# 1,3-DIPOLAR CYCLOADDITION BEHAVIOR OF PYRAZOLONE *N,N*-DIOXIDES TOWARD EPOXYNAPHTHALENE. EFFECTIVE SECONDARY N···O INTERACTION BETWEEN ADDENDS

Yasuyuki Yoshitake, Masashi Eto, and Kazunobu Harano[*†]

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-hon-machi, Kumamoto 862, Japan

Abstract- Cycloaddition of pyrazolone *N,N*-dioxides (**1**) with epoxynaphthalene (**2a**) gave *endo* 1,3-dipolar cycloadduct. The origin of the high *endo* selectivity was explored by MO analysis of the transition structure. *Ab initio* calculation at several levels indicates that the orientation complex (OC) forms prior to the formation of the transition state (TS). The interaction between the oxygen of **2a** and the nitrogen of the >N→O group of **1** binds two addends together in both OC and TS.

In the previous papers,[1] we reported the cycloaddition behavior of 3,5-disubstituted pyrazolone *N,N*-dioxides (**1**) toward various unsaturated compounds. In the 1,3-dipolar reaction of **1** with epoxynaphthalene (**2a**), the *endo-exo* cycloadduct was produced stereoselectively, whereas the reaction of **1** with norbornadiene gave a mixture of *endo-exo* and *exo-exo* isomers.
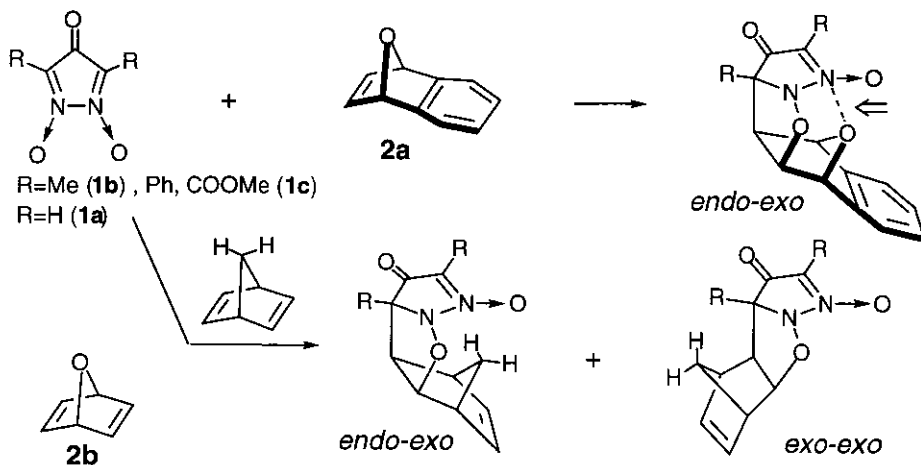
Scheme 1

In the X-Ray structure of the cycloadduct (**3ca**) of 3,5-dimethoxycarbonylpyrazolone N,N-dioxide (**1c**) with **2a**, we found the presence of very close contact between the epoxy oxygen and the nitrogen atom of the remaining $>N{\rightarrow}O$ group, which is reproduced by MP2/3-21G calculation (Figure 1).

2.757 X-Ray
3.151 AM1
3.411 PM3

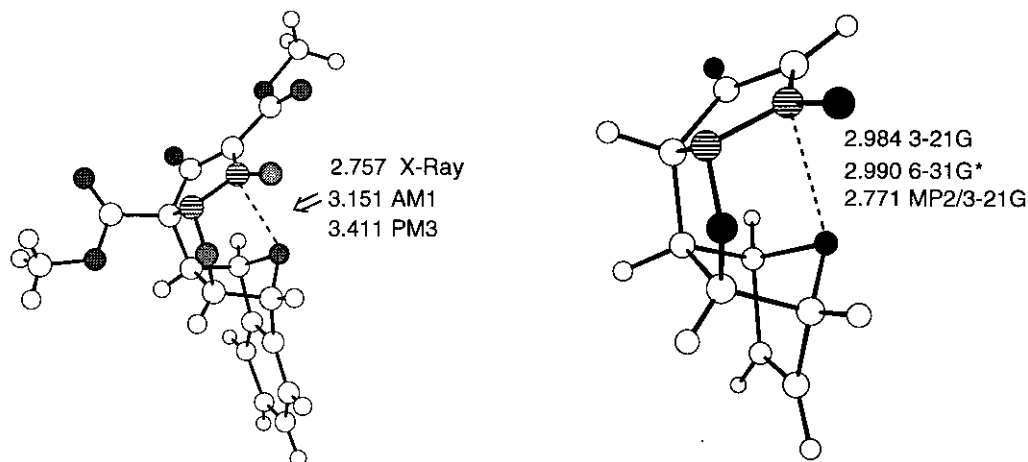2.984 3-21G
2.990 6-31G*
2.771 MP2/3-21G

Figure 1. X-Ray and Semiempirical MO Structures of the *endo* cycloadduct (**3ca**) of **1c** and **2a** and the *ab initio* structures of model cycloadduct (*endo* **3ab**) of **1a** and epoxybenzene (**2b**).

