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THE KINETIC ISOTOPE EFFECT IN THE REARRANGEMENT OF NEOPENTYLCHLOROCARBENE

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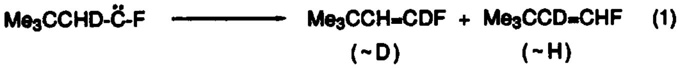
Summary. The kinetic isotope effect for the 1,2-H/1,2-D shift of neopentylchlorocarbene ranges from 2.5-3.5.

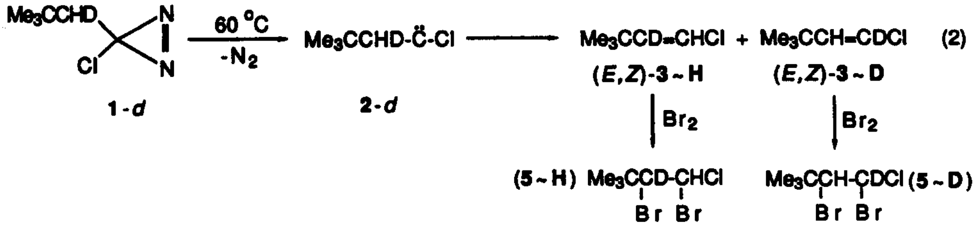
We recently reported a kinetic isotope effect (KIE) of extraordinary magnitude attending the 1,2-H(D) rearrangement of neopentylfluorocarbene, eq. (1).[1] At 22°C, in $CDCl_3$, k_H/k_D = 4.8-5.2, as calculated from the ~H/~D distributions of the *E* or *Z* product alkenes. Neither solvent (isopentane) nor temperature variation (k_H/k_D = 6.1-6.2 at -30°C) had much effect, consistent with a classical KIE. Given that the 1,2-H activation energy for neopentylfluorocarbene is only ~3 kcal/mol,[2] the magnitude of the KIE is striking.

It is of immediate interest to determine the corresponding KIE for neopentyl*chloro*carbene. Is it also unusually large, albeit smaller than that of the fluorocarbene? In the event, the measurement of this KIE is made difficult by technical problems in the product analysis, and by complications in the photochemistry of the diazirine precursor of neopentylchlorocarbene (see below). Nevertheless, we can now confirm that the KIE for the 1,2-H(D) rearrangement of neopentylchlorocarbene is "normal", relative to that of the corresponding fluorocarbene, but abnormally large in terms of conventional expectations. Moreover, we present suggestive evidence that a comparable KIE operates in direct nitrogen-loss, 1,2-H(D) rearrangements of an excited state of the carbene precursor.

We focused first on the *thermolysis* of monodeuterated neopentylchlorodiazirine, 1-d,[3] eq.(2), where contributions of an excited precursor to the KIE are unlikely,[4] and product analysis of the isomeric 3~H and 3~D alkenes should give a direct measure of the "intramolecular" KIE. Thermolysis of 1-d in $CDCl_3$ at 60°C afforded only (GC, GC-MS) *E* and *Z*-3~H and *E* and *Z*-3~D. The *E*/*Z* ratio was ~5-6:1, as compared to the ratio of



$$\underset{}{Me_3CCHD\text{-}\ddot{C}\text{-}F} \longrightarrow \underset{(\sim D)}{Me_3CCH{=}CDF} + \underset{(\sim H)}{Me_3CCD{=}CHF} \quad (1)$$



(2)

1-*d* 2-*d*

~12:1 observed for the photolytic decomposition of the undeuterated diazirine at 20°C.[2]

