## Communication

Exo-Selectivity in the Diels-Alder Reaction of Cyclopentadiene with Activated Cyclic Dienophiles in Flexible Conformation

Kwan Soo Kim* and Yung Hyup Joo

Department of Chemistry, Yonsei University, Seoul 120-749, Korea
Received January 15, 1999

Diels-Alder reaction is one of the most widely used reactions in organic synthesis due to its versatility and its high regio- and stereoselectivity. Although the *cis* rule is quite generally followed, the *endo* addition rule appears to be obeyed only in the addition of cyclic dienes to cyclic dienophiles.[1] It is well known that activated cyclic dienophiles in the rigid *s-trans* conformation such as maleic anhydride predominantly give *endo* cycloadducts in the reactions with cyclopentadiene. On the other hand, recent studies revealed that the Diels-Alder reaction of the cyclic dienophiles containing the exocyclic double bond in the rigid *s-cis* conformation such as itaconic anhydride, α-methylene-γ-butyrolactone, and 5-methylene-1,3-dioxolan-4-ones afforded predominantly *exo* cycloadducts.[2] Conformationally unconstrained cyclic dienophiles such as 1 have not been fully explored. There have been only some scattered reports on Diels-Alder reactions of activated cyclic dienophiles in flexible conformation and their results are not consistent.[3] We have previously observed complete *exo* selectivity in the Diels-Alder reaction of cyclopentadiene with activated cyclic sugar dienophiles in the flexible conformation.[4] Therefore, we investigated the stereoselectivity of the Diels-Alder reaction between cyclopentadiene and cyclic dienophiles having flexible conformation in order to know whether the *exo* selectivity in this type of reaction is general and in the hope to get some insight on the *exo* selectivity of the reaction. Although our theoretical study based on a part of the present results was published,[5] it could not provid us clear picture for the origin of the *exo* selectivity. Moreover, the calculation failed to explain the *exo* selectivity in the reaction of cyclopentadiene with 1 and with 3. Herein we report the *exo* selective Diels-Alder reaction of cyclopentadiene with model cyclic dienophiles 1-4 and the temperature effect and Lewis acid effect on the *exo* selectivity.
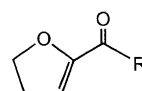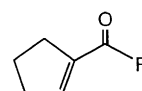

1 R = H   **3** R = H
2 R = CH$_3$ **4** R = CH$_3$

Reaction of 5-formyl-2,3-dihydrofuran (1)[6] with cyclopentadiene provided a mixture of *exo* cycloadduct **5a** and *endo* cycloadduct **5b** in 5 : 1 ratio in 71% yield at 160 °C in a sealed tube and 12 : 1 ratio in 33% yield at room temperature. On the other hand, complete *exo* selectivity was observed in the cycloaddition of 1 and cyclopentadiene in the presence of BF$_3$·OEt$_2$ at -78 °C in methylene chloride. Cycloaddition of 1 with cyclopentadiene catalyzed by Et$_2$AlCl also afforded predominantly the *exo* adduct, whereas the reaction in the presence of SnCl$_4$ provided more
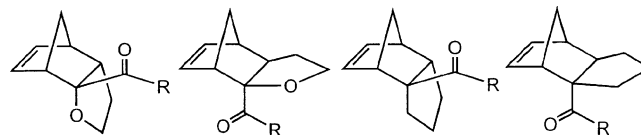
5a R = H   **5b** R = H   **7a** R = H   **7b** R = H
6a R = CH$_3$ **6b** R = CH$_3$ **8a** R = CH$_3$ **8b** R = CH$_2$

endo adduct than in the absence of the Lewis acid although the *exo* adduct were still predominant. The lower temperature appears to be favorable for the formation of *exo* adducts. The results of the cycloaddition of 1 with cyclopentadiene are summarized in entries 1-6 of Table 1. Because of the slight or substantial decomposition of reactants and products in certain cases, the *exo/endo* ratio and yield were determined at the point just before the appearance of any decomposition products. The prolonged reaction time, therefore,

Table 1. Diels-Alder Reaction of Cyclopentadiene with Cyclic Dienophiles **1** and **2**

