

Figure 3. Mixing of fluorescent vesicles (B and D) and quencher vesicles (A and C). The quencher vesicles were added at time indicated by the arrows (see text for vesicle compositions): (a) A (without quencher) + B at 40 °C; (b) A + B at 20 °C; (c) A + B at 40 °C; (d) C + D at 40 °C; (e) D + A at 40 °C.

in the intensity, apart from the instantaneous decrease. This indicates that the fluorocarbon vesicle does not undergo fusion and/or component exchange with the hydrocarbon or fluorocarbon vesicles.

In conclusion, double-chain, fluoroalkyl amphiphiles are shown to form stable bilayer membranes when dispersed in water. The fluoroalkyl bilayer is apparently much less permeable than the hydrocarbon counterpart and does not undergo facile mixing with other bilayers. The peculiar characteristics of the fluorocarbon bilayer such as strong aggregation, O₂ binding, and reduced permeability provide exciting possibilities.

Acknowledgment. We are grateful to Professor M. Takayanagi for the use of an electron microscope (Hitachi H-500).

Registry No. 1, 82838-63-9; 2, 82838-64-0; 3, 82838-65-1; 4, 82838-66-2; 5, 82838-67-3; 6, 79508-19-3; 7, 82838-68-4; TNBS, 5400-70-4; fluorescamine, 38183-12-9.

Hydrogen Bonding in Alcohols: Its Effect on the Carbene Insertion Reaction^{1a}

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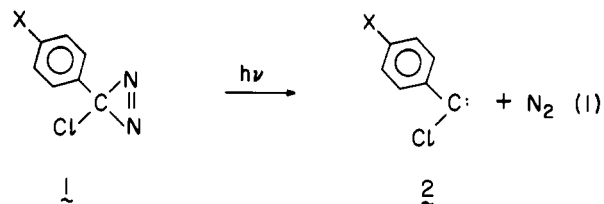
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Received April 30, 1982

The insertion reactions of carbenes into the O-H bonds of alcohols have received considerable attention.^{2,3} In many instances competitive kinetic studies have been carried out comparing rate constants for insertion of a carbene into different alcohols^{2,4} or comparing rate constants for O-H insertion with respect to those for olefin addition.^{2,5} The essential assumption has always been

that the reaction of the carbene with each of the substrates is first order with respect to that substrate. In this work we report that this simple assumption does not hold for the liquid-phase reactions of carbenes **2a** and **2b** with methanol or *tert*-butyl alcohol.

Laser flash photolysis⁶ of diazirines⁷ **1a** (0.004 M) and **1b** (0.0067 M) in acetonitrile solvent gave strong absorption spectra due respectively to transients with $\lambda_{\text{max}} = 326$ and 355 nm. The transient absorption spectrum obtained in the photolysis of **1a** has been characterized as due to phenylchlorocarbene, **2a**, in its singlet state.¹⁰ Using the same experimental criteria¹⁰ on the system containing **1b**, e.g., sensitivity of the transient signal to added oxygen, the failure to observe a triplet EPR signal of the matrix isolated transient at 4 K, etc.,¹¹ and finding essentially identical results, we assigned that transient absorption spectrum as being due to *p*-anisylchlorocarbene, **2b**, in its singlet state (reaction 1).



1g, 2g, X = H; 1b, 2b, X = CH₃O

In the absence of added quenchers, **2a** and **2b** decayed predominantly via second-order processes with initial half-lives in the 2–10- μ s range, depending on the laser dose.

The transient absorptions due to **2a** and **2b** could be quenched in the normal way by addition of substrates such as tetramethylethylene (TME).^{9,12} The reactions were first order with respect to such substrates as evidenced by the excellent linearity of plots obtained by using eq 2. This equation relates the observed

$$k_{\text{obsd}} = k_0 + k_2[\text{substrate}] \quad (2)$$

pseudo-first-order rate constant for transient decay, k_{obsd} , to the rate constant for decay in the absence of substrate, k_0 , and the rate constant for the reaction of carbene with substrate, k_2 .