These facts prompted us to consider that similar interaction must be operative in the transition state playing a leading role in determination of the stereoselectivity. This paper deals with the theoretical confirmation of the secondary interaction between the addends using the *ab initio* MO calculation.

RESULTS AND DISCUSSION

The model reaction selected for the present study is that of unsubstituted pyrazole N,N-dioxide (**1a**) with epoxybenzene (**2b**) which is a simplified form of epoxynaphthalene (**2a**). The energies of the *endo/exo* transition states for 1,3-dipolar cycloaddition reactions of **1a** with epoxybenzene are listed in Table 1. In PM3,[2] 3-21G and 6-31G* calculations,[3] the *exo* TS is slightly more stable than the *endo* TS, whereas the STO-3G and MP2/3-21G calculations predicted that the *endo* adduct is predominant.

Table 1. Energies of the Transition States for Cycloaddition of **1a** with Epoxybenzene (**2b**)[a]

Method	E_{endo}	E_{exo}	ΔE ($E_{endo} - E_{exo}$)
PM3	101.531[b]	101.211[b]	0.320[c]
STO-3G	-743.7612	-743.7608	-0.251
3-21G	-753.4320	-753.4332	0.753
6-31G*	-753.4466	-753.4479	0.816
MP2/3-21G	-750.7976	-750.7958	-1.130

a) *Exo* attack with respect to epoxybenzene.   b) Heat of formation (ΔHf)   c) ΔHf$_{endo}$ - ΔHf$_{exo}$

The exclusive *endo* cycloadduct formation is considered to be destined to occur by an additional factor before formation of the TS. As described above, the X-Ray structure of the *endo* adduct (**3ca**) and the *ab initio* TS structures gave us a clue to solve the problem.
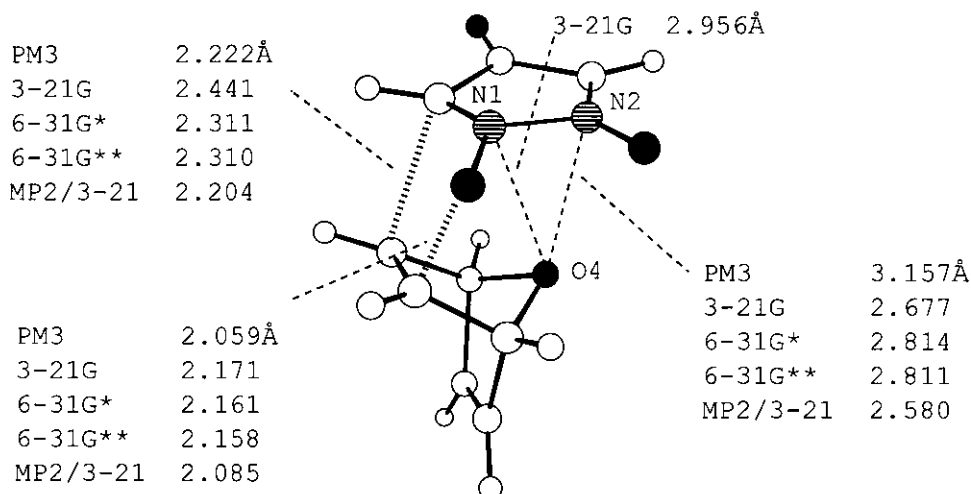

PM3	2.222Å
3-21G	2.441
6-31G*	2.311
6-31G**	2.310
MP2/3-21	2.204

PM3	2.059Å
3-21G	2.171
6-31G*	2.161
6-31G**	2.158
MP2/3-21	2.085

PM3	3.157Å
3-21G	2.677
6-31G*	2.814
6-31G**	2.811
MP2/3-21	2.580

3-21G   2.956Å

Figure 2. Partially formed C--C and C--O Bond Lengths and N--O Short Contacts in the *endo* Transition State (**TSab**)

