

Kinetic and Theoretical Studies of the [3 + 2] Cycloadditions of Alkynyl Fischer Carbene Complexes with *N*-Alkyl Nitrones

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The 1,3-dipolar cycloadditions of alkynyl Fischer carbene complexes with nitrones to give 2,3-dihydroisoxazole carbene complexes were found to undergo first-order kinetics both for the nitrones and alkynyl carbene complexes. The effects of metals, substituents of the nitrones and complexes, and solvents were studied. The rates increased with the more electron rich nitrones and less electron rich metal complexes. Ab initio theoretical calculations supported that the HOMO of nitrones and the LUMO of carbene complexes were the interacting frontier molecular orbitals. Only little dependence of solvent was observed, and therefore a concerted pathway is more likely.

Introduction

The [3 + 2] cycloaddition reactions of 1,3-dipoles have been intensely investigated in the last two decades,¹ and their importance in natural product synthesis has been thoroughly established.² α,β -Unsaturated Fischer carbene complexes have recently been found to undergo rapid and highly regioselective [4 + 2]³ and [2 + 2]⁴ cycloaddition reactions with a variety of dienes and alkenes, respectively. However, there are only a few examples of [3 + 2] cycloaddition of Fischer carbene complexes with 1,3-dipoles.⁵ It has been shown that the reaction of phenylethynylcarbene complexes with CH₂N₂ leads to competing reactions involving the formation of pyrazolylcarbene and *N*-pyrazolyl complexes in an overall low yield.⁶ However, with the same 1,3-dipole containing a TMS group, Me₃SiCHN₂, phenylethynylcarbene complexes give high yields of pyrazolylcarbene complexes in a highly regioselective and rate-enhancing manner compared to the analogues of organic esters with the carbene fragments replaced by an oxygen atom.⁷ Kalinin et al. found that another 1,3-dipole, α,N -diphenyl nitron,

undergoes [3 + 2] cycloaddition with trimethylsilyl ethynylcarbene complexes to yield oxazoline carbene complexes in low to moderate yields (accompanied with ca. 30% of unreacted carbene complexes).⁸ Recently, we reported the chemoselective and regioselective 1,3-dipolar cycloaddition of alkynyl Fischer carbene complexes with α -phenyl *N*-*tert*-butyl nitrones (PBN) to give essentially a quantitative yield of 2,3-dihydroisoxazole carbene complexes at room temperature.⁹

The detailed quantitative mechanistic aspects of this cycloaddition remains unaddressed. Since kinetic studies of cycloadditions often yield important insights into the mechanism of the reactions with special regard to the concertedness of the reaction, we therefore have undertaken kinetic studies and theoretical calculations on the cycloaddition reaction of nitrones with alkynyl carbene complexes and now report our results here.

Results and Discussion

Kinetic experiments on reaction 1 were carried out spectrophotometrically at constant temperature within 0.2 °C. Reaction 1 was accompanied by characteristic changes in the MLCT bands and exhibited clean isobestic points for at least 3 half-lives. Typically, [complex]

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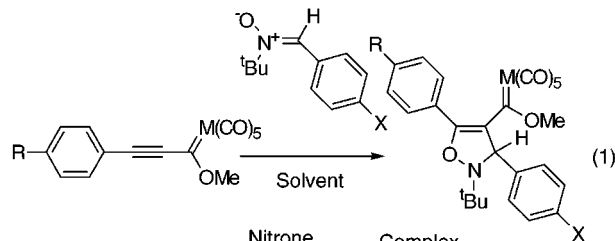
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	Nitron	Complex
1	R = H, M = Cr	x = Me ₂ N, 4a
2	R = H, M = W	MeO, 4b
3	R = Me, M = W	Me, 4c
	H, 4d	R = H, M = Cr, X = H, 5a
	Br, 4e	R = H, M = W
	Cl, 4f	x = Me ₂ N, 6a ; MeO, 6b ;
	NO ₂ , 4g	Me, 6c ; H, 6d ;
		Br, 6e ; Cl, 6f ;
		NO ₂ , 6g
		R = Me, M = W, X = H, 7a

= 6.0 × 10⁻⁵ M, and an at least 10-fold excess of nitron was used in order to establish pseudo-first-order condi-

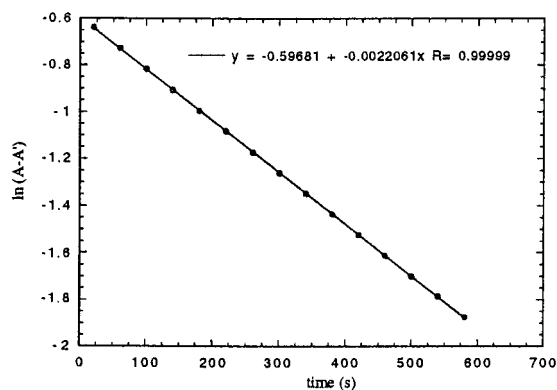


Figure 1. First-order plot of reaction of **2** with **4d** in acetone at 34.2 °C.

