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## Kinetic Isotope Effects on the 1,3-Intramolecular Insertion Reaction of <u>t</u>-Butylchlorocarbene

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**Summary.** The primary kinetic isotope effect for the 1,3-CH(D) insertion reaction of  $\underline{t}$ -butylchlorocarbene- $\underline{d}_6$  ranges from 3.25 at -12 °C to 2.14 at 118 °C; tunneling is not apparent in this temperature interval.

Recent studies of the kinetic isotope effects (KIE) associated with intramolecular carbenic insertions furnish surprising results, including unexpectedly high values of  $\underline{k}_{H}/\underline{k}_{D}$  (~3-5) for the ambient temperature 1,2-H(D) shifts of neopentylchlorocarbene,<sup>1</sup> neopentylfluorocarbene,<sup>2</sup> and dimethylcarbene.<sup>3</sup> Additionally, methylchlorocarbene and methylchlorocarbene- $\underline{d}_{3}$  exhibit curved Arrhenius plots of ln  $\underline{k}(1,2-H(D) \text{ shift})$  vs. 1/T over the temperature range 248-343 K, and a KIE that <u>increases</u> from 0.9-1.8 as the temperature <u>rises</u>.<sup>4</sup> Both quantum mechanical tunneling (QMT) and classical 1,2-H(D) shifts may contribute to the rearrangement of methylchlorocarbene to vinyl chloride, with QMT dominant at lower temperatures.<sup>4,5</sup>

Methylbromocarbene<sup>6</sup> and benzylchlorocarbene<sup>7</sup> similarly display curved Arrhenius correlations for both  $\alpha$ -H and  $\alpha$ -D carbenes, with QMT again a possible cause of the curvature. In the case of benzylchlorocarbene, matrix isolation studies of the  $\alpha, \alpha$ - $\underline{d}_2$  carbene at 10 K suggest a KIE ~ 2000, implicating QMT in the low temperature regime.<sup>8</sup>

Similarly, matrix isolation of <u>t</u>-butylchlorocarbene (<u>t</u>-BuCCl, 1) in nitrogen matrices shows that the 1,3-CH insertion to 1,2-dimethyl-2-chlorocyclopropane (2) occurs at a finite rate ( $\underline{k} \sim 3 \times 10^{-5} - 4 \times 10^{-4} \text{ s}^{-1}$ ) even at 11 K, and is temperature independent from 11-30 K.<sup>9</sup> In contrast, the perdeuterocarbene, 1-<u>d</u><sub>9</sub>, is persistent in the matrix; no C-D insertion occurs over 40 h at 14 K or 48 h at 30 K.<sup>9</sup>



The temperature independence of the insertion rate at very low temperature, together with the necessarily very large KIE, are strong evidence for QMT conversion of  $1\rightarrow 2$  at very low temperature.

Our prior studies of carbene 1 in solution revealed that photolysis of diazirine 3 afforded cyclopropane

**2**, the 1,2-Me shifted alkene, **4**, and azine **5**, eq. (1).<sup>10</sup> Importantly, carbene trapping experiments with 2-methyl-1-butene demonstrated that the cyclopropane arose from carbene **1** by intramolecular insertion,<sup>11</sup> whereas alkene **4** stemmed directly from an untrappable photoexcited state of diazirine **3**. The carbene could undergo a thermally-driven 1,2-Me shift to **4** (~10%) at higher temperature (79 °C), but did not appreciably do so at ambient temperature.<sup>10c,12</sup>

In view of the demonstrated importance of tunneling in the low temperature reactions of 1,<sup>9</sup> and the unusual KIE associated with methylchlorocarbene,<sup>4,5</sup> we have now determined (intramolecular) KIE's for the 1,3-CH insertion reaction of 1 from -12 to 118 °C. Over this temperature regime, the KIE's are of normal magnitude, exhibit normal temperature dependence, and afford no overt evidence for OMT.

The requisite carbene precursor  $[3-(\underline{t}-butyl-\underline{d}_6)-3$ -chlorodiazirine,  $3-\underline{d}_6]$  was prepared from pivalonitrile- $\underline{d}_6$  as outlined in Scheme 1. Reduction of acetone- $\underline{d}_6$  (>99%)  $d_6$ ) with LiAlH<sub>4</sub> (25 °C, 1 h, 63%) gave isopropanol- $\underline{d}_6$ , which was converted to the tosylate (TsCl, pyr, 20 °C, 3 h, 71%), and thence to isobutyronitrile- $\underline{d}_6$  (NaCN, HMPA,<sup>13</sup> 100 °C, 3 h, 18%). Methylation (LDA,<sup>14</sup> Et<sub>2</sub>O, N<sub>2</sub> atm., -78 °C, 40 min, then MeI, to 25 °C, 3 h, 93%) then gave pivalonitrile- $\underline{d}_6$ , **6**. Finally, nitrile **6** was converted to diazirine **3**- $\underline{d}_6$ by Pinner reaction (HCl, MeOH) to the iminoester, ammonolysis to the amidine hydrochloride (31%) and Graham oxidation to the diazirine (~50%).<sup>10,15,16</sup>