When methanol was used as a substrate in acetonitrile solvent, plots obtained by using eq 3 showed pronounced curvature (Figure 1). The flash photolysis experiments were repeated in isooctane as solvent, which does not strongly associate with methanol,¹⁴ and the data again showed pronounced curvature. This indicates that the reactions with the carbenes were not first order with respect to methanol. In addition, quenching by methanol was about 10 times more efficient in isooctane than in acetonitrile. Spectral properties were similar in both solvents.

Product studies were carried out to verify that the reactions being monitored were indeed the expected insertion processes. Thus, photolysis ($\lambda > 300$ nm) of an isooctane solution of **1a** (0.052

(6) The technique and instrument have been described in detail elsewhere; see: Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7747–7753.

(7) The diazirines were prepared following Graham's method⁸ and could be obtained analytically pure with appropriate IR and UV characteristics⁹ by using chromatographic purification on silica gel. They were always repurified before each experiment since they tend to deteriorate on storage. **Caution:** a cold sample of **1b** decomposed violently on rapid warming to room temperature.

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(11) We thank Drs. K. F. Preston and M. S. Platz for carrying out the EPR measurements.

(12) Griller, D.; Liu, M. T. H.; Scaiano, J. C.; Wong, P. C., to be submitted for publication.

(13) Products were analyzed by using gas chromatography with a mass spectrometer detector. Products could not be analyzed for the reactions of **2b** since the solutions became highly colored shortly after the start of photolysis and screened **1b** from further degradation.

(14) The behavior of neopentyl alcohol is similar to that of methanol and leads to positive curvature.

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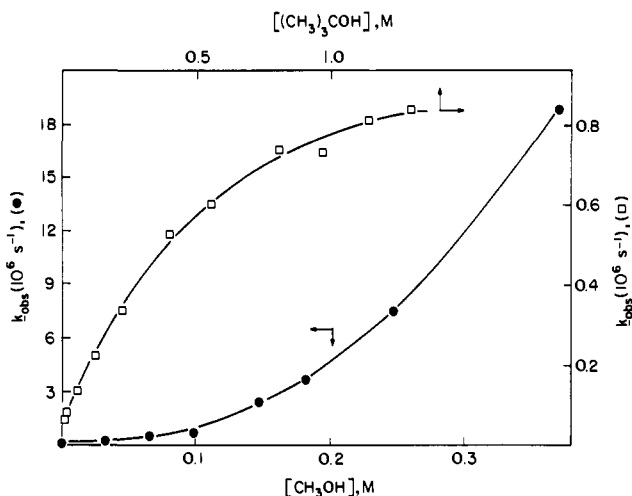


Figure 1. Quenching of *p*-anisylchlorocarbene by alcohols at 300 K: methanol in acetonitrile (●, left and bottom scales) and *tert*-butyl alcohol in isooctane (□, top and right scales). The continuous trace is an arbitrary fit to the data.

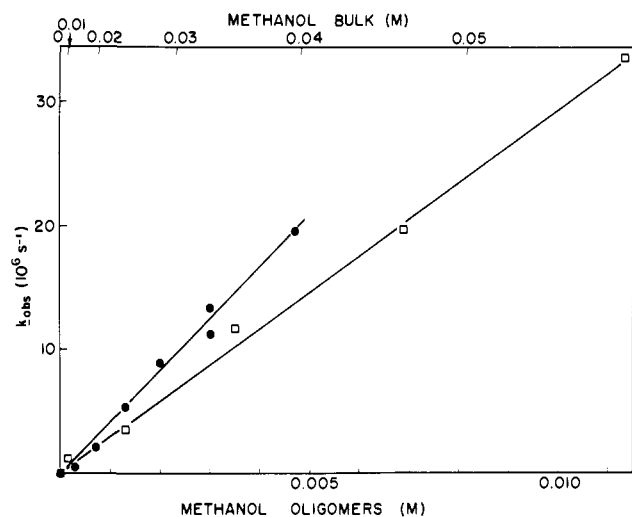
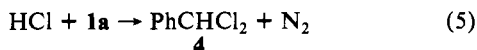
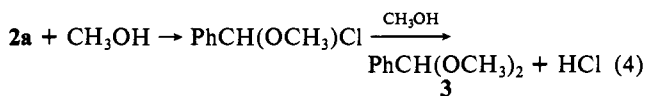


Figure 2. Quenching of **2a** (□) and **2b** (●) by methanol in isooctane at 300 K, plotted as a function of the oligomer concentration.

