The Kinetic Range of Carbene–Pyridine Ylide forming Reactions

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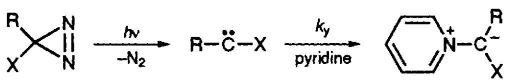
Absolute rate constants for the ylide-forming reactions of 16 carbenes with pyridine range from 1.4×10^{10} to 1.2×10^5 dm^3 mol^{-1} s^{-1}, and can be rationalized by frontier molecular orbital theory.

In 1988, Jackson *et al.* reported laser flash photolysis (LFP) experiments in which aryl- or alkyl-chlorocarbenes, R–C–Cl, reacted with pyridine in hydrocarbon solutions at near diffusion-controlled rates, affording pyridinium ylides that absorbed strongly at 376 (R = Me_3C) or 480 nm (R = Ph)[1] [eqn. (1)]. Correlations of the observed rates of formation of the ylides (k_{obs}) with the concentration of pyridine gave the second-order rate constants for the carbene–pyridine reactions (k_y) as 3.3×10^8 (R = Ph) and 2.4×10^9 dm^3 mol^{-1} s^{-1} (R = Me_3C), whilst the intercepts of these correlations at [pyr] = 0 provided kinetic data for the reactions of the carbenes in the absence of pyridine. Moreover, the quantitative response of k_{obs} to added carbene traps (*e.g.* alkenes) afforded kinetic data for intermolecular carbene reactions.[1] These methods have now become standard for following the rection kinetics of carbenes that lack usable UV absorptions.[2]

Alkyl-, dialkyl- and arylalkyl-carbenes react so rapidly with pyridine that it has become customary to take k_y as $\geqslant 10^9$ dm^3 mol^{-1} s^{-1}.[3] Additionally, a variety of alkylhalocarbenes, R–C–X, have been examined in eqn. (1) with R including Me,



(1)

Pr^i, $ArCH_2$, Me_3C and cyclopropyl, and X = Cl or in some cases Br. These examples gave k_y in the range 10^8–10^{10} dm^3 mol^{-1} s^{-1}.[4] We also found that R–C–X (R = $PhOCH_2$, Me_3CCH_2, cyclopropyl and cyclobutyl; X = Cl or F) reacted with pyridine with k_y *ca.* 10^8–10^{10} dm^3 mol^{-1} s^{-1}.[5]

The many reports of extraordinarily rapid ylide formation tend to obscure the fact that selectivity can be observed in these reactions. For example, there is an 8-fold rate retardation, probably steric in origin, for the reactions of 2,2-dimethylcyclopropylchlorocarbene ($k_y = 4.7 \times 10^7$ dm^3 mol^{-1} s^{-1})[6] *versus* cyclopropylchlorocarbene ($k_y = 3.6 \times 10^8$ dm^3 mol^{-1} s^{-1})[7] with pyridine. More impressively, although the analogous reactions of the dialkylcarbenes, bicyclo[2.1.1]hexan-2-ylidene[8] and homocuban-9-ylidene,[9] exhibit $k_y \geqslant 10^9$ dm^3 mol^{-1} s^{-1}, that of adamantanylidene is, for unknown reasons, extraordinarily slow, $k_y = 1.5 \times 10^6$ dm^3 mol^{-1} s^{-1}.[10]

Now, we report our findings with a series of oxycarbenes that expand the dynamic range of carbene–pyridine ylide-forming reactions down to 1×10^5 dm^3 mol^{-1} s^{-1}. The reactivity of these carbenes is in qualitative accord with expectations based on frontier molecular orbital theory.

The carbenes, listed in Table 1, were generated by LFP of diazirines that were either previously available, or were prepared by Graham oxidations[11] of amidines or isoureas, followed as necessary by exchange reactions[12] with alkoxides or other nucleophiles. LFP irradiation[13] at 351 nm and 23–25 °C of pentane (isooctane) or MeCN solutions of the diazirines in the presence of varying concentrations of pyridine gave rise to pyridinium ylides. The observed rate constants for ylide growth were linear in [pyridine], affording k_y [eqn. (1)]. For each carbene, Table 1 collects λ_{max} (or λ_{obs}) of the ylide, the concentration range of pyridine, and k_y.

