

# Cycloalkene budding: mass spectrometric studies of competitive and dual cycloalkene extrusion reactions from doubly unsaturated aldehyde *N,N*-dimethylhydrazones

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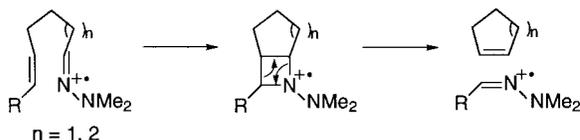
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Mass spectral fragmentation pathways of four doubly unsaturated aldehyde *N,N*-dimethylhydrazones were investigated using EI-MS and tandem mass spectrometry (MS/MS) under electron ionization and collisionally activated decomposition (CAD) conditions. Cyclopentene extrusion was found to be slightly favored over cyclohexene loss in a hydrazone capable of losing either cycloalkene. Evidence for the regeneration of a chain-shortened iminium radical cation as a result of cycloalkene extrusion was provided by studying substrates capable of undergoing successive cycloalkene budding sequences. EI-MS of these compounds shows sequential loss of both cyclopentene and cyclohexene, in accord with expectations for a cascade mechanism. Although these MS/MS experimental results are also compatible with alternative mechanisms which would entail the simultaneous loss of both neutral cycloalkenes or of a macrocyclic diene, a rapid cascade of cycloalkene budding accounts best for the experimental observations. Copyright © 2000 John Wiley & Sons, Ltd.

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Recently, we reported an unusual mass spectral fragmentation process undergone by *N,N*-dimethylhydrazones of 5- and 6-alkenals. This fragmentation gives rise to characteristic neutral losses of cyclopentene or cyclohexene (Scheme 1).<sup>1</sup> Along with our interest in this unanticipated fragmentation as a diagnostic tool for recognizing double bonds in the 5 or 6 positions of aldehydes,<sup>2–4</sup> we wanted to understand the pathway by which these cycloalkene extrusions occur. The results of a recent computational study implied that a cycloaddition between a carbon–carbon double bond and an iminium radical cation to form an azetidine radical cation intermediate, followed by a cycloreversion, provides a viable pathway for the observed fragmentations (Scheme 1).<sup>5</sup>

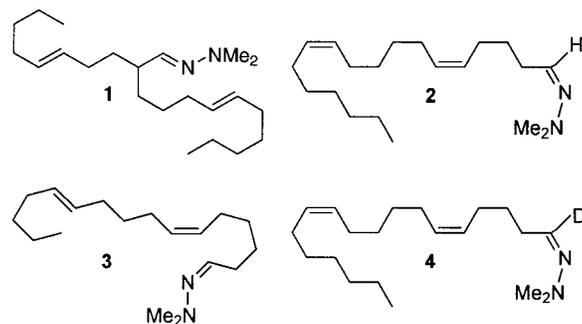


Scheme 1.

Although synchronous  $\pi 2_s + \pi 2_s$  cycloadditions are thermally forbidden processes by the conservation of orbital symmetry,<sup>6</sup> evidence for their ionic counterparts, involving  $[2 + 1]^+$  radical cation reactions, has been reported in the

gas phase.<sup>7–10</sup> Remarkably,  $[2 + 1]^+$  cycloadditions involving a neutral alkene and a vinylic radical cation have been found to be facile despite being symmetry forbidden.<sup>11–14</sup> Examples of  $[2 + 1]^+$  cycloadditions between electron-rich alkenes and styrenes in solution have also been documented,<sup>15,16</sup> and Bauld and co-workers have illustrated that triarylammonium radical cations can accelerate such cycloadditions<sup>17–19</sup> via ‘hole-catalyzed’ reactions, wherein orbital symmetry control appears to be largely negated.<sup>20</sup>

To determine whether a preference exists for cyclopentene or cyclohexene budding in a molecule which offers both possibilities, we synthesized 2-[(*E*)-3-octenyl]-(*E*)-6-dodecenal *N,N*-dimethylhydrazone (**1**) (Scheme 2) and studied its mass spectral fragmentations under EI and CAD conditions. To confirm that cycloalkene budding proceeds with regeneration of a new iminium radical cation, we synthesized (5*Z*,11*Z*)-5,11-octadecadienal *N,N*-dimethylhydrazone (**2**), (6*Z*,11*E*)-6,11-hexadecadienal *N,N*-dimethylhydrazone (**3**), and (5*Z*,11*Z*)-5,11-[1-<sup>2</sup>H<sub>1</sub>]octade-



Scheme 2.

