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Competitive Rearrangements of Alkylacetoxycarbenes

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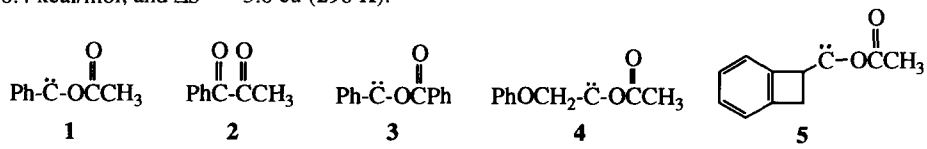
Summary. Absolute rate constants are determined for (1,2) acetyl, carbon, and hydride shifts in cyclobutylacetoxycarbene and isopropylacetoxycarbene; comparative reactivities are examined.

The signature intramolecular reaction of an acyloxycarbene is 1,2-acyl migration to give a 1,2-dione; the 1,2-acetyl shift of phenylacetoxycarbene (**1**) to dione **2** (k_{Ac} = 1.3 x 10^5 s^{-1}) is an archetypal example.[1-3] The analogous benzoyl shift of phenylbenzoyloxycarbene (**3**) to benzil occurs with k_{PhCO} = 6.7 x 10^5 s^{-1}, E_a = 8.4 kcal/mol, and $\Delta S^{\ddagger}$ = -5.0 eu (298 K).[2]



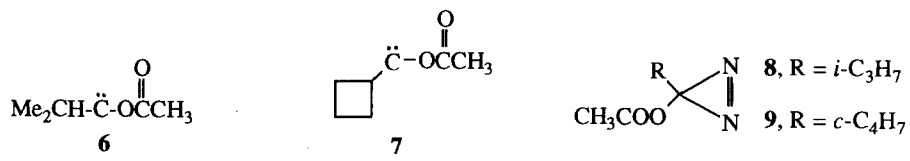
1 **2** **3** **4** **5**

These are relatively "slow" intramolecular rearrangements,[4] so that it is unsurprising that phenoxymethylacetoxycarbene (**4**) undergoes a phenoxy-stimulated 1,2-H shift (k_H = 4.1 x 10^6 s^{-1}) in kinetic preference to acetyl migration.[1,2] Similarly, benzocyclobutenylacetoxycarbene (**5**) offers a π-mediated, "phenyl" 1,2-C shift/ring expansion to 3-acetoxyindene (k_c = 8.5 x 10^6 s^{-1}) rather than acetyl migraton.[5]

Although acetyl shifts are not competitive for carbenes **4** or **5**, the (deactivating) *electronic* influence[2] of the acetoxy substituent is evident: k_H of **4** is 8.8 or 3.2 times smaller than in the analogous chloro- or fluorocarbenes, respectively.[6] Similarly, ring expansion of **5** is 4.4 times slower than that of benzocyclobutenylfluorocarbene (k_c = 3.8 x 10^7 s^{-1}).[5]

Can acetyl migrations effectively compete with carbon and hydride shifts in the *same* carbene? In affirmative response, we describe the chemistry, rearrangement kinetics, and comparative reactivities of isopropylacetoxycarbene (*i*-PrCOAc, **6**) and cyclobutylacetoxycarbene (CbCOAc, **7**).

The carbenes were generated from diazirines **8** and **9**, which were obtained from "modified" Graham oxidations[7] of isopropyl- or cyclobutylamidine[8] hydrochlorides. Diazirine exchange reactions of isopropyl- or cyclobutylbromodiazirine with acetate[9] failed to afford acetoxydiazirines **8** or **9**. Therefore, 0.3 mol of isopropylamidinium chloride in DMSO (containing 0.3 mol of LiOAc) and pentane was stirred and oxidized by excess 12% aqueous NaOCl solution (*saturated* with NaOAc) at 30-35 °C. Silica gel chromatography of the water-washed, dried, and concentrated pentane extract of the reaction mixture gave ~10% of **8** (1:2 CH_2Cl_2/

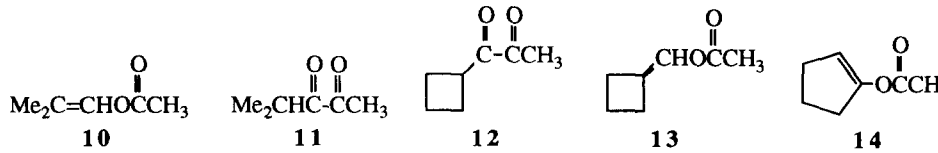


pentane, $R_f = 0.6$; the accompanying 40% of isopropylchlorodiazirine had $R_f = 0.9$). Diazirine **8** (λ_{max}, pentane, 338, 354 nm) gave an appropriate NMR spectrum. An analogous oxidation of cyclobutylamidinium chloride gave ~10% of diazirine **9** (λ_{max} 342, 356 nm, $R_f = 0.5$), accompanied by ~40% of the chlorodiazirine ($R_f = 0.8$).