Entry	Dieno-phile	Lewis Acid	Tempera-ture(°C)	Reaction Time[a]	Product	Ratio exo/endo	Yield (%)[b]
1	**1**		160	7 hr	**5a/5b**	5 : 1	71
2	**1**		RT	7 days	**5a/5b**	12 : 1	33
3	**1**	SnCl₄	-30	30 min	**5a/5b**	1.3 : 1	5
4	**1**	SnCl₄	-78	30 min	**5a/5b**	4 : 1	10
5	**1**	Et₂AlCl	-78	30 min	**5a/5b**	40 : 1	5
6	**1**	BF₃·OEt₂	-78	30 min	**5a/5b**	100 : 0	6
7	**2**		160	7hr	**6a/6b**	9 : 1	30
8	**2**		RT	4 days	**6a/6b**	12 : 1	23
9	**2**	SnCl₄	-30	30 min	**6a/6b**	2.7 : 1	20
10	**2**	SnCl₄	-78	50 min	**6a/6b**	3 : 1	16
11	**2**	Et₂AlCl	-78	30 min	**6a/6b**	15 : 1	10
12	**2**	BF₃·OEt₂	-78	1.5 hr	**6a/6b**	20 : 1	20

[a] The reaction was stopped just before appearance of any decomposition products. [b] Isolated yield. The yield could be enhanced when the reaction time was prolonged.

could enhance the yields in several reactions listed in Table 1 and Table 2. The Diels-Alder reaction of 5-acetyl-2,3-dihydrofuran (**2**), prepared from dihydrofuran and *N*,*N*-di-methylacetamide, with cyclopentadiene afforded a mixture of *exo* cycloadduct **6a** and *endo* cycloadduct **6b** in 9 : 1 ratio in 30% yield at 160 °C in a sealed tube and in 12 : 1 ratio in 23% yield at room temperature. The diastereomeric ratio in the reaction of **2** with cyclopentadiene showed the similar trend with that in the reaction of **1** and cyclopentadiene although the *exo* selectivity was less pronounced (entries 7~12 of Table 1). Thus, more *exo* cycloadducts were produced at higher temperature than at lower one and in the presence of BF₃·OEt₂ or Et₂AlCl than in the absence of Lewis acids.

Cycloaddition of carbocyclic enal **3**[7] with cyclopentadiene also afforded *exo* isomer **7a**, the major and *endo* isomer **7b**, the minor as shown in entries 1~4 in Table 2. The cycloaddition of carbocyclic enone **4**[7] gave an equal amount of *exo* adduct **8a** and *endo* adduct **8b**, independent to the reaction temperature and presence of Lewis acids (entries 5~8 of Table 2). The reactions of **3** and **4** with cyclopentadiene at

Table 2. Diels-Alder Reaction of Cyclopentadiene with Cyclic Dienophiles **3** and **4**

Entry	Dieno-phile	Lewis Acid	Tempera-ture(°C)	Reaction Time[a]	Product	Ratio exo/endo	Yield (%)[b]
1	**3**		160	4 days	**7a/7b**	2 : 1	12
2	**3**		90	7 days	**7a/7b**	5 : 1	24
3	**3**	SnCl₄	-30	60 min	**7a/7b**	2 : 1	30
4	**3**	Et₂AlCl	-78	60 min	**7a/7b**	7 : 1	62
5	**4**		160	4 days	**8a/8b**	1 : 1	12
6	**4**		90	7 days	**8a/8b**	2 : 1	20
7	**4**	SnCl₄	-78	30 min	**8a/8b**	1 : 1	44
8	**4**	Et₂AlCl	-78	30 min	**8a/8b**	1 : 1	66

[a] The reaction was stopped just before appearance of any decomposition products. [b] Isolated yield. The yield could be enhanced when the reaction time was prolonged.

room temperature were too sluggish to follow, while the reaction in the presence of BF₃·OEt₂ resulted in extensive decomposition even at -78 °C.