As seen in the *endo* **TSab**, the forming N--O and C--C bond distances calculated at RHF levels are longer than those obtained by MP2/3-21G calculation, which are comparable to the PM3 distances. The interatomic distance between N1 (and N2) and O4 is interesting. The 3-21G calculation indicates that the N2----O4 (2.677Å) is shorter than the N1----O4 (2.956Å). The 6-31G* and 6-31G** N2----O4 distances is 2.814 and 2.811 Å, respectively, slightly longer than the X-Ray distance (2.757Å) of the *endo* adduct (**3ca**).
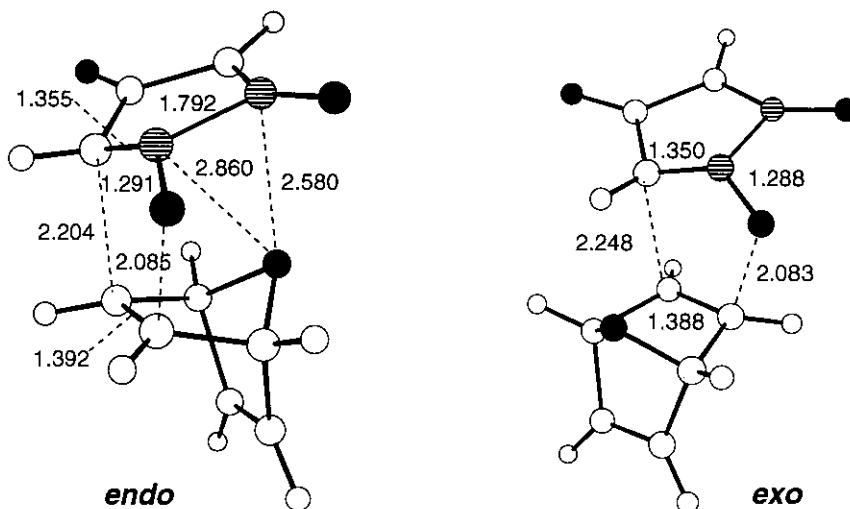

Figure 3. Geometries of MP2/3-21G **TSab**

The PM3 distance is 3.157Å, which may be overestimated than the actual value.[4]

The MP2/3-21G TS geometries leading to the *endo* and *exo* adducts are depicted in Figure 3, wherein the N----O close contact of the *endo* TS is 2.580 Å, considerably shorter than the sum of the VDW distance of N and O atoms.

Based on these consideration and observation of a charge-transfer (CT) complexation[5] between **1c** and electron-rich dipolarophiles such as *N*-vinylcarbazole,[1b] we arrived at the conclusion that the initial interaction leading to *endo* cycloaddition involves orientation complexes of CT type.

In order to obtain information about the formation of orientation complex between **1a** and **2b**, we calculated various geometries of the molecular complexes, in which two addends were placed 3.0Å apart and fully optimized. The most stable structure of complex calculated at the 6-31G* level is depicted in Figure 4. The stabilization energy due to complexation is 5.8 kcal mol^{-1}, in which the two N----O distances are 3.020 and 3.062Å, respectively.[6]
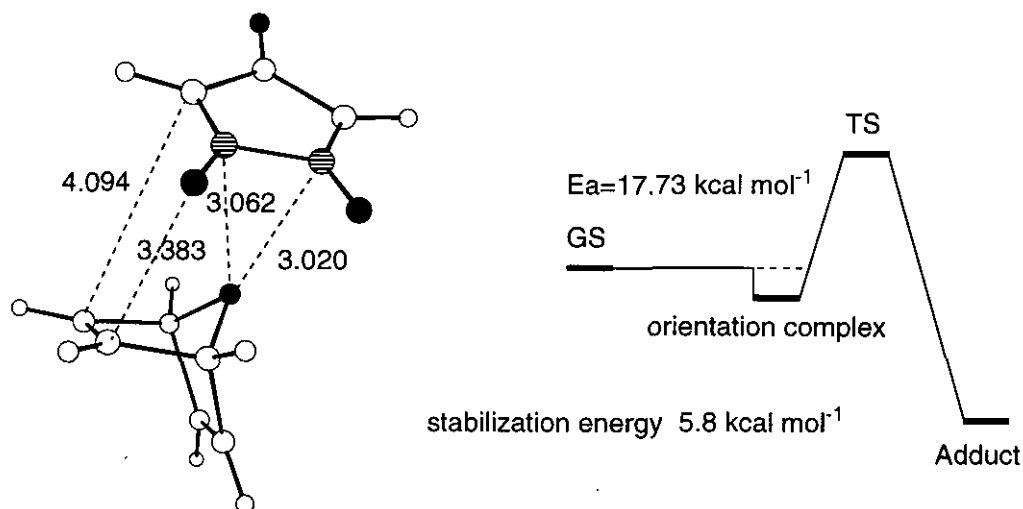

Figure 4. 6-31G* Geometry of Orientation Complex and Stabilization Energy

Along the progress of the cycloaddition (addends → orientation complex → TS → cycloadduct), the two addend are loosely united by the N2----O< interaction with the distance being kept among 2.8-3.0Å (Scheme 2).

