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Carbene Fragmentation in the Bicyclo[3.1.0]hexyl System: Disconnecting the Trishomocyclopropenyl Cation

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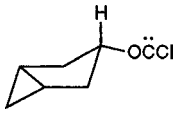
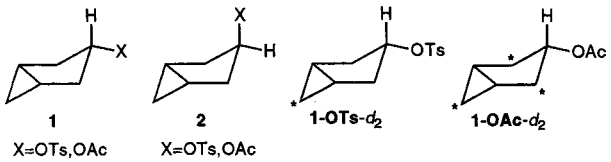
ABSTRACT



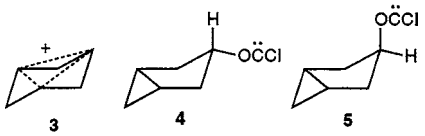
Fragmentation of *cis*-3-bicyclo[3.1.0]hexyloxychlorocarbene (4) affords *cis*- and *trans*-3-bicyclo[3.1.0]hexyl chlorides, *cis*- and *trans*-2-bicyclo-[3.1.0]hexyl chlorides, and 2-bicylo[3.1.0]hexene. The promiscuity of product formation, taken together with kinetics and labeling studies, suggests that the fragmentation of 4 proceeds via a 3-bicyclo[3.1.0]hexyl cation–chloride ion pair but largely bypasses a trishomocyclopropenyl cation intermediate.

Our understanding of carbocation chemistry is heavily influenced by numerous studies of solvolysis reactions, frequently involving tosylate or triflate substrates. Most of these reactions have activation energies in the 20−30 kcal/mol range and entail significant solvent or anchimeric assistance.

A classic example of the latter phenomenon occurs in the acetolysis of *cis*-3-bicyclo[3.1.0]hexyl tosylate, **1-OTs**.[1] To summarize the key findings: (a) **1-OTs** affords **1-OAc** with complete retention and no elimination in HOAc at 50 °C, whereas *trans*-**2-OTs** gives 66% of **1-OAc** with inversion, accompanied by 33% of elimination (at 75 °C). (b) Acetolysis of **1-OTs** at 50 °C ($k = 2.5 \times 10^{-5}$ s^{-1}) is ∼10 times faster than acetolysis of **2-OTs** ($k = 2.7 \times 10^{-6}$ s^{-1}). (c) Acetolysis of **1-OTs**-d_2, labeled at the cyclopropyl methylene position, yields **1-OAc**-d_2 with the label equally distributed over the three methylene groups. In contrast, there is minimal label scrambling during the acetolysis of **2-OTs**.



These results implicate the symmetrical trishomocyclopropenyl cation, **3**, as the key intermediate formed during the acetolysis of **1-OTs**.[1] Cation **3** forms with rear-side participation of the stereochemically apposite cyclopropyl σ bond in the acetolysis of (cis) **1-OTs**, but such participation is necessarily absent during the acetolysis of (trans) **2-OTs**, where the σ bond is not properly positioned; instead, solvent participation leads to inverted acetate, **1-OAc**. The σ-bond involvement accounts for rate acceleration in the acetolysis of **1-OTs**, and the intermediacy of **3** accounts for the observed stereochemical retention and label scrambling.[1]



Recently, we found that the fragmentation of alkoxychlorocarbenes provides entry to carbocations, related ion pairs, and their precursor transition states.[2] We could access such

(1) Winstein, S.; Sonnenberg, J. *J. Am. Chem. Soc.* **1961**, *83*, 3235; **1961**, *83*, 3244.
(2) Moss, R. A. *Acc. Chem. Res.* **1999**, *32*, 969.