Table 1. Determination of Reaction Order from Pseudo-First-Order Rate Constants using **2** with **4d**^a

[4d] _{initial} (10 ⁻⁴ M)	k _{obs} (10 ⁻⁴ s ⁻¹)	k (M ⁻¹ s ⁻¹)
6.3	1.33	0.21
12.0	2.86	0.24
30.0	6.93	0.23
60.0	13.70	0.23

^a [**2**]_{initial} = 6.0 × 10⁻⁵ M in THF at 24.7 °C.

tions. Wavelengths where maximum absorbance changes (λ_{\max}) occurred (λ_{\max} for **1** = 502 nm and λ_{\max} for **2** and **3** = 486 nm) were monitored for at least 3-half-lives. Then the collected kinetic data were treated with Guggenheim's method.¹⁰ By plotting $\ln(A - A_{t+\Delta})$ vs t (where A is absorbance at time t , $A_{t+\Delta}$ is the absorbance at time $t + \Delta$, and Δ is a period two to three times as great as the half-life period of the reaction), a linear pseudo-first-order plot with slope equal to k_{obs} was obtained for the reaction (e.g., reaction of **2** with **4d**), and hence the reaction was first-order with respect to complex (Figure 1).

Experiments were repeated at several nitrene concentrations, and from the pseudo-first-order plots, the pseudo-first-order rate constants were then determined. These data are shown in Table 1. The rate equation is now, $\text{rate} = k_{\text{obs}}[\text{complex}]$, $k_{\text{obs}} = k[\text{nitrene}]^n$. The third column of Table 1 lists the quotient $k_{\text{obs}}/[\text{nitrene}]_{\text{initial}}$, whose constancy shows that $n = 1$. Therefore, the cycloaddition is a bimolecular one, and the rate equation may be written as:

$$\text{rate} = k[\text{complex}][\text{nitrene}]$$

Similarly, the rate constants for other reactions were measured.

The activation parameters were determined by the temperature dependence of rate constants using the Eyring plot encompassing the temperature range from 14.2 to 44.2 °C, and the data are listed in Table 2. The small values of enthalpies, ΔH^\ddagger (between 19 and 34 kJ mol⁻¹) and large negative activation entropies, ΔS^\ddagger (-146 to -174 J K⁻¹mol⁻¹) (Table 2) indicate the reaction between a carbene complex and a nitrene goes through a highly structured or polar transition state.

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Substituent Effect on Nitrene. The data shown in Table 3 demonstrates that the reactions were accelerated by the electron rich substituents in nitrenes. This observation can be explained according to the Frontier Molecular Orbital Theory (FMO).¹ The electron rich nitrene raises the HOMO energy level, decreases the energy gap of the cycloaddition between that of nitrene and carbene complex, and consequently accelerates the reaction. A Hammett linear free energy treatment of the data (Table 3) gives a ρ value of -3.15 (coefficient of correlation, $R = 0.9191$) using σ_p^0 constants and a ρ^+ value of -1.19 (Figure 2, $R = 0.9839$) using σ_p^+ constant (Figure 2). It was found that R for σ_p^+ plot was larger than that of σ_p^0 plot. It implies that the reaction may involve an enhanced resonance transition state. The magnitude of ρ^+ obtained from the Hammett plot (-1.19) is quite different from those observed for typical ionic processes (-3.3 to -4.3)¹² and is comparable with other concerted [3 + 2] cycloaddition.¹³

Substituent Effect on Carbene Complex. The substituent effect on the carbene complex was briefly investigated. The methyl-substituted W complex **3** ($k = 1.18 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$) was found about 50% slower than the unsubstituted W complex **2** ($k = 2.27 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$) in the reactions with **4d** (Table 2). The electron-donating methyl group may raise the LUMO energy level of the complex to enlarge the energy gap of cycloaddition and therefore slow down the reaction.

