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Activation energies for the 1,2-carbon migration of ring-fused cyclopropylchlorocarbenes

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Abstract—Fused-ring cyclopropylchlorocarbenes **2** and **3** ring expand to fused-ring chlorocyclobutenes **10** and **11**, respectively, with activation energies of 3–4 kcal/mol and activation entropies of ∼−20 e.u. Carbon tunneling appears to be unimportant at low temperatures.

The rearrangements of cyclopropylcarbenes are complicated and have been extensively investigated.[1] Some simplification is possible upon substitution of a chlorine atom at the divalent carbon center, which stabilizes the cyclopropylcarbene by electron donation into the carbene's vacant p orbital.[2] In particular, the 1,2-carbon migration of cyclopropylchlorocarbene (**1**) to chlorocyclobutene (Eq. 1) has attracted significant attention. The rate constant for the rearrangement was determined by laser flash photolysis

(1)

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(LFP) employing a diazirine precursor for carbene **1**, and following the kinetics either by direct observation of the carbene at 250 nm[3,4] or by 'indirect' monitoring of the competitive growth of its *N*-ylide formed by reaction with added pyridine.[3–5] Values of $k_{1,2}$ ranging from 3.8×10^5 to $9 \times 10^5\ \mathrm{s}^{-1}$ (at 20–23 °C in isooctane) were observed, depending on method and source.[3,4] The activation energy of the rearrangement, however, remains somewhat uncertain. A value of 7.4±0.4 kcal/mol was determined by direct observation of **1** after correction for concurrent carbene dimerization.[3b] However, a significantly lower value of 3.0±0.4 kcal/mol was obtained by four different methods: direct observation of **1**; determination of $k_{1,2}$ by ylide methodology; by analysis of the kinetics of competitive carbene addition to an alkene; and from product analysis of temperature dependent, competitive rearrangement and alkene additions of **1**.[6] Dimerization was found not to be a complicating factor under the reaction conditions.[6]

Early computational studies gave $\Delta H^{\ddagger} \sim 8$ kcal/mol (in vacuo) for the ring expansion of **1**,[4,6] similar to the higher experimental value of E_a (7.4 kcal/mol).[3b] More recently, an exhaustive state-of-the-art theoretical study of reaction (1) reinforced the divergence between the computed and 'lower' experimental E_a; the computed E_a's were 10.7 kcal/mol in vacuo or 8.5 kcal/mol in isooctane.[7] An even larger discrepancy was found for the experimentally determined[8] and computed E_a of the analogous ring expansion of cyclopropylfluorocarbene to fluorocyclobutene (4.2 vs 11.9 kcal/mol, respectively).[9] Finally, both experiment[10] and theory[7,10] agree that carbon atom tunneling is not important in the ring expansion of carbene **1** at ambient temperature.

In view of the continuing divergence between our experimental values of E_a for the ring expansion of **1** and the corresponding computational values, we examined the analogous ring expansion of two novel ring-fused cyclopropylchlorocarbenes, **2** and **3**. The results are communicated here.

Keywords: Carbenes; Kinetics.

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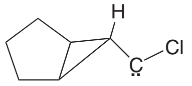

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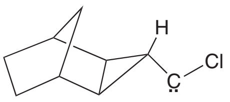

