

Isomerization and Fragmentation of Metastable Secondary Amine Radical Cations

Allan C. Petersen and Steen Hammerum*

Department of Chemistry, University of Copenhagen, The H.C. Ørsted Institute, DK-2100 Copenhagen Ø, Denmark

Petersen, A. C. and Hammerum, S., 1998. Isomerization and Fragmentation of Metastable Secondary Amine Radical Cations. – Acta Chem. Scand. 52: 1045–1050. © Acta Chemica Scandinavica 1998.

Metastable straight-chain secondary amine radical cations isomerize prior to unimolecular fragmentation by reversible hydrogen atom abstraction/exchange and by 1,2-migration of RCH_2NH_2 in intermediate β -distonic isomers.

The metastable molecular ions of primary amines are known to isomerize prior to fragmentation^{1–6} via reactions initiated by intramolecular hydrogen atom abstraction. However, the introduction of *N*-alkyl groups reduces the hydrogen atom affinity of the aminium nitrogen atom,⁷ and the present study was undertaken to determine whether this change would cause the unimolecular reactions of secondary amine molecular ions to take a different course. Further, we wished to examine whether skeletal isomerization by way of 1,2-migration of an alkylamino group in intermediate β -distonic isomers would be an important reaction of secondary amine molecular ions, in the same way that 1,2-migration of NH_3 is an important reaction of β -distonic isomers of primary amine molecular ions.^{2,8–10}

Experimental

The alkylamines examined were prepared by unexceptional methods, usually by reduction of the appropriate amide or carbamate with LiAlH_4 or LiAlD_4 . 2,2-²H₂-*N*-Methylhexylamine was prepared by *N*-methylation of 2,2-²H₂-capronitrile, followed by reduction with NaBH_4 , as described by Borch.¹¹ The *N*-deuteriated amine molecular ions were formed by H/D exchange in the mass spectrometer inlet system, after replacing most of the exchangeable, surface-bonded hydrogen with deuterium by admitting D_2O at a relatively high pressure for an extended period of time.

The reactions of metastable molecular ions formed by 70 eV electron ionization were studied on a Jeol HX/HX110A four-sector (EBEB) mass spectrometer in three-sector mode. The spontaneous reactions of the ions in question were studied by mass analyzed kinetic energy (MIKE) spectroscopy; the reactants were selectively

transmitted by the first magnet (B1), allowed to dissociate in the field-free region between B1 and the second electric sector (E2), whereupon the products were separated according to their kinetic energy (i.e. effectively mass analyzed) by scanning E2. The collision induced dissociation (CID) reactions of the molecular ions were studied after collision with nitrogen or oxygen in a collision cell situated after the first magnetic sector. Kinetic energy release measurements were based on the peak width at half height of the appropriate peaks in the MIKE spectrum, measured under conditions of relatively high energy resolution and corrected for the energy spread of the parent ion beam. Preliminary studies were carried out on VG ZAB-2F instruments at the University of Bielefeld, Germany, and Ecole Polytechnique, Palaiseau, France.

Results and discussion

Secondary aliphatic amine molecular ions formed by 70 eV electron ionization react in the mass spectrometer ion source predominantly by α -cleavage;¹² other reactions proceed only in low ion yield. However, metastable molecular ions behave differently, e.g., *N*-ethylhexylamine molecular ions react in the field-free regions of a double-focusing mass spectrometer by expulsion of four different alkyl radicals, methyl, ethyl, butyl and pentyl,⁸ whereas the major ion-source reactions just involve loss of methyl and pentyl radicals. Prior to fragmentation, isomerization of the molecular ions by intramolecular hydrogen atom transfer from carbon to nitrogen can take place, resulting in CH/NH exchange.^{3,5,6}

1,2-Migration of the alkylamino group. The identity of the alkyl radicals expelled from metastable secondary amine molecular ions depends on the length of the

* To whom correspondence should be addressed.

Table 1. Fragmentation of metastable secondary amine molecular ions (MIKE spectra).