Photolysis of diazirine **8** in pentane ($A_{338} = 0.8$, Rayonet reactor, 16, 8 W 350 nm lamps, 15 min 25 °C) afforded ~30% of 1-acetoxy-2-methylpropene (**10**), a comparable yield of 4-methylpentane-2,3-dione (**11**), 5% of the dimer of carbene **6**, and several unidentified minor products. The structures of **10** and **11** were established by NMR, GC-MS, and comparisons to authentic materials synthesized from acetic anhydride and isobutyraldehyde[10] (for **10**), or 4-methyl-2-pentene and $KMnO_4$ in cold acetic anhydride[11] (for **11**). Products **10** and **11** stem from 1,2-H or 1,2-acetyl rearrangements of **6**, respectively.[12]

Analogous photolysis of diazirine **9** ($A_{342} = 0.1$, 1 hr, 25 °C) afforded carbene **7**, and thence the Ac-shift product **12**, the H-shift product **13**, and the C-shift/ring expansion product acetoxycyclopentene (**14**), as well as the carbene dimer (3.8%). Primary products **12**, **13**, and **14** constituted ~70% of the crude photolysate, and were formed in a distribution of 32 : 1.0 : 2.5, respectively (capillary GC).

Again, products were identified by NMR, GC-MS, and comparisons to independently synthesized authentic samples. Enol acetates **13** or **14** were prepared from cyclobutanecarboxyaldehyde or cyclopentanone in reactions with acetic anhydride,[10] whereas dione **12** was obtained by $KMnO_4$ oxidation[11] of 1-cyclobutylpropene, prepared by Wittig olefination of cyclobutane carboxyaldehyde. The dimer of carbene **7** was identified by GC-MS (exact mass).



Absolute rate constants were obtained by laser flash photolysis (LFP)[2] using the pyridine ylide method.[13] LFP of **9** ($A_{342} = 0.1$, 20 °C) in pentane containing 1.1 - 5.5 mM pyridine gave carbene **7**, and thence its pyridine ylide (λ_{max} 390 nm). From the slope of the observed linear dependence ($r = 0.997$, 5 points) of the observed rate constants for ylide formation vs. [pyridine], we obtained $k_{ylide} = 4.85 \times 10^8$ $M^{-1}s^{-1}$ for the second order reaction between **7** and pyridine. Extrapolation of the correlation to [pyridine] = 0 gave an intercept (k) = 4.98×10^5 s^{-1}, taken as the aggregate rate constant for the processes that destroy carbene **7** in

Table 1. Rate Constants for Intramolecular Carbenic Rearrangements[a]

Carbene	Migrant	k_{re}, s^{-1}	Reference
1	Ac	1.3×10^5	2
4	H	4.1×10^6	2
$PhOCH_2CCl$	H	$3.6 \times 10^{7\,b}$	6
$PhOCH_2CF$	H	$1.3 \times 10^{7\,b}$	6
5	C	8.5×10^6	5
7	Ac	4.0×10^5	c
	C	3.2×10^4	c
	H	1.3×10^4	c
CbCCl[d]	C	5.6×10^7	16
	H	1.2×10^7	16
CbCF[d]	C	1.8×10^6	6
	H	5.3×10^5	6
6	Ac	4.0×10^6	c
	H	4.0×10^6	c
Me_2CHCCl	H	$>5.0 \times 10^{7\,e}$	17

[a]In hydrocarbon solvents, 20-25 °C. [b]At -32 °C. [c]This work. [d]Cb = Cyclobutyl. [e]At -90 °C.

the absence of pyridine. Partition of k according to the distribution of **12-14** (and dimer) afforded $k_{Ac} = 4.0 \times 10^5$ s^{-1} (**7**→**12**), $k_H = 1.3 \times 10^4$ s^{-1} (**7**→**13**), and $k_c = 3.2 \times 10^4$ s^{-1} (**7**→**14**).[14]