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The diazirine precursors for carbenes **2** and **3** were both prepared by the same sequence of reactions, illustrated for carbene **2** in Scheme 1. Thus, cyclopentene was converted to *exo*- and *endo*-bicyclo[3.1.0]hexane-6-carboxylate ethyl esters **4** with ethyl diazoacetate ($Rh_2(OAc)_4$, CH_2Cl_2, 6 h, rt, N_2 atm, 96%).[11] Without purification, the esters were hydrolyzed with epimerization, and then acidified to yield *exo*-acid **5**[12] (KOH, aq EtOH, refl., 6 h, then HCl, mp 58–59 °C, 72%), which was reesterified to *exo*-methyl ester **6** (MeOH, H_2SO_4, refl., 6 h, 94%). The ester was converted to amidine **7** by the Gielen–Garigipati reaction[13] ($MeAl(Cl)NH_2$ toluene, 80 °C, 40 h, then MeOH, rt, 1 h, mp 206–208 °C from *i*-PrOH/acetone, 56%; Anal. C, H, N). Compounds **4**–**7** were each characterized by ^1H and ^{13}C NMR spectroscopy. Finally, **7** was oxidized to diazirine **8** by aqueous NaOCl (12.5% 'pool chlorine', LiCl, DMSO, pentane, 0–15 °C, 15 min, ~45%).[14] Diazirine **8** was purified by chromatography over silica gel, and characterized by NMR,[15] IR (1566 cm^{-1}, film, N=N), and UV (λ_{max} 346 nm, pentane).

In a precisely parallel series of reactions, norbornene was transformed to diazirine **9**,[16] which was also purified by chromatography, and characterized by NMR,[17] IR (1565 cm^{-1}, film, N=N), and UV (λ_{max} 346 nm, pentane). Diazirines **8** and **9** were decomposed either photochemically (350 nm, 25 °C) or thermally (16 h, 70 °C) in $CDCl_3$ or 1,2-dichloroethane (DCE) to give the 1,2-C migration products **10** or **11**, anticipated from the intermediate carbenes **2** or **3**, respectively. The products were characterized by capillary GC, GC–MS, and ^1H and ^{13}C NMR spectroscopy. For 6-chlorobicyclo[3.2.0]hept-6-ene (**10**), we observed the vinyl proton at δ 5.69, as well as the allylic ring-junction protons at δ 3.2 and 3.09.[18] Similarly, for 3-chloro-*exo*-tricyclo[4.2.1.0^{2,5}]nona-3-ene (**11**), we found the vinyl proton at δ 5.74 and the allylic ring-junction protons at δ 2.72 and 2.41.[19] In the photolysis of **8**, about 17% of cyclopentene was formed by the fragmentation of carbene **2**; fragmentation was much reduced in the photolysis of **9**, but other impurities lowered the yield of **11** to about 81%.

The kinetics of the **2** → **10** and **3** → **11** rearrangements were examined by LFP using the pyridine ylide method.[5] LFP[20] at 351 nm and 25 °C of diazirine **8** ($A_{350} \sim 1$ in DCE) in the presence of pyridine produced an ylide absorbance at (λ_{max}) 385 nm. A correlation of the apparent rate constants for ylide formation, k_{obs} (2.8×10^6–6.4×10^7 s^{-1}) versus pyridine concentration (0.02–2.47 M), was linear (10 points, $r = 0.999$) with a slope of 2.6×10^7 M^{-1} s^{-1}, equivalent to the rate constant for ylide formation, k_y, and a *Y* intercept of 5.71×10^5 s^{-1}; cf. Figure 1. The intercept represents the sum of rate constants for processes that destroy carbene **2** when [pyridine] = 0. Given that alkene **10** is the principal product (>80%) formed from carbene **2**, we can take the extrapolated *Y* intercept of Figure 1 as a reasonable estimate of $k_{1,2}$ for the **2** → **10** rearrangement. Repetition of the determination gave a second value of $k_{1,2} = 5.87 \times 10^5$ s^{-1}, leading to an average value of $(5.79 \pm 0.08) \times 10^5$ s^{-1}.[21–23]

In a similar way, we determined $k_{1,2}$ for carbene **3**. Here, ylide formation was observed at λ_{max} 375 nm, and the quality of the kinetic data is illustrated in Figure 2, where $k_y = 3.40 \times 10^7$ $M^{-1}s^{-1}$, and the *Y* intercept ($k_{1,2}$) = 1.90×10^6 s^{-1}. Again, correlation of k_{obs} and [pyridine] is linear, with $r = 0.998$ for 8 points. Repetition of the experiment led to an average value of $k_{1,2} = (1.89 \pm 0.02) \times 10^5$ s^{-1} for the **3** → **11** rearrangement. The values of $k_{1,2}$ that we observe for carbenes