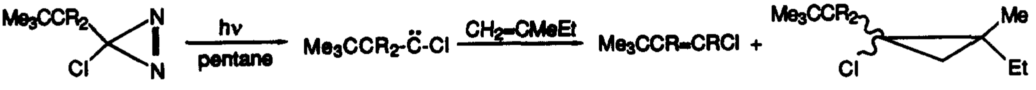
The vinyl protons of *E*-3-H and *E*-3-D were clearly visible in the 200 MHz NMR spectrum ($CDCl_3$) at δ5.89 and 5.94; each signal was a triplet, J~1.9 Hz, due to *cis*-H-D coupling.[5] The very similar chemical shifts of these key protons led us to seek definitive assignments. Accordingly, the alkene mixture was brominated (excess Br_2, pentane or $CHCl_3$, 25°C), giving a mixture of the diastereomeric, racemic dibromides, (*RS*,*SR*)/(*RR*,*SS*)-5-H and (*RS*,*SR*)/(*RR*,*SS*)-5-D.[6] The -C*H*ClBr (5-H) and Me_3CC*H*Br- (5-D) protons of the dibromides were now clearly differentiated, with the former diastereomers displaying singlets at δ6.26 and 6.18, whereas the latter absorbed at δ4.38 and 4.26. From the appropriate integral areas, these signals were readily correlated with the principal vinyl proton absorptions of the parent alkenes at δ5.89 (*E*-3-H) and δ5.94 (*E*-3-D), respectively.[7]

With the NMR assignments secured, integration of the appropriate vinyl protons of the alkenes afforded an overall (*E* + *Z*) KIE: k_H/k_D = 2.59 ± 0.13, for the thermolysis of 1-d at 60°C.

The absolute rate constant, k_H, for the 1,2-H shift of the undeuterated neopentylchlorocarbene has been measured as 1.4×10^7 s^{-1} by laser flash photolysis,[2] using the pyridine ylide methodology.[8] In precisely the same way,[2] we have now measured k_D for the 1,2-D shift of α,α-dideuteroneopentylchlorocarbene.[9] From 5 measurements of k_{obs} for the formation of the pyridine ylide, with [pyr] varied from 4×10^{-4} - 4×10^{-3} M, we obtained $k_{pyr} = 3.0 \times 10^9$ $M^{-1}s^{-1}$ for the formation of the ylide, and $k_o = 4.0 \pm 0.3 \times 10^6$ s^{-1} for the disappearance of the carbene at [pyr] = 0. Taking the latter value as k_D,[2,10] gives $k_H/k_D = 1.4 \times 10^7/4.0 \times 10^6 = 3.5 \pm 0.6$ at 20°C. Neglecting secondary isotope effects, this value is in good agreement with the product based KIE of 2.6 determined at 60°C.

What complexities attend the photolysis of neopentylchlorodiazirine? It is known that carbenic rearrangements that are initiated by the photolysis of alkylhalodiazirines can be accompanied by the simultaneous rearrangement of a second transient,[11],[12] probably the diazirine's first excited state.[11c,12] In the photolysis of neopentyl*fluoro*diazirine, we found that carbene formation and carbenic rearrangement, eq. (1), accounted for >94% of the overall reaction, with little involvement of other product-forming intermediates.[1] However, we should anticipate greater participation of a non-carbenic pathway in the photolysis of neopentyl*chloro*diazirine.[13]

In fact, the photolysis (λ > 330 nm) of neopentylchlorodiazirine,[2] 1, in varying concentrations of 2-methyl-1-butene in pentane, gives *Z*- and *E*-*t*-butylchloroethenes, 3,[2] by 1,2-H shifts, and cyclopropanes 4[14] by addition of carbene 2 to the alkene; eq. (3).



(3)

1 (R=H)
1-d_2 (R=D)

2 (R=H)
2-d_2 (R=D)

3 (R=H)
3-d_2 (R=D)

4 (R=H)
4-d_2 (R=D)

A plot of the product ratio [4]/[3] vs. [alkene] was curved (Figure 1A, trace 1), indicating that the product distribution was not the result of a straightforward competition between the intermolecular addition (giving 4) and intramolecular rearrangement (to 3) of a single intermediate (*e.g.*, carbene 2). Had this been the case, Figure 1A would have exhibited a linear correlation.[11b]

On the other hand, the *inverse* correlation of [3]/[4] vs. 1/[alkene] was rigorously linear (Figure 1b, line 1) consistent with a 2-intermediate mechanism, in which addition product 4 has a single precursor (carbene 2), but rearrangement product 3 has 2 precursors: the carbene and (presumably) the photoexcited diazirine, 1*.[11b,c,12,15]