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cadial *N,N*-dimethylhydrazone (**4**) and studied their mass spectral fragmentations under EI and CAD conditions. In this paper we report our findings.

## EXPERIMENTAL

### Mass spectrometry

GC/MS was performed using electron ionization (70 eV). Mass spectra were recorded using a Micromass (Beverly, MA, USA) Quattro I triple quadrupole mass spectrometer equipped with an EI source. The source temperature was held at 180 °C. For CAD experiments, argon gas pressure in the collision cell was adjusted to attenuate precursor ion signals by 50% (pressure about  $1.8 \times 10^{-4}$  mbar). Laboratory frame collision energy was optimized for each experiment as indicated in the corresponding figure captions. ESI mass spectra were recorded using a Micromass Quattro I triple quadrupole mass spectrometer equipped with an electrospray ion source. The source temperature was held at 85 °C.

### Characterization

<sup>1</sup>H NMR spectra were recorded at 500 MHz on a Varian (Palo Alto, CA, USA) Unity 500 spectrometer. <sup>13</sup>C NMR spectra were recorded at 100 MHz on a Varian VXR-400S spectrometer. IR spectra were recorded on a Hewlett Packard (Palo Alto, CA, USA) 5890 Series II gas chromatograph linked to a Hewlett Packard 5965A infrared detector.

### Materials

*2-[(E)-3-Octenyl]-(E)-6-dodecenal N,N-dimethylhydrazone* (**1**). Alkylation of (*E*)-1-iodo-4-decene with the lithium anion of (*E*)-5-decenal *N,N*-dimethyl hydrazone provided **1** as a clear oil after purification by flash column chromatography:  $R_f = 0.12$  (20:1 hexane/ethyl acetate); IR (gas phase)  $\nu$  2933, 2863, 2793, 1605, 1455  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t, 6H,  $J = 7$  Hz), 1.22–1.49 (m, 16H), 1.90–2.03 (m, 8H), 2.17–2.24 (m, 1H), 2.70 (s, 6H), 5.32–5.41 (m, 4H), 6.42 (d, 1H,  $J = 8$  Hz); <sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 14.2, 22.3, 22.7, 27.2, 29.5, 30.3, 31.5, 31.9, 32.4, 32.7, 32.8, 33.3, 34.0, 42.3, 43.7, 130.1, 130.2, 130.7, 130.8, 144.1. HRMS calcd for  $\text{C}_{22}\text{H}_{41}\text{N}_2$ : 333.3369. Found: 333.3344.

*(5Z,11Z)-5,11-Octadecadienal N,N-dimethylhydrazone* (**2**). 1,7-Octadiyne was treated with sodium amide followed by alkylation with 1-iodohexane. The resulting mono-substituted alkyne was purified and treated with sodium amide followed by regioselective alkylation of 1-chloro-4-iodobutane. Conversion to 5,11-octadecadiyn-1-ol was achieved by treatment of the chlorodiene with sodium acetate, followed by ester hydrolysis with potassium carbonate in methanol. 5,11-Octadecadiyn-1-ol was hydrogenated with  $\text{H}_2$  in the presence of Lindlar catalyst and subsequently oxidized to (*5Z,11Z*)-5,11-octadecadienal with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine-*N*-oxide (NMO). Treatment of (*5Z,11Z*)-5,11-octadecadienal with *N,N*-dimethylhydrazine and powdered 4 Å molecular sieves provided **2** as a clear oil after purification by flash column chromatography:  $R_f = 0.36$  (5:1 hexane/ethyl acetate); IR (gas phase)  $\nu$  3011, 2933, 2865, 1458, 1259  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t, 3H,

