Tetrahedron Letters, Vol. 34, No. 38, pp. 6025-6028, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

The α-Secondary Isotope Effect in the 1,2~C Rearrangement of Cyclopropylchlorocarbene

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Abstract: The experimental α-secondary kinetic isotope effect for the rearrangement of (2,2-dideuteriocyclopropyl)chlorocarbene, 2-d_2, to chlorocyclobutenes, 4 and 5, is k_H/k_D = 1.20 at 21 °C. The corresponding value calculated by ab initio electronic structure methods is 1.12. The isotope effect very largely originates in hybridization changes at the migrating carbon atom.

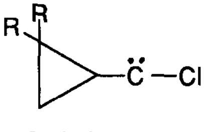
Recently, we reported strikingly large primary deuterium kinetic isotope effects (KIE's) attending 1,2~H migrations in the neopentylhalocarbenes, **1**: for the fluorocarbene, **1-F**, k_H/k_D ~ 6.5 in pentane or $CDCl_3$ at 20-22 °C,[1a] whereas for the analogous chlorocarbene, **1-Cl**, k_H/k_D ~ 3.5 (pentane, 20 °C).[1b] These KIE's greatly exceed the value reported for the parent methylchlorocarbene (≤ 1.3, heptane, 22 °C).[2] However, in keeping with the high values, Platz communicated k_H/k_D = 3.2 for the relative lifetimes of CH_3-C-CH_3 vs. CD_3-C-CD_3 (pentane, 25 °C), which are believed to be controlled by the rate constants for 1,2~H vs. 1,2~D shifts.[3] Similar effects also govern the relative lifetimes of the detected CD_3-C-D and the unobserved CH_3-C-H.[4]

What origins can be ascribed to these large KIE's that are associated with low activation energy (≤ 3-4 kcal/mol)[5] intramolecular rearrangements? Unusually negative activation entropies, low transmission coefficients, and quantum mechanical tunneling may all contribute.[2,4,5] Are *secondary* KIE's also abnormal in these reactions?

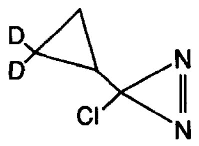
To answer this question, we have now determined the intramolecular α-secondary KIE for the CH_2 vs. CD_2 competitive 1,2~C shifts of (2,2-dideuteriocyclopropyl)chlorocarbene, **2-d_2**. The parent carbene, **2**, ring expands to 1-chlorocyclobutene with $k \sim 0.9\times10^6$ s^{-1} (20 °C, isooctane), E_a ~ 3.0 kcal/mol, and log A ~ 8.2 s^{-1} ($\Delta S^{\neq}$ ~ -23 e.u.).[6,7] The extraordinarily low $\Delta S^{\neq}$, which must be of dynamic origin, implies a transmission coefficient <<1.[6b] When the migrating cyclopropyl carbons are rendered structurally distinct (e.g., CH_2 vs. CMe_2 in **2-Me_2**), a kinetic selectivity of ~ 5, favoring CH_2, is observed and attributed to differential steric effects in the computed alternative rearrangement transition states.[8] Reduction of the structural difference to CH_2 vs. CD_2 (as in **2-d_2**) should mitigate the steric factors and permit unusual electronic effects or tunneling to come to the fore. Appropriate experimental and computational studies of **2-d_2** follow.

