through an extrapolation to the complete basis set second-order limit, *E*2(CBS), (ii) an interference correction which accounts for the difference in the CBS correction for the approximate full-CI (in this case CCSD(T)) and second-order energy, Δ*E*(INT), (iii) a correction to account for effects of spin contamination on the Møller–Plesset perturbation expansion, Δ*E*(SPIN). This is scaled by an empirical parameter to improve the calculated dissociation energies, (iv) an empirical correction which corrects the tendency to underestimate dissociation energies, Δ*E*(EMP) (these corrections, *E*2(CBS), Δ*E*(INT), Δ*E*(SPIN) and Δ*E*(EMP) are calculated at the 6-311++G(3d2f,2df,2p) basis level) and (v) two higher-order correction terms:

$$\Delta E(\text{MP3,4}) = \text{MP4(sdq)/6-31+G(d(f),p)} - \text{MP2/6-31+G(d(f),p)}$$ and

$$\Delta E(\text{CC}) = \text{CCSD(T)/6-31+G†} - \text{MP4(sdq)/6-31+G†}$$

The total CBS-RAD(B3LYP,B3LYP) energy (at 0 K) is then given by:

$$E_0 = \text{HF/6-311++G(3d2f,2df,2p)} + E2(\text{CBS}) + \Delta E(\text{INT}) + \Delta E(\text{SPIN}) + \Delta E(\text{EMP}) + \Delta E(\text{MP3,4}) + \Delta E(\text{CC}) + \text{ZPE}$$

Heats of formation at 298 K were calculated using the atomization method as outlined by Nicolaides *et al*.[20] using experimental 0 K heats of formation and thermal corrections for atoms.[21] For each of the separate components of the CBS-RAD(B3LYP,B3LYP) energy the HF wavefunction was verified to be stable. We have estimated the effect of solvent (benzene) on the calculated rates of cyclization using the SCI-PCM model, evaluated at the HF/6-31G(d) level. Relative permittivities of 2.17 (30 °C) and 2.27 (80 °C)[22] were used with an isodensity cut-off value of 0.001.

Results and discussion

We have previously reported results of *ab initio* calculations on the cyclization of *N*-methylpent-4-enylaminyl (**10**) at the UMP2/6-31G*//UHF/6-31G* level of theory.[23] The outcomes of that study were that (i) the 5-*exo* mode of cyclization is preferred by 6.6 kcal mol^{-1}, (ii) there is a significant barrier to cyclization *via* the 5-*exo* mode (14.1 kcal mol^{-1}) and (iii) the 5-*exo* cyclization of **10** to **23** is a highly exothermic process (14.8 kcal mol^{-1}). The results of that study were criticized by Newcomb and coworkers as being unreliable.[3] In response, these workers reinvestigated the cyclization of **10** at several levels of theory.[3] Surprisingly, their work focussed only on the thermodynamics (Δ*G*) of the conversion of **10** to **23**. *No effort was made to calculate the barrier to reaction (*$\Delta G^{\ddagger}$*) despite their focus on the kinetic aspects of these processes*. The conclusion of that study was that the conversion of **10** to **23** is only slightly exothermic with values of −1.0 and 0.0 kcal mol^{-1} being preferred for Δ*G*.[3] We now disclose the results of a more sophisticated theoretical analysis of the cyclization reactions of **10**.[24] Additionally, the 5-*exo*:6-*endo* reaction manifolds for hex-5-enyl (**11**) and pent-4-en-1-oxyl (**12**) radicals have also been investigated at the same level of theory. These latter studies were performed in order to assess the quality of the calculations at this level of theory through comparison with well established experimental data.