Platz and Jones found that k_y is relatively insensitive to solvent polarity,[14] and the comparisons of k_y in hydrocarbon or MeCN available in Table 1 support this conclusion, although k_y is 1–2.9 times greater in hydrocarbon than in MeCN. Apparently, the carbenes themselves are somewhat more stabilized by hydrocarbon–polar solvent 'transfer' than are the (presumably) polar transition states of ylide formation. One should note, however, that in some cases (*e.g.* entries 4 and 5) so much pyridine must be added to the hydrocarbon solvent to trap the carbene that the solvent is nearly half pyridine, and its polarity is enhanced accordingly.

The data in Table 1 indicate that the normally nucleophi-

Table 1 Kinetics of the reactions of carbenes with pyridine

			Hydrocarbon		MeCN		
Entry	Carbene	λ_{max}/nm[a]	[py]/ mmol dm^{-3} [b]	k_y/s^{-1} [c]	[py]/ mmol dm^{-3} [b]	k_y/s^{-1} [c]	Ref.[d]
1	MeC–OMe	380	5.5–6.7 (×10³)	6.6×10^5			16
2	MeC–OCH_2CF_3	380	183–476	1.6×10^7	260–2060	6.6×10^6	*e*
3	CHC–OMe[f]	*g*	3.1 (×10³)	($\leqslant 10^5$)[g]			15
4	CHC–OCH_2CF_3[f]	385	1127–2480	1.0×10^6	1329–3543	3.4×10^5	*e*
5	PhC–OMe	480	2060–10 590	1.2×10^5	2060–10 300	1.2×10^5	13
6	PhC–OCH_2CF_3	465	353–5300	1.8×10^6	353–5300	1.4×10^6	*e*
7	PhC–OAc	480	12.2–58.9	3.5×10^7	24.7–91.6	2.0×10^7	21
8	ClC–OMe	472[h]		—	2810–5620	9.0×10^5	11
9	ClC–OCH_2CF_3	400[h]		—	62–360	2.8×10^7	*e*
10	$PhOCH_2C$–OCH_2CF_3	390[h]	2.45–11.8	8.6×10^8		*h*	20
11	$PhOCH_2C$–OAc	390	1.87–6.24	1.0×10^9	1.98–9.52	6.4×10^8	21
12	$PhOCH_2C$–F[g]	380	0.20–1.0	1.4×10^{10}			5
13	$PhOCH_2C$–Cl[g]	380	0.40–3.0	1.2×10^{10}			5
14	PhC–F	460	0.31–3.3	1.5×10^9	1.22–6.80	9.5×10^8	26
15	PhC–Cl	480	0.61–3.6	1.5×10^9[j]	1.22–6.15	5.9×10^8	11
16	PhC–Br	480	0.615–4.75	1.2×10^9	0.615–9.16	5.2×10^8	11

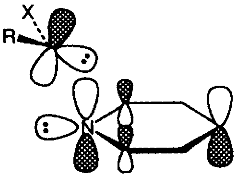
[a] λ_{max} in pentane or isooctane; λ_{obs} in MeCN. [b] Range of pyridine concentration used in kinetic runs. [c] Rate constant for pyridinium ylide formation at ambient temp.; errors are *ca.* ±10%. [d] Reference to precursor diazirine preparation. [e] This work. [f] C_3H_5 = cyclopropyl. [g] The ylide could not be detected; the reaction was too slow relative to competing processes. [h] The ylide was unstable. [i] Data at −32 °C. [j] Platz *et al.* report $k_y = 3.3 \times 10^8$ or 7.6×10^8 in hydrocarbon,[1,14] and 3.9×10^8 in MeCN.