$J = 7$  Hz), 1.23–1.38 (m, 12H), 1.53 (p, 2H,  $J = 7$  Hz), 1.96–2.12 (m, 6H), 2.07 (p, 2H,  $J = 7$  Hz), 2.24 (q, 2H,  $J = 7$  Hz), 2.72 (s, 6H), 5.31–5.40 (m, 4H), 6.65 (t, 1H,  $J = 5$  Hz); <sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.3, 22.8, 26.9, 27.2, 27.3, 27.4, 28.0, 29.1, 29.5, 29.6, 29.9, 31.9, 32.9, 43.6, 129.3, 129.8, 130.2, 130.5, 139.6. HRMS calcd for  $\text{C}_{20}\text{H}_{38}\text{N}_2$ : 306.3034. Found: 306.3036.

*(6Z,11E)-6,11-Hexadecadienal N,N-dimethylhydrazone* (**3**). A Wittig reaction between the ylide of 6-hydroxyhexyl-triphenylphosphonium bromide and (*E*)-5-decenal provided (*6Z,11E*)-6,11-hexadecadienol. Oxidation of the alcohol with TPAP/NMO provided (*6Z,11E*)-6,11-hexadecadienal, which was treated with *N,N*-dimethylhydrazine and powdered 4 Å molecular sieves to provide **3** as a clear oil after flash column chromatography:  $R_f = 0.21$  (5:1 hexane/ethyl acetate); IR (gas phase)  $\nu$  2933, 2864, 1456, 1032, 966  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 (t, 3H,  $J = 7$  Hz), 1.30–1.54 (m, 10H), 1.94–2.07 (m, 8H), 2.24 (dt, 2H,  $J = 7$  Hz), 2.72 (s, 6H), 5.33–5.43 (m, 4H), 6.65 (t, 1H,  $J = 5$  Hz); <sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 22.3, 26.9, 27.2, 27.6, 29.5, 29.8, 32.0, 32.3, 32.4, 33.1, 43.6, 129.9, 130.0, 130.1, 130.8, 139.6. HRMS calcd for  $\text{C}_{18}\text{H}_{34}\text{N}_2$ : 278.2721. Found: 278.2719.

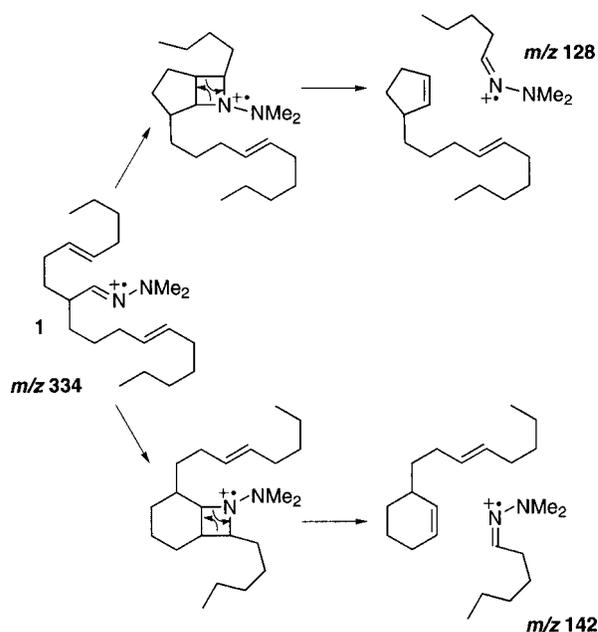
*(5Z,11Z)-5,11-[1-<sup>2</sup>H<sub>1</sub>]Octadecadienal N,N-dimethylhydrazone* (**4**). (*5Z,11Z*)-5,11-Octadecadien-1-ol was oxidized to (*5Z,11Z*)-5,11-octadecadienoic acid with pyridinium dichromate in dimethylformamide. Reduction of (*5Z,11Z*)-5,11-octadecadienoic acid with lithium aluminum deuteride provided (*5Z,11Z*)-5,11-[1-<sup>2</sup>H<sub>2</sub>]octadecadienol. Oxidation of the deuterated alcohol to (*5Z,11Z*)-5,11-[1-<sup>2</sup>H<sub>1</sub>]octadecadienal was achieved with TPAP/NMO. Treatment of (*5Z,11Z*)-5,11-[1-<sup>2</sup>H<sub>1</sub>]octadecadienal with *N,N*-dimethylhydrazine and powdered 4 Å molecular sieves provided **4** as a clear oil after flash column chromatography:  $R_f = 0.57$  (5:1 hexane/ethyl acetate); IR (gas phase)  $\nu$  3011, 2933, 2865, 1459  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 (t, 3H,  $J = 7$  Hz), 1.25–1.38 (m, 12H), 1.54 (p, 2H,  $J = 7$  Hz), 1.99–2.10 (m, 8H), 2.24 (t, 2H,  $J = 7$  Hz), 2.73 (s, 6H), 5.33–5.41 (m, 4H); <sup>13</sup>C NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.3, 22.8, 27.0, 27.32, 27.36, 27.4, 28.0, 29.2, 29.5, 29.6, 29.9, 30.5, 32.0, 32.8, 129.4, 129.8, 130.2, 130.5. HRMS calcd for  $\text{C}_{20}\text{H}_{37}\text{N}_2\text{D}$ : 307.5436. Found: 307.3098.