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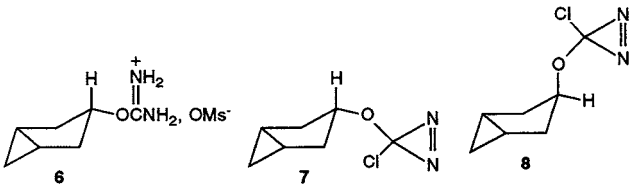
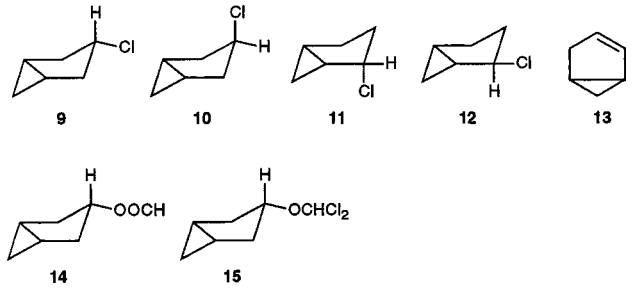
archetypal species as the 1-norbornyl[3a] and 2-norbornyl[3b] cations. Activation energies were low (<10 kcal/mol), so that solvent or anchimeric assistance should have been less important than in analogous solvolytic reactions. We wondered, therefore, whether the intermediacy of cation **3** would be suppressed in the fragmentation of *cis*-3-bicyclo[3.1.0]-hexyloxychlorocarbene (**4**) relative to the fragmentation of its trans isomer (**5**) and the solvolysis of **1-OTs**. Here, we provide an affirmative answer.

cis-3-Bicyclo[3.1.0]hexanol was prepared[1] from Δ^3-cyclopentenol[4] and converted[5] to isouronium mesylate **6**. The latter was oxidized with NaOCl[6] to diazirine **7** (λ_{max} 350 nm, pentane; υ 1540 cm^{-1}, film). Similarly, *trans*-3-bicyclo[3.1.0]-hexanol[1] was converted to diazirine **8** (λ_{max} 348 nm, pentane; υ 1541 cm^{-1}, film).



Products. Diazirines **7** and **8** were purified by chromatography over silica gel with pentane elution, and then photolyzed in various solvents at 350 nm to yield product mixtures that were analyzed by GC−MS and ^{1}H and ^{13}C NMR. From diazirine **7**, via carbene **4**, we obtained fragmentation products **9**−**13** in a total yield of ∼70%. Also present were formate **14** (20%, the product of carbene capture by water), and dichloride **15** (∼4%, the product of carbene capture by HCl). Several unknown products were also formed in a total yield of ∼6%.



The identities and distributions of products **9**−**13** were established by GC−MS, ^{1}H NMR, ^{13}C NMR, and NMR spiking experiments with independently prepared samples. Chlorides **9** and **10** were obtained in a ratio of 80:20 from the reaction of *cis*-3-bicyclo[3.1.0]hexanol with $SOCl_2$ and pyridine in ether.[7,8] Chlorides **11** and **12** were similarly[7] prepared in a 1.1:1 ratio from *cis*-2-bicyclo[3.1.0]hexanol.[9−11] 2-Bicyclo[3.1.0]hexene (**13**) was identified by its olefinic proton resonances at δ 5.30 and 5.87.[12] Finally, **14** and **15** were recognized by their low-field proton resonances (OOC*H* and OC*H*Cl_2) at δ 7.92 (**14**) and 7.15 (**15**). Additionally, **14** was augmented when the photolysis of **7** was carried out in the presence of water, whereas **15** was suppressed in the presence of pyridine, which scavenges HCl.[13]

The distributions of fragmentation products from carbene **4**, normalized to 100%, appear in Table 1.

Table 1. Product Distributions from Carbenes **4** and **5**[a]

carbene	solvent	**9**	**10**	**11**	**12**	**13**
4	C_6D_{12}	44	18	7		31
	DCE-d_4	30	9	17	13	31
	CD_3CN	20	10	27	17	26
5	C_6D_{12}	15	31		7	47
	DCE-d_4	7	28	7	19	39
	CD_3CN	6	19	17	19	39

[a] Photolysis at 25 °C; distributions in percent.

Experiments in solvents cyclohexane-d_{12}, dichloroethane d_4 (DCE-d_4), and CD_3CN are included; results in $CDCl_3$ were very similar to those in DCE-d_4. Photolyses of diazirine **8** in these solvents also gave mixtures of **9**−**13**, as well as the trans isomers of **14** and **15**. The relevant product distributions are also collected in Table 1.

We note the following: (a) Fragmentations of **4** and **5** are stereoselective for retention in the formation of **9** or **10**, but they are far from stereospecific. (b) There is substantial hydride shift, leading to chlorides **11** and **12**, which appears to increase with increasing solvent polarity.[14] (c) Elimination to **13** is a major pathway for both carbenes.