Similar results attended the photolysis of the α,α-dideuterodiazirine, 1-d$_2$,[9] eq. (3). The direct correlation of [4-d$_2$]/[3-d$_2$] vs. [CH$_2$=CHMeEt] was curved (Figure 1A trace 2), but the corresponding inverse plot was linear (Figure 1B, line 2).[16] It is immediately evident from the Figures that a sizeable KIE is operative in the diazirine photolyses. For instance, we see in Figure 1A at high [alkene] that the undeuterated diazirine[15] and carbene (1 and 2) afford much 1,2-H rearrangement, relative to trapping ([4]/[3] = 0.59 at 8.3 M alkene), whereas their deuterated analogues afford much more addition and less rearrangement ([4-d$_2$]/[3-d$_2$] = 2.1 at 7.4 M alkene). Neglecting secondary isotope effects, these observations are consistent with an aggregate KIE of ~2.1/0.59 ~ 3.6 that favors 1,2-H over 1,2-D.

At high [alkene], where carbenes 2 or 2-d$_2$ should be largely trapped by addition, the KIE should mainly reflect 1,2-H(D) from excited diazirines 1* or 1-d$_2^*$. Indeed, 25°C photolysis of 1-d in 9.2 M (neat) 2-methyl-1-butene, where >95% of the carbene should be trapped,[17] gave alkenes 3-H and 3-D eq. (2), with k_H/k_D = 2.83 ± 0.14 (from the product analysis). This can be associated with a KIE operating in a nitrogen-loss/rearrangement reaction of excited diazirine 1-d*.

It is clear from both product studies and laser flash photolytic measurements that KIE's of ~2.5-3.5 attend the 1,2-H(D) rearrangements of *both* the neopentylchlorocarbenes 2, 2-d, and 2-d$_2$, *and* (most probably) their corresponding, excited state diazirine precursors. Carbene isotope effects of this magnitude are large compared to expectations for these reactive species; *cf.*, the KIE of $\le$1.3 for CH$_3$-C-Cl/CD$_3$-C-Cl.[18,19] However, they are appropriate relative to k_H/k_D ~ 5, observed in the 1,2-H(D) rearrangement of neopentylfluorocarbene;[1] one would expect the more reactive chlorocarbene to exhibit a lower KIE than its fluoro analogue. It is clear that we still have much to learn about the genesis of isotope effects in carbenic rearrangements.

Acknowledgment. We thank the National Science Foundation for financial support.

References and Notes

(1) R.A. Moss, G-J. Ho, W. Liu, and C. Sierakowski, *Tetrahedron Lett.*, 33, 4287 (1992).
(2) R.A. Moss, G-J. Ho, and W. Liu, *J. Am. Chem. Soc*, 114, 959 (1992).
(3) See reference 1, notes (12) and (18), and reference 2, for the preparation of 1-d.
(4) There is suggestive evidence that even thermal decompositions of nitrogenous carbene precursors may not always afford "pure" carbene reactions: J.M. Fox, J.E.G. Scacher; K.G.L. Jones, M. Jones, Jr., P.B. Shevlin, B. Armstrong, and R. Sztyrbicka, *Tetrahedron Lett.*, 33, 5021 (1992).

(5) The signals for the Z(-D) and Z(-H) isomers were at δ5.67 and 5.91, respectively.

(6) These dibromides were correlated with authentic (non-deuterated) dibromides that were characterized by NMR, GC-MS, and elemental analysis.

(7) It is a surprise that the vinyl proton of E-3-H appears at slightly higher field than that of E-3-D.

(8) J.E. Jackson, N. Soundararajan, M.S. Platz, and M.T.H. Liu, J. Am. Chem. Soc., 110, 5595 (1988).

(9) See reference 1, note (12), and reference 2 for the preparation of the diazirine.