## RESULTS AND DISCUSSION

To discriminate between a preference for cyclopentene or cyclohexene budding, we studied the mass spectral fragmentations of compound **1**. The CAD daughter ion spectrum of the molecular ion of **1** revealed the formation of ions with  $m/z$  values of 128 and 142 (Scheme 3), arising from loss of 3-(4-decenyl)-cyclopentene or 3-(3-octenyl)-cyclohexene, respectively (Fig. 1).

Under the conditions used, the observed abundance ratio of the  $m/z$  128 and 142 ions is about 3:2, favoring cyclopentene loss to a small extent. In addition to these ions, we also observed a fragment ion at  $m/z$  224 arising from a McLafferty rearrangement,<sup>21</sup> as well as its cycloalkene budding product at  $m/z$  156 (Scheme 4). The  $m/z$  291 ion results from loss of  $\text{N}(\text{CH}_3)_2$  from the molecular ion.<sup>22,23</sup> High-resolution mass spectral data of **1** established the molecular composition of the  $m/z$  156 ion as  $\text{C}_9\text{H}_{20}\text{N}_2$  (calcd for  $\text{C}_9\text{H}_{20}\text{N}_2$  156.1626; found 156.1629).

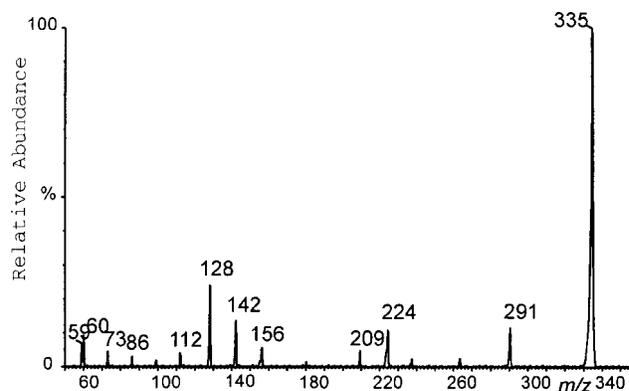
In order to investigate the regeneration of an iminium



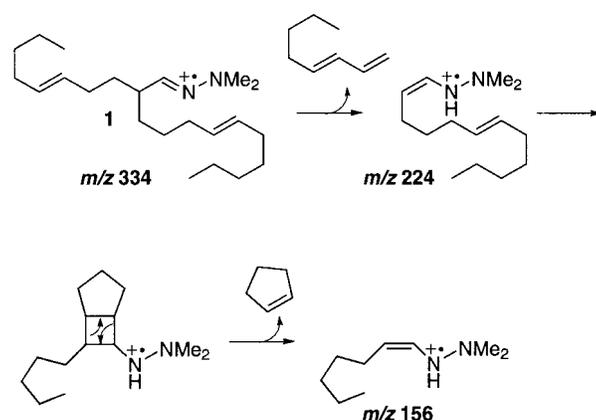
Scheme 3.

