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Absolute Kinetics of Alkoxychlorocarbene Fragmentation

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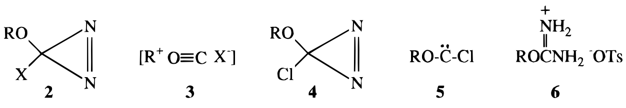
The reaction of an alkoxide with a dihalocarbene produces an alkoxyhalocarbene[1] (**1**) that can fragment to an alkyl cation with loss of halide and CO ("deoxideation");[2] *cf.*, eq 1.

$$RO^- + :CX_2 \longrightarrow RO\bar{C}X_2 \xrightarrow{-X^-} \underset{\mathbf{1}}{RO\text{-}\ddot{C}\text{-}X} \longrightarrow R^+ + O{\equiv}C + X^- \qquad (1)$$

Alternatively, **1** can be directly generated from an alkoxyhalodiazirine, **2**, by thermolysis (or photolysis).[3]



[(a) R = $PhCH_2$, (b) R = 1-$AdCH_2$, (c) R = Me_3CCH_2]

Subsequent studies have shown that the cations of eq 1 arise as ion pairs that afford substantial halide return even in neat alcoholic solvents (e.g., R = $PhCH_2$, X = Cl).[4] Moreover, return occurs with stereochemical retention,[5,6] whereas competitive solvent capture takes place with inversion,[6] as anticipated for ion pair intermediates. 1,2-Carbon shift rearrangements of the initial alkyl moiety intervene when R is (1-adamantyl)methyl (l-$AdCH_2$),[7] cyclopropylmethyl,[8] or neopentyl.[2,9] Indeed, the associated product ratios,[8] label distributions,[8] and stereochemistry of the 1,2-Me migration when R = neopentyl,[9] indicate that ion pairs **3** must be very tight. In the limit, the conversion of **1** to RX approaches the mechanistic paradigm of the S_Ni reaction.[10]

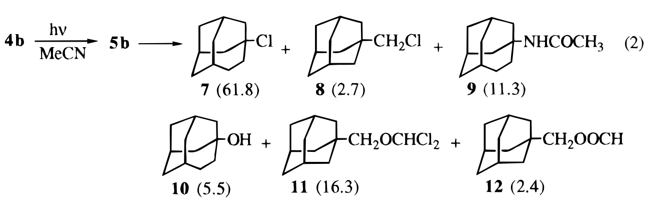
Despite this considerable body of product-based research, the *kinetics* of the actual carbene fragmentation are undetermined. Laser flash photolysis (LFP) of benzyloxychlorodiazirine (**4a**) failed to afford a transient absorption for benzyloxychlorocarbene, **5a**. Thermolysis of **4a** in methanol gave $PhCH_2Cl$ and $PhCH_2OMe$, from return and solvolysis of ion pair **3** (R = $PhCH_2$, X = Cl), but *no* products derived from methanolic capture of carbene **5a**.[4] If **5a** reacted with methanol at rates approaching diffusion control, like PhCOMe[11] or PhCCl,[12] then the fragmentation of **5a** must have occurred with $k_{\text{frag}} \sim 10^{10}$ s^{-1}.[4] However, we now know that *ambiphilic carbenes*, such as **5**, react "slowly" with methanol: the reaction of MeOCCl and neat MeOH occurred with $k \sim 2 \times 10^6$ s^{-1}.[13] The fragmentation of **5a** may therefore also be slow.

The introduction of the pyridine ylide methodology for the LFP visualization of carbenes that lack strong intrinsic UV absorptions,[14] together with the finding that MeOCCl reacts with pyridine (albeit slowly) to yield an ylide ($\lambda_{\max}$ 472 nm, k_y = 9.0×10^5 M^{-1} s^{-1}),[15] now permit us to apply the pyridine ylide LFP technique to the fragmentations of **5a**, (1-adamantyl)methoxychlorocarbene (**5b**), and neopentoxychlorocarbene (**5c**). The results constitute the first kinetic data for carbene fragmentation and demonstrate that this process occurs on the μsec timescale.

