

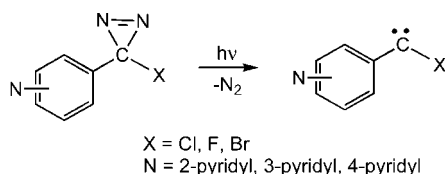
Absolute Reactivity of Halo(pyridyl)carbenes

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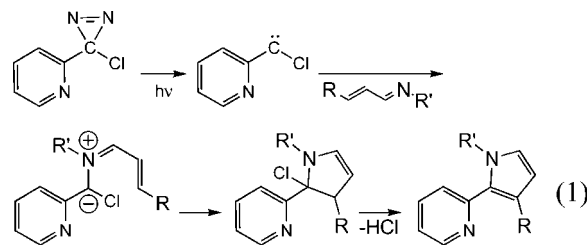


A comprehensive series of halo(pyridyl)carbenes was generated by laser flash photolysis of the appropriate diazirines. Only the chloro- and bromo(2-pyridyl)carbenes and the chloro- and bromo(3-pyridyl)carbenes could be directly observed, but the reactivity of all nine halo(pyridyl)carbenes could be directly studied using the standard and a modified pyridine–ylide approach. The carbenes were all ambiphilic, being highly reactive toward both electron-rich and electron-deficient alkenes. Second-order rate constants for these reactions ranged from 2.9×10^6 to $3.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and depended on both the position of the nitrogen atom within the pyridine ring and the nature of the halogen group, as well as the electrophilicity or nucleophilicity of the alkene. A reactivity trend with respect to the location of the nitrogen within the pyridine ring was observed, with the 4-pyridyl carbenes being the most reactive followed by the 2-pyridylcarbenes and then the 3-pyridylcarbenes being the least reactive. This observed reactivity trend is consistent with the pyridyl ring acting as an overall electron-withdrawing group. The results also show that resonance delocalization of electron density into the nitrogen atom of the 4-pyridyl- and 2-pyridylcarbenes in the transition state significantly reduces the effect of the adjacent halogen (F, Cl, or Br) on the reactivity of the pyridyl carbenes with a series of alkenes.

Introduction

There has been continuing interest in the use of carbenes containing aryl and heterocyclic groups to prepare novel heterocyclic compounds such as indolizines and heteroarylcyclopropanes.^{1–4} Of the wide variety of different carbenes that have been used in these reactions, halo(pyridyl)carbenes are distinctive in that they provide for the synthesis of pyridine-containing products, such as pyridyl-substituted pyrroles,⁵ eq

1, that are of pharmaceutical interest due to their antispasmodic,^{6,7} analgesic,⁸ anti-inflammatory,⁸ and kinase inhibitor activities.^{9,10}



At present, the chemistry of only a small number of halo(pyridyl)carbenes, such as α -chloro-^{1–3,5} and α -fluoro-substituted³ 2-pyridyl- and 3-pyridylcarbenes, has been investigated. The generation of these carbenes by thermal or photochemical decomposition of appropriate diazirines has been demonstrated,^{1–3,5} as has their ability to undergo classical reactions of carbenes, such as addition to alkenes to give pyridyl-

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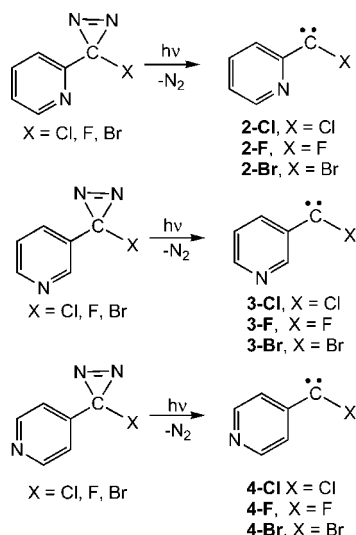
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SCHEME 1



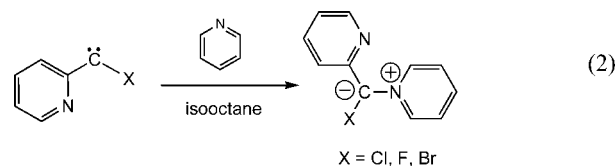
substituted cyclopropanes.^{2,3} In addition, the absolute reactivities of chloro(2-pyridyl)carbene and chloro(3-pyridyl)carbene have been studied in the presence of a series of electron-rich and electron-deficient alkenes.³ These results indicated that both the chloro(2-pyridyl)carbene and the chloro(3-pyridyl)carbene behave as ambiphilic species and that the 2-pyridyl derivative is considerably more reactive than the 3-pyridyl derivative. The results also demonstrated that both chloro(pyridyl)carbenes are several times more reactive than the related chloro(phenyl)carbene.³ The ability of chloro(4-pyridyl)carbene and chloro(3-pyridyl)carbene to form ylides with their diazirine precursors has also been demonstrated in laser photolysis studies.^{1,3} In these cases, ylides were generated without the need to add an additional reagent like pyridine, since the precursor diazirines already contain a pyridine ring that can add to the photochemically generated chloro(pyridyl)carbene.

In the present work, a systematic study of the absolute reactivity of the complete family of halo(pyridyl)carbenes generated in isooctane by laser flash photolysis (LFP) of the corresponding diazirines, Scheme 1, is described. Spectral features of the carbenes as well as their reactivity toward a set of alkenes were examined. Several aspects of the reactivity of these carbenes are addressed, such as the effect of the pyridyl nitrogen and the effect of the halogen substituent. The discussion is based on the experimental results as well as on theoretical calculations of halo(pyridyl)carbenes, with the expectation that these results can contribute to a better understanding of the interesting chemistry of these species.