Solvent Effect. Reaction of **2** with **4d** was examined in several solvents (Table 2). The observed rate constants did not exhibit a large significant solvent dependence, at the most a factor of 4. This supports that there is not a larger charge separation in the activated complex than in the reactants, so the reaction probably goes through one-step, polar, concerted pathway as suggested in the Hammett plot of the substituent effect of nitrenes.

Metal Effect on Carbene Complex. The data in Table 1 demonstrate that the reactivity of carbene complexes **2** ($22.7 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$) is 2.9 times faster than **1** ($7.7 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$) at 25 °C. This metal effect has also been observed in the [2 + 2] cycloaddition of alkynyl carbene complex with dihydropyran with the rate of W complex faster than that of Cr by 1.6 times.¹³

Theoretical Calculations. The HOMO and LUMO energies of substituted α -phenyl *N*-methyl nitrenes (PMN) as substitutes for PBN and methyl propiolate were calculated by ab initio method with basis set 3-21G using Gaussian 90 program¹⁴ on an IBM-RS6000 workstation (Table 4). It should be noted that kinetic studies of cycloaddition of tungsten complex **2** with PMN were not carried out since they were not clean enough to observe any isosbestic point, probably due to the fast decomposition of the thermal labile cycloadduct.^{9b} The HOMO and LUMO energies of PMN increase systematically except for that of the dimethylamino group, which shows a

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Table 2. Rate Constants and Activation Parameters of Cycloaddition Reactions

complex	X-PBN	temp (°C)	solvent	k ($10^{-4} \text{ M}^{-1} \text{ s}^{-1}$)	ΔH^\ddagger (kJ mol $^{-1}$)	ΔS^\ddagger (J mol $^{-1} \text{ K}^{-1}$)	ΔG_{498}^\ddagger (kJ mol $^{-1}$)
2	Me ₂ N (4a)	14.2	THF	93700	19.5	-158.2	66.6
		24.7		137000			
		34.2		154000			
		43.4		231000			
	MeO (4b)	14.8		6340	26.9	-154.7	73.0
		24.7		10100			
		34.7		14400			
		44.2		20100			
	Me (4c)	14.7		2480	31.9	-145.1	75.1
		24.7		4370			
		34.7		6340			
		44.2		9700			
	H (4d)	14.7		1370	31.2	-152.5	76.6
		24.7		2270			
		34.9		3640			
		44.2		5030			
	Br (4e)	15.1		390	30.0	-167.3	79.9
		24.7		673			
		34.0		960			
		43.7		1320			
	Cl (4f)	15.1		394	31.5	-161.8	79.7
		24.7		684			
		34.0		969			
		43.5		1420			
NO ₂ (4g)	15.0	34	33.9	-174.3	85.8		
	24.7	57					
	33.8	88					
	43.5	123					
H (4d)	15.2	1180	30.4	-157.1	77.2		
	24.7	1810					
	33.9	2660					
	43.5	4040					
H (4d)	15.2	2210	31.8	-146.8	75.5		
	44.7	3510					
	34.4	5380					
	43.4	7930					
H (4d)	15.3	1880	34.3	-146.5	76.0		
	24.7	3080					
	34.0	4460					
	43.7	7040					
1	H (4d)	15.1	THF	499	32.8	-156.0	79.3
		24.7		770			
		34.0		1220			
		43.7		1870			
3	H (4d)	15.2	THF	726	31.8	-156.1	78.3
		24.8		1180			
		33.8		1770			
		43.2		2570			

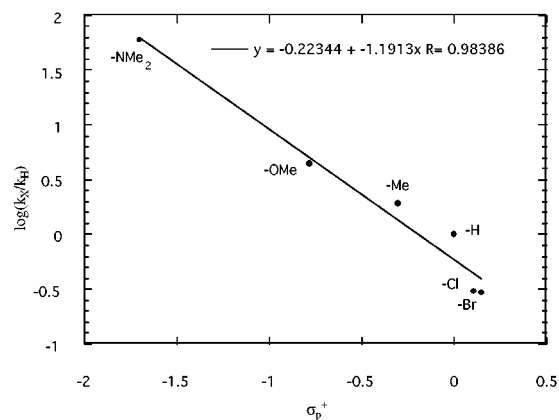
Table 3. Substituent Effect on Nitron (reaction of **2 with **4a–g**)**

nitron	X	σ_p^{0a}	σ_p^{+a}	k ($10^{-3} \text{ M}^{-1} \text{ s}^{-1}$)
4a	Me ₂ N	-0.32	-1.7	13700
4b	MeO	-0.12	-0.78	1010
4c	Me	-0.14	-0.3	440
4d	H	0	0	230
4e	Br	0.26	0.15	67
4f	Cl	0.34	0.11	68
4g	NO ₂	0.81	—	6