R/R' in RNHR'+	44	58	59	72	86	100	114	128	(M ⁺)
CH ₃ /n-C ₄ H ₉	100 ^a	—	—	—	—	—	—	—	87
CH ₃ /n-C ₅ H ₁₁	100 ^a	6	2	—	1 ^f	—	—	—	101
CH ₃ /iso-C ₅ H ₁₁	100 ^a	—	—	—	—	—	—	—	101
CH ₃ /n-C ₆ H ₁₃ ^c	16 ^a	100 ^b	—	—	—	2 ^g	—	—	115
CH ₃ /iso-C ₆ H ₁₃	100 ^a	3 ^b	50	—	—	—	—	—	115
CH ₃ /n-C ₈ H ₁₇	15 ^a	100 ^b	—	—	—	—	3	4	143
C ₂ H ₅ /n-C ₄ H ₉	34 ^d	100 ^a	—	3	35 ^a	—	—	—	101
C ₂ H ₅ /n-C ₆ H ₁₃	5	55 ^a	—	100 ^b	—	15 ^e	16 ^a	—	129

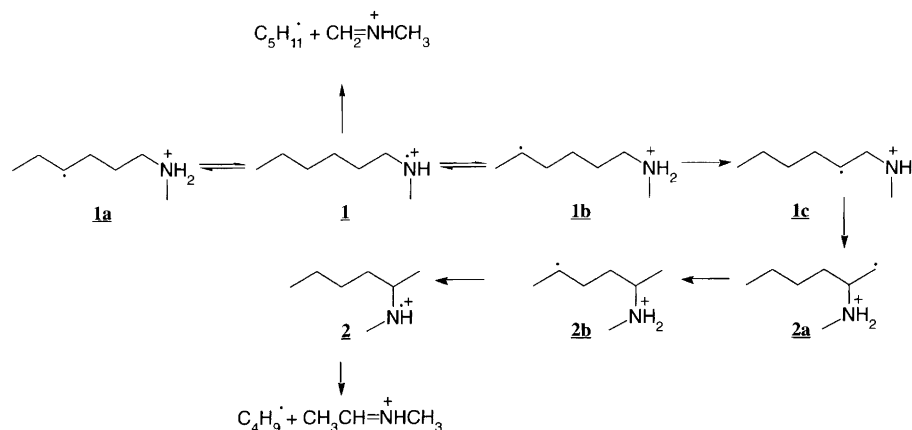
^aα-Cleavage peak. ^bβ-Cleavage peak. ^cIon-source reactions (*m/z*, rel. int.): 30, 9; 44, 100; 58, 4; 70, 1; 115, 15. CID spectrum (N₂, 80% transmission): 30, 3; 41, 3; 44, 100; 55, 3; 57.5, 0.5; 58, 99; 86, 1; 100, 3. CID spectrum (O₂, 80% transmission): 30, 3; 41, 2; 44, 90; 55, 3; 57.5, 25; 58, 100; 86, 1; 100, 2. ^dKER (*T*_{0.5}) 14 meV. ^eKER (*T*_{0.5}) 91 meV. ^fKER (*T*_{0.5}) 350 meV. ^gComposite peak, cf. Table 2.

N-alkyl groups. Relatively small *N*-methylamines (alkyl chains of five or fewer C-atoms) react predominantly by α-cleavage (see Table 1), whereas molecular ions with hexyl or longer alkyl groups react predominantly by loss of an alkyl group from the β-carbon atom, presumably via rearrangement reactions that involve intermediate distonic species such as **1a** and **1b** (Scheme 1). For example, the reactions of the metastable molecular ions of *N*-methylhexylamine, **1**, lead mainly to C₃H₈N⁺ and C₂H₆N⁺ ions. The reaction sequence shown in Scheme 1 is based on the mechanism proposed by Audier and coworkers² for the closely related reactions of primary amines. The key steps are (i) formation of the β-distonic intermediate, **1c**, by hydrogen atom transfer from C(5) to N and then from C(2) to C(5), and (ii) migration of the protonated alkylamino group from C(1) to C(2). Subsequent H-atom transfer from C(5) to C(1) and then from N to C(5) completes the isomerization to **2**, the *N*-methyl-2-hexylamine molecular ion, which finally fragments by α-cleavage.