The stereochemistry of the cycloadducts was assigned by NOE experiments. The NOE interaction existed between the acetyl proton H-12 (2.23 ppm in **6a** and 2.24 ppm in **8a**) and H-10 (1.79 ppm in **6a** and 1.85 ppm in **8a**) in *exo*-isomers **6a** and **8a**, while the NOE interaction existed between H-12 (2.17 ppm in **6b** and 2.14 ppm in **8b**) and the H-9 (6.05 ppm in **6b** and 6.01 ppm in **8b**) in *endo* cycloadducts **6b** and **8b** as shown in Figure 1. The chemical shifts of acetyl protons further confirmed the assignment made by NOE experiments. Thus, it is known that the ¹H NMR chemical shift of *exo* acetyl protons usually appears at lower field than that of *endo* acetyl protons in norbornene systems.[8] Aldehydes **5a** and **7a**, were converted into the corresponding benzoates **9a** and **10a**, respectively for the determination of stereochemistry. Irradiation of the H-11 signal of **9a** at 4.54 ppm enhanced the H-10 signal at 1.70 ppm. The NOE measured for the H-10 signal of **10a** at 1.82 ppm upon irradiation of the H-11 signal at 4.35 ppm was also in agreement with the structure of the *exo* cycloadduct depicted in Figure 1.

Furano-dienophiles **1** and **2** rendered the higher *exo* selectivity than carbocyclic dienophiles **3** and **4**. The origin of this difference is not clear yet; it might be the steric effect of the methylene group of the carbocycle, the electronic or stereoelectronic effect of the oxygen of the furanoid ring, or the combined effects of them. Temperature effect on the *exo*/*endo* ratio shown in Table 1 and Table 2 might be explained by assuming that, unlike in most other Diels-Alder reactions, the *exo* adducts are the kinetic products and the *endo* isomers are thermodynamic products. Yet, we were not able to observe the isomerization between *exo* and *endo* cycloadducts. Addition of Lewis acids affected dramatically the stereochemical course of the reactions of **1** and of **2** while the effect was much less pronounced in the reactions of **3** and of **4**. It is well known that Lewis acids usually enhance the *endo* selectivity in most of Diels-Alder reactions.[9] In the present study, the *exo* cycloadducts increased by addition of nonchelating BF₃·OEt₂ and Et₂AlCl while the *endo* isomers increased with SnCl₄ in the reactions of **1** and of **2**. In the presence of SnCl₄, the *s-trans* conformation of compounds **1** and **2** would be more favorable than the *s-cis* conformation owing to chelation by SnCl₄ (Figure 2). In fact, SnCl₄ has been regarded as a chelating Lewis acid and the direct evidence for the chelation of SnCl₄ with β-alkoxy aldehydes has also been obtained by NMR study.[10] On the other hand,

6a X = O **6b** X = O **9a** X = O
8a X = CH₂ **8b** X = CH₂ **10a** X = CH₂
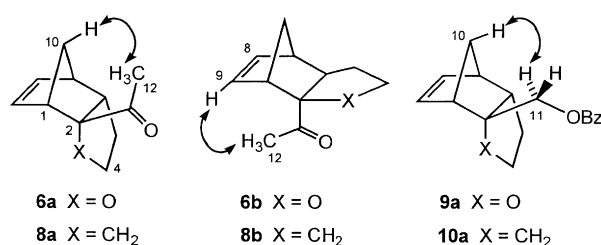
Figure 1. NOE interactions determined for cycloadducts **6a**, **6b**, **8a**, and **8b** and derivatives **9a** and **10a**.

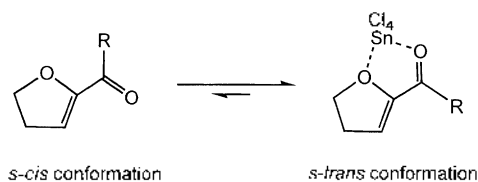s-cis conformation   s-trans conformation

Figure 2. Preferred s-trans conformation of compounds **1** and **2** by chelation with SnCl₄.