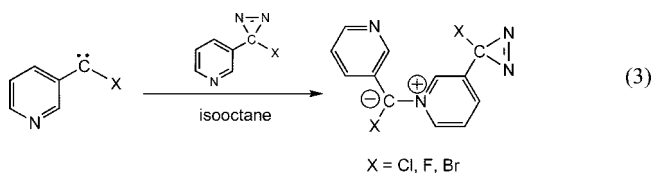
Results

Generation of Chloro(pyridyl)carbenes (2-Cl, 3-Cl, and 4-Cl). Laser irradiation (355 nm, <8 ns/pulse, ≤50 mJ/pulse) of 3-chloro-3-(2-pyridyl)diazirine in isooctane led to the formation of the previously reported^{1,3} chloro(2-pyridyl)carbene **2-Cl** with an absorption maximum at 310 nm and a first-order decay in isooctane of $1.8 \times 10^6 \text{ s}^{-1}$. After addition of pyridine, the first-order decay of the carbene at 310 nm increased in a linear manner with respect to pyridine concentration, and this decay was accompanied by concomitant growth in absorbance at 480 nm, Figure 1a. The absorbance at 480 nm is typical for carbene-

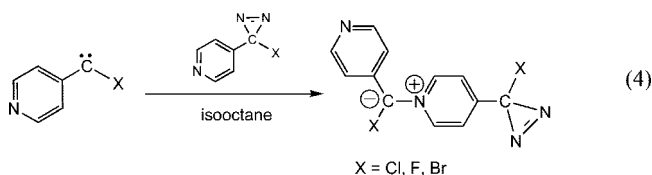
pyridine ylides,^{11,12} which allowed this band to be assigned to the chloro(2-pyridyl)carbene-pyridine ylide, eq 2 ($\text{X} = \text{Cl}$).



LFP of the 3-chloro-3-(3-pyridyl)diazirine in isooctane also gave results matching those published previously.³ The chloro(3-pyridyl)carbene **3-Cl** at 300 nm was observed immediately after the laser pulse, Figure 1b. It decayed rapidly with a rate constant that depended on the concentration of the diazirine to give a new band at 480 nm that was previously assigned³ to the chloro(3-pyridyl)carbene-diazirine ylide formed by reaction of the carbene with its diazirine precursor, eq 3 ($\text{X} = \text{Cl}$).



No absorption near 300 nm due to the chloro(4-pyridyl)carbene **4-Cl** was detected upon laser irradiation of 3-chloro-3-(4-pyridyl)diazirine in isooctane, Figure 1c. Instead, the ylide formed by addition of carbene **4-Cl** to its diazirine precursor, eq 4 ($\text{X} = \text{Cl}$) was observed with an absorption maximum at 500 nm.¹ Time-resolved growth of this ylide was readily observed, indicating that the carbene was sufficiently long-lived to be detected. The inability to detect the carbene therefore indicates that the chloro(4-pyridyl)carbene **4-Cl** has little absorption above 300 nm in the spectral region accessible under the conditions of the experiment.



Generation of Fluoro(pyridyl)carbenes (2-F, 3-F, and 4-F). Laser irradiation of 3-fluoro-3-(2-pyridyl)diazirine in isooctane produced no visible transient absorption above 300 nm. However, laser irradiation of the diazirine in the presence of pyridine (0.32 mM) led to the time-resolved formation of a transient species with a strong broad absorption band centered at 480 nm, Figure 1d. The transient species responsible for the absorption at 480 nm is assigned to the ylide obtained by trapping of the fluoro(2-pyridyl)carbene **2-F** with pyridine, eq 2 ($\text{X} = \text{F}$). This assignment is based on the following observations. First, the shape and position of the absorption band at 480 nm is very similar to other halo(aryl)carbene-pyridine ylides previously reported.¹¹ In addition, a plot of observed rate constant (k_{obs}) versus concentration of pyridine gave a straight

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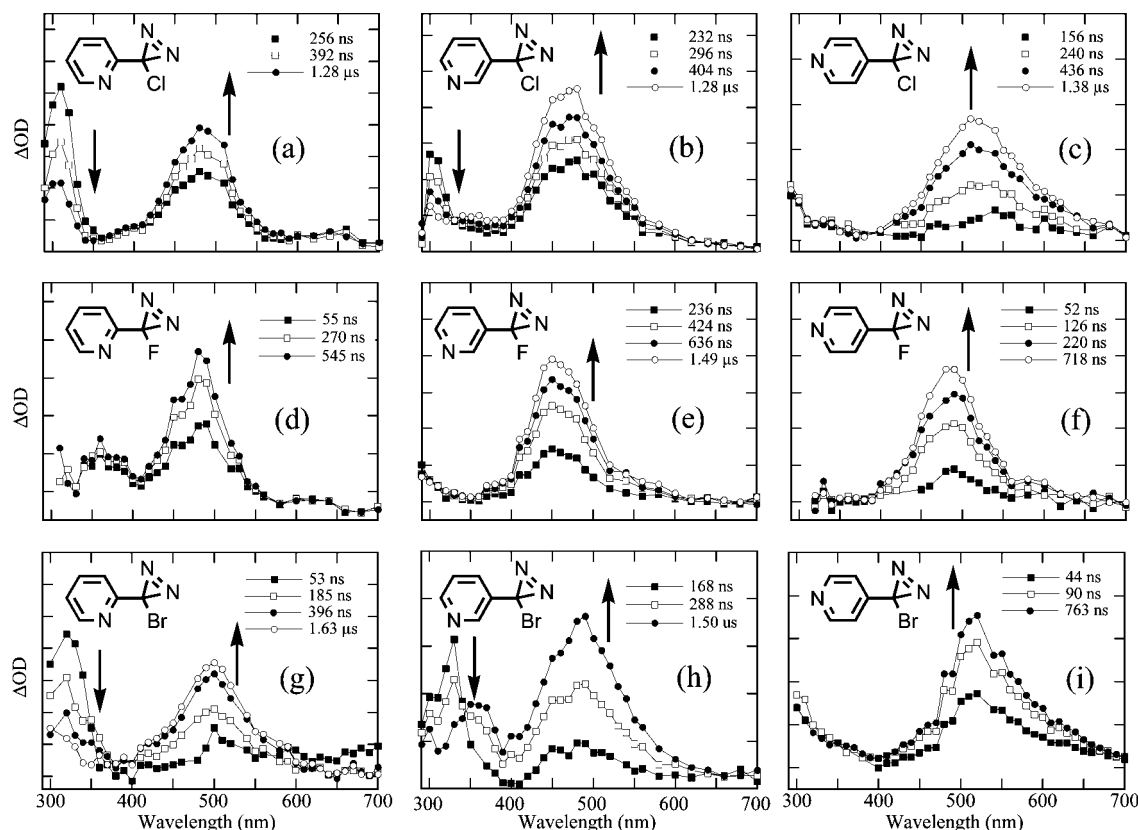