The contrast between the fragmentation of carbene **4** and the acetolysis of tosylate **1-OTs** is dramatic. The latter reaction occurs with chemo- and stereospecificity, and no elimination, whereas the carbene fragmentation manifests little control over stereochemistry, no suppression of 1,2-H shift, and no avoidance of elimination. There seems to be little participation of the internal cyclopropyl σ bond in the fragmentation of **4**. Instead, the fragmentations of carbenes **4** and **5** can be reasonably formulated as proceeding through

(3) (a) Moss, R. A.; Zheng, F.; Fedé, J.-M.; Ma, Y.; Sauers, R. R.; Toscano, J. P.; Showalter, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 5258. (b) Moss, R. A.; Zheng, F.; Sauers, R. R.; Toscano, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 8109.

(4) Hess, H. M.; Brown, H. C. *J. Org. Chem.* **1967**, *32*, 4138.

(5) Moss, R. A.; Kaczmarczyk, G. M.; Johnson, L. A. *Synth. Commun.* **2000**, *30*, 3233.

(6) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

(7) Freeman, P. K.; Raymond, F. A.; Grostic, M. F. *J. Org. Chem.* **1967**, *32*, 24.

(8) The signature ^{1}H NMR signals of **9** and **10** are those of the protons α to Cl: (δ, $CDCl_3$) 4.38 (**9**) and 3.80 (**10**) [lit.[7] (δ, CCl_4) 4.37 and 3.83, respectively].

(9) This alcohol was prepared by Simmons−Smith methylenation of Δ^2-cyclopentenol; cf. Dauben, W. G.; Berezin, G. H. *J. Am. Chem.* Soc. **1963**, *85*, 468.

(10) The signature ^{1}H NMR signals of **11** and **12** are those of the protons α to Cl: (δ, $CDCl_3$) 4.53 (**11**) and 4.40 (**12**) [lit.[7] δ 4.35 (CCl_4), lit.[11] 4.5 (neat) for **11**, and lit.[7] 4.29 (CCl_4) for **12**.

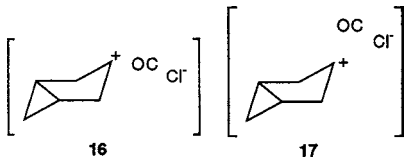
(11) Friedrich, E. C.; Holmstead, R. L. *J. Org. Chem.* **1972**, *37*, 2550.

(12) Dumartin, G.; Quintard, J.-P.; Pereyre, M. *J. Organomet. Chem.* **1983**, *252*, 37.

(13) See Moss, R. A.; Ge, C.-S.; Maksimovic, L. *J. Am. Chem. Soc.* **1996**, *118*, 9792. The persistence of products **11** and **12** in undiminished yield in the presence of pyridine indicates that they are not formed by the addition of HCl to alkene **13**.

(14) Note that H-shift with "inversion" (i.e., **4** → **12** or **5** → **11**) is absent in C_6D_{12}.

ion pairs **16** and **17**, respectively, which can collapse to **9** and **10**, undergo 1,2-H shift followed by chloride return to yield **11** and **12**, or lose HCl affording **13**. Leakage to delocalized cation **3** may compete with these processes, but only to a limited extent (see below). It is also clear from Table 1 that ion pairs **16** and **17** do not mutually equilibrate; the product distributions from **4** and **5** remain distinct.[15]



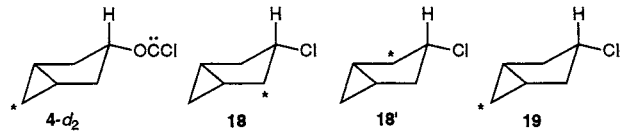
16 **17**

Kinetics. Absolute rate constants for the fragmentations of carbenes **4** and **5** were determined by laser flash photolysis[13] (LFP) at 351 nm and 25 °C of diazirines **7** and **8**. The pyridine ylide method[16] was used to visualize the carbenes. Thus, LFP of **7** in DCE containing pyridine produced an absorption at 425 nm assigned to the ylide formed from carbene **4** and pyridine. A correlation of the apparent rate constants for ylide formation ($(1.5-4.3) \times 10^5$ s^{-1}) vs pyridine concentration (1.6−8 M) was linear ($r = 0.996$, 9 points), with a slope equivalent to the rate constant for ylide formation ($k_y = 4.7 \times 10^4$ M^{-1} s^{-1}) and a *Y*-intercept which we take[13,16] as the rate constant for carbene fragmentation ($k_{frag} = 7.5 \times 10^4$ s^{-1}). An average value of k_{frag} (two runs) for carbene **4** is 8.5 (±0.9) $\times 10^4$ s^{-1}. Similarly, we determined $k_{frag} = 7.9$ (±0.1) $\times 10^5$ s^{-1} for carbene **5**.