Calculated heats of formation (ΔH_f°, 298 K) for each of the stationary points are presented in Table 2. Individual components of the CBS-RAD(B3LYP,B3LYP) energies and geometries (optimized at the B3LYP level of theory) are available as supporting information. The lowest energy conformation of **10** is the fully extended (all *trans*), **E**. Cyclization involves at least two other intermediates, either the $\mathbf{G_{12}}$ or $\mathbf{G_{23}}$ *gauche* conformations (in which the conformation about the C(1)–C(2) and C(2)–C(3) bonds, respectively, are *gauche*), and the $\mathbf{G_{12}G_{23}}$ conformation (in which the conformation about both the C(1)–C(2) and C(2)–C(3) bonds is *gauche*). $\mathbf{G_{12}}$ and $\mathbf{G_{23}}$ lie less than 0.5 kcal mol^{-1} higher in energy (Δ*H*, 298 K) than **E**, while $\mathbf{G_{12}G_{23}}$ lies roughly 1 kcal mol^{-1} higher than **E**. The lowest energy transition state leading to **23** lies 7.6 kcal mol^{-1} higher than **E**, and connects $\mathbf{G_{12}G_{23}}$ with a conformation of **23** in which the *N*-methyl lies in an axial position.[23] The lowest energy conformation of **23** lies 4.1 kcal mol^{-1} lower than this conformation and 9.1 kcal mol^{-1} lower than **E**. The transition state barriers for rotation about the C(1)–C(2) and C(2)–C(3) bonds and inversion at nitrogen in **23** are all expected to be less than the transition barrier for cyclization. The six-membered ring *endo* product lies 11.8 kcal mol^{-1} lower than **E** and proceeds through a transition state lying 10.7 kcal mol^{-1} higher than $\mathbf{G_{12}G_{23}}$ and 11.8 kcal mol^{-1} higher than **E**. For the hex-5-enyl (**11**) and pent-4-en-1-oxyl (**12**) radicals the extended geometry is also the lowest energy acyclic form and cyclization also proceeds *via* at least two intermediates analagous to those in the *N*-methylpent-4-enylaminyl radical (**10**).

Table 2 Calculated gas-phase radical heats of formation (ΔH_f°) at 298 K (kcal mol^{-1})

Radical	ΔH_f°
10	48.4
N-Methylpyrrolidinyl-2-methyl	39.3
N-Methylpiperidin-2-yl	36.5
11	41.7
Cyclopentylmethyl	26.4
Cyclohexyl	21.0
12	14.5
(2-Furanyl)methyl	−1.3
Pyran-2-yl	−2.7

Thermodynamic and kinetic parameters for the gas-phase cyclization reactions of radicals **10**, **11** and **12** are listed in Table 3. The cyclization of **10** through the 5-*exo* manifold at 80 °C is predicted to be exergonic ($\Delta G = -5.4$ kcal mol^{-1}), whereas the barrier to cyclization ($\Delta G^{\ddagger}$) is predicted to be 12.1 kcal mol^{-1}. These data translate to a gas-phase rate constant for cyclization for **10** of 2.5×10^5 s^{-1} at 80 °C. Incorporation of solvent effects decreases the rate constant to 7.8×10^4 s^{-1}. This value agrees well with that obtained for the *N*-butyl analogue **1** in boiling benzene ($k_c = 2.5 \times 10^4$ s^{-1} at 80 °C) (Table 4). The calculated *exo*:*endo* ratio for the cyclization of **6** is in accord with that observed experimentally for **1**.[1a,2] Furthermore, the rate constant for the ring opening of **23** in the gas phase is predicted to be 1.1×10^2 s^{-1} at 80 °C ($A = 2.0 \times 10^{12}$ s^{-1}; $E_a = 17.3$ kcal mol^{-1}) at this level of theory. The value in benzene is calculated to be 7.3×10^1 s^{-1}, differing by almost three orders of magnitude from the experimental value of Newcomb and coworkers for the ring opening of **5** (5.1×10^4 s^{-1}).[3]

The quality of the theoretical predictions for the cyclization of radicals **11** and **12** (Table 3) is particularly satisfying. In both cases, the experimentally observed *exo*:*endo* ratio is reproduced. The calculated rate constants for 5-*exo* cyclization of **11** (8.2×10^6 s^{-1} at 80 °C) and **12** (2.3×10^9 s^{-1} at 30 °C) in benzene are in very good agreement with experimental[25,26] and recent theoretical[27] values (Table 4). The level of agreement between theory and experiment is somewhat surprising, especially from conventional transition state theory and the approximate treatment of solvation effects used in the current procedure. However, the excellent agreement for the cyclization reactions of **11** and **12** does substantiate the reliability of the theoretical predictions for the cyclization of **10**. The structures of the *exo* and *endo* cyclization transition states for the radicals **10**, **11** and **12** are presented in Fig. 1.

