Structure-Reactivity Dependence in the Rearrangements of a Family of Alkylacetoxycarbenes

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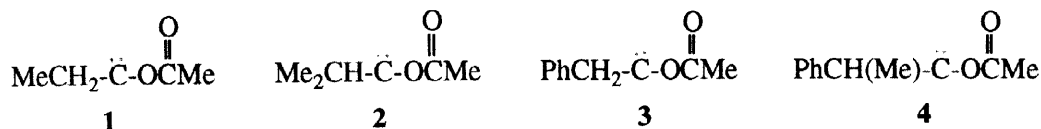New Brunswick, New Jersey 08903

Abstract. Absolute rate constants and activation parameters are presented for the 1,2-H and 1,2-acetyl migrations of a family of alkylacetoxycarbenes. © 1998 Elsevier Science Ltd. All rights reserved.
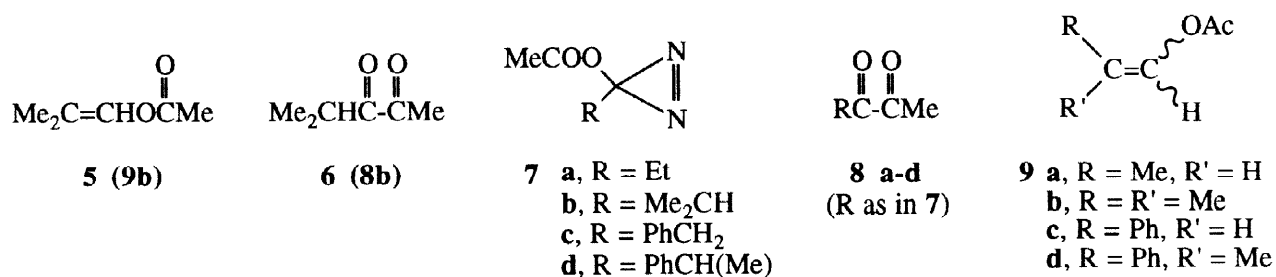
Intramolecular 1,2-H shifts of alkyl or alkylchlorocarbenes are often very rapid making it difficult to relate structure with reactivity in terms of absolute rate constants. For example, k_H in hydrocarbon solvents at 25 °C for Me_2CHCCl, $PhCH(Me)CCl$, or EtCCl exceeds 10^8 s^{-1},[1,2] while k_H for $PhCH_2CCl$ is 5-7 x 10^7 s^{-1}.[1,3] Recently, however, we found that the electron-donating, carbene-stabilizing effect of an acetoxy "spectator" substituent[4] slows the H-shift of $Me_2CHCOAc$ by >12 times, relative to Me_2CHCCl, while the H-shift of cyclobutylacetoxycarbene decreases >900 times, relative to the analogous chlorocarbene.[5] This suggests that a family of alkylacetoxycarbenes would be well-suited to an examination of H-shift kinetics as a function of structure.

Here, we describe the rearrangements in a family of these carbenes, RCOAc, where R is varied from ethyl (**1**) to isopropyl (**2**), and from benzyl (**3**) to α-methylbenzyl (**4**). Competitive 1,2-H and 1,2-acetyl shifts[6] occur with each carbene; e.g., $Me_2CHCOAc$ (**2**) yields both enol acetate **5** and dione **6**.[5] Determination of the product distributions, absolute kinetics, and activation parameters of these rearrangements affords a satisfying structure-reactivity correlation for the carbenes, and helps quantitate the relative abilities of methyl and phenyl substituents to stimulate 1,2-H carbenic migrations ("bystander" effects).[7,8]

Carbenes **1-4** were generated photochemically from diazirines **7a-d**. These were prepared by "modified" Graham reactions,[5,9] in which the appropriate amidine hydrochloride[10] in DMSO-pentane was oxidized with excess 12% aqueous HOCl, saturated with NaOAc.