Again, there is a marked contrast with the solvolyses of tosylates **1** and **2**, where the cis substrate (**1**) reacts ~10 times faster than its trans isomer (**2**) due to anchimeric assistance by the cyclopropyl σ bond.[1] In carbene fragmentation, such assistance is unimportant, and the trans carbene (**5**, axial OCCl) fragments ~9 times faster than the cis carbene (**4**, equatorial OCCl). Moreover, k_{frag} for *cis*-**4** is "normal" in that it is similar to k_{frag} for cyclohexyl-OCCl (3.3×10^4 s^{-1})[17] and cyclopentyl-OCCl (8.7×10^4 s^{-1}).[17]

We also note that the fragmentation of carbene **4** is ~9 orders of magnitude faster than the acetolysis of tosylate **1** due to the huge difference in activation parameters for the 2 reactions. Thus, $\Delta H^{\ddagger}$ for the acetolysis of tosylate **1** is 24.1 kcal/mol ($\Delta S^{\ddagger} = -5.0$ eu).[1] In contrast, a correlation of ln(k_{frag}) vs $1/T$ (233−303 K) for carbene **4** gives E_a ~2.4 kcal/mol ($r = 0.987$, 8 points).[18,19]

Label Scrambling. 6,6-Dideuterio-*cis*-3-bicyclo[3.1.0]-hexanol was prepared from Δ^3-cyclopentenol by Simmons−Smith methylenation with CD_2I_2.[1] Conversion to labeled diazirine **7**-d_2 proceeded as above, and photolysis led to **4**-d_2. If the fragmentation of **4**-d_2 gave (via **3**) complete equilibration and label scrambling over carbons 2, 4, and 6, then product chlorides **18** and **18′** should together be twice as abundant as chloride **19**. The product ratio (**18** + **18′**)/**19** was determined by ^{1}H NMR, integrating the cyclopropyl protons at C6 (δ 0.6 and 0.8) vs the proton α to Cl at C3 (δ 4.38). From this analysis, the percent scrambling in the fragmentation of **4**-d_2 was 8% in C_6D_{12}, 9% in $CDCl_3$, and 15% in CD_3CN.



4-d_2 **18** **18'** **19**

These results contrast with 100% scrambling observed in the acetolysis of **1-OTs**.[1] Clearly there is little involvement of the trishomocyclopropenyl cation **3** in the fragmentation of carbene **4**; chloride largely returns to the original carbon atom. There is perhaps a slight increase of scrambling in the more polar solvent CD_3CN, but even here, the results suggest only marginal leakage to cation **3**.

In conclusion, fragmentations of *cis*-3-bicyclo[3.1.0]-hexyloxychlorocarbene (**4**) in solvents of low to moderate polarity proceed through tight ion pairs which, in the limit, may functionally mimic a S_Ni reaction. The very low activation energy of 2.4 kcal/mol is consistent with an early transition state in which there is very little involvement of the C1−C5 cyclopropyl σ bond. At the same time, the very negative entropy of activation[18] indicates a highly ordered, probably cyclic transition state. The lack of chemospecificity, kinetic advantage, and label scrambling, phenomena associated with the acetolysis of **1-OTs**, suggests that the fragmentation of carbene **4** provides entry to a complementary "nonsolvolytic" carbocation chemistry. Related results in the 2-norbornyl system[3b] make it likely that the important difference between solvolysis and carbene fragmentation is general.

Acknowledgment. We are grateful to the National Science Foundation for financial support.

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(17) Johnson, L. A. Ph.D. Dissertation, Rutgers University, New Brunswick, NJ, 2001.

(18) $\Delta S^{\ddagger} \sim -30$ eu, indicating a high degree of order in the transition state for the fragmentation of **4**. The transition state may feature a cyclic array, akin to a "S_Ni" mechanism,[19] and proceed via tight ion pairs resembling **16**.

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