Kinetics of the 1,5-Dipolar Cyclization of 2-Vinylpyridinium Ylides to Indolizines. Determination of Rate Parameters by Laser Flash Photolysis

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Abstract

Nanosecond laser flash photolysis (λ = 355 nm) of an aqueous solution of 3-chloro-3-p-chlorophenyldiazirine in isooctane produces a transient absorption at 310 nm due to the formation of the carbene. In the presence of 2-vinylpyridine, a second transient with a broad absorption band peaking at 520 nm grows in. This absorption is attributed to 2-vinylpyridinium ylide. The ylide decays with a lifetime equal to 33 μs at 25°C independent of the concentration of 2-vinylpyridine. As the ylide decays, there is a concomitant growth of an absorption at 330 nm, attributed to the formation of indolizine. The activation parameters for the 1,5-dipolar cyclization of the ylide to indolizine were determined; E_a = 12.1 kcal mol^{-1} and log A = 13.4. © 1994 John Wiley & Sons, Inc.

Introduction

Indolizine, a heterocyclic system with 10 π delocalized electrons, is of interest to synthetic organic chemists [1]. The electrophilic substitution of the indolizine has been widely investigated [2]. The construction of indolizine usually involves the 1,3-dipolar cycloaddition of pyridinium ylide with ethylenic compounds to form dihydroindolizines; these can be isolated as intermediates which can be catalytically converted into indolizines. More recently, we reported a one-step synthesis for 3-substituted indolizines from the reaction of arylchlorocarbenes with 2-vinylpyridine [3]. We now report the kinetic studies on this intramolecular 1,5-dipolar cyclization process, $\underline{2} \rightarrow \underline{3}$.

1(a). $X = p\text{-}ClC_6H_4$;   1(b). $X = C_6H_5CH_2$;   1(c). $X = C_6H_5CD_2$
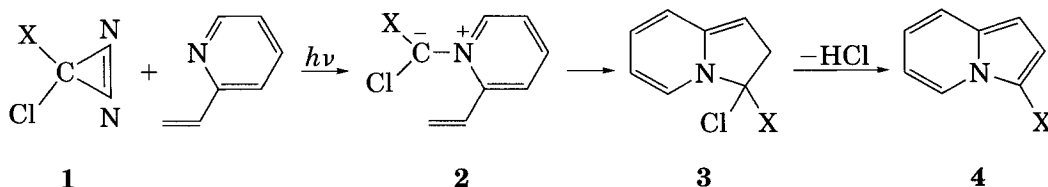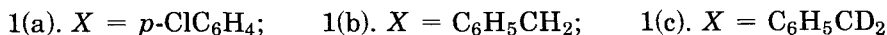
Experimental

Materials

All chlorodiazirines 1a–c were prepared [4] by oxidation of the corresponding benza-midine hydrochloride or benzylamidine hydrochloride in a freshly prepared solution of sodium hypochlorite in DMSO and purified by chromatography on 60–200 mesh silica gel. 2-vinylpyridine and isooctane were purchased from Aldrich and used as received.

Kinetics

The laser flash photolysis setup uses a crossed-beam arrangement. The sample in a 10 × 10 mm cell was excited at 355 nm by single light pulses (200 ps; 5-30 mJ) provided by a frequency tripled mode-locked Nd-YAG laser (Quantel). The detection system (pulsed Xe-arc, monochromator, photomultiplier, and Tektronix 7912 transient recorder) has a response time around 4 ns.

Product Studies

Irradiation (350 nm) of a solution of diazirine, 1a (0.2 M) and 2-vinylpyridine (1.0 M) in isooctane at 25°C resulted in the formation of a single product, 3-arylindolizine 4a. Due to the filtering effect of 4a, the diazirine is not totally used up in photolysis. Therefore product yield for 4a was determined by refluxing diazirine 1a with 2-vinylpyridine (vp) in benzene. The indolizine was isolated by column chromatography on basic Al_2O_3 in 55% yield [3]. Spectral data for indolizine 4a and 4b have been reported previously [3].

Results and Discussion

Platz and co-workers have systematically examined the weak fluorescence spectra of diazirines [5]. They have studied how variation of the nature of the alkyl group, isotopic substitution, and temperature all effect diazirine fluorescence intensities. This data, along with data concerning the yields of pyridine ylides demonstrate that diazirine excited states suffer 1,2 hydrogen migration and nitrogen extrusion, in competition with carbene formation. It is important to note that pyridine does not quench the fluorescence of diazirines. Thus diazirine excited states do not reach with pyridine to form ylides.