Each individual step has clear literature precedent: hydrogen atom transfer between C and N is reversible for primary amine molecular ions¹⁻⁶ (see also below), alkyl radicals isomerize readily by intramolecular hydro-

gen atom transfer with five-membered or larger cyclic transition states,¹³ and 1,2-migration of NH₃-groups takes place in β-distonic isomers of primary amine molecular ions.^{2,8-10} The spectra of the deuterium labeled amines provide direct support for this mechanism. In particular, the retention of *one* β-deuterium in the C₃H₈N⁺ product ion (Fig. 1 and Table 3) lends strong support to the proposed skeletal rearrangement; the formation of **2** is further confirmed by the loss of CHD₂[•] from 1-(1-1-D₂) (Table 2).

Taking the relative heats of formation of the products as a guide to the relative critical energies, we find that reaction via **2** (Scheme 1) provides an energetically favorable alternative to simple cleavage for the metastable molecular ions; α-cleavage in ion **2** requires some 12 kcal mol⁻¹ less than does α-cleavage in **1** (ΣΔ*H*_f for CH₃CH=NHCH₃⁺ + C₄H₉[•] = 163 kcal mol⁻¹; ΣΔ*H*_f for CH₂=NHCH₃⁺ + C₅H₁₁[•] = 175 kcal mol⁻¹).¹⁴ Reaction via rearrangement to **2** will in turn be possible for many of the surviving molecular ions that do not possess the energy required for direct α-cleavage of the straight-chain alkyl group. The critical energies of the hydrogen atom transfer steps in Scheme 1 are not known, nor is that for 1,2-migration of the amino group, but since



Scheme 1.

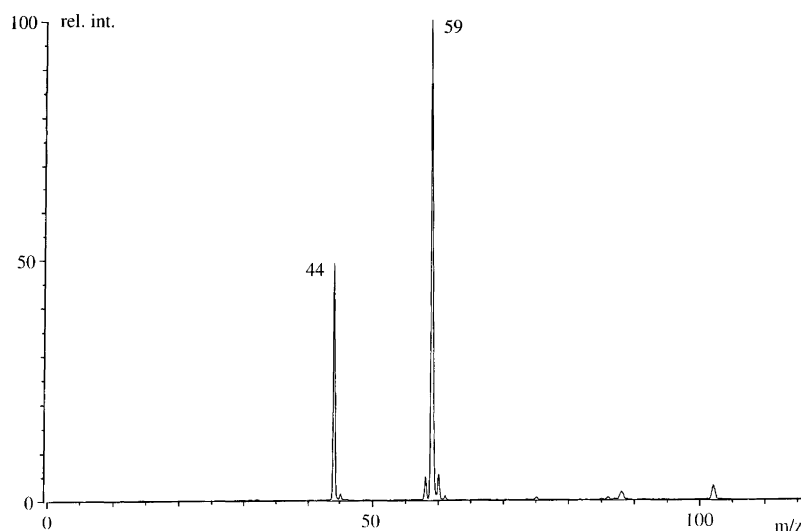


Fig. 1. MIKE spectrum of the (2,2- $^2\text{H}_2$)-*N*-methylhexylamine molecular ion (m/z 117).

Table 2. Loss of methyl and ethyl radicals from metastable deuterium-labeled *N*-methyl- and *N*-ethyl-hexylamine molecular ions (**1** and **4**).^a

	-15	-16	-17	-18	-29	-30	-31
1 - <i>N</i> -CD ₃	94	—	—	6	—	—	—
1 -1,1-D ₂	18 ^b	35	47 ^c	—	—	—	—
1 -2,2-D ₂	97	3	—	—	—	—	—
4 -1,1-D ₂	95	—	5	—	96	—	4
4 -1',1'-D ₂	100	—	—	—	9	—	91

^aRelative abundance within each peak group (cf. Table 1).