FIGURE 1. Transient spectra obtained upon 355 nm laser excitation of the diazirines shown in isooctane at 22 °C under the following conditions: (a) 1.3 mM diazirine and 0.32 mM pyridine, (b) 3.0 mM diazirine, (c) 0.6 mM diazirine, (d) 1.3 mM diazirine and 0.32 mM pyridine, (e) 1.0 mM diazirine, (f) 0.8 mM diazirine, (g) 1.3 mM diazirine and 0.32 mM pyridine, (h) 2.4 mM diazirine, and (i) 3.3 mM diazirine. Downward and upward arrows indicate time-resolved absorption decays and growths, respectively. Legends indicate the time at which the spectra were obtained after the laser pulse.

line with a slope corresponding to the bimolecular rate constant for the formation of the transient at 480 nm ($k_y = 2.9 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) that is consistent with the trapping of a carbene with pyridine.

Photolysis of 3-fluoro-3-(3-pyridyl)diazirine in isooctane produced the transient absorption spectra shown in Figure 1e. Again, the spectra showed no absorption in the 300 nm region due to the fluoro(3-pyridyl)carbene **3-F**. However, the spectra did show a strong absorption band centered at 450 nm that formed in a time-resolved manner. The growth of the transient at 450 nm was linearly dependent on the concentration of the diazirine precursor, giving a second order rate constant, $k_y = 2.6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. The spectral features of the transient at 450 nm, in addition to the large value of the bimolecular rate constant for its formation, are very similar to those observed for the chloro(pyridyl)carbene-diazirine ylides previously reported.^{1,3} Therefore, the absorption band at 450 nm can be confidently identified as the fluoro(3-pyridyl)carbene-diazirine ylide, eq 3, $X = \text{F}$, formed upon reaction of the fluoro(3-pyridyl)carbene **3-F** with its diazirine precursor.

Similarly, laser irradiation of 3-fluoro-3-(4-pyridyl)diazirine in isooctane yielded an absorption spectra with no significant absorption near 300 nm. Instead, the spectra showed intense absorption band centered at 480 nm that grew in as a function of time, Figure 1f, and was assigned to the fluoro(4-pyridyl)carbene-diazirine ylide, eq 4 ($X = \text{F}$). The second-order rate constant for the reaction of carbene **4-F** with its diazirine precursor was determined to be $5.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.

According to these results, none of the fluoro(pyridyl)carbenes could be directly observed after 355 nm laser excitation of their corresponding diazirine precursors. However, the observation of the growth curves for ylide formation indicates that in all cases these carbenes are sufficiently long-lived for study using the nanosecond laser system. These results are similar to those reported for fluoro(phenyl)carbene which absorbs at 270 nm and has no absorption above 300 nm in the UV-vis spectrum.¹³

Generation of Bromo(pyridyl)carbenes (2-Br, 3-Br, and 4-Br). Laser irradiation of 3-bromo-3-(2-pyridyl)diazirine in isooctane produced a transient spectrum that was dominated by an absorption band centered at 330 nm. This transient absorption band was assigned to the bromo(2-pyridyl)carbene **2-Br** based on the following observations. The location of the absorption maximum and narrow shape of the absorption band are similar to the known absorption spectrum for the bromo(phenyl)carbene in solution.¹³ In addition, the transient showed a reactivity pattern typical of carbenes, including a rapid reaction with pyridine ($k_y = 2.7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) to form a broad and intense absorption band at 500 nm, Figure 1g, assigned to the carbene-pyridine ylide, eq 2 ($X = \text{Br}$).