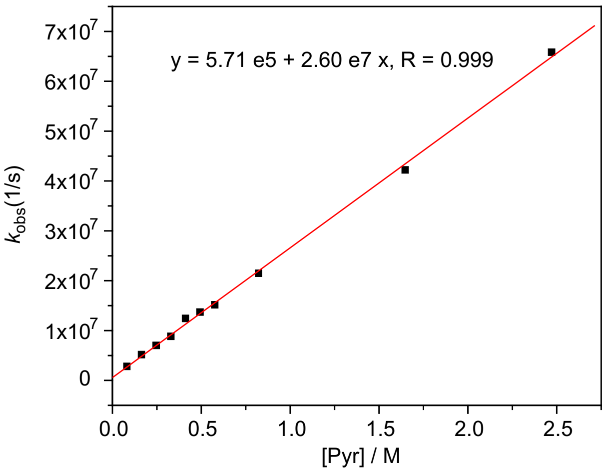
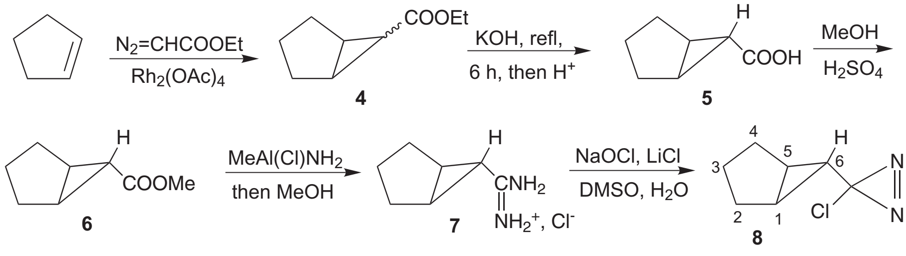


Figure 1. k_{obs} (s^{-1}) for ylide formation between carbene **2** and pyridine versus [pyr] (M); see text.



Scheme 1.

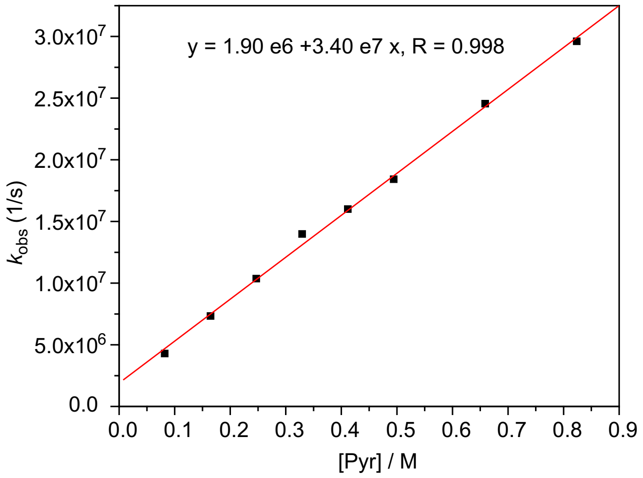


Figure 2. k_{obs} (s^{-1}) for ylide formation between carbene **3** and pyridine versus [pyr] (M); see text.

2 ($5.8 \times 10^5\ s^{-1}$) and **3** ($1.9 \times 10^5\ s^{-1}$) are comparable to the range of $k_{1,2}$ values ($3.8–9 \times 10^5\ s^{-1}$) reported for the parent cyclopropylchlorocarbene, **1**; see above.