Mixtures of **7a-d**, accompanied by the analogous alkylchlorodiazirines, were obtained and separated by silica gel chromatography (2:1 pentane/CH_2Cl_2) of the water-washed, dried, and concentrated pentane extracts of the reaction solutions.[11] This procedure was described in detail for diazirine **7b**.[5] The new diazirines exhibited appropriate NMR and UV spectra.

$$MeCH_2\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}OCMe \qquad Me_2CH\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}OCMe \qquad PhCH_2\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}OCMe \qquad PhCH(Me)\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}OCMe$$

$$\mathbf{1} \qquad\qquad\qquad \mathbf{2} \qquad\qquad\qquad \mathbf{3} \qquad\qquad\qquad \mathbf{4}$$

$$\underset{\underset{\textbf{5 (9b)}}{Me_2C=CHOCMe}}{\overset{\overset{O}{\|}}{}} \qquad \underset{\underset{\textbf{6 (8b)}}{Me_2CHC\text{-}CMe}}{\overset{\overset{O\ O}{\|\ \|}}{}} \qquad \underset{\underset{\underset{\textbf{d, R = PhCH(Me)}}{\underset{\textbf{c, R = PhCH_2}}{\underset{\textbf{b, R = Me_2CH}}{\textbf{7 \ \ a, R = Et}}}}}{\overset{MeCOO}{\underset{R}{\diagup\!\!\diagup}}\!\!\overset{N}{\underset{N}{\diagdown\!\!\diagdown}}} \qquad \underset{\underset{\textbf{(R as in 7)}}{\underset{\textbf{8 a-d}}{RC\text{-}CMe}}}{\overset{\overset{O\ O}{\|\ \|}}{}} \qquad \underset{\underset{\underset{\textbf{d, R = Ph, R' = Me}}{\underset{\textbf{c, R = Ph, R' = H}}{\underset{\textbf{b, R = R' = Me}}{\textbf{9 \ a, R = Me, R' = H}}}}}{\overset{R}{\underset{R'}{}}\!C\!=\!C\overset{OAc}{\underset{H}{}}}$$

Particularly clean carbene rearrangements were observed in tetrachloroethane (TCE).[12] Solutions of **7a-d** were photolyzed in TCE (A_{340} = 0.4 - 1.0) at 25 °C in a Rayonet reactor (350 nm, 16 8 W lamps) until the diazirines were destroyed. From each alkylacetoxycarbene thus generated, we obtained a 1,2-acetyl shift product (**8**) and a 1,2-H shift product (**9**). In the case of carbene **3**, 10% of carbene dimer also formed; no azine was observed (GC-MS). New products **8a,c,d** and **9a,c,d** were identified by GC-MS and by capillary GC comparisons to fully characterized synthetic samples. Product distributions at 298 K were measured by capillary GC (±3%), and are summarized in columns 2 and 3 of Table 1.

Absolute rate constants for the carbene rearrangements were determined over an average temperature range of 20-80 °C by laser flash photolysis (LFP).[6b] Using the pyridine ylide method,[5,6b,13] growth of the carbene-pyridine ylides (at [pyr] = 2.5 - 22 mM in TCE) was monitored at 378 nm (**1-3**) or 388 nm (**4**). Details of this methodology as applied to the carbenic rearrangements have been described.[5,6b]

In Table 1, we collect the aggregate rate constants (k_r) for the rearrangements of **1-4** in TCE at 25 °C (column 4), the constituent rate constants for 1,2-acetyl (k_{ac}) and 1,2-H (k_H) shifts partitioned according to the product distributions[14] (columns 5 and 6), and the Arrhenius parameters for the aggregate rearrangements (columns 7 and 8).

The carbenes display a range of comparative H/acyl migration efficiencies and associated rate constants. For example, substitution of an α-Me group on EtCOAc (**1**), produces $Me_2CHCOAc$ (**2**), and increases the H/acyl migration (product) ratio from 18/82 to 95/5, while k_T (for the sum of H and Ac shifts) increases from 8.9×10^4 s^{-1} to 2.0×10^6 s^{-1}, a factor of 22.8. *Partition* of k_T between k_H and k_{ac} according to the product distributions reveals that the overall gain in H migration accompanying α-methylation is due to a 121-fold enhancement in k_H, slightly offset by a 1.4-fold gain in k_{ac}.