Figure 1 shows the uv spectra of the starting materials (3-chloro-3-p-chlorophenyldi-azirine, 1a, and 2-vinylpyridine, vp) before and after irradiation at 366 nm for 60 s (less than 1% conversion). The differential spectrum is the uv absorption of 3-p-chlorophenylindolizine, 4a, $\lambda_{max} = 330$ nm. Laser flash photolysis of diazirine 1a at 355 nm in isooctane produces an absorption band at 310 nm (Fig. 1) due to the formation of carbene, $p\text{-}ClC_6H_4\text{-}C\text{-}Cl$ [6]. In the presence of vp, a new transient, attributed to pyridinium ylide, 2a, grows in with a rate equal to the rate of decay of the carbene as measured at 310 nm. The absorption spectrum is broad and the main band peaks around 520 nm (Fig. 1). The plot of the observed pseudo-first-
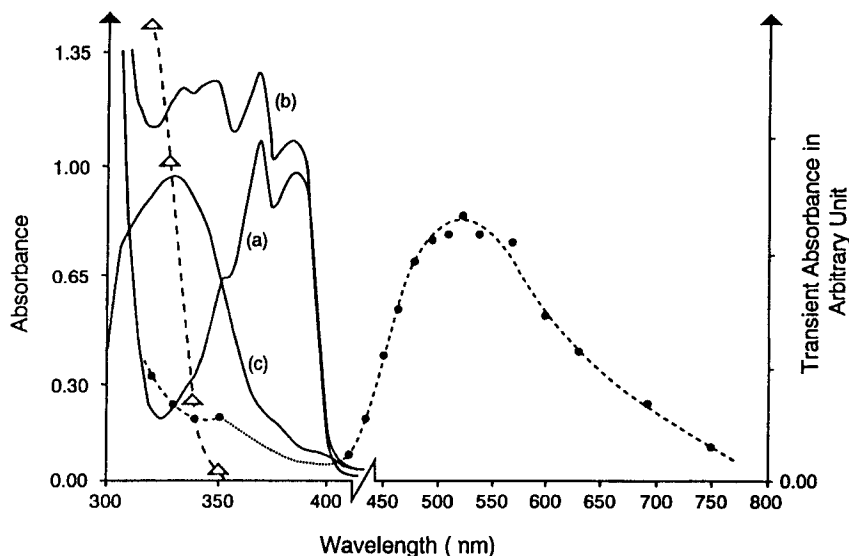
Figure 1. Spectroscopic evolution of a solution of diazirine $\underline{1a}$ (5×10^{-3} M) with 2-vinylpyridine (10^{-2} M) in isooctane. Conventional uv spectra (left scale). (a) Before irradiation, (b) after irradiation at 366 nm and (c) differential spectrum, (b-a), identical to the spectrum of the authentic sample of indolizine $\underline{4a}$. Transient absorption spectra, (right scale), recorded after laser excitation at 355 nm. △..........:△   delay 5 ns; assigned to the carbene. •..........:•   delay 1 μs; assigned to the ylide. Notice the change in the wavelength scale at 420 nm.

order rate constants for growth of the absorption at 520 nm vs [vp] is linear and yields the rate constant for the reaction of the carbene with [vp] at 25°C: $k_y = 2.0 \pm 0.5 \times 10^8$ M^{-1} s^{-1}. This value is similar to that measured for the reaction of arylchlorocarbenes with pyridine [6].

The ylide $\underline{2a}$ decays with a lifetime equal to 33 μs at 25°C independent of the concentration of 2-vinylpyridine. As the ylide decays, there is a concomitant growth of the absorption at 330 nm, attributed to the formation of indolizine, $\underline{4a}$. Kinetic analysis of the growth gives a first-order rate constant equal to 3×10^4 s^{-1} corresponding to a 33 μs lifetime for the precursor of $\underline{4a}$. Since the decay of the ylide $\underline{2a}$ matches the growth of $\underline{4a}$, the HCl elimination from $\underline{3a}$ to form $\underline{4a}$ must be much faster than the cyclization step. The aromatization of the system indeed provides a strong driving force for this elimination. The temperature dependence of the cyclization step has been studied by following both the decay of the ylide at 520 nm and the growth of the indolizine at 330 nm. The data in Figure 2 fall on a single Arrhenius line. Least squares analysis yielded the following parameters for 1,5-cyclization of the ylide: $E_a = 12.1 \pm 0.3$ kcal mol^{-1} and log $A = 13.4 \pm 0.2$. At 330 nm where all species (carbene, ylide, and the indolizine) absorb, the measured transient absorption, Figure 3, gives a complete description of the system.