lic,[13,15–17] stabilized[18] oxycarbenes react with pyridine several orders of magnitude more slowly than comparable halocarbenes; comparison of entries 3, 5 and 1 with 14–16 gives the reactivity sequence C_3H_5C–OMe (C_3H_5 = cyclopropyl) < PhC–OMe < MeC–OMe ≪ PhC–Hal. Similarly, ClC–OMe (entry 8) reacts with pyridine *ca.* 8000 times more slowly than CCl_2 ($k_y = 7.9 \times 10^9$ dm^3 mol^{-1} s^{-1}).[19]

Within the oxycarbene family, modulation of the reactivity can be acheived by modifying the oxy substituent. The trifluoroethoxycarbenes, for example, are 15–30 times more reactive than comparable methoxycarbenes because the CF_3CH_2O substituent is a poorer electron donor than MeO[20] (compare entries 2 *vs.* 1, 4 *vs.* 3, 6 *vs.* 5, and 9 *vs.* 8). Further decreases in oxy substituent potency with concomitant increases in k_y can be seen with PhC–OAc[21] (entry 7 *vs.* 6 or 5) and PhC–$OSiMe_3$ (k_y *ca.* 10^8 dm^3 mol^{-1} s^{-1}).[22]† Related, but compressed trends can be discerned amongst even the very reactive alkylcarbenes; *cf.* entries 10–13.

In terms of frontier molecular orbital theory,[17,18] the ylide-forming reactions of RC–X with pyridine involve both 'electrophilic' orbital interactions (**E**, carbene p–pyridine σ) and 'nucleophilic' orbital interactions (**N**, pyridine π*–carbene σ). From the charge distribution of the product ylide, we might expect the **E** term to dominate in the transition state for phenylhalocarbenes. Indeed, electron-withdrawing substituents in XC_6H_4CCl enhance carbenic reactivity towards pyridine[14,23] (Hammett $\rho = +1.5$[23]). However, the differential orbital energies[17,18] corresponding to the **E** and **N** interactions of (*e.g.*) PhC–F[13] and pyridine[24] are equal ($\Delta\varepsilon_E$ *ca.* 11.2 eV, $\Delta\varepsilon_N$ *ca.* 11.1 eV), so that, neglecting orbital overlap, the nucleophilic component of the PhC–F/pyridine transition state is comparable to the electrophilic component.

For the nucleophilic carbenes, MeC–OMe and PhC–OMe, $\Delta\varepsilon_N$ (both 10.3 eV) is more favourable than $\Delta\varepsilon_E$ (13.7 and 12.1 eV, respectively), so that the transition states for these carbenes' reactions with pyridine should feature extensive carbene σ-electron donation into (*e.g.*) the π_5^* orbital of pyridine,[24] as well as pyridine σ donation to the carbene's p orbital, possibly as in transition state **1**. (π_4^* and π_5^* of pyridine are not degenerate, but possess very similar energy levels; 2.99 and 3.01 eV, respectively.[24])



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Note that 'nucleophilic' carbenic attack on pyridine does not seem to be as effective as 'electrophilic' attack, though characterized by lower (more favourable)[17,18] values of $\Delta\varepsilon_N$ (10.3 eV). Ylide formation by MeC–OMe or PhC–OMe is >1000 times slower than the analogous reaction of PhC–F, where both $\Delta\varepsilon_E$ and $\Delta\varepsilon_N$ (11.1–11.2 eV) are higher. Clearly, *ab initio* calculations and details of orbital overlap in the transition state are needed for a more precise analysis. Meanwhile, our studies of these and related reactions continue.

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Footnote

† An exception is a glycosylidene carbene that should approximate an alkoxycarbene, yet reacts very rapidly with pyridine (k_y *ca.* 8×10^8 dm^3 mol^{-1} s^{-1}).[25]

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