Laser irradiation of 3-bromo-3-(3-pyridyl)diazirine in isooctane solution led to a transient absorption spectrum containing one absorption band at 330 nm and a second at 490 nm, Figure 1h. The decay of the transient species at 330 nm is concurrent with the growth of the species at 490 nm, showing that the

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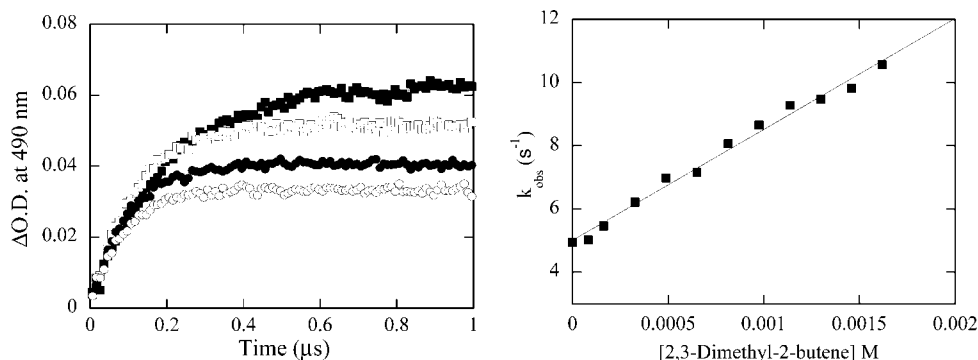


FIGURE 2. (a) Time-resolved changes in absorbance at 490 nm upon laser irradiation of 3-fluoro-3-(4-pyridyl)diazirine (1.2×10^{-3} M) in isooctane containing (■) 0 M, (□) 0.81 mM, (●) 1.3 mM, and (○) 1.8 mM of 2,3-dimethyl-2-butene. (b) Relationship between the observed rate constant for the growth of the ylide at 490 nm, formed by addition of the fluoro(4-pyridyl)carbene to the 3-fluoro-3-(4-pyridyl)diazirine, and the concentration of 2,3-dimethyl-2-butene in isooctane at 22 °C.

transient at 490 nm is a product from the reaction of the transient at 330 nm. These results are analogous to those reported for chloro(3-pyridyl)carbene in isooctane,³ and the absorption band at 330 nm can be assigned to bromo(3-pyridyl)carbene **3-Br**, and the broad absorption band at 490 nm to the bromo(3-pyridyl)carbene-diazirine ylide, eq 3 ($X = \text{Br}$). The second order rate constant for the formation of carbene-diazirine ylide was determined to be $k_y = 1.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$.

Laser irradiation of 3-bromo-3-(4-pyridyl)diazirine in isooctane yielded a transient absorption spectrum dominated by a single broad absorption band centered at 520 nm, Figure 1i. The shape and position of this absorption band are similar to the other pyridyl carbene-diazirine absorption bands described above and previously reported.^{1,3} Thus, the 520 nm absorption band is assigned to the bromo(4-pyridyl)carbene-diazirine ylide, eq 4 ($X = \text{Br}$), formed by addition of bromo(4-pyridyl)carbene **4-Br** to its diazirine precursor. The carbene-diazirine ylide is formed with a bimolecular rate constant, $k_y = 3.7 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. The bromo(4-pyridyl)carbene **4-Br** presumably has no strong absorbance above 300 nm, similar to chloro- and fluoro(4-pyridyl)carbenes described above.

Study of the Reactivity of Halo(pyridyl)carbenes with Alkenes. Moss and co-workers studied the reactivity of chloro(2-pyridyl)carbene **2-Cl** and chloro(3-pyridyl)carbene **3-Cl** toward electron-rich and electron-deficient alkenes.³ Their study was carried out by monitoring the decay of the absorption band of the two carbenes at 310 nm as a function of the concentration of alkene. In the present work, only four of the nine halo(pyridyl)carbenes investigated have significant absorption in the UV region above 300 nm and therefore the methodology used in the previous study could not be applied in this work to all nine carbenes. In view of this, an alternative approach based on monitoring the time-resolved evolution of ylides was used. The advantage of using ylide-forming reactions to study carbenes is well documented.^{11,12} The ylide method is particularly useful when the carbenes that are being investigated are “invisible” in the accessible UV–vis region of the absorption spectrum, such as the five carbenes not directly observed in the present work, or when the absorption band of the carbene overlaps strongly with the absorption band of their precursor.

Typically, the ylide method requires the addition of pyridine as a reagent to quench the carbene and generate the detectable carbene-ylide. However, in the current work, a pyridine ring was already present as a structural feature on the diazirines used as the carbene precursors, and as described above the halo(4-pyridyl)- and halo(3-pyridyl)carbenes reacted with their precursors

to generate readily observed carbene-diazirine ylides. Therefore, in order to determine the reactivity of the halo(4-pyridyl)- and halo(3-pyridyl)carbenes with a set of alkenes, the growths of the carbene-diazirine ylides were measured at a known concentration of diazirine but at different concentrations of the alkene quencher. Under these conditions, the observed rate constant (k_{obs}) for the formation of a carbene-diazirine ylide is given by eq 5

$$k_{\text{obs}} = k_0 + k_{\text{diaz}}[\text{diazirine}]_0 + k_q[\text{alkene}] \quad (5)$$

where k_0 is the first-order rate constant that represents all the first-order and pseudo-first-order processes that the carbene undergoes other than the reaction with the diazirine precursor, k_{diaz} is the second-order rate constant for the reaction of the carbene with the diazirine, $[\text{diazirine}]_0$ is the known, initial concentration of diazirine, k_q is the second-order rate constant for the reaction of the carbene with the alkene, and $[\text{alkene}]$ is the known concentration of the alkene added to the solution. According to this equation, a plot of k_{obs} versus alkene concentration at a constant diazirine concentration should be linear with the slope giving the second-order rate constant for the reaction of the carbene with the alkene.

Figure 2a shows the time-resolved growth kinetics of the ylide formed upon reaction of the fluoro(4-pyridyl)carbene **4-F** at various concentrations of 2,3-dimethyl-2-butene. As shown in Figure 2b, the observed rate constant for the growth of the ylide increased in a linear manner with respect to 2,3-dimethyl-2-butene concentration, and treatment of these data with eq 5 led to the second-order rate constant for reaction of carbene **4-F** with the 2,3-dimethyl-2-butene of $k_q = 3.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. Rate constants for quenching of the each 3-pyridyl- (**3-F**, **3-Cl**, and **3-Br**) and 4-pyridylcarbenes (**4-F**, **4-Cl**, and **4-Br**) with a variety of alkenes were obtained in a similar manner, and these rate constants are summarized in Table 1.