$Me_3CCXY\text{-}\ddot{C}\text{-}Z$

1, X,Y=H_2, HD, or D_2
Z=F or Cl

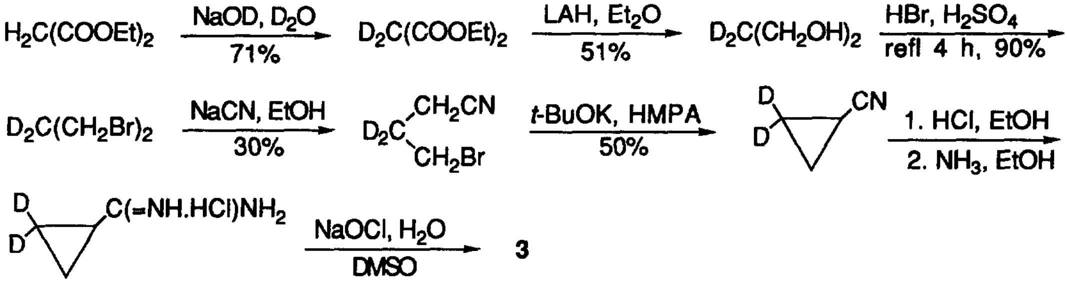


2, R=H
2-d_2, R=D
2-Me_2, R=Me



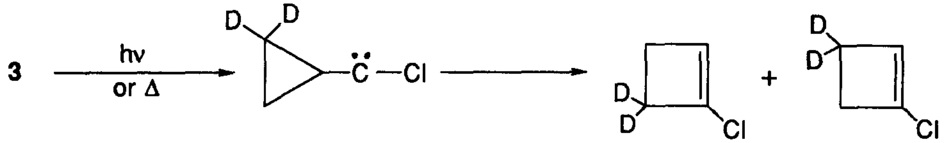
3

Scheme I



The requisite 3-(2,2-dideuteriocyclopropyl)-3-chlorodiazirine precursor (**3**) of carbene **2**-$\underline{d}_2$ was synthesized by the sequence outlined in Scheme I. Exchange of diethyl malonate with 2M NaOD/D_2O afforded the $\underline{d}_2$ ester (>97% $\underline{d}_2$ by NMR).[9] Reduction with $LiAlH_4$ (refluxing ether/pentane, 2 h) gave the labeled propane diol,[9] which was converted[10] to the corresponding dibromide. The latter, with 0.81 equiv. of NaCN in 84% aq. EtOH (R.T., 1 h, refl., 45 min), gave 1-bromo-2,2-dideuterio-3-cyanopropane[11] ($\delta(CDCl_3)$ 2.52, 3.46, 2 2-proton singlets, >97% 2-$\underline{d}_2$). Treatment with KO-$\underline{t}$-Bu in HMPA (100 - 120 °C with vacuum distillation) closed the bromocyanopropane to the cyanocyclopropane, the conversion of which to the amidinium salt[12a] and thence to **3**[12b] via Graham's oxidation[13] have been previously described.[5,6]

Decompositions of **3** were carried out photochemically ($CDCl_3$, $\lambda > 320$ nm) or thermolytically with analysis by ^1H NMR. Photolysis of **3** ($\underline{A}_{348} = 1.0$, 21 °C, 40 min) destroyed the diazirine and afforded a reaction mixture that contained the $\underline{\text{proximal}}$-$\underline{d}_2$ chlorocyclobutene, **4**, and its $\underline{\text{distal}}$ isomer, **5**; cf., eq. (1).[14] These isomers can be differentiated by noting the deshielding by Cl of the adjacent allylic protons of **5** ($\delta(CDCl_3)$ 2 .75), relative to the "para" CH_2 of **4** (δ 2.39);[15] parallel chemical shift behavior was observed with the isomeric cyclobutenes derived from **2**-Me_2, the dimethyl analogue of **2**-$\underline{d}_2$.[8]



2-$\underline{d}_2$ **4** **5** (1)

The distal/proximal product ratio is equivalent to the ~CH_2/~CD_2 migration ratio of carbene **2**-$\underline{d}_2$,[16] and thus to $\underline{k}_H/\underline{k}_D$, the α-secondary KIE. For the 21 °C photolysis, $\underline{k}_H/\underline{k}_D = 1.20$ by electronic integration of the appropriate NMR signals. Photolysis of **3** at -30 °C gave $\underline{k}_H/\underline{k}_D = 1.28$, while either photolysis or thermolysis (20 min) of **3** in $CDCl_3$ at 60 °C led to $\underline{k}_H/\underline{k}_D = 1.18$.[16] Conservatively, we attach 10% errors to these ratios, so that the isotope effect and its temperature dependence are both small.[17]

We have carried out ab initio electronic structure calculations to analyze the magnitudes of the observed KIE's. The geometries of the reactant (**2**) and the transition state for 1,2~C rearrangement to chlorocyclobutene were optimized at the Hartree-Fock level with the 6-31G* split valence plus polarization function basis set (HF/6-31G*//6-31G*) and fully characterized by harmonic normal mode analysis.[8,18] Isotopic mass substitution subsequently provided the vibrational frequencies for the dideuterio-labelled species. The full statistical mechanical expressions based on conventional transition state theory[19] were used to evaluate $\underline{k_H/k_D}$. The transmission coefficient ratio was set to unity and all vibrational frequencies were scaled by a factor of 0.87.[20]

