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Regioselectivity of ring closure of the 2-azonia-2,2,5-trimethyl-5-hexenyl radical

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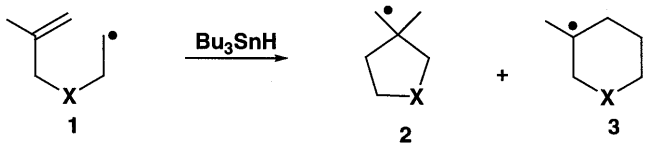
Abstract—The 2-azonia-2,2,5-trimethyl-5-hexenyl radical **9**, derived from treatment of 1-iodo-2,2,5-trimethyl-2-azonia-5-hexenyl iodide **12** with tributyltin hydride, is found to give an 8:3:1 mixture of the isomeric 5-*exo*, 6-*endo* and acyclic ammonium salts. A rationale for the observed regioselectivity is proposed, and a comparison is made with the behaviour of the corresponding all-carbon radical.

Investigations into the regioselectivity associated with ring closure have been reported for a number of 5-methyl substituted hexenyl radicals, with particular interest directed towards determining the factors which influence the 5-*exo* versus 6-*endo* modes of intramolecular addition. The parent radical **1** ($X = CH_2$), which was investigated some years ago by Beckwith and his associates,[1] was shown to yield a 40:60 ratio of the rearranged species **2** and **3** ($X = CH_2$). Intuitively, this observation suggests that the thermochemical stability of the 6-*endo* product **3** dominates those factors which otherwise favour *exo* closure. In fact, a comparison between the kinetic data for cyclisation of the 5-hexenyl radical and **1** ($X = CH_2$) demonstrates that the predominance of 6-*endo* product in the case of the latter is caused primarily by a decrease in the rate of 1,5-closure as a result of the added methyl group.

Table 1. Regioselectivity of ring closure of the radicals **1**

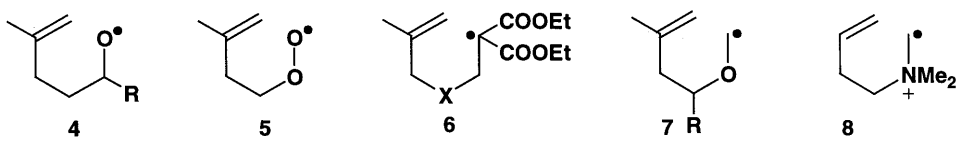
Radical	X	*exo*:*endo*
1	CH_2	40:60
1	O	98:2
1	NTs	100:0

Subsequently, it was discovered that introduction of a heteroatom such as O[2] or N[3] at the 3-position results in a return to prominence of 5-*exo* product, as illustrated by the rearrangement of radicals **1** (X = O) and **1** (X = NTs) (Table 1). This phenomenon was ascribed to an increase in the rate of 5-*exo* closure associated with the more acute C–X–C bond angle present in the hetero-substituted radicals, which has the effect of bringing the two reacting centres closer.



1 2 3

Highly reactive radicals, such as the alkoxy radical **4**, have been shown[4] to produce only the 5-*exo* product, at an extremely rapid rate ($k_c = 10^8$ s^{-1}). Alkenylperoxy radicals such as **5** also undergo regiospecific *exo* ring closure but at a decreased rate.[5] In contrast, the highly stabilised, electrophilic radical **6** has been shown to cyclise with high regioselectivity giving a product derived from 6-*endo* addition exclusively.[6] In the iodine atom-transfer process employed in this ring closure it was shown that ring opening was not competitive with atom transfer; hence this reaction is under kinetic control. The radical **7** however, leads to a 3.2:1 mixture of 5-*exo* and 6-*endo* products.[7]



4 5 6 7 8

Keywords: α-ammonio radicals; heterocyclic synthesis; regioselectivity; radical cyclisation.

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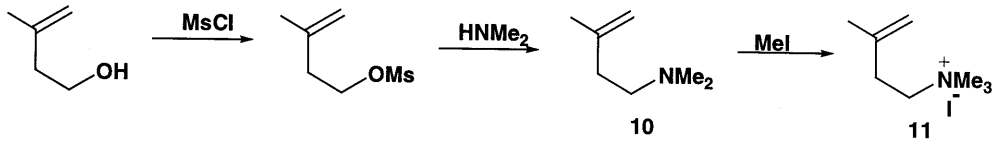
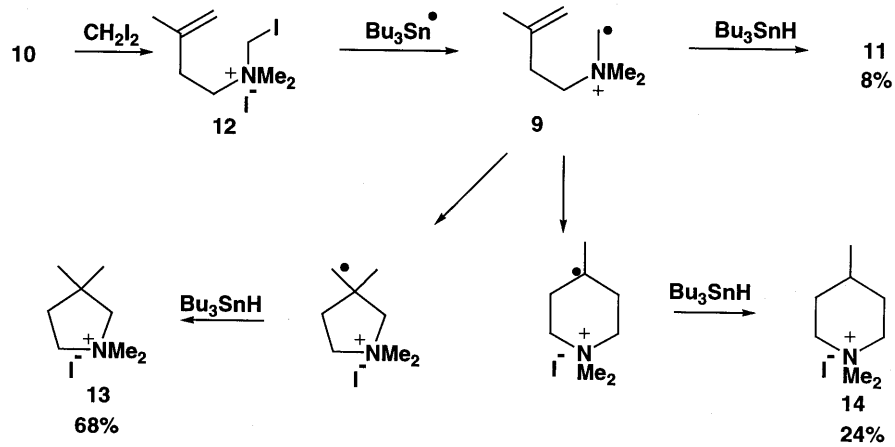