To maintain experimental consistency, it would have been ideal to examine the reactivity of the 2-pyridyl carbenes with alkenes in the same manner as described for the 3-pyridyl- and 4-pyridylcarbenes. However, none of the 2-pyridylcarbenes reacted with their diazirine precursors to form ylides. On the other hand, all three 2-pyridylcarbenes formed strongly absorbing ylides when generated in the presence of small amounts of pyridine. Thus, absolute rate constants for the addition of carbenes **2-Cl**, **2-F**, and **2-Br** to the alkenes were measured using the conventional pyridine-ylide method. This method is same as that described above, except that the relevant rate expression shown in eq 6 contains a term, $k_{\text{pyr}}[\text{pyridine}]_0$, that defines the

TABLE 1. Second-Order Rate Constants (k_q) for the Reaction of the Halo(pyridyl)carbenes with a Series of Alkenes in Isooctane at 22 °C

alkene	k_q ($10^6 \text{ M}^{-1} \text{ s}^{-1}$) ^a								
	2-F	3-F	4-F	2-Cl	3-Cl	4-Cl	2-Br	3-Br	4-Br
(CH ₃) ₂ C=C(CH ₃) ₂	1900	520	3500	1700 (1100) ^d	710(420) ^d	2400	1700	1400 ^b	2400
(CH ₃) ₂ C=CHCH ₃	970 ^b	210	2100	930 (720) ^d	420(180) ^d	870	860	640 ^b	1400 ^b
cyclohexene	130	8.6	140	100	15 ^b	150 ^b	150	44	320 ^c
<i>n</i> -BuCH=CH ₂	40	2.9	54	30 (20) ^d	9.1(6.2) ^d	66	39	17	90 ^c
CH ₂ =CHCO ₂ CH ₃	44	27	55	36	15	42	45	26	100 ^b
CH ₂ =CClCN	460	150	260	790 (460) ^d	300(190) ^d	780	1300	660 ^b	1100 ^c

^a Errors are 10 ± 5% unless otherwise indicated. ^b Error is 20 ± 5%. ^c Error is 50 ± 5%. ^d Data taken from ref 3.

TABLE 2. HOMO and LUMO Energies and Mulliken Atomic Charges at the Carbenic Carbon of Halo(pyridyl)carbenes in the Gas Phase and Carbenic Carbon–Pyridyl Ring Carbon Bond Lengths ($d(\text{C}(\text{carbenic})-\text{C})$ of Halo(pyridyl)carbenes and Halo(phenyl)carbenes in the Gas Phase Calculated at the B3LYP/6-31G* Level

compd	HOMO energy (eV)	LUMO energy (eV)	Mulliken charge on C: carbon	$d(\text{C}(\text{carbenic})-\text{C})$ (Å)
2-PyFC: (2-F)	-5.951	-2.808	+0.1868	1.493
3-PyFC: (3-F)	-6.092	-2.826	+0.1463	1.470
4-PyFC: (4-F)	-6.279	-3.074	+0.1628	1.483
fluoro(phenyl)carbene				1.470
2-PyClC: (2-Cl)	-5.940	-3.268	-0.08562	1.480
3-PyClC: (3-Cl)	-6.043	-3.269	-0.1503	1.455
4-PyClC: (4-Cl)	-6.211	-3.512	-0.1347	1.470
chloro(phenyl)carbene				1.456 (1.457) ^a
2-PyBrC: (2-Br)	-5.965	-3.280	+0.0006390	1.467
3-PyBrC: (3-Br)	-6.002	-3.322	-0.06180	1.453
4-PyBrC: (4-Br)	-6.157	-3.561	-0.04542	1.473
bromo(phenyl)carbene				1.453

^a Data taken from ref. 14

rate constant for the addition of the carbene to pyridine at a constant pyridine concentration rather than a term describing the addition of the carbene to a diazirine precursor.

$$k_{\text{obs}} = k_0 + k_{\text{pyr}}[\text{pyridine}]_0 + k_{\text{q}}[\text{alkene}] \quad (6)$$

Since k_0 and $k_{\text{pyr}}[\text{pyridine}]_0$ in eq 6 are constant for a given concentration of pyridine, the relationship between the observed rate constant and alkene concentration should be linear, with k_{q} being obtained from the slope. In all cases, plots obtained from the variation of observed rate constant of the halo(2-pyridyl)-carbene-pyridine growth as a function of alkene concentration were linear. From the slopes of these graphs, the second-order rate constants for the carbene addition to the alkenes reported in Table 1 were obtained.

Theoretical Calculations on Halo(pyridyl)carbenes. The halo(pyridyl)carbenes and halo(phenyl)carbenes¹⁴ were computed at the B3LYP/6-31G* level of theory to be singlet ground-state carbenes with X–C–C angles in the range of 106–112°, consistent with singlet state species.^{14–16} Data obtained from the calculations that are relevant to the discussion of the experimental results are given in Table 2 and include C(carbenic)–C bond lengths, Mulliken atomic charges on the carbenic carbon, and the HOMO and LUMO energies for all halo(pyridyl)carbenes studied in the present work. Other results from the computations are included as Supporting Information.