Irradiation of solutions of benzylchlorodiazirine ($\underline{1b}, X$ = C$_6$H$_5$CH$_2$) and vp in isooctane at 25°C, only produced Z-and E-β-chlorostyrenes and, contrary to expectations, no indolizines appeared. LFP of diazirine $\underline{1b}$ in isooctane in the presence of vp produces a transient species with an absorption at 420 nm attributed to ylide $\underline{2b}$. The plot of the observed pseudo-first-order rate constant for growth at 420 nm vs. [vp] is linear and yields the rate constant for the reaction of the C$_6$H$_5$CH$_2$—C—Cl with vp at 25°C,
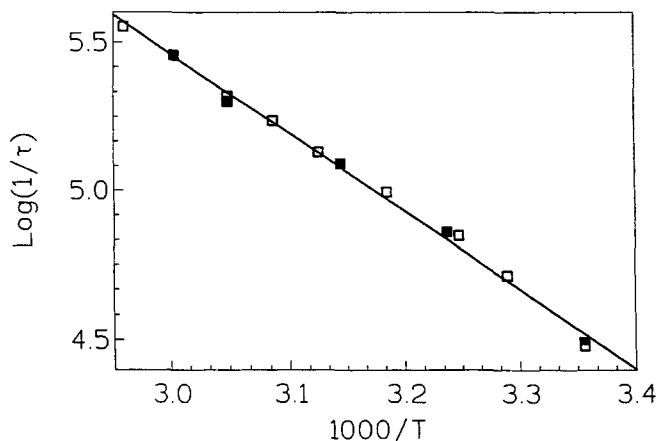
Figure 2.   Arrhenius plot for 1,5-cyclization of ylide 2a. (□), Decay of ylide at 520 nm and (■) the growth of 4a at 330 nm.

$k_y = 3 \pm 1 \times 10^9$ M^{-1} s^{-1}. Ylide 2b decays with a lifetime equal to 5.6 μs at 25°C. The temperature dependence of this decay process has been studied over the 25°–70°C range. Least-squares analysis yielded the following parameters: $E_a = 8.0 \pm 0.2$ kcal mol^{-1} and log $A = 11.2 \pm 0.1$. Ylide 2 is formed in both cases, but its fate is different. Ylide 2a disappears by a cyclization reaction, whereas ylide 2b suffers a 1,2-H shift followed by (or concerted with) the release of vp, since: (1) Chlorostyrenes are the only products and (2) The frequency factor for the process responsible for the decay of 2b is about the same as the one measured for 1,2-H shift in carbene 1b (but it is at least 100 times smaller than the frequency factor for cyclization of ylide 2a).
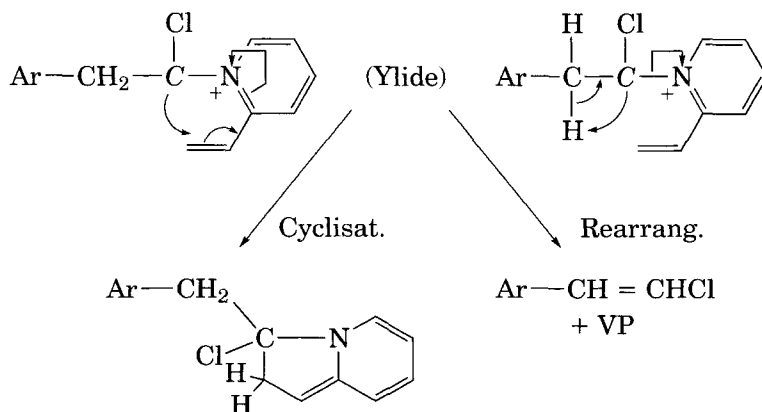
Irradiation of a solution of a 0.01M diazirine 1b with 1M tetramethylethylene (TME) in isooctane at 25°C resulted in the formation of chlorostyrenes and cyclopropane with chlorostyrenes/cyclopropane = 0.50. When 1M vp was added to the above solution, the chlorostyrenes/cyclopropane ratio increased to 2.6. This five-fold increase of the products ratio can be explained by the formation of ylide 2b which subsequently leads to the chlorostyrenes.
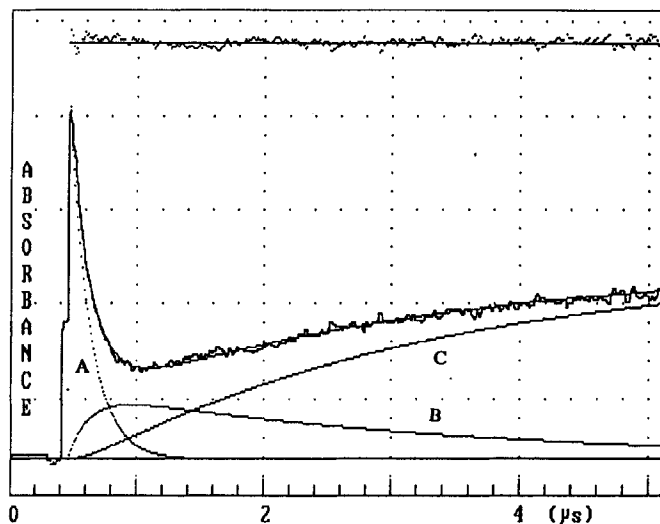
Figure 3. Transient absorption at 330 nm analyzed as the sum of the absorptions of three species involved in a $A \rightarrow B \rightarrow C$ kinetic scheme with $\tau_A = 160$ ns and $\tau_B = 2800$ ns. Species A is the carbene, B is the ylide, and C is the indolizine. Experimental conditions: in isooctane solvent at 65°C with [2−vinyl pyridine] = 1.8×10^{-2} M.