Reactions and Products. Diazirines **4a**−**c** were prepared by Graham oxidations[16] of *O*-alkylisouronium tosylates (**6**); the latter were synthesized from the appropriate alcohol, cyanamide, and anhydrous *p*-toluenesulfonic acid in $CHCl_3$ or THF[3a,4,6] and fully characterized. In MeCN, diazirines **4a**−**c** ($\lambda_{\max}$ 356 nm) had half-lives of 96 (**4b**)−155 (**4a**)[4] min at 25 °C.

Photochemical decomposition (λ > 330 nm) of **4a** in MeCN affords 63% of benzyl chloride via carbene **5a**, followed by fragmentation to ion pair **3a**, and subsequent collapse.[4] Additionally, 37% of $PhCH_2NHCOMe$ forms in a Ritter reaction initiated by benzyl cation capture by MeCN. Fragmentation is therefore the entire fate of carbene **5a**.

Product mixtures from carbenes **5b** and **5c** are more complex, however. Photolysis of (1-adamantyl)methoxychlorodiazirine (**4b**) (A_{356} = 1.0 in MeCN at 25 °C) gave **7**−**12** with the capillary GC distribution shown in eq 2; thermal decomposition at 25 °C afforded the same products in similar yields. Excepting **11**, products were characterized by ^1H NMR, GC-MS, elemental analysis, and GC-spiking with authentic samples. Dichloride **11** was identified by NMR and hydrolysis to formate **12**.



Products **7**−**10** arise by *fragmentation* (81%) of carbene **5b** via ion pair **3b**. Most of the 1-$AdCH_2$ moiety ring expands to the homoadamantyl cation, from which **7** (Cl^- return), **9** (Ritter attack on MeCN), and **10** (adventitious water) derive. 1-$AdCH_2$-Cl (**8**), which retains the original alkyl moiety, also descends from **3** but is not a displacement product since its yield does not increase when **4b** is decomposed in the presence of 0.1 M benzyltriethylammonium chloride. Products **11** and **12** represent *interception* (19%) of carbene **5b** by HCl (released during fragmentation) and water, respectively. When **4b** is decomposed in 4 M pyridine−MeCN, HCl is scavenged, and **11** disappears in favor of **12**, formed by hydrolysis of a carbene-pyridine ylide (see below). Fragmentation or pyridine capture are the two fates of carbene **5b** in pyridine−MeCN.[17]

Decomposition of diazirine **4c** affords the products (and capillary GC distribution) illustrated in eq 3;[18] product identities

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[17] Carbene dimer is *not* observed in MeCN, but in hexane, where fragmentation is slower,[4] dimer is the major product (55−60%).

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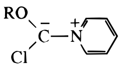
follow from GC-MS and spiking experiments with authentic samples.

$$\mathbf{4c} \xrightarrow[\text{MeCN}]{h\nu} \mathbf{5c} \longrightarrow \underset{\mathbf{13}\ (13.8)}{Me_2C{=}CHMe} + \underset{\mathbf{14}\ (26.5)}{CH_2{=}CMeEt} + \underset{\mathbf{15}\ (4.0)}{Me_2CClEt} \qquad (3)$$

$$\underset{\mathbf{16}\ (51.6)}{Me_3CCH_2OCHCl_2} + \underset{\mathbf{17}\ (3.4)}{Me_3CCH_2OOCH}$$

Dichloride **16** was characterized by NMR, GC-MS, and hydrolysis to formate **17** in aqueous MeCN. Products **13**−**15** arise by fragmentation (44%) of carbene **5c**, proceeding via ion pair **3c** (X = Cl), where rearrangement to the *tert*-amyl cation is total: loss of H^+ then generates **13** and **14**,[19] while return of chloride affords **15**. Dichloride **16** and formate **17** reflect interception (55%) of **5c** by HCl or water, respectively; the large alkene yield of fragmentation produces enough HCl to render trapping product **16** dominant. In the presence of 4 M pyridine, HCl is removed, **16** is entirely suppressed, and formate (74.5%) from hydrolysis of the carbene-pyridine ylide becomes the major product. Under these conditions, the fate of **5c** is fragmentation (23%)[20] or pyridine capture.

