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FACTORS CONTROLLING C=C VS. C=O ATTACK IN CYCLOADDITION OF A 1,3-DIENE TO AN AMBIDENT DIENOPHILE. DIELS-ALDER REACTION OF 2-PHENYL-Δ^2-PYRROLINE-4,5-DIONES (1)

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The [4+2] cycloaddition using an enone as a dienophile is on a balance with the normal C=C attack (ene-addition) and the unusual C=O attack (one-addition) of a diene. Steric hindrance on the C=C (caused by such phenomena as restricted free rotation of the substituent on C=C) retards the C=C attack, thus increasing the ratio of one-addition. Lewis acids greatly increase not only the reactivity of C=O but also the ratio of one-addition.

KEYWORDS —— 1-methoxy-3-trimethylsilyloxybutadiene; Diels-Alder reaction; dioxopyrroline; ambident dienophile; ene-addition; one-addition; steric hindrance; Lewis acid

It was recently suggested that enones are inherently ambident as dienophiles in Diels-Alder reaction.2) As particular examples, thermal cycloaddition of silyloxydienes to dioxopyrrolines (an enone system) exclusively takes place at C=O (one-addition) for a benzazepinopyrrolinedione (2), while normal C=C attack (ene-addition) occurs for an isoquinolinopyrrolinediones (1). The change of reactive site in the former compound was attributed to the aromatic ring being prohibited from taking coplanarity with the C=C of the dioxopyrroline ring, for conformational reasons, and thus interfering with the approach of the diene to C=C.2)

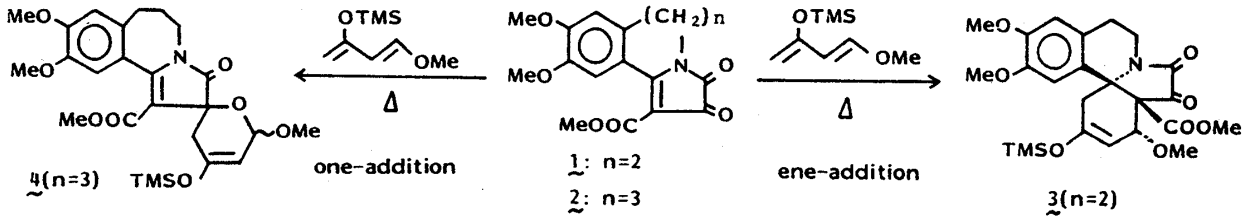


Chart 1

The above reported evidence suggests that steric hindrance on the C=C of an enone is one of the major factors controlling the ambidentness of a dienophile. Here we treat retardation of the C=C attack in connection with the degree of steric hindrance (though qualitative), and also discuss another factor that would accelerate the C=O attack of a diene.

In order to clarify the factor of steric hindrance we chose six 3-ethoxycarbonyl-Δ^2-pyrroline-4,5-diones with N-substituents of various bulkiness (5a-f)[3] and examined their cycloaddition reaction to 1-methoxy-3-trimethylsilyloxybutadiene. The UV spectra of 5a-f (Fig.) clearly show that conjugation of the phenyl group and the dioxopyrroline ring depends largely on the bulkiness of the N-substituents. The conjugation is more strictly prohibited by the compounds of bulkier N-subsituents. The degree of restriction of free rotation of phenyl, and thus the non-coplanarity of Ph with C=C, can be qualitatively estimated from the intensity of the absorption band at 280 nm.

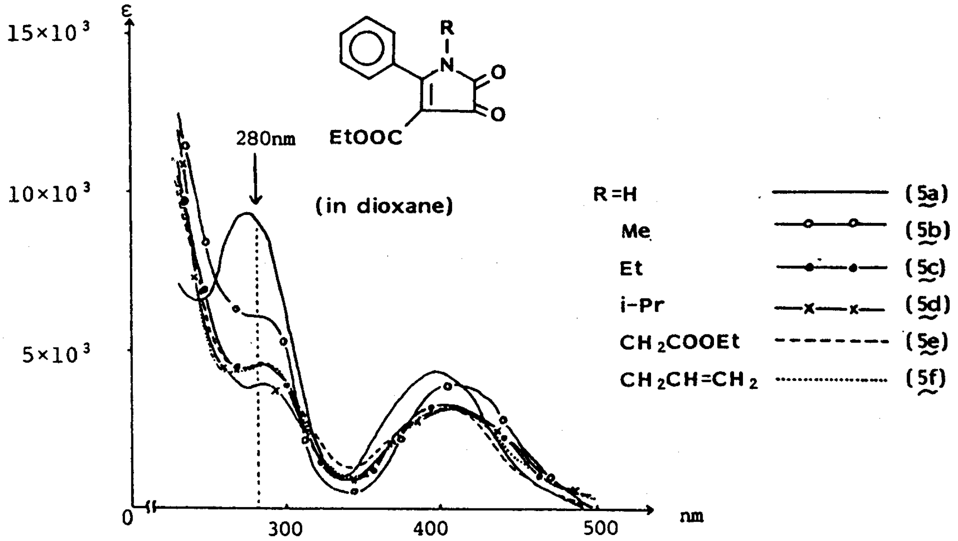


Fig. UV Spectra of 3-Ethoxycarbonyl-2-phenyl-Δ^2-pyrroline-4,5-diones (5a-f)