M) containing methanol (0.125 M) gave only products **3** and **4** each in 50% yield (by GC-MS). That product **4** was formed via reaction 5 was demonstrated in a separate experiment where a solution of **1a** was treated with hydrogen chloride (see eq 3-5).



The simplest interpretation of these results is that the hydrogen bonded oligomers, which are increasingly formed as the methanol concentration is increased, are substantially more reactive toward the carbenes than methanol monomer. That is, the O-H bonds involved in hydrogen bonding are more reactive toward carbenes **2a** and **2b** than those in unassociated molecules, presumably as a result of a decrease in bond dissociation energy.

The lower efficiency of methanol as a quencher in acetonitrile is attributed to hydrogen bonding to the latter, which decreases the abundance of methanol oligomers. This implies that the effect of methanol as a quencher in isooctane should be partially reversed by addition of small amounts of acetonitrile. Such was indeed the case since the lifetime of **2a** in isooctane containing methanol

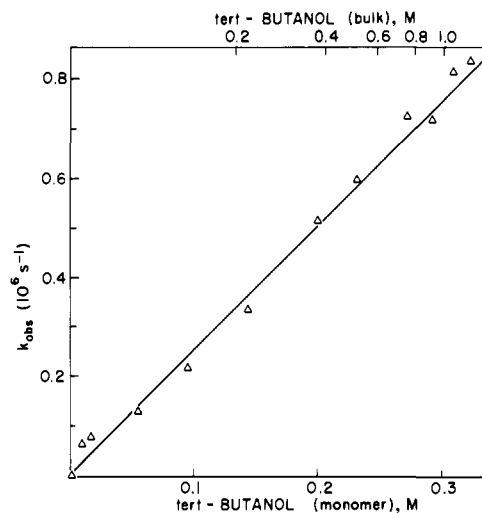


Figure 3. Quenching of **2b** by *tert*-butyl alcohol in isooctane at 300 K, plotted as a function of the monomer concentration.

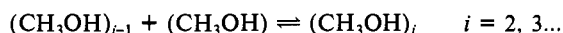
(0.062 M) was 32 ns and increased to ca. 100 ns by addition of 2% acetonitrile.

When *tert*-butyl alcohol was used in place of methanol, plots of k_{obsd} vs. $[(\text{CH}_3)_3\text{COH}]$ were again curved, but now the curvature was negative (Figure 1). Following the above interpretation, this result implies that the carbenes were less reactive toward *tert*-butyl alcohol oligomers than to its monomer. Presumably, the bulky *tert*-butyl groups protect the hydrogen bonded O-H from attack.¹⁴

The observed rate constants for carbene decay can be expressed as

$$k_{\text{obsd}} = k_0 + \sum_{i=1}^n k_i [m_i]$$

where the subscript "i" refers to the number of monomer units in the oligomer m_i , and both k_i and m_i are expressed in units of monomer. The kinetic data can then be treated by calculating the distributions of monomer, dimer, and oligomers by using data obtained in the analysis of vapor-pressure experiments.¹⁵⁻¹⁷ In this model the equilibria



are described by two equilibrium constants.¹⁵ The first, K_2 , represents the monomer-dimer equilibrium, while K_3 represents all higher equilibria. This approximation is equivalent to setting $k_3 = k_4 = \dots = k_n$. The simplicity of the model and the sensitivity of K_2 and K_3 to the methods of data analysis¹⁷ are such that it offers only a crude representation of the distribution of structures on the alcohol.

The mole fraction of monomer, X_1 , in a given mole fraction of alcohol, X_A , is given by eq 6. From Wilson's approach¹⁶⁻¹⁸

$$X_1^3(K_3^2 - K_2K_3) - X_1^2(2[K_3 - K_2] + X_A[K_3^2 + K_2]) + X_1(1 + 2K_3X_A) - X_A = 0 \quad (6)$$

the values of K_2 and K_3 at 300 K for methanol in hexane¹⁹ are 31.6 and 80.0 while for *tert*-butyl alcohol in isooctane the corresponding values are 7.50 and 12.77, respectively. With these data the mole fractions of monomer and hence dimer and oli-

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(19) It was assumed that the distribution of methanol monomer, dimer, and oligomers in isooctane was the same as in hexane for the same methanol molarity. The data reported at 333 and 313 K were extrapolated to 300 K (from a $\log K_i$ vs. T^{-1} plot), i.e., the temperature of the present experiments.

omers were calculated for different mole fractions of methanol and *tert*-butyl alcohol. Equation 6, which does not contain any adjustable parameters, was solved under the restrictions X_1 real, $K_3X_1 < 1$, $X_1 \leq X_A$.