Table 3 Calculated thermodynamic and kinetic parameters for the gas-phase cyclization reactions of *N*-methylpent-4-enylaminyl (**10**), hex-5-enyl (**11**) and pent-4-en-1-oxyl (**12**) radicals[a]

	10		**11**		**12**	
	5-*exo*	6-*endo*	5-*exo*	6-*endo*	5-*exo*	6-*endo*
T/°C	80		80		30	
ΔH/kcal mol^{-1}	−9.2	−12.0	−15.5	−20.9	−15.8	−17.2
ΔS/cal K^{-1} mol^{-1}	−10.6	−14.5	−4.9	−12.5	−4.8	−9.0
ΔG/kcal mol^{-1}	−5.4	−6.9	−13.7	−16.5	−14.4	−14.5
$\Delta H^{\ddagger}$/kcal mol^{-1}	7.4	11.7	5.6	8.0	2.0	3.9
$\Delta S^{\ddagger}$/cal K^{-1} mol^{-1}	−13.1	−14.2	−10.5	−11.4	−8.2	−9.5
$\Delta G^{\ddagger}$/kcal mol^{-1}	12.1	16.7	9.3	12.0	4.5	6.8
E_a/kcal mol^{-1}	8.1	12.4	6.3	8.7	2.6	4.5
A/s^{-1}	9.8×10^9	5.7×10^9	3.8×10^{10}	2.3×10^{10}	1.0×10^{11}	5.2×10^{10}
k_c/s^{-1}	2.5×10^5	3.4×10^2	1.2×10^7	2.7×10^5	3.5×10^9	8.2×10^7

[a] $\Delta G = \Delta H - T\Delta S$; $E_a = \Delta H^{\ddagger} + RT$; $A = (k_B T/h)\exp(\Delta S^{\ddagger}/R)$; $k_c = A\exp(-\Delta H^{\ddagger}/RT)$ is the rate constant for cyclization.

Table 4 Comparison of calculated and experimentally derived 5-*exo* cyclization rate constants for radicals **10**, **11** and **12** in benzene

	5-*exo* Cyclization rate constants/s^{-1}		*exo*:*endo*	
	Calculated	Experiment	Calculated	Experiment
10[a]	7.8×10^4	(2.5×10^4)[b]	100:0	100:0[b]
11[a]	8.2×10^6	1.5×10^6[c]	98:2	98:2
12[d]	2.3×10^9	$(4 \pm 2) \times 10^8$[e]	98:2	98:2

[a] 80 °C. [b] k_c for *N*-butylpent-4-enylaminyl (**1**); this work. [c] Ref. 25. [d] 30 °C. [e] Ref. 26.

