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A Theoretical and Experimental Investigation of the Kinetics of Ring Closure of the 3-Methyl-3-azahex-5-enyl Radical

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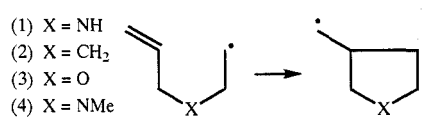
Abstract

Evaluation of the Arrhenius parameters for ring closure of the 3-methyl-3-azahex-5-enyl radical is reported. Cyclization of the radical is found to occur with high regioselectivity giving the *exo-trig* product exclusively with an activation energy of 22 kJ mol^{-1} and log A value of 11·1. The experimental activation barrier compares favourably with that determined by force field calculations which predict a value of 21 kJ mol^{-1}. The 3-methyl-3-azahex-5-enyl radical is therefore found to undergo ring closure some 70 times faster than the parent hex-5-enyl radical, in accord with predictions based upon geometrical considerations.

Introduction

We have recently shown[1–3] that radical-induced ring closure of modified hex-5-enyl radicals provides a convenient and high-yielding entry to bridgehead-substituted bicycloalkanes. In order to investigate the potential of this procedure for the synthesis of analogous heterocyclic systems—specifically, those containing nitrogen at the bridgehead—it seemed appropriate as a preliminary step to examine the details of cyclization of the 3-azahex-5-enyl radical (1). While it is well documented[4–6] that in the case of the all-carbon species (2) 5-*exo* ring closure occurs to give (6) almost exclusively, to our knowledge a corresponding examination of the behaviour of the 3-aza analogue (1), including an evaluation of the activation parameters for its ring closure to (5), has not been reported. Calculations performed by Spellmeyer and Houk[7] predict that the 3-azahex-5-enyl radical (1) cyclizes to give a 99:1 ratio of *exo/endo* products.



[1] Della, E. W., Knill, A. M., and Pigou, P. E., *J. Org. Chem.*, 1993, **58**, 2110.
[2] Della, E. W., and Knill, A. M., *Aust. J. Chem.*, 1994, **47**, 1833.
[3] Della, E. W., and Knill, A. M., *J. Org. Chem.*, 1995, **60**, 3518.
[4] Beckwith, A. L. J., *Tetrahedron*, 1981, **37**, 3073.
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[6] Newcomb, M., *Tetrahedron*, 1993, **49**, 1151.
[7] Spellmeyer, D. C., and Houk, K. N., *J. Org. Chem.*, 1987, **52**, 959.

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On the basis of differences in individual structural features such as C–N, C–C and C–O bond lengths, and CNC, CCC, COC bond angles, it has been suggested[4] that the hetero-substituted hex-5-enyl radicals (1) and (3) should undergo cyclization more rapidly than the parent (2). Beckwith and Glover[8] have obtained supporting evidence for their prediction in the case of the oxa species (3), cyclization of which was found to occur with greater facility than that of the all-carbon radical (2). In fact, we elected to investigate the behaviour of the 3-methyl-3-azahex-5-enyl radical (4) rather than its parent (1) because the former would resemble more closely the situation encountered in the projected syntheses of the 1-azabicycloalkanes. We now disclose the results of our study.

Table 1. Theoretical and experimental Arrhenius parameters for hex-5-enyl radical cyclizations

Cyclization reaction	E_a (kJ mol^{-1}) Theoretical	Experimental	log A	k_c (s^{-1})[A]
(1) → (5)	23	—	—	—
(2) → (6)[B]	31	28	10·4	2·3×10^5
(3) → (7)[C]	28	17	9·9	9·0×10^6
(4) → (8)	21	22	11·1	1·7×10^7

[A] At 25°C. [B] Taken from ref. 9. [C] Taken from refs 8, 9.