BF₃·OEt₂ and Et₂AlCl have been known as nonchelating Lewis acids although there has been recent reports that certain trivalent boron and aluminum species are capable of forming pentacoordinate complexes.[11] It is, therefore, reasonable to assume that the population of s-trans conformation of **1** and **2** in the presence of SnCl₄ would increase by chelation of SnCl₄ with the ring oxygen and the carbonyl oxygen and consequently the decreased exo selectivity might be related to the decreased population of s-cis conformation. It is, however, not yet clear whether the overwhelming exo selectivity in the presence of BF₃·OEt₂ or Et₂AlCl is owing to the preferred s-cis conformation of **1** and **2**. Decreased exo selectivity of **2** and **4** compared with **1** and **3**, respectively, might be attributable to the nonbonding interaction between the methylene group of cyclopentadiene and the methyl group of the compounds **2** and **4** in the exo transition state.

In conclusion, we found that the exo cycloadduct is the major product in the cycloaddition of cyclopentadiene with cyclic dienophiles having the flexible conformation 1~3. We also found that BF₃·OEt₂ is the Lewis acid of choice for predominant generation of exo cycloadducts and the lower temperature is desirable for the exo selectivity. We are currently involved in the synthesis of natural products employing this useful exo selective Diels-Alder reaction.

References

1. (a) Carruthers, W. Cycloaddition Reactions in Organic Synthesis; Pergamon Press: Oxford, U. K., 1990; p 56. (b) Sauer, J. Angew. Chem. Int. Ed. Engl. 1967, 6, 16. (c) Martin, J. G.; Hill, R. K. Chem. Rev. 1961, 61, 537.
2. (a) Roush, W. R.; Sciotti, R. J. J. Am. Chem. Soc. 1998, 120, 7411. (b) Roush, W. R.; Brakley, B. B. J. Org. Chem. 1992, 57, 3380. (c) Fotiadu, F.; Michel, F.; Buono, G. Tetrahedron Lett. 1990, 31, 4863. (d) Roush, W. R.; Essenfeld, A. P.; Warmus, S.; Brown, B. B. Tetrahedron Lett. 1989, 30, 7305. (e) Mattay, J.; Mertes, J.; Mass, G. Chem. Ber. 1989, 122, 327.
3. (a) Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J. J. Am. Chem. Soc. 1986, 108, 5908. (b) Sundin, A.; Frejd, T.; Magnusson, G. Tetrahedron Lett. 1985, 26, 5605. (c) Grieco, P. A.; Yoshida, K.; Garner, P. J. Org. Chem. 1983, 48, 3137. (d) Yokoyama, K.; Kato, M.; Noyori, R. Bull. Chem. Soc. Jpn. 1977, 50, 2201.
4. Kim, K. S.; Cho, I. H.; Joo Y. H.; Yoo I. Y.; Song, J. H.; Ko, J. H. Tetrahedron Lett. 1992, 33, 4029.
5. Kim, C. K.; Lee, I. Y.; Lee, B. S.; Lee, I.; Kim, K. S.; Joo, Y. H. J. Korean Chem. Soc. 1996, 40, 483.
6. Lozanova, A. V.; Surkova, A. A.; Moiseenkov, A. M. Izv. Akad. Nauk. SSSR. Ser. Khim. 1989, 734; English Translation 1989, 659.
7. Jones, N.; Taylor, H. T. J. Chem. Soc. 1959, 4017.
8. Moen, R. V.; Makowski, H. S. Anal. Chem. 1971, 43, 1629.
9. (a) Carruthers, W. Cycloaddition Reactions in Organic Synthesis; Pergamon Press: Oxford, U. K., 1990; p 50. (b) Santelli, M.; Pons, J.-M. Lewis Acids and Selectivity in Organic Synthesis; CRC Press: Boca Raton, U. S. A., 1996; p 267.
10. (a) Keck, G. E.; Castellino, S. Tetrahedron Lett. 1987, 28, 281. (b) Keck, G. E.; Castellino, S. J. Am. Chem. Soc. 1986, 108, 3847.
11. (a) Ooi, T.; Uraguchi, D.; Maruoka, K. Tetrahedron Lett. 1998, 39, 8105. (b) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. J. Am. Chem. Soc. 1998, 120, 5327.