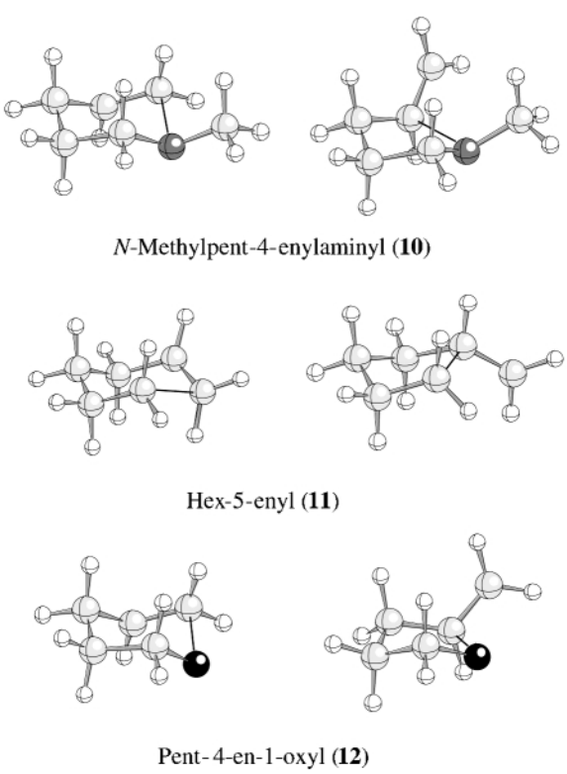

Fig. 1 Structures of the 6-*endo* and 5-*exo* cyclization transition states for the radicals **10**, **11** and **12**.

In the light of the above results a comment on the theoretical studies of Newcomb and coworkers[3] is in order. Newcomb and coworkers used the results of a *selected* set of calculations to support their claim that 5-*exo* cyclization of **10** is reversible. Their results show that a large free energy difference (−10.8 to −11.8 kcal mol^{-1}) is predicted by conventional molecular orbital methods when electron correlation is applied with even a rather modest-sized basis set, for example UMP2/6-31G(d). Small differences in free energy were predicted only in those cases where basis sets without polarization functions were used, UHF/3-21G and MP4/6-31G, or where correlation effects were ignored, UHF/6-31G(d). Accurate energies cannot be expected under these circumstances. This is confirmed by their calculations on the addition of aminyl to ethylene.[3] Substantial free energy differences (−9.3 to −11.7 kcal mol^{-1}) were predicted with reliable procedures, such as the G2 method.[3] On the other hand, the use of unpolarized basis sets along with the omission of electron correlation produced energy differences which are considerably smaller (−3.6 kcal mol^{-1}),[3] whereas density functional (DFT) methods predicted a large free energy difference for the addition of aminyl to ethylene, which is in reasonable agreement with the results from conventional molecular orbital (MO) methods.[3] Interestingly, DFT predicts a small energy difference for the 5-*exo* cyclization reaction.[3] While DFT can provide accurate energies, it is also subject to occasional (and often unpredictable) errors.[28]

Table 5 Comparison of calculated and experimental dissociation energies (298 K, kcal mol^{-1})

	CBS-RAD (B3LYP, B3LYP)	B3LYP/ 6-311+ G(3df,2p)	Expt.[a]
$CH_3NH_2 \rightarrow NH_2 + CH_3$	85.2	79.0	84.9 ± 1.1
$(CH_3)_2NH \rightarrow CH_3NH + CH_3$	82.3	74.0	82.2 ± 2.5

[a] Ref. 29.

In Table 5 we present the calculated C–N dissociation energies of methylamine and dimethylamine at the CBS-RAD(B3LYP,B3LYP) and B3LYP/6-311++G(3d2f,2df,2p) levels and compare these with experimental estimates.[29] The CBS-RAD(B3LYP,B3LYP) method performs exceptionally well in reproducing the experimental energies to within 0.2 kcal mol^{-1}. The B3LYP method, however, shows quite large errors, 5.9 and 8.2 kcal mol^{-1}, larger than the energy difference between **10** and **23** at the CBS-RAD(B3LYP,B3LYP) level. Substantial improvement in the DFT results can be seen with use of the BLYP and B3P86 functionals for these reactions.[30] Regrettably, Newcomb and coworkers used the results of B3LYP calculations and small basis set MO to drive home their argument for a reversible cyclization reaction.[3] Our calculations have been performed at a level of theory that was designed to produce accurate heats of formation for free radical systems. Moreover, this level of theory has also been shown to perform well for radical addition reactions.[31] In particular, the CBS-RAD method should provide reliable results for systems that experience large amounts of spin contamination. In the calculations reported here, $\langle S^2 \rangle$ is no greater than 1.02 for

the transition states, and no greater than 0.80 for the minima. The spin contamination correction, therefore, accounts for no more than 1.5 kcal mol^{-1} in the calculated barrier,[32] and has little effect on the values of ΔG.[33]