Arrhenius LFP studies of the carbene rearrangements were conducted over the temperature range of 243 (**3**) or 253 (**2**) to 303 K. Correlations of $\ln k_{1,2}$ versus $1/T$ are reproduced in Figure 3 for carbene **2** and Figure 4 for carbene **3**. The quality of the data is good, with $r = 0.994$ (7 points) for **2**, and $r = 0.983$ (8 points) for **3**. The corresponding activation parameters are **2** → **10**: $E_a = 3.1$ kcal/mol, $A = 4.3 \times 10^8\ s^{-1}$, $\Delta S^{\ddagger}_{298}$ −21 e.u.; and **3** → **11**: $E_a = 3.8$ kcal/mol, $A = 6.8 \times 10^8\ s^{-1}$, and $\Delta S^{\ddagger}_{298} - 20$ e.u. Both sets of activation parameters are similar, and they are also similar to those we measured for the ring expansion of the parent carbene **1** ($E_a = 3$ kcal/mol, $\Delta S^{\ddagger} \sim -20$ to -24 e.u.).[6] As a control experiment, the photolysis of diazirine **8** was examined at −30 to −40 °C. The product mixture, dominated by **10**, was unchanged from the room temperature photolysis.

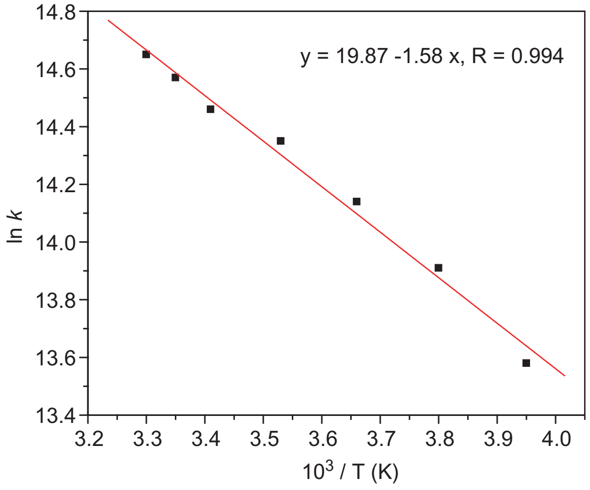


Figure 3. Arrhenius correlation for the **2** to **10** rearrangement in DCE; $\ln k_{1,2}$ (s^{-1}) versus $1/T$ (K^{-1}).

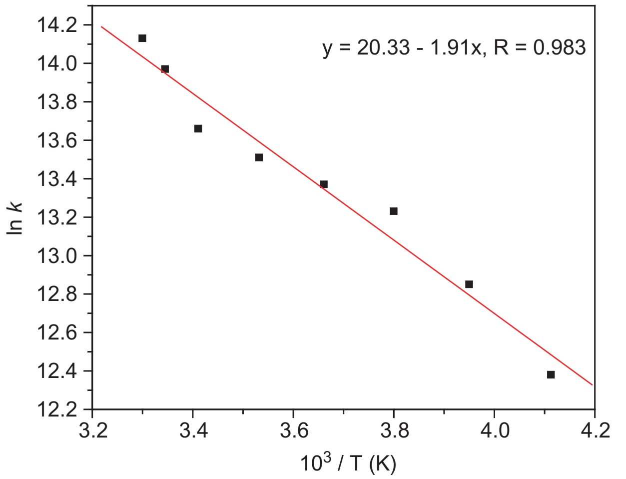
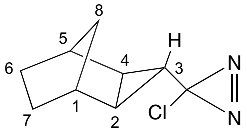


Figure 4. Arrhenius correlation for the **3** to **11** rearrangement in DCE; $\ln k_{1,2}$ (s^{-1}) versus $1/T$ (K^{-1}).

Although the present results do not explain the discrepancy between the experimental[6] and computed[7] values of E_a for the rearrangements of **1**, they parallel the 'low' experimental E_a of ∼3 kcal/mol, and suggest that the separation between the measured and computed activation energies is 'persistent.' Indeed, we computed $\Delta H^{\ddagger}_{298}$ for the rearrangement of carbene **2** to product **10** at the B3LYP/6-31G(d) level. Our value of 11.5 kcal/mol (in vacuo) compares well with $\Delta H^{\ddagger}_{298}$ 10.1 kcal/mol (HDFT, in vacuo) reported for rearrangement of the parent carbene (Eq. 1),[7] reinforcing the persistence of a 'gap' between the 'low' experimental and 'high' computed E_a's or $\Delta H^{\ddagger}$'s for these rearrangements.