Discussion

Reactivity of Halo(pyridyl)carbenes with Alkenes. The data in Table 1 show that the rate constants for the reactions of the halo(pyridyl)carbenes with electron-rich and electron-deficient alkenes are faster than the rate constants for the reaction of the halo(pyridyl)carbenes with 1-hexene. These results are the same as those previously observed for the reactions of chloro(2-pyridyl)carbene **2-Cl** and chloro(3-pyridyl)carbene **3-Cl** with a similar set of alkenes,³ although the rate constants measured in the earlier work are slightly smaller than those obtained in the present work. In fact, the trend where carbenes are more reactive with both electron-rich and electron-poor alkenes is often seen^{17,18} and in the present case leads to the conclusion that all of the halo(pyridyl)carbenes studied in the present work are ambiphilic species, behaving as electrophiles when reacting with electron-rich alkenes such as 2,3-dimethyl-2-butene and as nucleophiles when reacting with electron-poor alkenes such as 2-chloroacrylonitrile.

Effect of the Position of the Pyridyl Nitrogen on the Halo(pyridyl)carbene Reactivity. In previous work, Moss and co-workers found that the reactivity of the chloro(2-pyridyl)-carbene **2-Cl** toward alkenes was roughly 2.5–4 times greater than that of the chloro(3-pyridyl)carbene **3-Cl**,³ Table 1. The higher reactivity of **2-Cl** compared to **3-Cl** was attributed to the fact that the electronegative nitrogen atom in **2-Cl** is closer to the carbenic center than in **3-Cl**, which causes the pyridine ring in **2-Cl** to have a stronger electron-withdrawing inductive effect than the pyridine ring in **3-Cl**. As can be seen in Table 1, this trend does not extend to the chloro(4-pyridyl)carbene **4-Cl**. In this carbene, the pyridyl nitrogen is furthest from the carbenic center, but its reactivity with the different alkenes is considerably higher than the reactivity of the chloro(3-pyridyl)carbene **3-Cl** and in most cases slightly higher than the reactivity of **2-Cl**. This order of reactivity as a function of nitrogen position is not restricted to the α -chloro carbenes but was also observed for the fluoro(pyridyl)- and bromo(pyridyl)carbenes. Based on these observations, the proximity of the pyridyl nitrogen to the carbene center does not appear to be the only factor that contributes to the reactivity of the halo(pyridyl)carbenes. Instead, the fact that halo(4-pyridyl)carbenes react faster than the halo(3-pyridyl)carbenes and similar to the halo(2-pyridyl)carbenes suggests that the mesomeric effects are also important. In particular, resonance electron donation from the pyridine ring to the vacant p orbital on the carbene center induces a partial positive charge on positions 2 and 4 of the pyridine ring, but not on position 3. When this partial positive charge is located on the electronegative nitrogen atom as occurs for the 4- and

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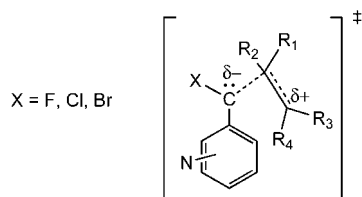
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SCHEME 2



2-pyridyl carbenes, the carbenes are destabilized and their reactivity increases. This is consistent with the known effect of the nitrogen atom in pyridine rings on electrophilic substitution reactions,¹⁹ which are most disfavored at the 2- and 4-positions since substitution at those positions produces an unstable intermediate with positive charge on the electronegative nitrogen.

The position of the nitrogen atom in the ring may also influence the relative stabilities of the transition states for the addition of the pyridyl carbenes to alkenes. The transition state for such reactions is considered to be asymmetric,²⁰ with charge build-up at both the carbenic carbon and at the olefinic carbon. For electrophilic addition of carbenes to alkenes, a partial negative charge is found at the carbenic carbon in the transition state as shown in Scheme 2. Such a transition state resembles the structure of pyridylmethyl anions, which are strongly stabilized by the resonance electron-withdrawing ability of 2- and 4-pyridyl rings. For example, 2- and 4-methylpyridine are much more acidic than 3-methylpyridine, and 4-methylpyridine is approximately 3 orders of magnitude more acidic than 2-methylpyridine.²¹ Thus, the transition state for electrophilic addition of halo(4-pyridyl)- and halo(2-pyridyl)carbenes to alkenes should also be stabilized by resonance delocalization of the negative charge to the nitrogen, and reactions progressing through these transition states should be more rapid than reactions involving the halo(3-pyridyl)carbenes.

The relative reactivities of carbenes toward alkenes has been explained by differences in the HOMO and LUMO energies of carbenes.²² In particular, the electrophilic addition of carbenes to electron-rich alkenes is predicted to be more favorable for carbenes having low-lying LUMO orbitals that increase the electron-accepting ability of the carbene in comparison to carbenes with higher energy LUMO orbitals. LUMO energies calculated for halo(pyridyl)carbenes have been plotted in a potential energy diagram, Figure 3. As can be seen, the LUMO energies of halo(4-pyridyl)carbenes are in all cases significantly lower than those for the halo(2-pyridyl)- and halo(3-pyridyl)carbenes, suggesting a higher reactivity of the former. This agrees well with our experimental results showing that the halo(4-pyridyl)carbenes were in every case more reactive toward electron-rich alkenes than the other two groups of isomers. On the other hand, the LUMO energies in Figure 3 for the halo(2-pyridyl)carbenes are slightly higher than for the halo(3-pyridyl)carbenes, which leads to the prediction that the halo(2-pyridyl)carbenes should be the least reactive isomers. In this case, the experimental results do not agree with the theoretical prediction, since the reactivities of halo(2-pyridyl)carbenes