Conclusions

In this paper the results of a new high level molecular orbital study of the cyclization reaction of *N*-methylpent-4-enylaminyl (**10**) have been described. The salient features of this study are (i) that **10** undergoes exclusive cyclization through the 5-*exo* cyclization mode, (ii) that there is a significant barrier to cyclization (12.1 kcal mol^{-1}) and (iii) that the overall process is exergonic (−5.4 kcal mol^{-1}). These parameters are consistent with a relatively slow, *irreversible* cyclization. Indeed, the calculated (solvent corrected) rate constant for cyclization of **10** at 80 °C of 7.8×10^4 s^{-1} is in good agreement with the experimental value for **1** at 80 °C ($k_c = 2.5 \times 10^4$ s^{-1}). In order to validate the data obtained from this theoretical study we also investigated the cyclization reactions of hex-5-enyl (**11**) and pent-4-en-1-oxyl (**12**) radicals at the same level of theory. To this end, we were delighted to find that the experimental data for the cyclizations of **11** and **12** were effectively reproduced. Experimentally, the role of $(Bu_3Sn)_2O$ in the reactions of the arenesulfenamides **6**–**9** with Bu_3SnH has been reassessed. We now suggest that the role of $(Bu_3Sn)_2O$ was to ensure a *thiol-free* reaction environment through the scavenging of MBT. Additionally, both Bu_3SnH[4] and $(Bu_3Sn)_2O$ are capable of reacting with PhSeH, with the latter being more effective. Finally, a reinvestigation of the reaction of the phenyl selenide **15** with Bu_3SnH provided no evidence of acyclic amine **17**. We conclude, therefore, that the rate of ring opening of **5** is not competitive with hydrogen transfer from Bu_3SnH under the conditions employed.

Experimental[1a]

Reaction of 2-mercapto-1,3-benzothiazole with $(Bu_3Sn)_2O$[5]

A solution of 2-mercapto-1,3-benzothiazole (1.7 g, 10.2 mmol) and $(Bu_3Sn)_2O$ (2.6 ml, 5.1 mmol) in benzene (40 ml) was heated under reflux for 1 h. The cooled solution was concentrated to dryness under reduced pressure. The ^1H and ^{13}C NMR spectra of the crude (4.6 g, colourless oil) were consistent with literature data for the stannyl sulfide **14**.[5]

Reaction of bis(1,3-benzothiazol-2-yl) disulfide with Bu_3SnH and $(Bu_3Sn)_2O$

A mixture of bis(1,3-benzothiazol-2-yl) disulfide (780 mg, 2.35 mmol), Bu_3SnH (1.2 ml, 4.5 mmol), $(Bu_3Sn)_2O$ (1.2 ml, 2.36 mmol) and a catalytic quantity of AIBN in dry, thiophene free, degassed benzene (25 ml) was heated under reflux for 1 h under an atmosphere of nitrogen. Evaporation of the cooled solution to dryness afforded a colourless oil. ^1H and ^{13}C NMR analysis of the crude revealed a mixture of Bu_3SnH and stannyl sulfide **14**.[5] There was no evidence of bis(1,3-benzothiazol-2-yl) disulfide.

Reaction of phenyl selenide 15 with Bu_3SnH

A mixture of phenyl selenide **15** (1 ml of 0.0187 M solution, 0.0187 mmol), AIBN (few crystals), and Bu_3SnH (54 mg, 0.185 mmol), in dry degassed benzene (17.6 ml) was heated at 80 °C for 3 h. GC analysis of the reaction mixture indicated the presence of only cyclic amine **16**.