Scheme 1.

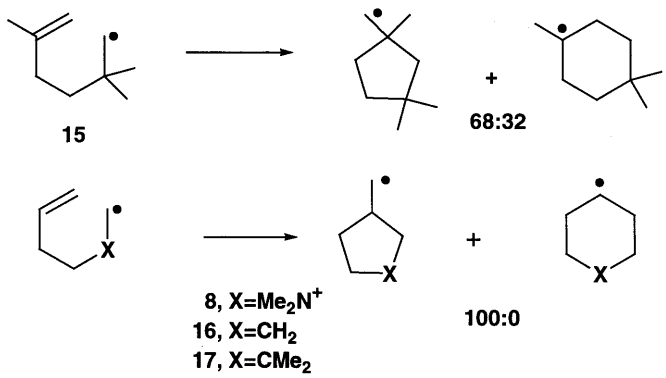


Scheme 2.

We have shown[8] previously that the highly reactive, electrophilic α-ammonium radical **8** undergoes exclusive 5-*exo* ring closure. It was therefore of interest to investigate the species **9** in order to determine whether the added methyl group at C5 has any influence on the regioselectivity of reaction. Employing standard chemistry highlighted previously[8] allowed easy access[9] to the amine **10**, which was converted into an authentic sample of the acyclic reduced product **11** (Scheme 1).

The required precursor **12** was synthesised by treatment of **10** with diiodomethane (Scheme 2). Treatment of the salt **12** with tributyltin hydride under standard conditions[8] led to a product shown by NMR analysis to consist of a mixture of the reduced material **11** (8%), together with the 5-*exo* **13** (68%) and 6-*endo* **14** (24%) salts. The analysis was facilitated by comparison of the ^{1}H and ^{13}C spectra of the mixture with those of **11** and the reported data for the 6-*endo* material **14**.[10] Recrystallisation of the product allowed separation of a pure sample of the major isomer **13** which was identified by comparison of its melting point with that reported[11] and which had NMR spectral properties consistent with those expected for **13**.

It was anticipated that kinetic effects would still govern the cyclisation of the highly reactive α-ammonium radical **9**. Moreover, by analogy with the behaviour of the all-carbon radicals **15** and **17**, the '*gem*-dialkyl effect'[12] would be expected to enhance considerably the formation of the 5 membered ring from **9**. It is noteworthy that the 5-*exo*:6-*endo* ratio increases from 40:60 for **1** ($X = CH_2$)[1] to 68:32 for **15**[13] through the introduction of the *gem*-dimethyl substituents at C2.



Although the regioselectivity displayed in the ring closure of **9** is significantly reduced in contrast with that of the parent α-ammonium radical **8**,[8] which gives the 5-*exo* product exclusively, the species **9** shows a higher regioselectivity (5-*exo*:6-*endo* = 3:1) than its carbocyclic analogue **15** (5-*exo*:6-*endo* = 2:1). This may be ascribed to the effect of the shorter C–N bond lengths in **9**, which would favour 1,5 addition. Interestingly, the polar effect appears to have little impact on the regioselectivity of the reaction. It is noteworthy that the radical **8** is quite electrophilic and, because the methyl substituent is slightly electron-donating, Frontier Molecular Orbital Theory predicts that addition to the unsubstituted terminus would be a favourable process.

In summary, it is proposed that the principal controlling factors in the cyclisation of the α-ammonium radical **9** are kinetic. In common with the behaviour of the all-carbon analogue **15**, the formation of the 5-*exo*-product results from a combination of a stereoelectronic preference for 1,5 addition and a favourable

gem-dimethyl effect. These factors are, however, counterbalanced by a steric retardation in the rate of 1,5 addition by the added methyl group at C5; the 6-*endo*-mode of ring closure now assumes greater significance than in those cases, such as the 2,2-dimethyl-5-hexenyl radicals **8** and **17**, in which the steric effect is absent.