Results and Discussion

Theoretical Estimate of the Activation Energy, E_a, for the Aza Radical Cyclizations

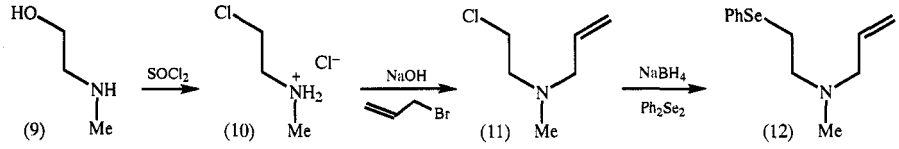
As a prelude to the experimental work we calculated the activation energy expected for rearrangement of the 3-methyl-3-azahex-5-enyl radical (4) to the isomeric radical (8) by a molecular mechanics approach based on that developed by Beckwith and Schiesser[9] and employed with considerable success by them on a series of related hex-5-enyl radicals. For comparison, we have included a similar calculation for cyclization of the parent radical (1) → (5) in order to determine whether the nature of the substituent on the nitrogen atom affected the transition state for cyclization and hence the activation energy. The theoretical data thus determined are collated in Table 1 along with those determined previously for the hex-5-enyl[9,10] and the 3-oxahex-5-enyl[9] radicals. The value of E_a for ring closure of (4) via the chair-to-*cis* transition state thus determined is 21 kJ mol^{-1} which is comparable with the barrier to cyclization (23 kJ mol^{-1}) of the 3-azahex-5-enyl radical (1). Inspection of Table 1 reveals that, in accordance with predictions[4] based on consideration of molecular models, force field calculations suggest that both cyclizations (1) → (5) and (4) → (8) should occur more readily than the ring closure (2) → (6).

Kinetic Results

Although it is general practice to employ a bromoalkane as precursor to radicals of type (2), we were precluded from doing so in the present case because of the

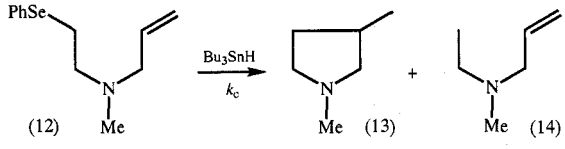
[8] Beckwith, A. L. J., and Glover, S. A., *Aust. J. Chem.*, 1987, **40**, 157.
[9] Beckwith, A. L. J., and Schiesser, C. H., *Tetrahedron*, 1985, **41**, 3925.
[10] Beckwith, A. L. J., and Schiesser, C. H., *Tetrahedron Lett.*, 1985, **26**, 373.

ease of internal displacement of halogen by the nucleophilic nitrogen atom in the required β-aminohaloalkane. The selenide (12) was selected as a convenient source instead, and its synthesis was accomplished in three steps from commercially available *N*-methylethanolamine (9) as illustrated in Scheme 1.



Scheme 1

Upon exposure to tributyltin hydride (10 equiv.) in the presence of initiator (azobisisobutyronitrile) in a minimal amount of benzene (2 M), the selenide (12) was found to give mixtures of the monocycle 1,3-dimethylpyrrolidine (13) and its acyclic isomer, *N*-allyl-*N*-ethyl-*N*-methylamine (14) (Scheme 2). The isomeric amine *N*-methylpiperidine, which would have arisen from *endo-trig* cyclization of (4), was not detected in the product, in agreement with the predictions from calculations cited above.[7] An authentic sample of 1,3-dimethylpyrrolidine (13) was obtained as the (sole) product of reduction of selenide (12) with 1 equiv. of tributyltin hydride under more dilute conditions (0·1 M), providing a clear demonstration of the expected ease of cyclization of the radical (4). A specimen of the reduced amine (14) was prepared by reduction of *N*-allyl-*N*-methylacetamide with lithium aluminium hydride; *N*-methylpiperidine was available commercially.