The inefficiency of the reaction to produce 3-benzylindolizine <u>4b</u> from <u>1b</u> is due to the fact that, in ylide <u>2b</u>, the 1,2-H shift is faster than the cyclization reaction, at least, at room temperature. Assuming that the kinetic parameters, E_a and A, for the cyclization of ylides <u>2a</u> and <u>2b</u> are (nearly) the same, the calculated rates for cyclization and 1,2-H shift are, respectively, 3.8×10^4 and 2.6×10^5 s^{-1} for <u>2b</u> at 25°C. The yield of indolizine, <u>4b</u>, would be only 12%, which may be difficult to detect as an isolated product.

However, since E_a is much larger for cyclization than for 1,2-H shift, the yield of indolizine formation should increase with rising temperature. At 80°C, the calculated rates for cyclization and 1,2-H shift are 9×10^5 and 1.9×10^6 s^{-1}, respectively, so that indolizine, <u>4b</u>, should be formed with a 32% yield at this temperature. In fact, when diazirine <u>1b</u> was refluxed in benzene in the presence of vp, the major products were still chlorostyrenes but indolizine <u>4b</u> was formed with 27% isolated yields compatible with the above calculated value.

Both the product yields [3] and the LFP results point to the fact that the p-chloro-phenylchloroylide, <u>2a</u>, undergoes cyclization but the benzylchloroylide, <u>2b</u>, does not, presumably because hydrogen shift occurs faster. The postulate of a 1,2-H shift in a carbene complex is not without precedent. In our recent studies, the combination of LFP and product analysis demonstrated that, even though (phenoxymethyl) chlorocarbene [7] reacts with its diazirine precursor with a substantial rate constant of 3.5×10^8 M^{-1} s^{-1}, the predicted azine product is not formed. These results indicate either carbene/diazirine reversibility or subsequent hydrogen migraiton of the carbene/diazirine adduct. If the rate of hydrogen shift from the ylide is similar to the rate of 1,2-H shift in a free carbene, then (phenyldideuteromethyl) diazirine, <u>1c</u>, would be a good test.

LFP of diazirine 1c in isooctane in the presence of vp produces a transient species with an absorption at 400 nm attributed to ylide 2c. Ylide 2c decays with a lifetime equal to 10.5 μs at 23°C. Similarly, the temperature dependence of this decay process has been studied over the 23°–70°C range. Least-squares analysis yielded the following parameters: $E_a = 8.70 \pm 0.20$ kcal mol^{-1} log $A = 11.43 \pm 0.10$. The kinetic isotope effect for the benzylchloroylide, τ_D/τ_H, is approximately equal to 2.0 which is similar to the KIE of ca. 3.0 observed for the 1,2-H shift in benzylchlorocarbene [8]. Goodman and co-workers [9] have proposed the application of quantum mechanical tunneling for 1,2-H(D) shifts in methylchlorocarbene. According to these authors, the formation of vinyl chloride could arise from two pathways. One occurs by movement over the classical barrier, while the other occurs via quantum mechanical tunneling. The curved Arrhenius plot could be the result of two competing pathways having different activation energies. Similar to the Goodman results, the curved Arrhenius plot was also noted in our benzylchlorocarbene system [8]. We believe that quantum mechanical tunneling or the influence of the solvent may be responsible for these observations.

In conclusion, the cyclization of the vinyl pyridinium ylides of chlorocarbene leading to indolizines followed by a fast elimination of HCl is not restricted to arylchlorocarbenes. Cyclization also occurs, with similar rate parameters, for benzylchlorocarbene and, probably, for alkylchlorocarbene as well. But, in the latter two cases, the efficiency of the reaction is hampered by its high activation energy and its competition with a rearrangement reaction. Therefore, the cyclization is limited to arylchlorocarbenes from a synthesis standpoint.

Acknowledgment

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