Kinetics. Absolute rate constants for the fragmentations of carbenes **5a**−**c** were determined by LFP[21] using pyridine ylide methodology;[14] carbene **5a** is illustrative. LFP at 351 nm and 25 °C of diazirine **4a** in MeCN ($A_{356} \sim 1.0$) in the presence of pyridine produced an absorption due to ylide **18a** at 460 nm. (Ylide **18**, R = Me, absorbs at 472 nm.[15])



18 (a-c as above)

A correlation of the apparent rate constants for ylide formation, k_{obs} (8.35×10^5 - 3.27×10^6 s^{-1}) vs pyridine concentration (0.41−5.36 M) was linear (eight points, $r = 0.997$) with a slope of 4.85×10^5 M^{-1} s^{-1}, equivalent to the rate constant for ylide formation, k_y,[22] and a *Y*-intercept of 6.9×10^5 s^{-1} (see supporting information, Figure S-1). The latter value can be equated with k_{frag} for **5a** → **3a** (X = Cl), because the product studies indicate that only fragmentation products result from the decay of benzyloxychlorocarbene.

We also determined k_{frag} by a double reciprocal analysis,[14b] in which we measured the absorbance (I_{rel}) of ylide **18a** as a function of pyridine concentration. A correlation of $1/I_{rel}$ vs 1/[pyr] was linear (12 points, $r = 0.996$); see supporting information, Figure S-2. Division of the correlation's intercept by its slope gave 0.369, which represents the lifetime (τ) of **5a** multiplied by k_y (4.85×10^5 s^{-1}, see above). Thus, $\tau_{\mathbf{5a}} = 7.6 \times 10^{-7}$ s, and $k_{frag} = 1.3 \times 10^6$ s^{-1}, in reasonable agreement with the directly measured value.

Similarly, LFP afforded k_{frag} for carbene **5b** as 5.2×10^6 s^{-1}, with $k_y = 2.0 \times 10^5$ M^{-1} s^{-1} for the formation of ylide **18b** ($\lambda_{max} = 468$ nm); see supporting information, Figure S-3. Here, the double reciprocal correlation gave $k_{frag} = 2.8 \times 10^6$ s^{-1} (see supporting information, Figure S-4). In contrast to carbene **5a**, where fragmentation in MeCN was quantitative, fragmentation of **5b** accounted for only ∼80% [eq 2], with ∼16% of the carbene diverted to **11** by HCl. However, in the presence of pyridine, under conditions analogous to those of LFP, HCl was removed, **11** was not formed, and fragmentation or pyridine capture were the principal modes of carbene decay. Therefore, the extrapolated Y-intercept of correlation S-3 fairly represents k_{frag} of (1-adamantyl)methoxychlorocarbene, **5b**.[23]

The absorbance of ylide **18c** (λ_{max} 465 nm), formed from LFP-generated **5c** and pyridine was too weak to reliably determine k_{obs}. However, the intensity of the absorbance did track pyridine concentration; a double reciprocal correlation of $1/I_{rel}$ vs 1/[pyr] was linear (six points, $r = 0.996$, supporting information Figure S-5) and led to $k_{frag} = 1.3 \times 10^6$ s^{-1} for neopentoxychlorocarbene, **5c**, assuming that k_y for the formation of **18c** is identical to k_y for the formation of ylide **18b** (see above).