(10) The complexities of the photochemistry of neopentylchlorodiazirine (see below) do not affect ylide-based kinetic studies which reflect only the chemistry of the carbene. There was also no apparent interference from azine formation in these reactions.

(11) (a) M.T.H. Liu, N. Soundararajan, N. Paike, and R. Subramanian, J. Org. Chem., 52, 4223 (1987). (b) J.A. LaVilla and J.L. Goodman, Tetrahedron Lett., 31, 5109 (1990). (c) W.R. White III and M.S. Platz, J. Org. Chem., 57, 2841 (1992).

(12) D.A. Modarelli, S. Morgan, and M.S. Platz, J. Am. Chem. Soc., 114, 7034 (1992).

(13) For example, the photolysis of cyclobutylfluorodiazirine involves only ~12% of non-carbenic rearrangement, whereas the analogous process with cyclobutylchlorodiazirine involes >60% of 1,2-C and 1,2-H rearrangements from an intermediate other than the carbene: R.A. Moss and G-J. Ho, submitted for publication.

(14) These products were characterized by NMR and GC-MS.

(15) Assuming that the second intermediate is 1*, its extent of intervention is ~58%, as determined[11b] from the intercept (1.4) of line 1 in Figure 1B.

(16) The intercept of line 2 in Figure 1B is 0.37, corresponding to (reduced) intervention of the second intermediate (i.e. 27%). Parallel effects of the α-deuteration of diazirines have been reported.[11c,12]

(17) The addition of carbene 2 to 2-methyl-1-butene has $k_{addn} = 5.9 \times 10^7$ $M^{-1}s^{-1}$, as measured by laser flash photolysis (pyridine ylide method). At [alkene] = 9.2 M, this leads to a pseudo-first-order $k_{addn} \sim 5.4 \times 10^8$ s^{-1}, which is ~39 times faster than 1,2-H for carbene 1 ($k_H = 1.4 \times 10^7$ s^{-1}).[2]

(18) J.A. LaVilla and J.L. Goodman, J. Am. Chem. Soc., 111, 6877 (1989).

(19) However, Platz et al. report an isotope effect of ~3.2 on the lifetime of CH_3-C-CH_3/CD_3-C-CD_3 in pentane.[12]

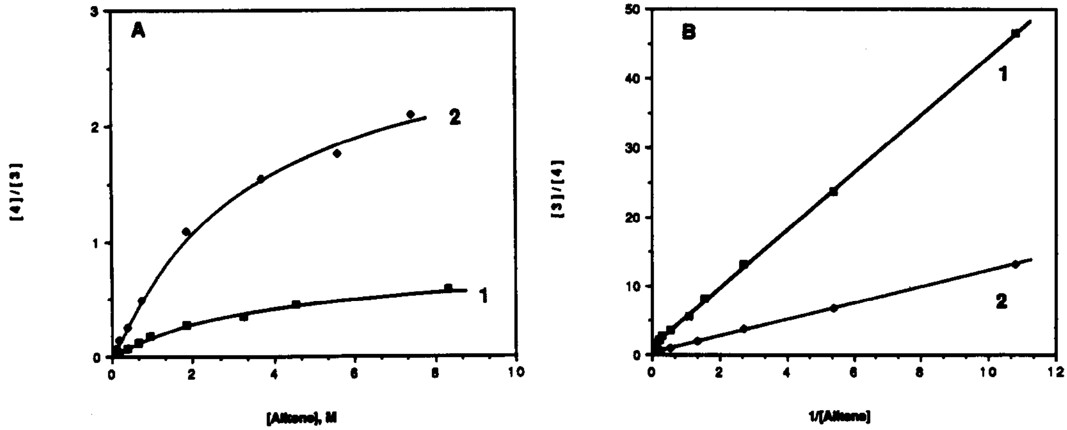


Figure 1. (A) Product ratio [4/3] *vs* [2-methyl-1-butene] for photolyses of 1 (trace 1) and 1-d_2 (trace 2). (B) Product ratio [3/4] *vs*1/[2-methyl-1-butene] for photolyses of 1 (line 1) and 1-d_2 (line 2).

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