The experimental rate constants, k_{obsd} were plotted against the total concentration of methanol oligomers higher than dimer while for *tert*-butyl alcohol they were plotted against the free monomer concentration (Figures 2 and 3). Despite the limitations of the two-constant model, straight lines of excellent quality were obtained. Thus to a good approximation the reactions of **2a** and **2b** with methanol were first order with respect to methanol oligomers, which were far more reactive than monomer or dimer, i.e. $k_1 \sim k_2 \ll k_3 \sim k_4 \dots k_n$. By contrast, the reactions were first order with respect to *tert*-butyl alcohol monomer, which was more reactive than dimer or oligomer, i.e. $k_1 \gg k_2 \sim k_3 \dots k_n$.

The rate constants for the reactions of **2a** and **2b** with methanol oligomers were $(2.9 \pm 0.2) \times 10^9$ and $(4.3 \pm 0.4) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (per methanol unit), respectively, which implies that the rate constant for the reaction was close to diffusion controlled. By contrast, the rate constants for the reaction of **2b** with methanol monomer were ca. $2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (extrapolated to $[\text{CH}_3\text{OH}] \rightarrow 0$) in isooctane and $6.5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ in acetonitrile. For *tert*-butyl alcohol monomer reacting with **2b** in isooctane, the rate constant was found to be $(2.52 \pm 0.15) \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.

If the above interpretation is correct, it follows that k_{obsd} for methanol quenching should decrease while that for *tert*-butyl alcohol quenching should increase as the temperature is increased. This is because the association energies^{16,17} for dimer and oligomers are such that the concentrations of these species decrease substantially with increasing temperature. Thus, the lifetime of **2b** in acetonitrile containing 0.23 M methanol gave a good Arrhenius plot with $E_a = -4.7 \pm 0.3 \text{ kcal mol}^{-1}$ for data in the 245–323 K range, this value being in the range of the hydrogen bond strength in methanol.^{16,17,20} In the case of *tert*-butyl alcohol, the reactivity was low enough that **2b** could be easily monitored in *tert*-butyl alcohol as solvent, where the lifetime at 300 K was 650 ns. An Arrhenius plot between 300 and 348 K led to $E_a = +3.23 \pm 0.60 \text{ kcal mol}^{-1}$.²¹

The formation of **3** as a product raises the interesting question of whether it is formed in a rapid reaction involving two methanol molecules contained in the oligomer chain or whether $\text{PhCH}(\text{OCH}_3)\text{Cl}$ diffuses away from the reaction site to react with a second molecule of methanol at a later stage. This question does not have a bearing on the interpretation of the reaction kinetics, but it clearly warrants further investigation.

To summarize, it was found that the reactions of carbenes **2a** and **2b** with methanol and *tert*-butyl alcohol were not first order with respect to the bulk concentrations of those substrates. The results were thought to suggest that oligomers of methanol reacted more readily with these carbenes than its monomer while the converse was true for *tert*-butyl alcohol, where steric effects play a dominant role. Analysis of the distributions of monomers, dimers, and oligomers in the alcohols showed that while methanol monomer was about 2 orders of magnitude less reactive than its oligomers, it was nevertheless somewhat more reactive than *tert*-butyl alcohol monomer. Methanol oligomers reacted at the diffusion-controlled rate on a per methanol unit basis, while *tert*-butyl alcohol oligomers were essentially inert in the time scale of these experiments. At this point it is not clear whether these properties are characteristic of chlorocarbenes or whether they would also apply to other systems.

Registry No. **1a**, 4460-46-2; **1b**, 4222-26-8; **2a**, 19807-41-1; **2b**, 82849-42-1; methanol, 67-56-1; *tert*-butyl alcohol, 75-65-0.