^a From ref 11.

deviation from the linear correlation of Hammett constants. Since the rate of the cycloaddition increases with electron-donating nitrones, it is reasonable to conclude that the HOMO of the nitrones are the frontier orbitals.

Scheme 1 demonstrates the results of theoretical calculations^{15,16} of the three given compounds and the

**Figure 2.** Plot of $\log(k_X/k_H)$ versus σ_p^+ for reaction of **2** with substituted PBN.

cycloaddition processes of the chromium carbene complex¹⁶ and its organic ester analogue¹⁵ with the *N*-methyl nitron (PMN) in an attempt to understand the cycloaddition. Both of the dipolarophiles adapt their LUMO to

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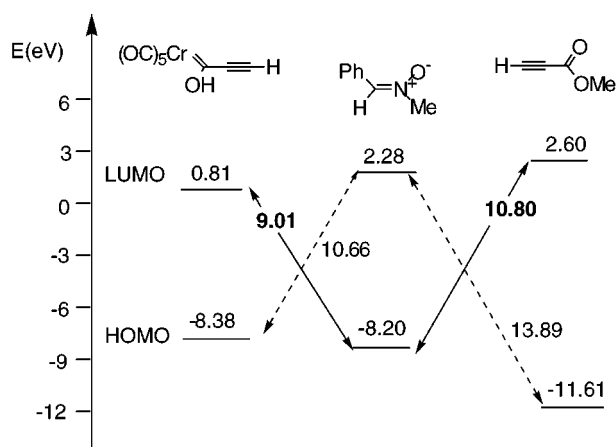
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Table 4. HOMO and LUMO Energies of PMN, Calculated by ab Initio Method (Basis Set: 3-21G) Using Gaussian 90 Program

X-PMN	σ_p^+ ^a	HOMO (eV)	LUMO (eV)
Me ₂ N (6a)	-1.70	-8.073	2.339
MeO (6b)	-0.78	-7.821	2.505
Me (6c)	-0.30	-8.025	2.360
H (6d)	0.00	-8.198	2.275
Br (6e)	0.15	-8.347	1.968
Cl (6f)	0.11	-8.514	1.883

^a From ref 11.

Scheme 1. Frontier Orbital Energies Relationships of Reactants



interact with HOMO of PMN, as the energy differences are smaller than the LUMO of the dipoles and the HOMO of the dipolarphiles. The energy gap between the carbene complex and PMN is 9.01 eV, while that between the organic ester and PMN is 10.80 eV. The energy gap for

carbene complex is 1.71 eV (equivalent to 154 kJ mol⁻¹) smaller than that for the organic ester analogue. The smaller energy gap of cycloaddition of carbene complex with PMN supports its rate enhancement over the organic ester analogue.^{3,7,9}

Conclusion

Alkynyl Fischer carbene complexes have been demonstrated to undergo polar, concerted [3 + 2] cycloaddition with *N*-alkyl nitrones to give 2,3-dihydroisoxazole carbene complexes. The reactions have been found to be controlled by HOMO (nitron)–LUMO (carbene complex) interaction both theoretically and experimentally.

Experimental Section

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Kinetic measurements were performed on a spectrophotometer equipped with a temperature controller. The temperature was measured with a digital thermometer (± 0.1 °C) with type K thermal couple wire. The solvents used, hexane (CaH₂), THF (Na/benzophenone ketyl), acetone (K₂CO₃) and acetonitrile (CaH₂), were distilled prior to use. All the solvents and stock solutions were deoxygenated by the freeze–pump–thaw method (–195 to 45 °C, at least five cycles). Reactants were transferred inside a drybox to a Schlenk type UV-cuvette. The progress of reaction was monitored spectrophotometrically. The rate constants were calculated using the computer program KaleidaGraph to find out the slopes of best linear straight lines. The rate constants and activation parameters were within 10% error.

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