Scheme 1

$$\begin{array}{c} O \\ D_{3}CCCD_{3} & \underbrace{\text{LiAlH}_{4}}_{\text{Et}_{2}O} & D_{3}CCHCD_{3} & \underbrace{\text{TsCl}}_{\text{pyr}} & OTs \\ 1 \\ D_{3}CCHCD_{3} & \underbrace{\text{NaCN}}_{\text{HMPA}} & D_{3}CCHCD_{3} & \underbrace{\text{LDA}}_{\text{HMPA-Et}_{2}O, \text{then Mel}} \\ CH_{3}-C-CN & \underbrace{1. \text{HCl}, \text{MeOH}}_{\text{CD}_{3}} & CH_{3}-CCHCD_{4} & \underbrace{\text{NaOCl}}_{\text{LD}_{3}} & \underbrace{\text{NaCN}}_{\text{HMPA}} & D_{3}CCHCD_{3} & \underbrace{\text{LDA}}_{\text{HMPA-Et}_{2}O, \text{then Mel}} \\ CH_{3}-C-CN & \underbrace{1. \text{HCl}, \text{MeOH}}_{\text{CD}_{3}} & CH_{3}-CCHCD_{2} & \underbrace{\text{NaOCl}}_{\text{H}_{2}O, \text{DMSO}} & (CD_{3})_{2}(CH_{3})C \\ CD_{3} & \underbrace{\text{CD}_{3}}_{\text{LDA}} & \underbrace{\text{CDA}}_{\text{H}_{2}O, \text{DMSO}} & \underbrace{\text{CD}_{3}}_{\text{LDA}} & \underbrace{\text{NaOCl}}_{\text{Cl}} & \underbrace{\text{NaOCl}}_{\text{LDA}} & \underbrace{\text{NaOCl}} & \underbrace{\text{$$

Photochemical decomposition of  $3-\underline{d}_6$  was carried out in CDCl<sub>3</sub>,<sup>17</sup> with product analysis by 200 MHz <sup>1</sup>H NMR on CDCl<sub>3</sub> solutions that were first concentrated by careful fractional distillation, and then flash distilled to rid the samples of azine. The products<sup>10</sup> obtained from  $3-\underline{d}_6$  are shown in eq. (2), where the cyclopropanes **2a** and (isomers) **2b**, **2b'** stem from C-H or C-D insertion, respectively, whereas the alkenes **4a** and (isomers) **4b**, **4b'** arise from CH<sub>3</sub> or CD<sub>3</sub> shifts. Only the cyclopropanes are considered to be products of the carbene when it is generated photochemically.<sup>10c</sup> Thermal decompositions of  $3-\underline{d}_6$  yield the same products as photolysis, with cyclopropanes and alkenes both attributable to the carbene.<sup>10c</sup>

Cyclopropane **2a** exhibits <sup>1</sup>H NMR multiplets for its 3 cyclopropyl protons that are centered at ( $\delta$ ) 0.54, 0.84, and 2.88. The isomeric pair of cyclopropanes **2b**, **2b**' display CH<sub>3</sub> singlets at 1.07 and 1.23. From



the appropriate ratio of integral areas, corrected for the 2:1 CD<sub>3</sub>/CH<sub>3</sub> bias in carbene 1- $\underline{d}_6$ , 200 MHz NMR analysis of the reaction product mixture affords  $\underline{k}_{\text{H}}/\underline{k}_{\text{D}}$  for the 1,3-insertions of 1- $\underline{d}_6$ . Data appear in Table 1 for decompositions of 3- $\underline{d}_6$  under varied conditions.

The CH<sub>3</sub> resonances of the methyl shift alkene products **4a** and **4b**, **4b'** appear at 2.08 and 1.81, 1.72, respectively, so that NMR integration also affords the 4a/(4b + 4b') ratio. Statistical correction then yields the secondary KIE for CH<sub>3</sub> vs. CD<sub>3</sub> shifts of carbene 1- $\underline{d}_6$ . These data also appear in Table 1, where the KIE's are seen to be small.

