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

Ming Lok Yeung,† Wai-Kee Li,† Hui-Jean Liu,‡ Yu Wang,‡ and Kin Shing Chan*,†

Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong and Department of Chemistry, National Taiwan University, Taipei, Taiwan, ROC

Received March 2, 1998

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, substitutents 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 regionelective $[4 + 2]^3$ 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 nitrone,

† The Chinese University of Hong Kong.

[‡] National Taiwan University.

undergoes [3 + 2] cycloaddition with trimethylsilylethynylcarbene complexes to yield oxazoline carbene complexes in low to moderate yields (accompanied with ca. 30% of unreacted carbene complexes). 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.

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 alknyl 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 isosbestic points for at least 3 half-lives. Typically, [complex]

 $=6.0\times10^{-5}$ M, and an at least 10-fold excess of nitrone was used in order to establish pseudo-first-order condi-

⁽¹⁾ Padwa, A. 1,3 Dipolar Čycloaddition Chemistry, Wiley-Interscience: New York, 1984; Vols. 1 and 4.

⁽²⁾ Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P.; Eds. *Natural Products Synthesis Through Pericyclic Reactions*, American Chemical Society: Washington, DC, 1983.

^{(3) (}a) Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1983**, *105*, 6746. (b) Wulff, W. D.; Yang, D. C. *J. Am. Chem. Soc.* **1984**, *106*, 7565. (c) Dotz, K. H.; Kuhn, W. *J. Organomet. Chem.* **1985**, *486*, C43. (d) Wulff, W. D.; Tang, P. C.; Chan, K. S. McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813. (e) Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 7418. (f) Bao, J.; Dragisich, V.; Wenglowsky, S.; Wulff, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 9873. (4) (a) Faron, K. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1988**, *110*, 8747.

^{(4) (}a) Faron, K. L.; Wulff, W. D. J. Am. Chem. Soc. 1988, 110, 8747. (b) Camps, F.; Moreto, J. M.; Ricart, S.; Vinas, J. M.; Molins, E.; Miravitlles, C. J. Chem. Soc., Chem. Commun. 1989, 1560. (c) Faron, K. L.; Wulff, W. D. J. Am. Chem. Soc. 1990, 114, 6419. (d) Camps, F.; Llebaria, M. G.; Moreto, J. M.; Ricart, S.; Vinas, J. M. Tetrahedron Lett. 1990, 31, 4479. (e) de Meijere, A.; Wessjohann, L. Synlett. 1990, 40. (f) Merlic, C. A.; Xu. D. J. Am. Chem. Soc. 1991, 113, 7418. (g) Pipoh, R.; van Eldik, R.; Wulff, W. D.; Wang, S. L. B. Organometallics 1994, 11, 490.

⁽⁵⁾ For leading reference: Barluenga, J.; Fernandez-Mari, F.; Argimiro, L. V.; Aguilar, E.; Olano, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2267.

⁽⁶⁾ Kreissl, F. R.; Fischer, E. O.; Kreiter, C. G. *J. Organomet. Chem.* **1973**, *57*, C9.

⁽⁷⁾ Chan, K. S.; Wulff, W. D. J. Am. Chem. Soc. 1986, 108, 5229.

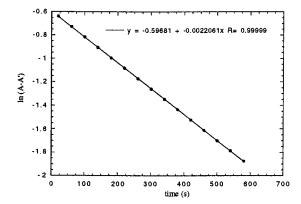


Figure 1. First-order plot of reaction of **2** with **4d** in acteone at 34.2 °C.

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

$[{f 4d}]_{initial} \ (10^{-4} { m M})$	$k_{\rm obs}~(10^{-4}~{\rm s}^{-1})$	$k (\mathrm{M}^{-1} \; \mathrm{s}^{-1})$
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 $\mathbf{1} = 502$ nm and λ_{max} for $\mathbf{2}$ and $\mathbf{3}$ = 486 nm) were monitored for at least 3-half-lives. Then the collected kinetic data were treated with Guggenheim's method. 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-firstorder plot with slope equal to $k_{\rm obs}$ was obtained for the reaction (e.g., reaction of 2 with 4d), and hence the reaction was first-order with respect to complex (Figure

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

rate = k[complex][nitrone]

Similarly, the rate constants for other reactions were measured.

The activation parameters were determined by the temperature dependence of rate constants using the Erying 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^{\dagger} (between 19 and 34 kJ mol⁻¹) and large negative activation entropies, ΔS^{\dagger} (-146 to -174 J K⁻¹mol⁻¹) (Table 2) indicate the reaction between a carbene complex and a nitrone goes through a highly structured or polar transition state.

Substituent Effect on Nitrone. The data shown in Table 3 demonstrates that the reactions were accelerated by the electron rich substituents in nitrones. This observation can be explained according to the Frontier Molecular Orbital Theory (FMO).1 The electron rich nitrone raises the HOMO energy level, decreases the energy gap of the cycloaddition between that of nitrone 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 $\sigma_{\rm p}{}^{\rm o}$ 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 $(-3.3 \text{ to } -4.3)^{12}$ 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 = $1.18\times 10^{-2}\ M^{-1}\ s^{-1)}$ was found about 50% slower than the unsubstituted W complex 2 ($k = 2.27 \times 10^{-2} \text{ M}^{-1}$ s⁻¹)in the reactions with **4d** (Table 2). The electrondonating 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 substitutent effect of nitrones.