The computed KIE arises almost exclusively from differences in vibrational zero-point energies. The rate constant ratios formed by the mass-moment of inertia and thermal excitation partition functions are both 1.00 ± 0.01. At 21 ^{o}C, the computed $\underline{k_H/k_D} = 1.09$, normal and weak. The temperature dependence is predicted to be small, in agreement with the experimental data, since the computed $\underline{k_H/k_D} = 1.10$ at -30 ^{o}C and 1.07 at 60 ^{o}C. The magnitudes of the computed KIE's are slightly less than the observed values but they do not include any corrections for quantum mechanical tunneling effects. A tunneling correction factor to the rate constant (k_t) based on the assumption of an infinitely high parabolic activation energy barrier ($k_t = u^{\neq}/\sin(u^{\neq})$, $u^{\neq} = 0.5h|v^{\neq}|/k_BT$, $v^{\neq}$ = transition state imaginary frequency)[21] may be readily evaluated on the basis of the vibrational frequency analysis of the transition state. Using this expression, the KIE's arising from tunneling are slightly larger than unity with weak temperature dependence. Thus, at -30 ^{o}C the ratio is $k_{tH}/k_{tD} = 1.05$, at 21 ^{o}C we obtain $k_{tH}/k_{tD} = 1.03$, and finally $k_{tH}/k_{tD} = 1.02$ at 60 ^{o}C. Multiplication of the two sets of KIE's leads to final computed α-secondary kinetic isotope effects of $\underline{k_H/k_D} = 1.16$ (-30 ^{o}C), 1.12 (21 ^{o}C), and 1.09 (60 ^{o}C), all within 10% of the experimental values. It is well understood that the tunneling correction expression is very approximate.[21] The choreography of the 1,2~C rearrangement is very intricate and the activation energy barrier for this highly exothermic reaction is certainly not parabolic.[6,22] Considering the approximate nature of the calculations and the expressions used to evaluate the KIE, as well as the complete omission of any dynamical effects,[23] the overall agreement between computed and experimental values is highly satisfactory.

The magnitude of a secondary kinetic isotope effect is used to infer changes in hybridization at the reacting center as it passes from the reactant to the transition state. From the classical analysis by Streitwieser,[24] the complete change from sp^3 to sp^2 hybridization at a carbon atom is expected to produce a normal secondary KIE of magnitude ~ 1.4. The present observed and computed values are considerably smaller than this extremum and the 1,2~C rearrangement might thus be expected to involve small hybridization changes at the migrating center. A natural bond orbital analysis was carried out on the reactant and transition state wavefunctions.[25] The localized molecular orbitals provided by this scheme show that the cyclopropane type C-H bonds in **2** effectively employ $sp^{2.6}$ hybrids from carbon. In the transition state, the hybridization of the carbon orbitals in the C-H bonds of the migrating methylene group changes to $sp^{2.4}$. Thus, the normal but weak secondary KIE for the present rearrangement is fully consistent with small hybridization changes that decrease the amount of C(2p) character in the C-H bonds attached to the carbon undergoing the 1,2-shift. The minor changes in hybridization give rise to only small changes in the vibrational zero-point energies.

Two additional points deserve brief mention. Firstly, we doubt that the observed secondary kinetic isotope effect reflects steric factors differentiating deuterium from protium. In the transition state, the distances between the methylene hydrogens on the migrating carbon and the carbenic carbon atom are of the order 2.2 - 2.5 Å,[8] which indicates possible steric hindrance because $R_{VDW}(H) = 1.2$ Å and $R_{VDW}(C) = 1.6$ Å.[26] A C-D bond is shorter (0.009 Å)[24] than a C-H bond and hence a D atom will be closer to the carbenic carbon. Steric interactions, if present, will thus tend to favor CH_2 migration, but we do not believe that distance differences of the order of 0.01 Å can be important. Secondly, if substantial charge buildup occurs on the migrating center, differences in the electron donating ability of H vs. D could conceivably play a factor. Presumably, D is the better electron donor (poorer electron acceptor) due to the shorter C-D bond length. The change in partial atomic charge on the migrating carbon atom, between the reactant and the transition state, is positive but very close to zero.[8] Therefore, the relative H vs. D electron donating ability should not play a role. These two factors are not recognized in the ab initio calculations where isotopic substitution does not alter the molecular geometries.

In summary, whereas primary kinetic isotope effects involving hydrogen migration in carbenes can be large, the α-secondary effects appear normal. The present measured values are reproduced well by ab initio calculations which also provide a detailed mechanism in terms of small differential zero point energy changes related to small hybridization changes at the migrating carbon center.

Acknowledgements. We thank the National Science Foundation for financial support and Mr. F. Abu-Hasanayn for assistance with the kinetic isotope effect calculations.

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(Received in USA 2 June 1993; accepted 22 July 1993)