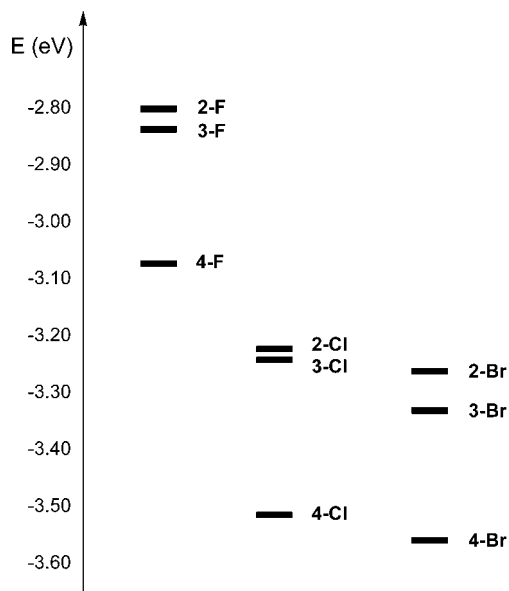


FIGURE 3. LUMO energies calculated for halo(pyridyl)carbenes at the B3LYP/6-31G* level.

toward electron-rich alkenes were significantly higher than those of halo(3-pyridyl)carbenes.³ Thus, the calculated LUMO energies do not provide a comprehensive explanation for the experimental order of reactivity observed for these two groups of carbenes.

Other computational results are consistent with the higher reactivity of the 2- and 4-pyridylcarbenes relative to the 3-pyridylcarbenes, but these do not provide a complete explanation for the higher reactivity of the 4-pyridyl carbenes relative to the 2-pyridylcarbenes. In particular, the Mulliken charge densities²³ in Table 2 indicate that the carbenic carbons of the 2- and 4-pyridylcarbenes have larger positive charges (or smaller negative charges) compared to the 3-pyridylcarbenes, which in turn suggests higher electrophilicity of the 2- and 4-pyridylcarbenes. However, the charges at the carbenic carbon of the 2-pyridyl carbons are more positive than those of the 4-pyridylcarbenes, which contradict the experimental results showing that the latter are more reactive toward electron-rich alkenes. The computations also show that the bond between the carbenic carbon and the aromatic carbon is substantially elongated in the 2- and 4-pyridylcarbenes relative to the 3-pyridylcarbenes, which in turn have C(carbenic)—C bond lengths that are almost identical to the length of the same bond in halo(phenyl)carbenes. These observations are consistent with the reduced resonance electron-donating ability of the pyridine rings in the 2- and 4-pyridylcarbenes that leaves the carbenic carbon on those carbenes with a greater positive charge (or smaller negative charge) than the 3-pyridylcarbene. In addition, a reduction in double bond character due to the unfavorable resonance interaction between the vacant p-orbital of the carbene and the pyridine ring in the 2- and 4-pyridylcarbenes increases the C(carbenic)—C bond distance in 2- and 4-pyridylcarbenes compared to the same bond distance in the halo(3-pyridyl)carbene as well as the halo(phenyl)carbenes.

Overall, the computational parameters help to understand the higher reactivity of the 4-pyridylcarbenes, but no single

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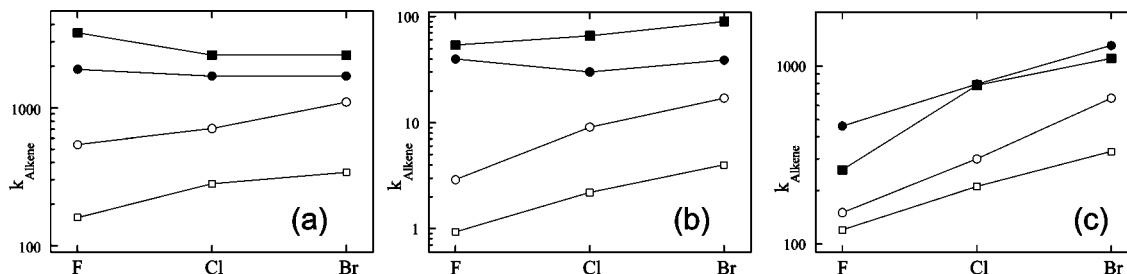


FIGURE 4. Second-order rate constants for the reaction of (□) halo(phenyl)carbenes (from ref ¹³), (○) halo(3-pyridyl)carbenes, (●) halo(2-pyridyl)carbenes, and (■) halo(4-pyridyl)carbene with (a) 2,3-dimethyl-2-butene, (b) 1-hexene, and (c) 2-chloroacrylonitrile in isooctane at 22 ± 1 °C.

parameter provides a complete explanation for the overall reactivity trend, 4-pyridyl > 2-pyridyl > 3-pyridyl. Thus, it is likely that factors that affect the fundamental reactivity of the carbenes, such as relative LUMO energies and positive charge density, and those that affect the stability the transition state combine to cause the observed difference in reactivities of the carbenes as a function of the position of the nitrogen atom in the pyridine rings. The high reactivity of 2-pyridylcarbenes toward electron-rich carbenes, despite having high LUMO energies, clearly indicates that the inductive-withdrawing effect of the nitrogen atom in the pyridine ring has a major influence on the reactivity of 2-pyridylcarbenes with alkenes. In contrast, the reactivity of 4-pyridylcarbenes seems to be greatly dictated by the low-lying LUMO energy of these species.