Metal Effect on Carbene Complex. The data in Table 1 demonstrate that the reactivity of carbene complexes 2 (22.7 \times 10⁻² M⁻¹ 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 nitrones (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

⁽⁸⁾ Kalinin, V. N.; Shilova, O. S.; Kovredov, A. I.; Petrovskii, P. V.; Batsanov, A. S.; Struchkov, Y. T. Organomet. Chem. USSR 1989, 4

^{(9) (}a) Chan, K. S. J. Chem. Soc., Perkin Trans. 1 1991, 2602. (b) Chan, K. S. Yeung, M. L.; Chan, W.-K.; Wang, R.-J.; Mak, T. C. W. J. Org. Chem. 1995, 60, 1741.

⁽¹⁰⁾ Frost, A.; Pearson R. G. Kinetics and Mechanism; John Wiley & Sons: New York, 1961; p 49.

⁽¹¹⁾ Exner, O. Chapter 10 of *Prog. Phys. Org. Chem.* **1973**, *10*, 1. (12) Baldwin J. E.; Kapecki, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 8 and references there in.

⁽¹³⁾ Pipoh, R.; van Eldik, R.; Wulff, W. D.; Wang, S. L. B. Organometallics 1992, 11, 490.

⁽¹⁴⁾ Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schelgel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; DeFrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. GAUSSIAN 90, Gaussian Inc., Pittsburgh, PA,

Table 2. Rate Constants and Activation Parameters of Cyclcoaddition Reactions

Table 2. Rate Constants and Activation Parameters of Cyclcoaddition Reactions							
complex	X-PBN	temp (°C)	solvent	$^{k}_{(10^{-4}\mathrm{M}^{-1}\;\mathrm{s}^{-1})}$	ΔH^{\sharp} (kJ mol ⁻¹)	ΔS^{\ddagger} (J mol $^{-1}$ K $^{-1}$)	ΔG^{\sharp}_{498} (kJ mol ⁻¹)
2 Me ₂ N (4a)	14.2	THF	93700	19.5	-158.2	66.6	
	2 (2)	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
	Di (IC)	24.7		673	00.0	107.0	70.0
		34.0		960			
		43.7		1320			
	Cl (4f)	15.1		394	31.5	-161.8	79.7
	OI (II)	24.7		684	01.0	101.0	70.7
		34.0		969			
		43.5		1420			
	NO_2 (4g)	15.0		34	33.9	-174.3	85.8
	110 ₂ (4g)	24.7		57	33.3	174.5	00.0
		33.8		88			
		43.5		123			
	H (4d)	15.2	hexane	1180	30.4	-157.1	77.2
	11 (40)	24.7	пехапе	1810	30.4	137.1	11.2
H (4d)		33.9		2660			
		43.5		4040			
	П (49)	15.2	acetone	2210	31.8	-146.8	75.5
	11 (4u)	44.7	acetone	3510	31.0	-140.6	75.5
		34.4		5380			
	34.4 43.4		7930				
	45.4 15.3	CH ₃ CN	1880	34.3	-146.5	76.0	
	П (40)	24.7	CH ₃ CN	3080	34.3	-140.5	70.0
			4460				
	34.0		7040				
	II (4.3)	43.7	TITE		20.0	1500	70.9
1	H (4d)	15.1	THF	499	32.8	-156.0	79.3
		24.7		770			
		34.0		1220			
	TT (4 T)	43.7	TO THE	1870	01.0	150 4	70.0
3	H (4d)	15.2	THF	726	31.8	-156.1	78.3
		24.8		1180			
		33.8		1770			
	43.2		2570				

Table 3. Substitutent Effect on Nitrone (reaction of 2 with 4a-g)

with 4a g)				
nitrone	X	$\sigma_{\rm p}{}^{\rm o}$ a	σ_{p}^{+} a	$k (10^{-3} \mathrm{M}^{-1} \mathrm{s}^{-1})$
4a	Me_2N	-0.32	-1.7	13700
4b	MeO	-0.12	-0.78	1010
4c	Me	-0.14	-0.3	440
4d	Н	0	0	230
4e	\mathbf{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

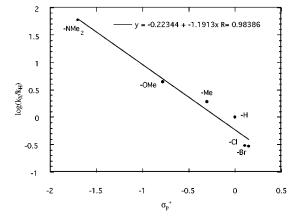


Figure 2. Plot of $\log(k_{\rm X}/k_{\rm H})$ verse $\sigma_{\rm p}^{+}$ for reaction of **2** with substituted PBN.

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

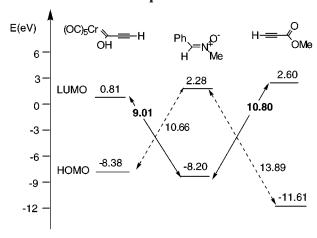
⁽¹⁵⁾ Liu, H. J. M. Philos. Doctoral, Deformation Electron Density Study of Ficher Carbene Complex. National Taiwan University, 1991. (16) Wang, C.-C.; Wang, Y.; Liu, H.-J.; Lin, K.-J.; Chou, L.-K.; Chan, K. S. *J. Phys. Chem. A* **1997**, *101* (47), 8887.

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

X-PMN	$\sigma_{ m p}^{+\;a}$	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 (nitrone)-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.

Acknowledgment. We thank the Research Grants Council of Hong Kong (CUHK 88/93E) for financial support.

JO9803840