radical cation during mass spectral fragmentations, we studied dimethylhydrazones **2–4**, which could give rise to sequential loss of both cyclopentene and cyclohexene. With hydrazone **2** in hand, we examined whether this compound would suffer an initial loss of cyclopentene to give a chain-shortened iminium radical cation which would again cyclize and ‘bud off’ cyclohexene. Under 70 eV EI conditions, we recorded peaks at  $m/z$  238 and 156, resulting from loss of cyclopentene alone and of cyclopentene plus cyclohexene. In order to determine the direct lineage of the  $m/z$  156 and 238 peaks, we carried out MS/MS experiments with the assumption that EI and CAD fragmentation mechanisms are similar. As expected, we found that the  $m/z$  238 ion originates from the molecular ion ( $m/z$  306) while the  $m/z$  156 ion stems from the  $m/z$  238 chain-shortened iminium radical cation. However, there also is a formal possibility that the parent  $m/z$  306 radical cation could be serving as a direct precursor of the  $m/z$  156 ion (Fig. 2 (a), Scheme 5).

To ascertain whether the tandem budding process also operates with a substrate for which the first step would be

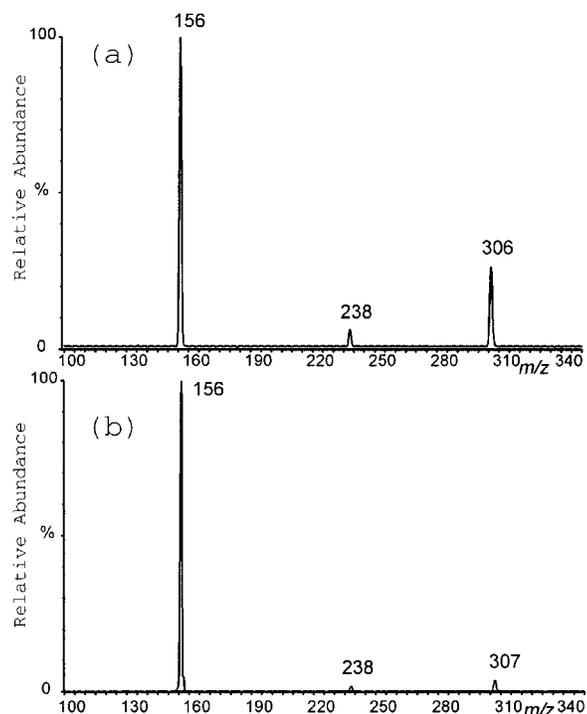


**Figure 1.** Daughter-ion CAD spectrum of the molecular ion produced by 70 eV electron ionization of 2-[(*E*)-octenyl]-(*E*)-6-dodecenal *N,N*-dimethylhydrazone (**1**). Collision energy 28 eV.