^bKER 295 meV. ^cKER 72 meV.

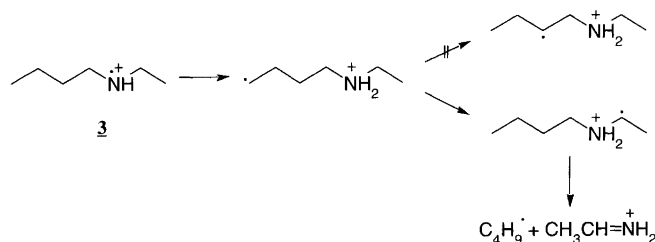
fragmentation via **2** competes successfully, the intermediate steps presumably have critical energies lower than 10 kcal mol⁻¹.

The formation of distonic ions. The metastable molecular ions of the smaller *N*-methylamines, such as *N*-methylbutylamine and *N*-methylpentylamine, do not undergo amino group migration, even though considerable exchange of C-bonded and N-bonded hydrogen atoms precedes alkyl radical loss (Table 3). This shows that H-atom abstraction from the alkyl group by the aminium nitrogen does occur and that it is reversible (see the following section). However, the hydrogen

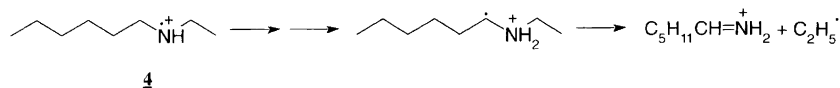
Table 3. C₃(H,D)₈N⁺ and C₂(H,D)₆N⁺ ions formed from metastable deuterium labeled *N*-methylalkylamine molecular ions.^a

	m/z							
	44	45	46	47	58	59	60	61
<i>n</i> -C ₄ H ₉ NDCH ₃	69	31	—	—	—	—	—	—
<i>n</i> -C ₅ H ₁₁ NDCH ₃	79	21	—	—	62	38	—	—
1 -ND	80	20	—	—	75	25	—	—
1 -NCD ₃	—	—	4	96	—	—	3	97
1 -1,1-D ₂	8	37	55	—	5	31	64	—
1 -2,2-D ₂	98	2	—	—	5	90	5	—
<i>n</i> -C ₈ H ₁₇ NDCH ₃	82	18	—	—	77	23	—	—

^aRelative abundance within each peak group; cf. Table 1.



Scheme 2.



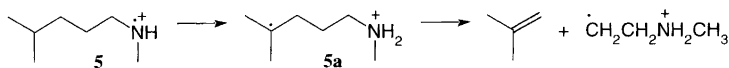
Scheme 3.

abstraction is not followed by skeletal isomerization when the alkyl chain is only four or five carbon atoms long, since subsequent formation of the key intermediate, the β -distonic isomer, does not take place; the alkyl groups are too short to allow the required H-transfer from C(2) (Scheme 2). Instead, transfer of a hydrogen atom from C(1) can occur, leading to formation of an α -distonic isomer (Scheme 3). This ion can dissociate by C-N cleavage, viz., loss of the *N*-methyl group from *N*-methylpentylamine and *N*-methylhexylamine and of the intact ethyl group from *N*-ethylhexylamine (Scheme 3). These reactions are accompanied by unusually high kinetic energy release.¹⁵

When the second *N*-alkyl group is larger than methyl, the initial hydrogen atom abstraction by the aminium nitrogen can be followed by hydrogen atom exchange between the alkyl chains. This can lead to the formation of other α -distonic ions, and these react by way of C-N cleavage, viz., the formation of m/z 44 from *N*-ethylbutylamine, **3** (Scheme 2); a closely related process has been described for *N*-isopropylpentylamine.⁸