For carbene **6**, the rearrangement rate constants were determined indirectly because of the low yields. Photolytically generated **6** could be trapped in >90% yield by methyl acrylate (MeAcr).[15] LFP of diazirine **8** ($A_{338} = 0.8$, 25 °C) in pentane containing 12.4 mM pyridine and variable concentrations (0 - 0.52 M) of MeAcr afforded the ylide derived from **6** and pyridine (λ_{max} 380 nm). A correlation of the observed rate constants for ylide formation with [MeAcr] was linear ($r = 0.993$ for 6 points, $k_{ylide} = 1.28 - 1.93 \times 10^7$ s^{-1}) with a slope of 1.30×10^7 $M^{-1}s^{-1}$ which can be taken[13] as k_{add} for the addition of **6** to MeAcr. Photolysis of **8** in 0.556 M MeAcr in pentane gave **10**, **11**, and the carbene/MeAcr adducts.[15] From the (corrected) capillary GC product ratios (0.55 : 0.56 : 1), and k_{add}, we calculate $k_{Ac} = 4.0 \times 10^6$ s^{-1} and $k_H = 4.0 \times 10^6$ s^{-1} for the intramolecular acetyl and hydride migrations of *i*-PrCOAc.

Table 1 collects rate constants for the present rearrangements, as well as analogous processes of related carbenes.[16,17] Clearly, for CbCOAc (**7**) and *i*-PrCOAc (**6**), 1,2-acetyl shifts are highly competitive with 1,2-C and 1,2-H migrations. In the former case, ~Ac is an order of magnitude faster than the more common processes, whereas with **6**, ~Ac and ~H are comparable in rate.

On the other hand, the electron-donating stabilizing effect of OAc^2 slows the H-shift of *i*-PrCOAc by >12 times, relative to *i*-PrCCl,[17] here permitting the first reasonably precise kinetic measurement of the 1,2-H shift of an isopropylcarbene.[18] Kinetic stabilization by OAc as a "spectator substituent" is strikingly apparent upon comparison of CbCOAc to CbCCl and CbCF (Table 1). The 1,2-C and 1,2-H migrations of **7** are,

respectively, 1750 and 923 times slower than the analogous rearrangements of CbCCl (56 and 41 times slower in comparison to CbCF).

Relative to *i*-PrCOAc, the 1,2-acetyl shift of CbCOAc is 10 times slower, presumably due to superior electron-donating cyclobutyl stabilization of the vacant carbenic p orbital.[8] At the same time, the 1,2-H shift of *i*-PrCOAc is 308 times faster than that of CbCOAc. H-shifts of cyclobutylcarbenes are slower than those of acyclic *sec*-alkylcarbenes[19] because the imposition of δ^+ on the cyclobutyl carbon during hydride migration is unfavorable, and because the Cb-H bond is stronger than the Me_2C-H bond. Strain in product **13** may also impede this rearrangement.

Finally, comparison of CbCOAc with its benzo analogue (**5**) reveals that the "π-mediated" C-shift of the latter[5] is 21 times faster than the Ac-shift of CbCOAc, and 266 times faster than the 1,2-C shift of CbCOAc. These kinetic advantages are in accord with the observed exclusive, chemospecific ring expansion.

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(12) Capillary GC gives **10**:**11** as 0.96:1. The dione is unstable to photolysis at λ<350 nm, but is stable under the described photochemical conditions.
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(14) These rate constants are likely to be too high by 10-15% because **12**-**14** only account for ~70% of the carbene; there are several minor unknowns. Product formation directly from excited diazirine[4] is an unlikely complication because diazirine-generated alkylacetoxycarbenes (e.g., **4**,[2] and **6**, see below) can be almost quantitatively scavenged by alkenes with the disappearance of rearrangement products.
(15) The isomeric cyclopropane products were characterized by NMR and an exact mass measurement.
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(17) Liu, M.T.H.; Bonneau, R. *J. Am. Chem. Soc.* **1996**, *118*, 8098.
(18) Parallel decelerations of 1,2-H shifts were noted above in comparisons of acetoxycarbene **4** with its Cl and F analogues; see also Table 1.
(19) Compare the 1,2-H shifts of CbCCl and *i*-PrCCl in Table 1.

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