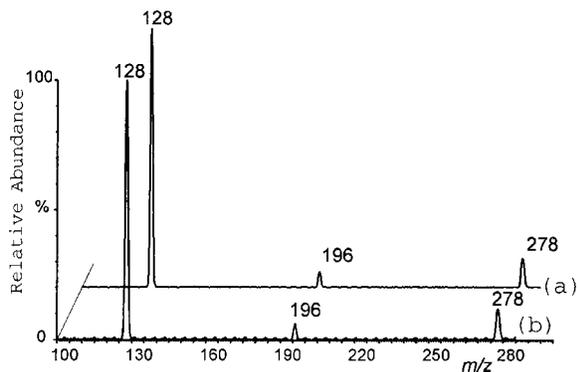
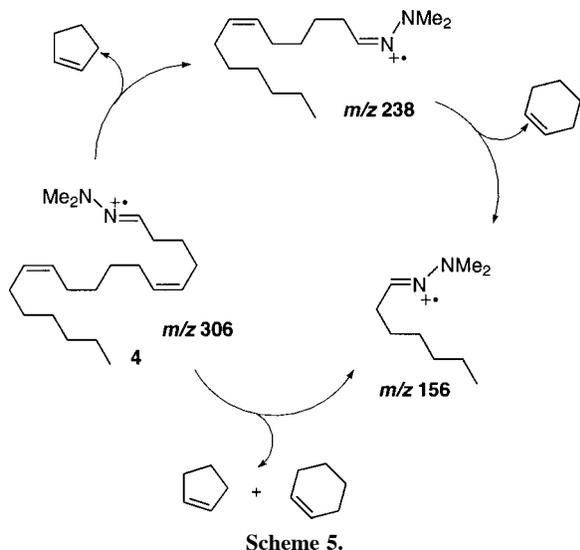


Scheme 4.

loss of cyclohexene, we studied a mixture of stereoisomers (*Z,E* and *E,E*) of **3** which could be separated by gas chromatography (GC) and individually investigated by CAD. The 70 eV EI mass spectrum of **3** is entirely analogous to that of **2**; it revealed an ion at  $m/z$  196 corresponding to cyclohexene loss, and  $m/z$  128 resulting from loss of both cyclohexene and cyclopentene from the molecular ion ( $m/z$  278). To determine the lineage of the  $m/z$  196 and 128 peaks, we carried out CAD precursor ion experiments under GC/MS conditions. The results demonstrated that the  $m/z$  196 ion comes directly from the  $m/z$  278 molecular ion, whereas the  $m/z$  128 ion stems from both the  $m/z$  196 and 278 ions (Fig. 3). These observations again allow the possibility of two pathways for double cycloalk-



**Figure 2.** CAD spectra of (a) (5*Z*,11*Z*)-5,11-octadecadienal *N,N*-dimethylhydrazone (**2**), and (b) (5*Z*,11*Z*)-5,11-[1-<sup>2</sup>H]octadecadienal *N,N*-dimethylhydrazone (**4**) showing the precursor ions of  $m/z$  156. Collision energy 12 and 28 eV, respectively.



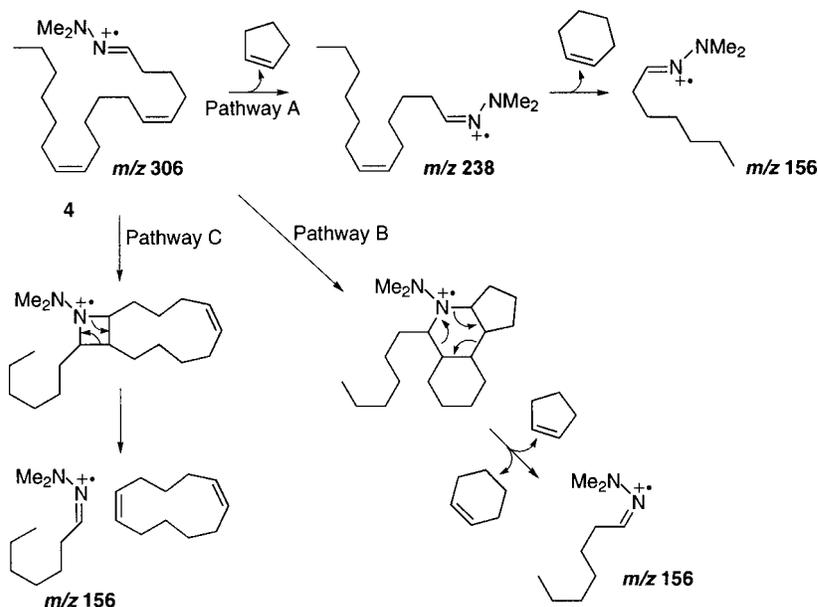
**Figure 3.** CAD spectra, obtained under GC/MS conditions, of (a) (6*Z*,11*E*)-6,11-hexadecadienal *N,N*-dimethylhydrazone (**3**) and (b) (6*E*,11*E*)-6,11-hexadecadienal *N,N*-dimethylhydrazone (**3**) showing the precursor ions of *m/z* 128. Collision energy 17.5 eV.

ene budding, and demonstrate that the change in position of the double bond still permits tandem fragmentation. As expected, the configuration of the double bond does not affect the outcome of these processes since the precursor ion CAD spectra of both (*Z,E*)- and (*E,E*)-isomers are virtually identical (Fig. 3).