Parallel substitution of α-Ph on EtCOAc (**1**) affords PhCH(Me)COAc (**4**). Here, k_H increases by 9.9 times while k_{ac} increases only 1.3 times, so that the efficiency of H vs. acetyl migration climbs from 18/82 to 62/38. Note that α-Me is ~12 times (121/9.9) more effective than α-Ph substitution at driving the 1,2-H shift. A similar conclusion emerges from a comparison of the k_H values attending "mutation" of **4** into **2**, where the α-Ph is replaced by an α-Me substituent: k_H increases by a factor of 12.2 as the H/acetyl migration ratio climbs from 62:38 to 95:5. Surprisingly, however, the α-Me substitution that converts PhCH_2COAc (**3**)

Table 1. Product Distributions,[a] Rate Constants, and Activation Parameters[b] in TCE

R in RCOAc	1,2-Ac (%)	1,2H (%)	$10^{-5}k_T$ (s⁻¹)	$10^{-5}k_{ac}^{c}$ (s⁻¹)	$10^{-5}k_H^{c}$ (s⁻¹)	E_a (kcal/mol)	log A (s⁻¹)
Et, 1	82.2	17.8	0.894	0.735	0.159	13.4	14.8
Me₂CH, 2	5.19	94.8	20.4	1.06	19.3	5.78	10.6
PhCH₂, 3	82.6	6.83[d]	8.29	6.85	0.566	2.49	7.70
PhCH(Me), 4	37.6	62.4	2.54	0.955	1.58	5.10	9.17

[a]Rate constants and product distributions refer to 298 K; errors are within ±3%. [b]Activation parameters were obtained from Arrhenius correlations with r>0.975. E_a values are within 11%; log A values are within ±4%. [c]Calculated from the observed total rate constant for carbene disappearance (k_T) using the observed product distribution.[14] [d]Carbene dimer (10.6%) is also formed; rate constants are corrected for dimer formation.

to PhCH(Me)COAc (4) is only attended by a 2.8-fold enhancement in k_H. The 20-fold increase in H/Ac migration that goes along with this α-methylation mainly derives from a 7-fold decrease in k_{ac}.

The 1,2-H shift enhancements due to α-Me substitution,[3] and the superiority of Me over Ph in this bystander role, have been described by Nickon,[8] based on competitive reactivity data. Related observations were made in absolute kinetic studies of alkylchlorocarbenes by Liu and Bonneau[1] and Goodman[2] in studies of alkychlorocarbenes.[15] Presumably, the electron releasing inductive effect of an α-Me substituent stabilizes developing positive charge at the migration origin during the hydride-like 1,2-H shift,[15] whereas the electron-withdrawing inductive effect of the α-Ph substituent mitigates the positive influence of its geometry-dependent, entropically unfavorable resonance effect.[16]

The aggregate rearrangement activation energies collected in Table 1 range from 2.5 kcal/mol for 3 to 13.4 kcal/mol for 1, the largest E_a reported for a carbenic rearrangement in solution. The structural metamorphoses of 1 to 2 (α-Me substitution) and 1 to 4 (α-Ph substitution) are each accompanied by reductions in E_a (~8 kcal/mol) and log A (4-6 log units). Although α-methylation of 3 to 4 generates a 2.6 kcal/mol increase in E_a (offset by a 1.5 unit increase in log A), preliminary temperature dependent product studies (which allow partition of the aggregate E_a and log A into H-shift and acetyl shift components) indicate that the 3 → 4 α-methylation reduces E_a^{H} from 6.2 to 3.4 kcal/mol, while E_a^{ac} increases from 2.5 to 6.5 kcal/mol.

Examination of the Arrhenius parameters reveals an underlying *compensation* between E_a and log A, whereby a decrease in E_a is opposed by a decrease in log A. The compensation also appears in the corresponding Eyring parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$; carbenic structural changes that lead to lower, more favorable enthalpies of activation engender oppposing entropic changes. Compensation was reported by

Giese for the differential activation parameters derived from the relative addition rates of dihalocarbenes with alkenes,[17] but the present results are based on absolute kinetics.

Finally, we comment on hydrocarbon vs. TCE solvent effects. Polar solvents promote 1,2-H shifts.[15] Indeed, the 1,2-H/1,2-acetyl migration ratio of **2** increases from 50/50 to 95/5 as the solvent is changed from isooctane to TCE; a parallel alteration [26/74 to 62/38] is observed for carbene **4**. Additionally, the activation energy for the rearrangements of **2** is lowered by ~5 kcal/mol on changing from hydrocarbon to TCE solvent. However, solvent-mediated compensation is observed; the decrease in E_a or $\Delta H^{\ddagger}$ is accompanied by an unfavorable entropic loss of ~13 eu. Solvation of the transition state for H migration lowers the E_a or $\Delta H^{\ddagger}$, but ties down solvent molecules, decreasing entropy.

References and Notes

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