Scheme 2

Analysis of the mixtures of (13) and (14) obtained from reductions performed at five different temperatures allowed the Arrhenius function for cyclization and trapping to be determined by the procedure described previously.[1,3] Insertion of the value for k_H, the rate of hydrogen abstraction of a primary radical from Bu_3SnH,[11] leads to the following expression for the Arrhenius function for cyclization:

$$\log k_c = (11 \cdot 10 \pm 0 \cdot 31) - \frac{22 \cdot 1 \pm 1 \cdot 5}{2 \cdot 303RT}$$

The activation energy of 22 kJ mol^{-1} is in excellent agreement with that derived from the molecular mechanics calculations above and is lower than the value for cyclization of the hex-5-enyl radical (2), as predicted.[4] Similarly, the experimental rate constant for cyclization of the *N*-methyl-3-azahex-5-enyl radical, k_c, at 25°C is $1 \cdot 7 \times 10^7$ s^{-1} which is larger than that observed for the corresponding all-carbon analogue. The magnitude of the preexponential term,

[11] Chatgilialoglu, C., Ingold, K, U., and Scaiano, J. C., *J. Am. Chem. Soc.*, 1981, **103**, 7739.

log A, is 11·1 which is in the range of values typically observed for log A for the cyclization of the analogous radicals (2)[6] and (3).[8]

This work demonstrates that ring closure of N-substituted 3-azahex-5-enyl radicals is an extremely facile process and it augurs well for our planned objective in synthesizing bicycloalkanes with nitrogen at the bridgehead, work we hope to report upon favourably at a future date.

Experimental

Molecular mechanics calculations[12] were carried out on a Macintosh IIvx computer by using PCMODEL. Kinetic experiments[13] and general experimental procedures[14] were performed as described. N-Methyl-2-chloroethylamine hydrochloride (10) was prepared as reported[15] from N-methylethanolamine.

N-*Allyl*-N-*methyl-2-chloroethylamine (11)*

Allyl bromide (5·1 g, 42·3 mmol) was slowly added to a two-phase mixture consisting of N-methyl-2-chloroethylamine hydrochloride (10) (5 g, 38·5 mmol) in CH_2Cl_2 (50 ml) and NaOH (3·38 g, 84·6 mmol) in water (35 ml). The mixture was stirred at room temperature for 3 h after which time a further aliquot of CH_2Cl_2 (50 ml) was added and the two phases were separated. The aqueous phase was reextracted with CH_2Cl_2 (2×) and the combined extracts were washed once with saturated sodium chloride solution. Removal of the solvent and distillation (Kugelrohr: 95°/20 mm) (lit.[16] 63–66°/35 mm) of the residue afforded the title compound (11) as a light yellow oil (3·8 g, 74%). ^{1}H n.m.r. δ ($CDCl_3$) 5·9–5·7, m, 1H; 5·2–5·0, m, 2H; 3·5, t, 2H; 3·0, d, 2H; 2·65, t, 2H; 2·23, s, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 134·96, 117·46, 60·62, 58·02, 41·86, 41·22.

N-*Allyl*-N-*methyl-2-(phenylseleno)ethylamine (12)*

Sodium borohydride was slowly added to a solution of diphenyl diselenide (1·17 g, 3·75 mmol) in dry ethanol (20 ml) until the bright yellow solution became colourless. N-Allyl-N-methyl-2-chloroethylamine (11) (1 g, 7·5 mmol) in ethanol (1 ml) was added in a single portion and the reaction mixture was heated at 80° for 3 h. Ethanol was removed from the cooled solution under vacuum and 5% HCl (30 ml) was added to the residue which was washed once with hexane. The aqueous solution was basified (pH 10) and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed once with saturated sodium chloride solution and then dried ($MgSO_4$) and the solvent evaporated yielding the title compound (12) as a light yellow viscous oil (1·6 g, 84%). ^{1}H n.m.r. δ ($CDCl_3$) 7·5, m, 2H; 7·2, m, 3H; 5·9–5·7, m, 1H; 5·2–5·1, m, 2H; 3·0, m, 4H; 2·7, m, 2H; 2·23, s, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 135·32, 132·25, 130·34, 128·94, 126·62, 117·62, 60·53, 56·84, 41·76, 25·29. The derived picrate crystallized from ether/hexane as fine yellow *needles*, m.p. 90° (Found: C, 44·8; H, 4·2; N, 11·6. $C_{18}H_{20}N_4O_7Se$ requires C, 44·7; H, 4·2; N, 11·6%).