If we neglect the secondary KIE on the CH<sub>3</sub> migration of  $1-\underline{d}_6$ , then the primary KIE's for the 1,3insertion reactions can also be derived from  $(\underline{k}_{ins}/\underline{k}_{-Me})_{1-\underline{d}_0}/(\underline{k}_{CD ins}/\underline{k}_{-Me})_{1-\underline{d}_6}$ , where we compare the ratio of C-H insertion to CH<sub>3</sub> migration of carbene 1 with the ratio of C-D insertion (2b, 2b') to CH<sub>3</sub> migration (4a) of carbene  $1-\underline{d}_6$ . Appropriate NMR integrations give these data (shown in parentheses in Table 1), which are in good agreement with the KIE's derived from the insertion products 2a and 2b, 2b'.

The data are consistent with a classical primary KIE operative during the 1,3-CH(D) insertions of  $1-\underline{d}_6$ in the temperature range -12 to 118 °C (261-391 K). The tunneling mechanism, so strongly evident at 30 K,<sup>9</sup> is not readily detectable at the higher temperatures,<sup>18,19</sup> where the KIE decreases with increasing temperature, as expected for a classical insertion mechanism.<sup>20</sup>

The "normal" behavior of the 1,3-CH insertion KIE of carbene 1 resembles that observed for the 1,2-H(D) shift primary KIE's of the neopentylhalocarbenes,<sup>1,2</sup> but markedly contrasts to that reported for methylchlorocarbene.<sup>4</sup> In this latter case, the (small) KIE increases from 0.9 - 1.8 as the temperature rises from 248-343 K, and it is at least conceivable that tunneling may significantly contribute even at ambient temperatures.<sup>4</sup> More to the point, the "blends" of classical and QMT contributions to the 1,2-H migration of methylchlorocarbene and the 1,3-CH insertion of <u>t</u>-butylchlorocarbene differ, so that the associated KIE's and their temperature dependences diverge. Apparently, the influence of QMT persists at higher temperatures in the 1,2-H shift more than in the 1,3-CH insertion.

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Decomposition of 3- <u>d</u> <sub>6</sub> <sup>b</sup>	$\underline{k}_{\rm H}/\underline{k}_{\rm D}$ , 1,3-insertion <sup>c</sup>	<u>k<sub>H</sub>/k<sub>D</sub>, ~CH<sub>3</sub>/~CD<sub>3</sub></u>
hv (-12)	3.25	······································
hv (22)	2.92	1.10
Δ (61)	2.72 (2.74)	1.07
Δ (88)	2.48 (2.49)	1.07
Δ (100)	2.52 (2.52)	1.09
Δ (118)	2.14 (2.19)	1.02

**Table 1.** Isotope Effects in the Reactions of t-Butylchlorocarbene-d<sub>6</sub><sup>a</sup>

<sup>a</sup>Errors in the isotope effects are  $\pm 10\%$ ; decomposition temperatures were held to  $\pm 2$  °C. <sup>b</sup>Temperatures (°C) are shown in parenthesis. <sup>c</sup>Data in parentheses are derived from the ratios of C-H (C-D) insertion to CH<sub>3</sub> migration; see text.

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- (11) Laser flash photolysis gave the  $1 \rightarrow 2$  rate constant as  $-9 \times 10^5$  s<sup>-1</sup> in isooctane at 25 °C.<sup>10b,c</sup>
- (12) Not surprisingly, carbone 1 does not significantly rearrange to 4 in low temperature matrices.<sup>9</sup>
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- (16) <sup>1</sup>H NMR analysis of the amidine salt indicated >98%  $\underline{d}_6$ .
- (17) Conditions: focused Osram XE UV lamp,  $\lambda > 320$  nm, <u>A<sub>346</sub> of 3-d<sub>6</sub>=0.8</u>, 7 h.
- (18) Attempts to study the insertion KIE in solution at temperatures much lower than -12 °C were frustrated by large scale formation of azine 5 ( $d_{12}$ ).
- (19) An Arrhenius treatment of the data in Table 1 gives  $\Delta E_a \sim 0.56$  kcal/mol for the C-H vs. C-D insertions of 1-<u>d</u><sub>6</sub>. Extrapolation to 30 K generates a very large KIE, consistent with the observed persistence<sup>9</sup> of perdeutero-1.
- (20) The magnitude and temperature dependence of the KIE's for the conversion of 1-<u>d</u><sub>6</sub> to cyclopropanes 2a and 2b, 2b' are similar to those for conversion of α-iodoneopentyllithium-<u>d</u><sub>6</sub> [CH<sub>3</sub>(CD<sub>3</sub>)<sub>2</sub>CCHILi] to the corresponding isomeric <u>d</u><sub>6</sub>-dimethylcyclopropanes.<sup>21</sup> The latter (carbenoid) C-H/C-D insertions afford KIE's of 2.76 and 2.43 at -90 and -44 °C, respectively.
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