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(21) A few experiments were carried out to examine the possibility of traces of water leading to complications in the measurements reported herein. It was concluded that in the concentrations in which it may be present as an impurity in carefully dried solvents ($\ll 0.2\%$) water cannot account for the effects observed. Preliminary experiments suggest that water quenching also leads to curvature. UV spectroscopy of diazirine-methanol samples shows no evidence of complexation at concentrations of methanol three times higher than those used in our experiments.

Total Synthesis of the Complement Inhibitor K-76 in Racemic Form. Structural Assignment to "K-76 Monocarboxylic Acid"

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Received July 14, 1982

Activation of the complement system contributes to the inflammatory processes associated with diseases such as rheumatoid arthritis, lupus erythematosus, and glomerulonephritis, and in consequence great interest is attached to the discovery of agents that are potent inhibitors of complement.¹ Among the most exciting developments in this area is the recent finding by the Otsuka group of a fungal metabolite from *Stachybotrys complementi* nov. sp. K-76, which inhibits the crucial complement C₅ step at concentrations of ca. 10 $\mu\text{g}/\text{mL}$.^{2,3} The active substance, termed K-76, was formulated as the tetracyclic dialdehyde **1** (Chart I) on the basis of X-ray crystallographic studies of a derivative.⁴ We report herein a total synthesis of (\pm)-K-76 (**1**) by a route that allows access to a wide variety of structural analogues as well. The general course of this synthesis follows from methodology developed recently for the total synthesis of (\pm)-aphidicolin⁵ and (\pm)-stemodin,⁶ which makes the bicyclic keto ester **2**⁶ readily available in five steps from geranyl bromide.

Treatment of **2**, mp 76–80 °C, with sodium hydride in ether at 0 °C followed by triflic anhydride afforded the vinyl triflate **3**⁷ (90%), which by reaction with 3 equiv of lithium dimethylcopper in ether (–78 °C, 2 h, –50 °C, 2 h, and –30 °C, 1 h) gave the β -methylated α,β -unsaturated ester **4** (90%). Reduction of ester **4** (lithium aluminum hydride in ether at 23 °C for 4 h) provided the corresponding primary alcohol, mp 87–88.5 °C (95%), which was quantitatively converted to the allylic bromide **5** in one flask by (1) mesylation (1.2 equiv. of mesyl chloride, 2 equiv of triethylamine in methylene chloride at –50 °C for 10 min) and (2) bromide displacement (addition of excess lithium bromide in tetrahydrofuran (THF) and reaction at –50 to 0 °C for 1 h).

The aromatic unit was derived from the symmetrical acetal **6**, which was synthesized from methyl 3,5-dihydroxybenzoate by the sequence (1) conversion to the bis(methoxymethyl) (MOM) derivative (77%) by treatment with sodium hydroxide (4 equiv) in methanol and subsequent reaction with 4 equiv of chloromethyl methyl ether at 0 °C, (2) reduction to the primary alcohol (96%) (lithium aluminum hydride in ether at 23 °C), (3) oxidation to the aldehyde (95%) (1.2 equiv of pyridinium chlorochromate and sodium acetate in methylene chloride at 23 °C for 6 h), and (4) acetalization with tosic acid in methanol at 0 °C for 1 h (90%). Reaction of **6** with 1 equiv of *n*-butyllithium in 2:1 THF-tetra-methylethylenediamine at –20 to 0 °C for 1 h afforded the lithio derivative **7**, which was coupled to the bromide **5** at –78 °C in the presence of added hexamethylphosphoric triamide (HMPA) (one-third by volume) for 1 h (–78 to 0 °C) to give **8** in 75% yield. Treatment of **8** with 1:3 1 N hydrochloric acid-THF at 23 °C for 1 h produced the aldehyde **9**, mp 76–78 °C (93%), which upon exposure to 15:1:3 THF-ethylene glycol-6 N hydrochloric acid at 45–50 °C for 6 h resulted in cleavage of the MOM protecting

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(7) Satisfactory proton magnetic resonance and infrared spectroscopic data were obtained for each synthetic intermediate. In addition, high-resolution mass spectra, obtained on chromatographically purified and homogeneous samples, confirmed the molecular formula of each thermally stable intermediate.