C-C bond cleavage after H-atom transfer to produce $\cdot\text{CH}_2\text{NH}_2\text{CH}_3^+$ or $\cdot\text{CH}_2\text{CH}_2\text{NH}_2\text{CH}_3^+$ by loss of an alkene molecule from the metastable molecular ions^{9,15} is observed in only a few instances, notably the loss of C_4H_8 from *N*-methylisohexylamine radical cations, **5**, which gives rise to $\cdot\text{CH}_2\text{CH}_2\text{NH}_2\text{CH}_3^+$ in reasonable ion yield (Table 1), in preference to loss of $\text{C}_4\text{H}_9\cdot$ by cleavage after amino group migration. Both reactions require an initial H-abstraction step, but transfer of the tertiary hydrogen atom to nitrogen, with a six-membered cyclic transition state, will be highly favored over transfer of a hydrogen atom from one of the terminal methyl groups (Scheme 4). The resulting δ -distonic ion, **5a**, undergoes direct C-C bond cleavage, since further isomerization by 1,3-hydrogen atom transfer to give the pivotal β -distonic intermediate required for amino group migration is not favorable; 1,3-hydrogen atom transfers in alkyl radicals are exceedingly rare, presumably for kinetic reasons,¹⁶ and H-atom transfer from secondary to tertiary carbon is known to be slow.¹³

The metastable *N*-methylisopentylamine molecular ion does not react in a similar fashion, to produce $\cdot\text{CH}_2\text{NH}_2\text{CH}_3^+$; this reaction would require some 40 kJ mol^{-1} more energy than does simple cleavage.



Scheme 4.

Conversely, the energy required for simple cleavage and for formation of the distonic fragment ion is almost the same for ion **5**.¹⁷

The metastable molecular ions of long, straight-chain primary amines undergo isomerization and fragmentation via the β -distonic isomer almost to the exclusion of simple cleavage by fission of the α -CC bond.² For secondary amines the difference is less pronounced (Table 1), but β -cleavage still proceeds in higher ion yield when the alkyl chain is sufficiently long. The increased tendency to undergo α -cleavage presumably reflects that the hydrogen atom affinity of the aminium nitrogen atom in secondary amine radical cations is lower than that of the less substituted aminium nitrogen in their primary counterparts,⁷ and that the hydrogen atom abstraction in turn competes less efficiently with simple cleavage. An additional contributing factor is that the surviving secondary amine molecular ions will, on average, possess higher internal energy than their primary amine counterparts, owing to the higher critical energy for simple cleavage. The effective energy distribution of the metastable molecular ions will therefore be wider, and the reactions will in consequence resemble the reactions observed in the ion source more closely.¹⁸

It is worth noting that $\text{C}_3\text{H}_8\text{N}^+$ ions, the major product of the spontaneous reactions of metastable *N*-methylhexylamine molecular ions, are also formed in appreciable abundance (15%) in the collision-induced reactions of the molecular ions, whereas $\text{C}_3\text{H}_8\text{N}^+$ ions are not among the important products of the ion-source reactions. This suggests that a significant proportion of the surviving molecular ions undergo rearrangement prior to the collision event. This is supported by the formation of prominent doubly charged molecular ions by collision with oxygen molecules (Table 1) (see Ref. 19).

Hydrogen exchange between C and N prior to fragmentation. The interchange of the nitrogen-bonded and carbon-bonded hydrogen atoms in metastable secondary amine molecular ions possessing three-carbon or longer alkyl groups demonstrates that the formation of distonic isomers of the molecular ion (Scheme 1) is a reversible process. The extent of CH/NH exchange can be determined from the deuterium incorporation in the fragment