Effect of the Halogen Substituent on the Halo(pyridyl)carbene Reactivity. The halogen attached to the carbene center of halo(phenyl)carbenes is known to have a significant effect on the reactivity of the carbenes with alkenes,¹² with fluoro(phenyl)carbene being the least reactive and bromo(phenyl)carbene being the most reactive. This order of reactivity²⁰ is due to fluorine being best able to stabilize the carbene by resonance donation to the empty 2p orbital and by inductive withdrawal of electron density from the filled, nonbonding sp² orbital. The reactivity of the halo(3-pyridyl)carbenes, **3-F**, **3-Cl**, and **3-Br**, with alkenes in Table 1 followed the same order, Figures 4a,b (open circles), presumably for the same reasons as described for the halo(phenyl)carbenes. The order of reactivities also correlates nicely with the LUMO energies of the halo(3-pyridyl)carbenes. The most reactive halo(3-pyridyl)carbene, the bromo derivative **3-Br**, has the lowest calculated LUMO energy, and the least reactive fluoro(3-pyridyl)carbene **3-F** has the highest calculated LUMO energy, Table 3. The effect of halogen substituents on the reactivity of the halo(2-pyridyl)- and halo(4-pyridyl)carbenes with electron-deficient alkenes like 2-chloroacrylonitrile was the same as that observed for the halo(3-pyridyl)carbenes and halo(phenyl)carbenes, namely that the fluoro derivatives were least reactive, and the bromo derivatives most reactive, Figure 4c. However, the effect of halogen substituents on the reactivity of halo(2-pyridyl)- and halo(4-pyridyl)carbenes with electron-rich alkenes is surprisingly small as illustrated in Figure 4a,b, and in some cases shows a reverse order, with the fluoro(2-pyridyl)- and fluoro(4-pyridyl)carbenes being slightly more reactive than the chloro and bromo derivatives. Thus, the pyridine rings in halo(2-pyridyl)- and halo(4-pyridyl)carbenes seem to produce a leveling effect on the carbene reactivity that reduces the effect of the halogen atom on the reactivity of the carbene.

A possible explanation lies in the combined effects of the halogen and the pyridine nitrogen on the stability of the transition state. The transition state for the electrophilic addition

of the carbenes to alkenes is presumed to have a partial negative charge at the carbenic carbon. For halo(phenyl)carbenes, the halogen substituent can significantly affect the stability of this transition state, with the strongly electronegative fluorine imparting more stabilization than the less electronegative bromine and increasing the rate constant for the addition reaction. In the transition state for the reaction of the 2- and 4-pyridylcarbenes, the negative charge may be delocalized into the electron-withdrawing nitrogen group. As a result, the magnitude of the negative charge at the benzylic center is reduced, and ability of the α-halo groups to influence the stability of the reaction is diminished. On the other hand, for halo(3-pyridyl)carbenes, the negative charge is more localized on the carbene carbon and thus depends more on the electron-withdrawing inductive effect of the halogen atom to stabilize their transition states in the reactions with alkenes.

Conclusion

The results described demonstrate that all of the halo(pyridyl)carbenes studied in the present work are ambiphilic species, a property that they share with the well-studied halo(phenyl)carbenes. In addition, the results also show that the location of the nitrogen within the pyridyl ring has a strong influence on the reactivity of the carbenes, with the nitrogen in the 2- or 4-positions providing the greatest rate enhancement due to a combination of effects of the nitrogen on the stability of the carbene as well as the stability of the transition state for reaction with alkenes. The presence of the nitrogen also reduces the influence of the different halo groups on the reactivity of the halo(2-pyridyl)- and halo(4-pyridyl)carbenes, presumably due to the charge developed in the transition state being delocalized into the ring nitrogen, thus reducing the effectiveness of the halogen in stabilizing the negative charge.

Experimental Section

Materials. The synthesis of 3-chloro-3-(2-pyridyl)diazirine,^{1,2} 3-chloro-3-(3-pyridyl)diazirine,^{1,2} 3-chloro-3-(4-pyridyl)diazirine,^{1,2} 3-fluoro-3-(2-pyridyl)diazirine,³ and 3-fluoro-3-(3-pyridyl)diazirine³ have been reported previously. 3-Fluoro-3-(4-pyridyl)diazirine was prepared^{3,27} by exchange reactions of 3-chloro-3-(4-pyridyl)diazirine with molten tetra-*n*-butylammonium fluoride. The 3-bromo-3-(pyridyl)diazirines were prepared from the corresponding pyridylamine hydrochlorides^{25,27} following a modified method²⁷ of the Graham reaction. Complete details regarding the synthesis and characterization of these diazirines are provided in the Supporting Information.

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Laser Flash Photolysis. The computer-controlled nanosecond laser flash photolysis system employed in this study has been previously described.²⁸ The excitation source was the third harmonic of a Nd:YAG laser (355 nm, 20 mJ/pulse, <8 ns/pulse). Sample cells for laser experiments were constructed of 7 × 7 mm² Suprasil quartz tubing. Each sample contained 2 mL of aerated spectrograde isooctane to which was added 10–20 μL of a diazirine stock solution (made in dichloromethane). The final concentration of diazirine precursor was in the range of 0.5–2 mM, with absorption at the excitation wavelength of 355 nm in the 0.2–0.4 range. In addition, pyridine concentrations in the range of 0.2–5 mM were used in experiments with 3-halo-3-(2-pyridyl)diazirines. In the quenching experiments, small amounts (1 to 50 μL) of alkene stock solution were added to the sample cells. Samples were shaken after every laser shot to ensure their homogeneity. All experiments were conducted at room temperature (22 ± 1 °C).

Computational Method. The geometries of the halo(pyridyl)carbenes and halo(phenyl)carbenes used in this work were optimized using the Gaussian03 suite of programs.²⁹ Geometry optimizations were carried out at the B3LYP/6-31G* level of theory. All stationary points were characterized by normal coordinate analysis.

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Supporting Information Available: Synthesis and NMR characterization of 3-fluoro-3-(4-pyridyl)diazirine and the 3-bromo-3-(pyridyl)diazirines. Cartesian coordinates and absolute energies for the halo(pyridyl)carbenes and halo(phenyl)carbenes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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