The thermal cycloaddition reaction and the product analyses were done as follows, the results being summarized in Tables 1 and 2. Solutions of the dioxopyrrolines (5a-f) and the diene (5 eq.) in toluene were heated at 130°C for 10-30 min in a sealed tube. The ene-adducts (6a-b) were crystallized when the reaction mixtures were triturated with n-hexane-ether and obtained in pure form by filtration. The one-adducts (7) were characterized as the desilylated compounds (9 and/or 10) which were isolated after treatment of the reaction mixture (in the cases of 5e-f) or the mother liquor of 6a-b with KF in THF (at room temp.) followed by purification with medium pressure LC (silica gel, elution with AcOEt-n-hexane). The structures of the ene-adducts (6a and 6b) were confirmed by comparison with the authentic samples reported before.[4] The structures of the one-adducts (9 and 10)[5] were elucidated spectroscopically by comparing with analogous compounds derived from 4[2),6] (see Table 2).

Table 1 indicates that ene-adducts (normal adduct) predominate when the N-substituents are small and the free rotation of the phenyl is not restricted, while one-adducts are increased and predominate with the compounds of bulkier N-substituents where free rotation of the phenyl is restricted. It is clear, in the latter cases, that the phenyl group causes steric hindrance for the approach of the diene to the C=C, thus retarding the ene-addition path, since it can not be coplaner with the C=C.

Another factor that may influence the [4+2] cycloaddition reaction is the addition of a Lewis acid. Great acceleration of the reaction under catalysis of Lewis acids is very often observed,[7] and a recent study by Danishefsky et al.[8]

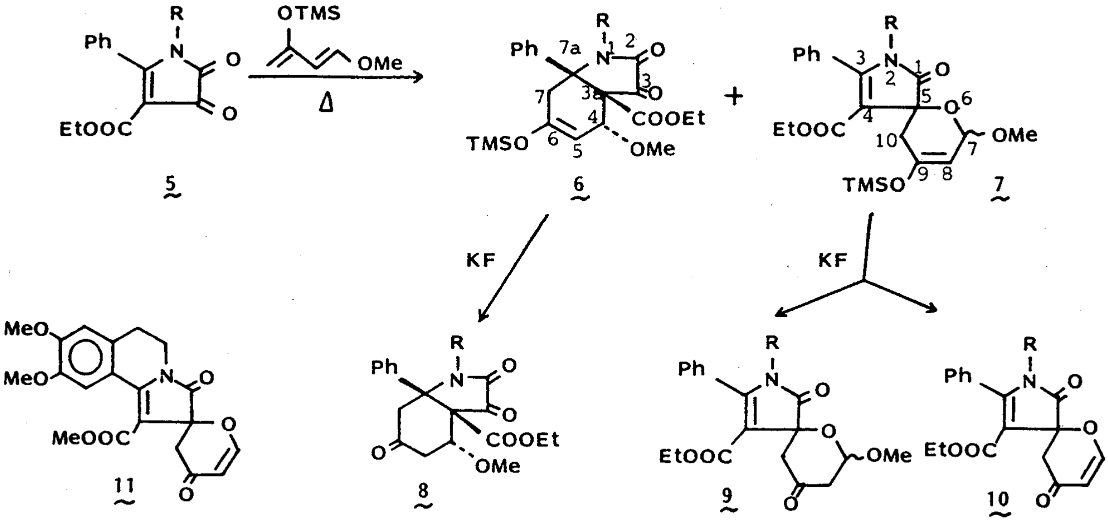


Chart 2

Table 1. [4+2]Cycloaddition Reaction of 1-Methoxy-3-trimethylsilyloxybutadiene to 2-Phenyl-Δ^2-pyrroline-4,5-diones (5a–f)

		Thermal cycloaddition (130°C)		ZnCl$_2$ Catalysed cycloaddition(r.t.)
5	R	ene-adduct (%)	one-adduct (%)	one-adduct (%)
a	H	32 { 6: 27 8^{a}(R=TMS) : 5	10 (9)	63 (10)
b	Me	63 { 6: 60 8^{b}: 3	25 { 9: 22 10: 3	68 (10)
c	Et	——	96 { 9: 68 10: 28	
d	i-Pr	——	81 (9)	
e	CH$_2$COOEt	——	71 (9)	
f	CH$_2$-CH=CH$_2$	——	57(10)	

a) 8a(R=TMS): mp168-169°C, νmax cm^{-1}(Nujol): 1750, 1740, 1725.
b) Yield given is a sum of stereoisomers at C$_4$-OMe configuration (see ref. 4b). 8b(C$_4$-αOMe): mp172-174°C, νmax cm^{-1}(Nujol): 1770, 1730, 1710. 8b(C$_4$-βOMe): mp154-155°C, νmax cm^{-1}(Nujol): 1775, 1705.