ions formed from specifically labeled *N*-alkylhexylamine ions (Tables 3 and 4). Only 20% of the α -cleavage ions formed from $C_6H_{13}NDCH_3^+$ or $C_8H_{17}NDCH_3^+$ retain the deuterium atom (Table 3), which suggests that the nitrogen-bonded hydrogen can undergo rapid exchange with four other hydrogen atoms, presumably those initially located at C(4) and C(5) (see Scheme 1). The same mechanism predicts D-incorporation in the $C_3H_8N^+$ ions of 30% (somewhat less if the conversion of **2b** into **2** is reversible), in good agreement with the 25% observed. In other words, for secondary amine molecular ions, the hydrogen atom on the nitrogen undergoes exchange with the methylene hydrogens almost only via 1,5- and 1,6-H-shifts (six- and seven-membered cyclic transition states). By comparison, six-, seven-, and eight-membered ring cyclic transition states are involved in the intramolecular hydrogen atom exchange of long-chain primary alkylamine radical cations.⁴

The less extensive CH/NH exchange observed on going from primary to secondary amines, in particular the lower tendency to undergo intramolecular H-abstraction with an eight-membered cyclic transition state, is probably another consequence of the lower hydrogen atom affinity of the aminium nitrogen atom in secondary amine radical cations.

The results in Tables 3 and 4 also show that the hydrogen atoms on C(1) are, to a large extent, retained in the immonium ions formed by loss of butyl and pentyl radicals; the abundance of the m/z 59 and m/z 45 ions from (1,1-²H₂)-*N*-methylhexylamine and the m/z 73 and m/z 59 ions from (1,1-²H₂)-*N*-ethylhexylamine shows that intramolecular H-exchange involving the α -hydrogen atoms takes place for roughly 25% of the molecular ions. The retention of the α -deuterium appears to be higher for the ions formed via skeletal rearrangement, as also observed for the *N*-deuteriated ions. This suggests that also the exchange of the α -hydrogen atoms involves the C(4) and C(5) methylene groups, from which one H is transferred to the incipient product ion when **2a** is converted into **2b** (Scheme 1).

Very little exchange involves the hydrogen atoms on the *N*-methyl or *N*-ethyl groups. This could be taken to suggest that the preferred sizes of the cyclic transition states for carbon-to-carbon hydrogen atom transfer are five and six, rather than seven, whereas for carbon-to-nitrogen hydrogen atom transfer, the preferred transition

Table 4. $C_4(H,D)_{10}N^+$ and $C_3(H,D)_8N^+$ ions formed from metastable deuterium-labeled *N*-ethylhexylamine molecular ions.^a

	m/z					
	58	59	60	72	73	74
1,1-D ₂	1	19	80	—	16	84
<i>N</i> -CD ₂ CH ₃	—	6	94	—	6	94

^aRelative abundance within each peak group; cf. Table 1.

state sizes appear to be six and seven, rather than five. An additional reason could be that abstraction of hydrogen atoms α to an ammonium group is not a particularly favorable reaction, in contrast with abstraction of H α to amino groups; similar observations have been made for H-abstraction reactions involving amines and ammonium ions in condensed phase radical reactions.²⁰

Conclusions. The hydrogen atom affinity of the nitrogen atom is lower for secondary amine molecular ions than for primary amines, which results in less extensive intramolecular exchange of hydrogen atoms; for the same reason, rearrangement by 1,2-migration of the alkylamino group in metastable β -distonic isomers is less important for secondary amine molecular ions.

Acknowledgements. Support from *Statens Naturvidenskabelige Forskningsråd* and the Human Capital and Mobility program of the EU is gratefully acknowledged.

