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The Kinetic Isotope Effect on the Carbenic 1,2-H(D) Shift Originating at a Tertiary Carbon Atom

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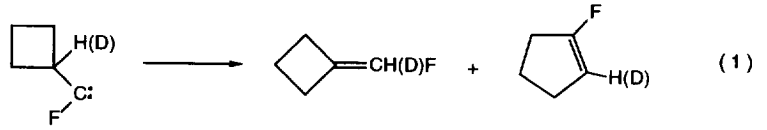
Summary. The kinetic isotope effect for the 1,2-H(D) shift of cyclobutylfluorocarbene to fluoromethylenecyclobutane varies from ~1.7-2.6 over the temperature range -15 to 138 °C; the isotope effect appears to increase slightly with increasing temperature.

Renewed attention has recently been focused on the magnitude and mechanism of intramolecular carbene kinetic isotope effects (KIE). Of particular interest is the 1,2-H migration, the most common singlet intramolecular carbenic reaction.[1] At *primary* carbon migration origins, methylchlorocarbene and methylchlorocarbene-d_3 exhibit curved Arrhenius correlations of ln*k*[1,2-H(D) shift] vs. 1/T over the 248-343 K temperature range, and a KIE that increases from 0.9-1.8 as the temperature *rises*.[2] Both quantum mechanical tunneling (QMT) and classical 1,2-H(D) shifts may contribute, with QMT dominant at lower temperatures.[2,3] Arrhenius correlations of methylbromocarbene and methylbromocarbene-d_3 are similarly nonlinear, with the KIE ranging from 0.92-1.35 (T = 223-343 K).[4] Note, however, that the KIE at primary carbons can be considerably larger: the KIE derived from the lifetimes of dimethylcarbene and dimethylcarbene-d_6 is 3.2.[5]

At *secondary* carbon migration origins, there is great variability in 1,2-H(D) carbenic KIE's, which can be quite large at ambient temperatures: *viz*: k_H/k_D ~ 3-5 for neopentylchlorocarbene and neopentylfluorocarbene.[6,7] Benzylchlorocarbene affords curved Arrhenius correlations for both the α,α-h_2 and α,α-d_2 species in isooctane, with the directly observed k_H/k_D increasing from 0.87-2.62 as the temperature increases from 213-303 K,[8] paralleling the results obtained with methylchlorocarbene,[2,3] and suggesting the incursion of QMT. Indeed, matrix isolation studies of benzylchlorocarbene-α,α-d_2 at 10 K are consistent with a KIE ~ 2000, implicating QMT in the low temperature regime.[9] Other reported KIE's at secondary origins are smaller, ranging from 1.2-1.6 with ArCHD-C-CH_3,[10] to 2.3 for homobrexan-2-ylidene at 120-160 °C,[11] although KIE's in other cyclic carbenes are complicated by conformational factors.[1d,12]

KIE's for 1,2-H(D) shifts originating at *tertiary* centers do not appear to be known. These rearrangements are usually so rapid that precise absolute kinetic determinations of k_H and k_D present formidable problems.[13] Simultaneously, opportunities to determine intramolecular (competitive) KIE's are limited at tertiary migration origins, where α-CHD carbenes are obviously precluded.

Cyclobutylfluorocarbene, **1**, provides a system in which a 1,2-H(D) KIE originating at a tertiary carbon can be conveniently measured against an internal "clock." Generated by the photolysis of the appropriate diazirine, **1** undergoes competitive 1,2-H and 1,2-C shifts to yield alkenes **2** and **3**, respectively; eq. (1).[14] If



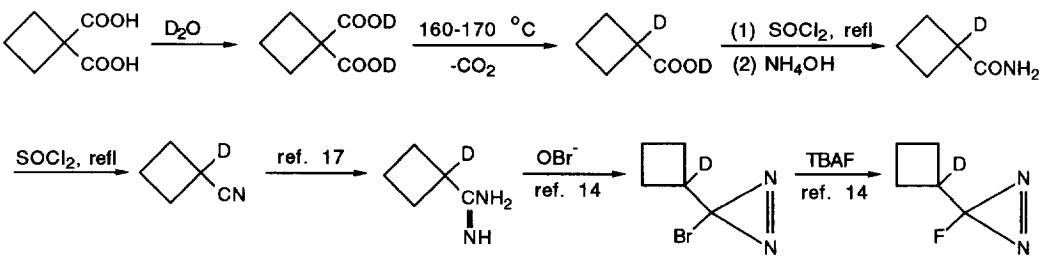
(1)

1-H(1-D) **2-H(2-D)** **3-H(3-D)**

we neglect the secondary KIE on the 1,2-C shift of carbene **1-D** to cyclopentene **3-D**,[15] then the 1,2-C migration can be used as a kinetic reference or clock ($k_c = 1.8 \times 10^6\ s^{-1}$).[14] The primary KIE for the 1,2-H(D) shifts of carbenes **1-H** or **1-D** to methylenecyclobutanes **2-H** or **2-D** is then given by the ratio (**2-H/3-H**)/(**2-D/3-D**), obtained from product analyses for unlabeled and labeled carbenes generated under identical conditions. Here, we describe experiments leading to the determination of the KIE for the 1,2-H(D) shift of cyclobutylfluorocarbene.