Acknowledgements

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References

1. Beckwith, A. L. J.; Blair, I. A.; Phillipou, G. *Tetrahedron Lett*. **1974**, 2251.
2. Smith, T. W.; Butler, G. B. *J. Org. Chem*. **1978**, *43*, 6.
3. Nimmesgern, H.; Padwa, A.; Wong, G. K. S. *Tetrahedron Lett*. **1985**, *26*, 957; Nimmesgern, H.; Padwa, A.; Wong, G. K. S. *J. Org. Chem*. **1985**, *50*, 5620.
4. Surzur, J. M.; Bertrand, M. P.; Nouguier, R. *Tetrahedron Lett*. **1969**, *48*, 4197.
5. Porter, N. A.; Nixon, J. R.; Gilmore, D. W. *Organic Free Radicals*, A.C.S. Chemical Symposium Series 69; Am. Chem. Soc.: Washington, 1978; Chapter 6.
6. Curran, D. P.; Chang, C. T. *J. Org. Chem*. **1989**, *54*, 3140.
7. (a) Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem*. **1991**, *56*, 5245. (b) Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem*. **1993**, *58*, 7718.
8. (a) Della, E. W.; Knill, A. M.; Smith, P. A. *J. Chem. Soc., Chem. Commun*. **1996**, 1637. (b) Della, E. W.; Smith, P. A. *J. Org. Chem*. **1999**, *64*, 1798.
9. **2,2,5-Trimethyl-2-azonia-5-hexenyl iodide 11**: Treatment of amine **10** with an excess of iodomethane in ether afforded a quantititive yield of the salt **11** which crystallised from EtOH/EtAc as colourless crystals mp 196–198°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 4.92 (s, 2H), 3.75 (m, 2H), 3.44 (s, 9H), 2.54 (m, 2H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 138.7, 114.2, 64.5, 53.3, 30.8, 22.4. Anal. calcd for $C_8H_{18}IN$: C, 37.7%; H, 7.1%; N, 5.5%. Found: C, 37.7%; H, 7.2%; N, 5.5%.
1-Iodo-2,2,5-trimethyl-2-azonia-5-hexenyl iodide 12: 2,5-Dimethyl-2-aza-5-hexene **10**[14] (1.7 g, 15 mmol) was treated with diiodomethane to give the salt **12** which crystallised from EtOH/EtOAc as colourless needles (4.4 g, 77%) mp 126–128°C; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 5.5 (s, 2H), 4.94 (s, 1H), 4.92 (s, 1H), 3.75 (m, 2H), 3.46 (s, 6H), 2.53 (m, 2H), 1.85 (s, 3H). ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 138.1, 113.8, 62.9, 51.1, 33.0, 30.2, 21.9. Anal. calcd for $C_8H_{17}I_2N$: C, 25.2%; H, 4.5%; N, 3.7%. Found: C, 25.5; H, 4.4; N, 3.7%.
Treatment of 12 with tributyltin hydride: **1,1,3,3 tetramethyl 1-azoniacyclopentane iodide 13**: A 0.01 M solution of 1-iodo-2,2,5-trimethyl-2-azonia-5-hexenyl iodide **12** (0.20 g, 0.52 mmol) in 2-methyl-2-butanol was deoxygenated and then heated to reflux before being treated with a solution of tributyltin hydride (0.18 g, 0.62 mmol) and AIBN (ca. 10 mg) in 2-methyl-2-butanol (1 mL) over 10 min. Work up yielded fine white crystals (0.11 g, 88%). The product was shown to consist of a mixture of **11** (8%), **13** (68%) and **14** (24%) by comparison of its ^{1}H and ^{13}C NMR spectra with those of authentic materials.[10,11] Recrystallisation of the mixture twice from EtOH/EtOAc yielded a pure sample of the 5-*exo* species **13** mp 328–330°C (lit. mp[11] 330–332°C).
10. (a) Tsuda, M.; Tsuda, M.; Kawazoe, Y.; Casey, A. F.; Hassan, M. *Chem. Pharm. Bull*. **1974**, *22*, 809. (b) Sugiura, M.; Takao, N. *Org. Magn. Res*. **1982**, *20*, 37.
11. Anderson, A. G.; Wills, M. T. *J. Org. Chem*. **1968**, *33*, 3046.
12. Allinger, N. L.; Zalkow, V. *J. Org. Chem*. **1960**, *25*, 701.
13. Beckwith, A .L. J.; Lawrence, T. *J. Chem. Soc., Perkins Trans. 2* **1979**, 1535.
14. Krafft, M. E.; Juliano, C. A.; Scott, L.; Wright, C.; McEachin, M. D. *J. Am. Chem. Soc*. **1991**, *113*, 1693.