References

- (a) Audier, H. E., Milliet, A. and Denhez, J. P. *Org. Mass Spectrom.* 18 (1983) 131; (b) Audier, H. E., Milliet, A., Sozzi, G. and Denhez, J. P. *Org. Mass Spectrom.* 19 (1984) 79; (c) Audier, H. E., Denhez, J. P., Milliet, A. and Sozzi, G. *Can. J. Chem.* 62 (1984) 931.
- Audier, H. E., Sozzi, G. and Denhez, J. P. *Tetrahedron* 42 (1986) 1179.
- (a) Hammerum, S. *Tetrahedron Lett.* 22 (1981) 157; (b) Hammerum, S., Christensen, J. B., Egsgaard, H., Larsen, E., Derrick, P. J. and Donchi, K. F. *Int. J. Mass Spectrom. Ion Phys.* 47 (1983) 351.
- Sozzi, G., Denhez, J. P., Audier, H. E., Vulpius, T. and Hammerum, S. *Tetrahedron Lett.* 26 (1985) 3407.
- Hammerum, S. *Acta Chem. Scand., Ser. B* 38 (1984) 707.
- Sozzi, G. *Thèse d'Etat*, Université de Paris-Sud, Centre d'Orsay, 1984.
- Aue, D. H. and Bowers, M. T. In: Bowers, M. T., Ed., *Gas Phase Ion Chemistry*, Academic Press, New York 1979, Vol. 2, Ch. 1.
- Bjørnholm, T., Hammerum, S. and Kuck, D. *J. Am. Chem. Soc.* 110 (1988) 3862.
- Hammerum, S., Kuck, D. and Derrick, P. J. *Tetrahedron Lett.* 25 (1984) 893.
- Hammerum, S. *Mass Spectrom. Rev.* 7 (1988) 123.
- Borch, R. F. *J. Org. Chem.* 34 (1969) 627.
- (a) Gohlke, R. S. and McLafferty, F. W. *Anal. Chem.* 34 (1962) 1281; (b) McLafferty, F. W. and Turecek, F. *Interpretation of Mass Spectra*, 4th ed., University Science Books, Mill Valley, CA 1993.
- (a) Hardwidge, E. A., Larson, C. W. and Rabinovitch, B. S. *J. Am. Chem. Soc.* 92 (1970) 3278; (b) Larson, C. W., Chua, P. T. and Rabinovitch, B. S. *J. Phys. Chem.* 76 (1972) 2507; (c) Nedelec, J. Y. and Lefort, D. *Tetrahedron* 31 (1975) 441; (d) Dearden, D. V. and Beauchamp, J. L. *J. Phys. Chem.* 89 (1985) 5359.
- Heats of formation of immonium ions from Lossing, F. P., Lam, Y.-T. and Maccoll, A. *Can. J. Chem.* 59 (1981) 2228.
- Hammerum, S., Petersen, A. C., Sølling, T. I., Vulpius, T. and Zappey, H. *J. Chem. Soc., Perkin Trans. 2* (1997) 393.
- (a) Beckwith, A. L. J. and Ingold, K. U. In: de Mayo, P., Ed., *Rearrangements in Ground and Excited States*, Academic Press, New York 1980, Vol. 1, p. 161; (b) Reutov, O. A. *Uspekhi Khimi* 53 (1984) 462; *Russ. Chem. Rev.* 53 (1984) 274.

17. Heats of formation (298 K, in kJ mol^{-1}): $\text{CH}_2=\text{NHCH}_3$, 707; $\text{CH}_2\text{NH}_2\text{CH}_3$, 821; $\text{CH}_2\text{CH}_2\text{NH}_2\text{CH}_3$, 765; isobutyl, 57; isobutene, -17; isopentyl, 44. Heats of formation from Ref. 15 and from Lias, S. G., Bartmess, J. E., Liebman, J. F., Holmes, J. L., Levin, R. D. and Mallard, W. G. *J. Phys. Chem. Ref. Data* 17, suppl. Vol. 1 (1988).
18. Hammerum, S., Bojesen, G., Haugshøj, K., Sølling, T. I., Vulpius, T. and Zappey, H. *Manuscript in preparation*.
19. Maquin, F., Stahl, D., Sawaryn, A., Schleyer, P. v. R., Koch, W., Frenking, G. and Schwarz, H. *J. Chem. Soc., Chem. Commun.* (1984) 504; see also Stahl, D. and Maquin, F. *Chimia* (1983) 87.
20. Auricchio, S., Bianca, M., Citterio, A., Minisci, F. and Ventura, S. *Tetrahedron Lett.* 25 (1984) 3373.

Received January 7, 1997.