3-Fluoro-3-(1-deuteriocyclobutyl)diazirine (**4-D**) was prepared as outlined in Scheme 1. Cyclobutane-1,1-dicarboxylic acid[16] was exchanged to the dideuterio acid (4 × 15 ml of D_2O to 0.19 mol of diacid, with

Scheme 1



4-D

repetitive lyophilization), where upon decarboxylation[16] afforded α-deuteriocyclobutanecarboxylic acid in 89% yield. NMR indicated 97.3% α-deuterium based on integration of the residual α-H at δ 3.0-3.2 ($CDCl_3$). Conversion of the acid to the acid chloride ($SOCl_2$, refl. 30 min, distilled at 132-134 °C, 88%), followed by reaction with conc. NH_4OH (<10 °C, 1 h, 60%) gave cyclobutanecarboxyamide-1-*d*. Dehydration of the amide ($SOCl_2$, refl. 1 h, 83%) yielded 1-cyanocyclobutane-1-*d*, 97% α-deuterated by integration of the α-H quintuplet centered at δ 3.4 ($CDCl_3$). Finally, conversion of the nitrile to the amidine,[17] Graham oxidation to 3-bromo-3-cyclobutyldiazirine,[14,18] and fluoride exchange with tetrabutylammonium fluoride,[14] afforded diazirine **4-D** (97% α-D by NMR).

Photochemical[19] or thermal decompositions of diazirines **4-H** or **4-D** were carried out in decane solutions until UV spectroscopy indicated that all of the diazirine had decomposed. Product ratios [**2-H(D)**/

Table 1. Isotope Effects in the 1,2-H(D) Shifts of Cyclobutylfluorocarbene[a]

Decomposition Cond.[b]	(**2-H/3-H**)[c]	(**2-D/3-D**)[c]	KIE[d]
hυ (-15)	0.240	0.144	1.67 ± 0.03
hυ (-5)	0.230	0.131	1.76 ± 0.08
hυ (5)	0.228	0.111	2.05 ± 0.05
hυ (15)	0.207	0.103	2.01 ± 0.03
hυ (25)	0.227	0.107	2.12 ± 0.09
hυ (35)	0.230	0.108	2.13 ± 0.14
hυ (45)	0.246	0.117	2.10 ± 0.04
Δ (100)	0.250	0.097	2.58 ± 0.26
Δ (112)	0.280	0.110	2.55 ± 0.30
Δ (138)	0.330	0.132[e]	2.50 ± 0.10

[a]Carbene **1-H** or **1-D** was generated from diazirine **4-H** or **4-D**. [b]Decomposition temperatures (°C) are shown in parenthesis. [c]Product ratios are averages of at least 4 GC determinations; average deviations were determined in each case and propagated to afford the errors attached to the KIE's. [d]Ratio of (**2-H/3-H**)/(**2-D/3-D**). [e]A control experiment showed that the **2-D/3-D** product ratio was unchanged after an additional 36 h at 138 °C.

3-H(D)][20] were determined by flame ionization capillary GC analysis (CP-Sil 5 CB or HP-1 columns) with electronic integration, and are collected in Table 1. The KIE's were then obtained from the product ratios and are also gathered in the table.[22]

The 1,2-H and 1,2-C shifts of carbene **1** are relatively slow (5.3×10^5 and 1.8×10^6 s^{-1} at 23 °C, respectively),[14,21] so that at low temperatures (≤ 5 °C) azine and dimer formation become significant and make more difficult the determination of product ratios. We are therefore somewhat tentative in our trust of the first 3 KIE's entered in Table 1. Nevertheless, the totality of data suggests that the KIE associated with the 1,2-H(D) shift of cyclobutylfluorocarbene ranges from ~1.7-2.6 over the temperature range -15 to 138 °C (258-411 K).

Importantly, the temperature dependence of the KIE is unusual: the KIE does not decrease with increasing temperature. Allowing for the variance in the data, the KIE manifests a slight increase with rising temperature. In this regard, it resembles the 1,2-H(D) KIE's reported for methylchlorocarbene[2] or benzylchlorocarbene[8] (see above), and stands in contrast to the apparently classical temperature dependence of the KIE's observed for the 1,2-H(D) shift of neopentylfluorocarbene[7] or the 1,3-CH(D) insertion reaction of *t*-butylchlorocarbene[23] (in similar temperature regimes).

Although a KIE of ~2 seems reasonable for a carbenic 1,2-H(D) shift originating at a tertiary carbon atom, the unusual temperature dependence reminds us that there is much that we do not understand about

intramolecular carbenic KIE's. For instance, the activation energies for the 1,2-H shifts of **1** and neopentylfluorocarbene are similar (3.8 and 3.3 kcal/mol, respectively[14]), but their KIE's at ambient temperature (2.1 and 5.0[7]) are quite different. These 1,2-H (and presumably 1,2-D) shifts have strongly negative entropies of activation (~-20 e.u.)[14] which, together with an unknown contribution of QMT,[2,3] make difficult the correlation of the KIE with carbenic structure. It is this latter problem that calls for continued experimental and theoretical attention.

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(22) There is a 12% contribution of the photoexcited state of diazirine **4** to product formation during the photolytic generation of carbene **1** at ambient temperature.[21] This complication is disregarded in the "photochemical" KIE's of Table 1.

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