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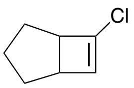

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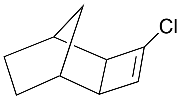

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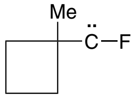

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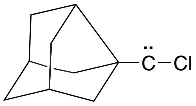

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Heavy atom quantum mechanical tunneling (QMT) is important in the ring expansions of 1-methylcyclobutylfluorocarbene (**12**) to 1-fluoro-2-methylcyclopentene,[24] and of noradamantyl chlorocarbene (**13**) to 2-chloroadamantene.[25] In contrast, calculations suggest that carbon QMT is unimportant in the ring expansion of **1**.[7] Our preliminary experiments with matrix-isolated **2** and **3** similarly failed to demonstrate QMT at low temperatures. Irradiation (334 nm, 75 min) of diazirine **8** isolated in a N_2 matrix (ca. 1:400) at 9 K cleanly produced carbene **2**. DFT calculated vibrational spectra (B3LYP/6-31+G**) of ca. 50:50 *syn*/*anti*-mixture of **2** gave a good fit to the experimental IR. Concurrently, a broad absorption in the UV/vis at 400–600 nm (max 490 nm) was observed to grow in. No changes were observed in the IR or UV/vis spectra of **2** after standing in the dark for 7 days at 8 K.

However, irradiation of **2** at 546 nm for 30 min resulted in its disappearance with the simultaneous growth of a series of new bands, some of which belonged to chloroacetylene (2110 cm^{-1}) and cyclopentene (assigned by comparison to the IR spectrum of an authentic sample). Other new bands, although of low intensity, were consistent with the IR spectra calculated for **10**.[26] Interestingly, irradiation of **2** at 435 nm caused more rapid disappearance of the IR bands that fit predictions for the carbene conformer with H and Cl *syn* (strongest bands at 1323 and 734 cm^{-1}), compared to the bands assigned to *anti*-**2** (strongest at 1386 and 646 cm^{-1}).

Similarly, photolysis of matrix-isolated **9** (ca. 1:400, N_2, 8 K) at 334 nm gave a mixture of *syn* and *anti*-carbene **3**, matching the calculated IR spectra. Carbene **3** showed UV/vis absorption very similar to **2** with a broad band in the 400–600 nm region and a maximum at 500 nm. Although no changes in the spectra could be detected after the matrix was maintained in the dark for 5 days at 8 K, **3** could be easily destroyed by irradiation at 546 nm for 3 h, producing norbornene (assigned by comparison to the IR spectrum of an authentic sample), chloroacetylene, and **11**.[26] Again, 435 nm irradiation caused selective reaction of *syn*-**3** (strongest bands at 1126 and 824 cm^{-1}) compared to *anti*-**3** (strongest bands at 1136 and 651 cm^{-1}).[27]

In conclusion, fused-ring cyclopropylchlorocarbenes **2** and **3** ring-expand to fused-ring chlorocyclobutenes **10** and **11** with activation energies of ∼3–4 kcal/mol and activation entropies ∼−20 e.u. These parameters are similar to those observed for the parent cyclopropylchlorocarbene **1**,[6] suggesting that the difference between the experimental values and the computed E_a of ∼8.5 kcal/mol[7] for the ring expansion of **1** is real and may be significant.