As a further check on our understanding of cycloalkene budding, we investigated the mass spectral fragmentations of deuterium-labeled compound **4**. The EI mass spectrum of diene **4** showed that the deuterium atom was exclusively lost as deuteriocyclopentene. Thus, the EI mass spectrum revealed the formation of fragment ions at *m/z* 156 and 238, corresponding to extrusion of both [<sup>2</sup>H<sub>1</sub>]cyclopentene/cyclohexene, and of [<sup>2</sup>H<sub>1</sub>]cyclopentene, respectively (Fig. 2 (b)). A MS/MS study of **4** revealed that the ion at *m/z* 156 has as parents both the *m/z* 238 ion and the molecular ion at *m/z* 307.

To rationalize the formal possibility of a simultaneous extrusion of two cycloalkenes (or one cycloalkadiene) from the parent radical cations in these experiments, we consider three distinct pathways, illustrated in Scheme 6 for the case of compound **2**. Pathway A involves a rapid, second cycloalkene budding from the initially formed chain-shortened iminium radical cation (*m/z* 238) within the collision cell, giving rise to what appears to be the 'direct' loss of both cyclopentene and cyclohexene from the *m/z* 306 parent. We have estimated the dwell time of ions in the collision cell to be 3–5 μs.

Pathway B involves formation via a [2 + 2 + 1]<sup>+</sup> cycloaddition of an intermediate *N,N*-dimethylaminopiperidine radical cation, followed by a [2 + 2 + 1]<sup>+</sup> cyclor-eversion<sup>24</sup> to give rise to the simultaneous production of both cycloalkenes. We computed the CBS-4 energy of both *N*-aminopiperidine (−63 kcal/mol) and *N*-aminopiperidine radical cation (−97 kcal/mol), and found these to be thermodynamically favorable intermediates. Energies calculated from experimentally determined gas phase enthalpies<sup>25–27</sup> were −66 and −105 kcal/mol, respectively. Despite its thermodynamic stability, the formation of a six-membered heterocycle from an imine radical cation and two non-conjugated double bonds is to our knowledge an



**Scheme 6.**

unprecedented process, and would clearly be kinetically unfavorable.

Pathway C, which requires a preliminary cycloaddition between the iminium radical cation and the remote double bond (C-11), would result in the direct loss of 1,6-cycloundecadiene. However, since we have shown that the *N,N*-dimethylhydrazone of 11-alkenals fails to undergo cycloalkene budding, this mechanism is also unlikely.<sup>1</sup> Based on these considerations, we favor rapid, sequential budding reactions (Pathway A) as the most likely mechanism responsible for our observations. The proposed radical cation mechanism is supported by the observation that even-electron, quasi-molecular ions  $[M+H]^+$  formed by electro-spray ionization of these hydrazones do not produce fragments similar to those observed in cycloalkene budding.

## CONCLUSIONS

The experiments we have described provide some additional understanding of the recently discovered cycloalkene budding reaction. A slight preference for cyclopentene over cyclohexene formation is established. Based on results obtained with suitably constructed doubly unsaturated substrates, an initial cycloalkene budding process has been demonstrated to produce a new nitrogen radical cation, capable of undergoing further ring extrusion events in a cascade fashion. Although alternative mechanisms that involve either the simultaneous loss of two cycloalkene moieties or the loss of a large ring diene from the initial molecular ion appear to be formal possibilities, our results are best accommodated by the assumption that the second cycloalkene budding reaction follows the first one in a time which is comparable to the residence time of these intermediates in the collision cell.

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