Reaction of phenyl selenide 15 with Bu_3SnH in the presence of $(Bu_3Sn)_2O$

A mixture of phenyl selenide **15** (6.6 mg 0.022 mmol), AIBN (few crystals), Bu_3SnH (62 mg, 0.213 mmol), $(Bu_3Sn)_2O$ (12.5 mg, 0.021 mmol) and nonane (3.1 mg) in dry degassed benzene (12 ml) was heated at 80 °C. GC analysis of the reaction mixture after 35 min indicated the presence of only cyclic amine **16**.

Reactions of *N*-(2-bromoethyl)-*N*-(prop-2-enyl)benzenesulfonamide (18) with Bu_3SnH in the presence of PhSeSePh and $(Bu_3Sn)_2O$

A stock solution of the sulfonamide **18**[12] (932 mg, 3.1 mmol), Bu_3SnH (1.15 ml, 4.3 mmol) and AIBN (33 mg) in dry, thiophene-free benzene (25 ml) was prepared at room temperature under nitrogen.

Experiment 1. A 5 ml aliquot of the stock solution was placed in a test tube, sealed and placed in a thermostatted oil bath at 80 °C for 2 h. CCl_4 (0.5 ml) was then added to the solution and heating continued for 2 minutes. The cooled solution was concentrated under reduced pressure. ^1H NMR analysis of the reaction crude indicated a mixture **19** and **20** in a ratio of 98 : 2.

Experiment 2. A 5 ml aliquot of the stock solution and diphenyl diselenide (38 mg, 0.12 mmol, 20 mol%) were placed in a test tube, sealed and placed in a thermostatted oil bath at 80 °C for 2 h. CCl_4 (0.5 ml) was then added to the reaction mixture and heating continued for 2 minutes. The cooled solution was concentrated under reduced pressure. ^1H NMR analysis of the reaction crude indicated a mixture **19** and **20** in a ratio of 91 : 9. (Note: a small quantity of grey precipitate (presumably elemental Se) was also produced.)

Experiment 3. A 5 ml aliquot of the stock solution, diphenyl diselenide (38 mg, 0.12 mmol, 20 mol%) and $(Bu_3Sn)_2O$ (305 μl, 0.6 mmol, 100 mol%) were placed in a test tube, sealed and placed in a thermostatted oil bath at 80 °C for 2 h. CCl_4 (0.5 ml) was then added to the solution and heating continued for 2 minutes. The cooled solution was concentrated under reduced pressure. ^1H NMR analysis of the reaction crude indicated a mixture **19** and **20** in a ratio of 98 : 2.

Reactions of 7-bromoheptene with Bu_3SnH

A mixture of 7-bromoheptene (100 μl of 0.29 M solution, 0.0029 mmol), AIBN (few crystals), Bu_3SnH (80 μl, 0.03 mmol) and dry, degassed benzene (10 ml, total volume) was heated at 65 °C for 6 h. GC analysis (uncorrected) of the cooled reaction mixture indicated the presence of methylcyclohexane and hept-1-ene in a ratio of 0.85 : 1. The same reaction in the presence of PhSeSePh (600 μl of 0.0071 M solution, 0.00043 mmol, 15 mol%) gave rise to a mixture of methylcyclohexane and hept-1-ene in a ratio of 1 : 1.

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33 The CBS method composes energies from calculations at a variety of basis levels and methods of electron correlation, with underlying assumptions of the additivity across calculations using the same basis set or level of electron correlation and the cancellation of errors. Thus, provided any error in the component energies remains roughly constant, it ought to approximately cancel. For example, in the CBS-RAD method, if the MP2 component has an inherent error, provided it remains roughly constant in both the MP2/6-311++G(3d2f,2df,2p) and MP2/6-31+G(d(f),d,p) calculations (where the MP2 energy is used), the error should approximately cancel. It is possible to estimate the error in the cancellation by examining the difference in the MP2 energies at these two basis levels. The MP2 energy difference between structures **10** and **23** is −14.5 and −14.6 kcal mol^{-1} at the MP2/6-311++G(3d2f,2df,2p) and 6-31+G(d(f),d,p) basis levels, respectively. Thus, the likely error (in this component of the CBS-RAD energy) is less than 0.1 kcal mol^{-1}.

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