1,3-Dimethylpyrrolidine (13)

Tributyltin hydride (0·86 g, 2·95 mmol) in dry benzene (1 ml) containing a few crystals of azobisisobutyronitrile was added to a solution of N-allyl-N-methyl-2-(phenylseleno)ethylamine

[12] Allinger, N. L., *J. Am. Chem.. Soc.*, 1977, **99**, 8127; Allinger, N. L., and Yul, Y. H., Quantum Chem. Program Exch., Nos 395, 423.
[13] Pigou, P. E., *J. Org. Chem.*, 1989, **54**, 4943.
[14] Della, E. W., Pigou, P. E., Schiesser, C. H., and Taylor, D. K., *J. Org. Chem.*, 1991, **56**, 4659.
[15] Akaboshi, S., Ikegami, S., and Uoji, K., *Tetrahedron*, 1974, **30**, 2077.
[16] Aiko, I., *Chem. Pharm. Bull.*, 1961, **9**, 343.

(12) (0·5 g, 1·96 mmol) in refluxing benzene (20 ml). The extent of reaction was monitored by gas chromatographic analysis and, upon completion, the mixture was cooled and extracted with 5% HCl (3×). The combined aqueous extracts were washed with hexane (2×) before being basified (pH 10) and reextracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and concentrated carefully to give the title amine (13) (0·15 g, 77%) whose ^{13}C n.m.r. data were identical to those reported.[17] ^1H n.m.r. δ ($CDCl_3$) 2·8–1·9, m, 6H; 2·3, s, 3H; 1·4–1·25, m, 1H; 1·0, d, 3H.

N-*Allyl*-N-*ethyl*-N-*methylamine (14)*

N-Methylacetamide (2 g, 27·4 mmol) was converted into *N*-allyl-*N*-methylacetamide as described.[18] ^1H n.m.r. δ ($CDCl_3$) 5·9–5·7, m, 1H; 5·3–5·1, m, 2H; 4·0, d, *J* 6·5 Hz, and 3·94, d, *J* 6·5 Hz, 2H; 3·0 and 2·95, 3H; 2·12 and 2·08, 3H.* ^{13}C n.m.r. δ ($CDCl_3$) 170·11; 169·67; 132·22; 131·72; 116·34; 115·69; 52·29; 48·98; 34·79; 32·69; 21·01; 20·39. A solution of the derived amide (1·3 g, 11·4 mmol) in ether (2 ml) was added dropwise to a stirred solution of $LiAlH_4$ (1·7 g, 44·7 mmol) in dry ether (20 ml), and the solution heated under reflux for 3 h. The cooled mixture was quenched with saturated aqueous sodium sulfate and then filtered, and the solids were washed thoroughly with ether. The combined filtrate was dried ($MgSO_4$) and the solvent carefully removed to afford the amine (14) as a light yellow liquid (0·91 g, 80%). ^1H n.m.r. δ ($CDCl_3$) 5·95–5·70, m, 1H; 5·20–5·10, m, 2H; 3·0, d, 2H; 2·42, q, 2H; 2·2, s, 3H; 1·05, t, 3H. ^{13}C n.m.r. δ ($CDCl_3$) 135·51; 117·53; 60·51; 50·91; 41·26; 12·20. The derived hydrochloride crystallized from dichloromethane/hexane as fine *needles*, m.p. 215° (Found: C, 53·2; H, 10·6; N, 10·3. $C_6H_{14}ClN$ requires C, 53·1; H, 10·4; N, 10·3%).

Acknowledgment

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* The presence of double peaks in the proton and carbon-13 n.m.r. spectra of *N*-allyl-*N*-methylacetamide is ascribed to its existence as rotational isomers as a result of the restriction to rotation about the amide group. Confirmation for this phenomenon was provided by the observation that the signals were found to coalesce when spectra were recorded on heated samples.

[17] Hawthorne, D. G., Johns, S. R., and Willing, R. I., *Aust. J. Chem.*, 1976, **29**, 315.
[18] Linkies, A., Pietsch, H., and Reuschling, D., *Tetrahedron Lett.*, 1978, **7**, 615.