A referee has pointed out that this assumption, coupled with the product ratio of **5c** fragmentation to pyridine capture (∼1:3 in 4 M pyridine; see above) leads to an estimated value of $k_{frag} \sim 3 \times 10^5$ s^{-1}, which is ∼4 times smaller than the value that emerges from the double reciprocal analysis of the ylide absorbance data. We believe that the double reciprocal method is not as accurate as the direct correlation of k_{obs} with [pyridine] and agree with the referee that it may be suspect in the case of carbene **5c**. Alternatively, the assumption that carbenes **5b** and **5c** have equal rate constants for ylide formation (k_y) may be poor. In the absence of better data, an inclusive range for k_{frag} of **5c** is $0.3{-}1.3 \times 10^6$ s^{-1}.

For carbene **5c** the product distribution, eq 3, is less favorable than for **5b**; only 44% of **5c** products arise by fragmentation in MeCN, where the major product (52%) is HCl-intercept dichloride **16**. However, in the presence of ≥4 M pyridine (where most of the LFP data is collected), HCl and **16** are suppressed, so that the kinetics should reflect a simple competition between ylide formation and fragmentation.[24]

The measured k_{frag} values are $0.69{-}1.3 \times 10^6$ s^{-1} (**5a**), $2.8{-}5.2 \times 10^6$ s^{-1} (**5b**), and $0.3{-}1.3 \times 10^6$ s^{-1} (**5c**).[25] Clearly, ROCCl fragmentation at 25 °C is not extraordinarily fast; the three carbenes have lifetimes of ∼0.2−3.3 μs. Most intriguingly, k_{frag} for the benzyloxycarbene, **5a**, is rather similar to k_{frag} for the adamantylmethoxy and neopentoxy species **5b** and **5c**. If fragmentation of **1** occurs in a single step, as in eq 1, with concerted cleavage of R−O and C−X, then one might expect benzyloxychlorocarbene to fragment (to delocalized $PhCH_2^+$) most rapidly. By this analysis, the fragmentations of **5b** and **5c** seem unusually fast, suggesting acceleration due to concerted fragmentation with alkyl participation.[9,26]

Alternatively, the similarity of all three fragmentation rates might indicate that the rate limiting step is actually scission of the C−X bond, forming [RO-C$^+$ X$^-$], which is followed by rapid cleavage of the R−O bond, affording **3**. However, the complete fragmentation of carbene **5a** in MeOH,[4] as opposed to the efficient trapping of isobutoxychlorocarbene in MeOH,[3a] suggests that two-bond concerted fragmentation is the more likely mechanism, at least for **5a**. Now that fragmentation kinetics can be readily visualized further mechanistic discrimination is possible and will be pursued.

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Supporting Information Available: Figures S-1−S-5; see text (5 pages). See any current masthead page for ordering and Internet access instructions.

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[18] Photochemical and thermal decompositions were similar. Carbene dimer (0.5%) and a trace of azine were detected. In hexane, dimer was the major product (58−75%).

[19] The predominance of alkene **14** suggests an intraion pair proton acceptor role for chloride.

[20] Yields are **13** (7.5%), **14** (13.7%), and **15** (1.7%).

[21] See ref 11 for a description of our LFP system.

[22] Ambiphilic carbenes react "slowly" with pyridine; for MeOCCl,[15] $k_y = 9.0 \times 10^5$ M^{-1} s^{-1}.

[23] The enhanced yield of formate **12b**, formed from carbene **5b** in place of **11** in the presence of pyridine, is mainly due to hydrolysis of ylide **18b** by adventitious water. Formate yield increases with added water, and direct LFP monitoring of the rate of ylide decay as a function of [H_2O] at [pyr] = 6.2 M in MeCN gives $k = 2.1 \times 10^6$ M^{-1} s^{-1} for the reaction of **18b** with water. The analogous hydrolysis of ylide **18a** had $k = 6.6 \times 10^5$ M^{-1} s^{-1}.

[24] Ylide **18c** eventually gives formate **17** upon hydrolysis; see above and ref 23.

[25] The rate constants for **5a** and **5b** are cited as ranges of direct and double reciprocal values. The range cited for **5c** is discussed above.

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