The highly negative entropies of activation $(\Delta S^{\ddagger})$[7] which were observed in the reactions of 3,5-disubstituted pyrazolone *N*,*N*-dioxides (**1b,c**) with **2a** reflect crowded transition states in which freedom of motion is unduly hindered. The 1,3-dipolar reactions exhibit entropies of activation ranging from -29 to -33 e.u. For example, the $\Delta S^{\ddagger}$ for the reaction of **1b** with **2a** is about 12 e.u. lower than that reported for the reaction of phenyl-*N*-methylnitrone with methyl methacrylate (Table 2). The extra N2--O< interaction besides the N1--O< attraction in pyrazolone *N*,*N*-dioxides obviously adds to the crowding in the transition state.
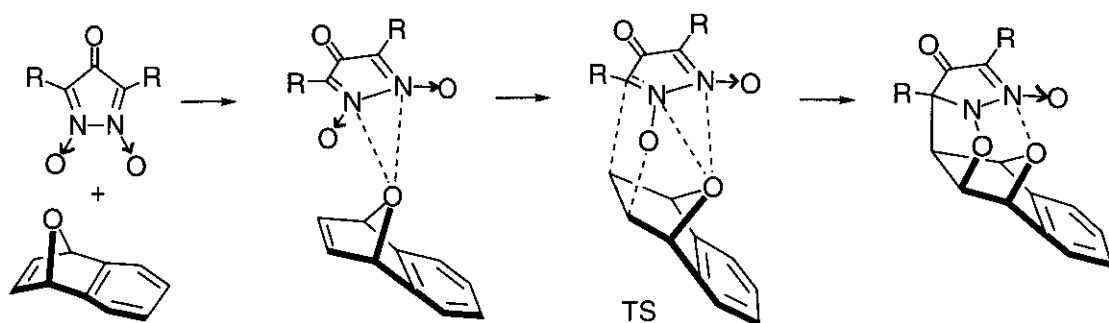
Scheme 2

Table 2. Activation Parameters for the 1,3-Dipolar Reactions of Phenyl-N-methylnitrone and Pyrazolone
N,N-Dioxides with Some Dipolarophiles.

1,3-Dipole/Dipolarophile[a]	$\Delta H^{\ddagger}$(kcal mol^{-1})	$\Delta S^{\ddagger}$(e.u.)
phenyl-N-methylnitrone/methyl methacrylate[b]	15.7	-32
phenyl-N-methylnitrone/2-vinylpyridine[b]	10.7	-29
1b/2a	12.7	-46
1c/2a	9.4	-43

a) in toluene. b) ref. 8.

As shown in Figure 4, the 6-31G* geometry of the orientation complex is very similar to the TS structure,
which is favorable for the movement to the *endo* TS. On the other hand, the transformation from the
orientation complex to the *exo* TS is considered to require a large structural change which is energetically
unfavorable.

At present, the ^{1}H-NMR spectral evidence for the presence of the orientation complex among **1b,c** and **2a**
in solution could not be obtained.

The study of weak interactions to control the stereo, peri and regioselectivities is in progress.

ACKNOWLEDGMENT

REFERENCES AND NOTES

† E-mail: harano@gpo.kumamoto-u.ac.jp

1. a) M. Eto, K. Harano, Y. Yoshitake, and T. Hisano, *J. Heterocycl.Chem.*, 1993, **30**, 1557.

    b) M. Eto, Y. Yoshitake, K. Harano, and T.Hisano, *J. Chem. Soc., Perkin Trans.* 2, 1994, 1337.

2. a) J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.

b) J. J. P. Stewart, *J. Comp. Chem.*, 1989, **10**, 209; *J. Comp. Chem.*, 1989, **10**, 221.

c) AM1 and PM3 calculation are performed using MOPAC; J. J. P. Stewart, *QCPE Bull.*, 1989, **9**, 10.

3. Gaussian 94, Revision D.4, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, *Gaussian, Inc.*, Pittsburgh PA, 1995.

4. The distance was calculated to be 2.811Å at the 6-31G** level which has been proposed to reproduce the experimental values for bond lengths in pyridine *N*-oxide. R. B.Perni, P. J. Kowalczyk and A. D. Treasurywala, *Tetrahedron Lett.*, 1995, **36**, 699.

5. R. Sustmann, W. Sicking, and R. Huisgen, *J. Am. Chem. Soc.*, 1995, **117**, 8679.

6. The PM3 stabilization energy is 2.2 kcal mol^{-1}.

7. The second-order rate constants were determined by following the decrease of the visible absorption band (n-π^*) of **1b,c**. The rate constants for **1b** (**1c**) at 40, 50, 60 and 70° are 7.1×10^{-6} (5.0×10^{-3}), 13.3×10^{-6} (8.4×10^{-3}), 24.5×10^{-6} (12.1×10^{-3}) and 42.1×10^{-6} (19.2×10^{-3}) sec^{-1} mol^{-1} l, respectively.

8. R. Huisgen, *Angew. Chem.*, 1963, **75**, 742 and references cited therein.