Table 2. Physical and Spectral Data of the One-adducts (9 and 10)

	R	mp	IR(cm^{-1})	UV λmax nm(ε) in EtOH
9a	H	175-177°C	1730, 1690$^{a)}$	242(10,600), 312(7,500)
9b	Me	118-121°C	1730, 1685$^{a)}$	238(sh. 6,700), 309(6,900)
9c	Et	oil	1735, 1690$^{b)}$	308(6,900)
9d	i-Pr	oil	1730, 1685$^{b)}$	309(6,700)
9e	-CH$_2$COOEt	oil	1740, 1690$^{b)}$	302(8.400)
10a	H	144-145°C	1735, 1680$^{a)}$	250(14,000), 297(7,700)
10b	Me	117-118°C	1740, 1685$^{a)}$	247(9,600), 303(6,500)
10c	Et	94-95 °C	1735, 1685$^{a)}$	250(10,000), 300(6,900)
10f	CH$_2$-CH=CH$_2$	103-104°C	1735, 1695, 1680^{a}	254(10,600), 300(7,200)

a) Nujol. b) CHCl$_3$.

suggested that Lewis acids greatly enhanced the reactivity of a carbonyl group to 1,3-dienes. We found that, in the above particular system, addition of Lewis acid not only accelerated the reaction but also completely changed the reaction path to enforce the C=O addition of the diene. The reaction of 5a and 5b and the diene (5 eq.) in CH_2Cl_2 in the presence of $ZnCl_2$ (1 eq.) rapidly proceeded at room temp. and was completed within 2 min. affording the one-adducts 10a and 10b as sole products, in 63% and 68% yield, respectively. Similarly, the isoquinolinopyrrolinedione (1) which could not be found in the non-catalysed thermal reaction produced only the one-adduct (11)[9] (in 61% yield) on reaction with the diene under catalysis with $ZnCl_2$ (1 eq.)(in CH_2Cl_2, r.t., 2 min).

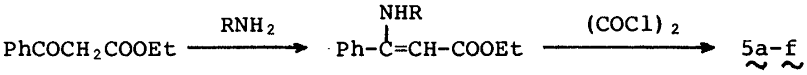
We consider that conclusions obtained from the above particular examples must be generally applicable to any [4+2] cycloadditions using an enone as a dienophile. For the system on a balance of C=C vs C=O addition, the reaction path is greatly affected and controlled by steric and electronic factors. Increase of steric hindrance on the C=C retards ene-addition. Lewis acids enforce the dienophile character of the C=O more than that of the C=C.

REFERENCES AND NOTES

1) Dioxopyrrolines XXVI. Part XXV: ref. 2.

2) Y. Tsuda, T. Ohshima, T. Sano and J. Toda, Heterocycles, 19, 2053 (1982).

3) The compounds 5a-f were prepared as follows.



$$PhCOCH_2COOEt \xrightarrow{RNH_2} Ph\text{-}\overset{NHR}{\overset{|}{C}}\text{=CH-COOEt} \xrightarrow{(COCl)_2} 5a\text{-}f$$

4) a) T. Sano, J. Toda, N. Kashiwaba, Y. Tsuda, and Y. Iitaka, Heterocycles, 16, 1151 (1981); b) Y. Tsuda, T. Ohshima, T. Sano, and J. Toda, Heterocycles, 19, 2027 (1982).

5) We consider that 9 and 10 were directly and independently produced from 7, since attempted transformation of 9 to 10 by action of SiO_2, F^-, or $ZnCl_2$ failed.

6) For example, 9b and 10b gave the following NMR data. 9b: ^{1}H-NMR δ($CDCl_3$): 5.22(1H, t, J=4 Hz, C_7-H), 3.57(3H, s, C_7-MeO), ^{13}C-NMR δ($CDCl_3$): 42.6(t, C-10), 44.9(t, C-8), 78.2(s, C-5), 100.4(d, C-7), 111.4(s, C-4), 157.2(s, C-3), 162.7(s, C-1), 176.0(s, COOEt), 202.0(s, C-9). 10b: ^{1}H-NMR δ($CDCl_3$): 5.53(d, J=6 Hz, C_8-H), ^{13}C-NMR δ($CDCl_3$): 39.6(t, C-10), 82.1(s, C-5), 106.2(d, C-8), 108.6(s, C-4), 158.8 (s, C-3), 160.0(d, C-7), 161.6(s, C-1), 174.6(s, COOEt), 189.2(s, C-9).

7) W. Carruthers, "Some Modern Methods of Organic Synthesis," p.198, 1978, Cambridge Univ. Press, Cambridge.

8) E. R. Larson and S. Danishefsky, Tetrahedron Lett., 1982, 1975. Stepwise mechanism for this cyclocondensation was suggested. Very recently change of the reactive site of enones by Lewis acid was also reported. S. Danishefsky and J.F. Kerwin. Jr., J. Org, Chem., 47, 3183 (1982).

9) 11: mp 185°C(dec.), ν_{max} cm^{-1}(Nujol): 1730, 1675, λ_{max}^{EtOH} nm(ε): 245(11,200), 289 (7,000), 360(9,000).

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