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15. Diazirine **8**. ^1H NMR (400 MHz, $CDCl_3$, δ): 0.96–1.1 (m, 1H, H3), 1.29 (d, $J = 1$ Hz, 2H, H1, H5), 1.39 (t, $J = 1$ Hz, 1H, H6), 1.54–1.62 (m, 1H, H3′), 1.64–1.78 (m, 4H, H2, H4). ^{13}C NMR (300 MHz, $CDCl_3$, δ): 20.52, 25.08, 25.12, 27.40, 49.04.
16. The initial addition reaction between norbornene and ethyl diazoacetate was catalyzed by CuCN: Sauers, R. R.; Sonnet, P. E. *Tetrahedron* **1964**, *20*, 1029.
17. Diazirine **9**. ^1H NMR (400 MHz, $CDCl_3$, δ): 0.68 (d, $J = 11$ Hz, 1H, H8), 0.77 (d, $J = 2.4$ Hz, 2H, H2, H4), 0.87 (dt, $J = 11$ Hz, 1.8 Hz, H8′), 1.22–1.48 (m, 4H, H6, H7), 1.57 (t, $J = 2.4$ Hz, 1H, H3), 2.29 (s, 2H, H1, H5). ^{13}C NMR (300 MHz, $CDCl_3$, δ): 20.40, 22.98, 28.43, 29.09, 35.87, 48.91.
18. Alkene **10**. ^1H NMR (400 MHz, $CDCl_3$, δ): 1.14–1.28 (m, 2H, H3), 1.50–1.90 (m, 4H, H2, H4), 3.09 (m, 1H, H1), 3.32 (dd, $J = 3.2$, 7.6 Hz, 1H, H5), 5.69 (d, $J = 0.4$ Hz, 1H, H6). ^{13}C NMR (300 MHz, $CDCl_3$, δ): 22.90, 24.54, 26.64, 44.37, 54.15, 117.80, 131.42. MS (*m*/*e*): 128, 130 [M^+, $(M+2)^+$].
19. Alkene **11**. ^1H NMR (400 MHz, $CDCl_3$, δ): 1.03 (m, 2H, H9), 1.47 (m, 2H, H7), 1.59 (m, 2H, H8), 2.02 (t, $J = 1.6$ Hz, 1H, H6), 2.10 (t, $J = 1.6$ Hz, 1H, H1), 2.41 (d, $J = 3.2$ Hz, 1H, H5), 2.72 (d, $J = 3.2$ Hz, 1H, H2), 5.74 (s, 2H, H4). ^{13}C NMR (300 MHz, $CDCl_3$, δ): 22.99, 28.29, 30.49, 32.84, 36.37, 46.34, 56.38, 117.42, 131.56. MS (*m*/*e*): 154, 156 [M^+, $(M+2)^+$].
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21. Some alkene **10** could arise directly by rearrangement concerted with nitrogen loss of diazirine **8**.[22,23] To estimate this contribution, **8** was photolyzed in 2-methyl-2-butene and the reaction products were examined by capillary GC. Formation of ∼61% of the cyclopropane adducts of carbene **2** and 2-methyl-2-butene was verified by GC–MS; the proportion of cyclobutene **10** was ∼39%. The extensive quenching of **10** by the added alkene proves that most of the **10** formed in the absence of alkene (>60%) stems from

carbene **2**, and not from an excited state of diazirine **8**. The pyridine ylide LFP kinetics are therefore valid as a measure of the rearrangement of carbene **2**. The method is independent of excited diazirine because it follows reactions of the carbene; the excited diazirine does not live long enough to react with pyridine.[23]

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26. Only minor amounts of the fragmentation or rearrangement products of the carbenes were observed in initial irradiations of matrix isolated diazirines **8** or **9**, suggesting at most only minor excited state diazirine participation at low temperature. See also, note 21.
27. TD B3LYP/6-31+G** calculations predict shorter wavelength absorptions for the *syn* conformations of carbenes **2** and **3** (488 and 489 nm, respectively), compared to the *anti* conformers (553 and 555 nm, respectively). Preliminary experiments suggest that irradiations at 590 nm induce selective photochemistry of the *anti* carbenes. Mixtures of both rearrangement and fragmentation products are observed from **2** and **3** irrespective of the irradiation wavelength, although further experiments probing whether the *syn* and *anti* conformers of the carbenes may favor different products are in progress.