Substituent Effects on Two Orthogonal π-Systems in Pseudopericyclic Ring-opening Reactions of 5-Alkoxy-2-aminooxazoles

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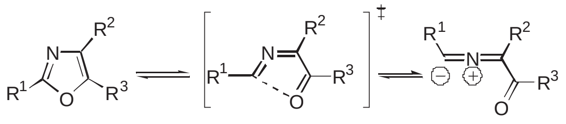
Using the density functional theory calculations, the nature of the effects of electron-donating substituents on pseudopericyclic ring-opening reactions of oxazole derivatives have been explained. The reactions involve interactions in two kinds of orthogonal π-systems at the transition states. A 2-amino group interacts with a horizontal π-system at the transition state, while a 5-alkoxy group interacts with a vertical one. Owing to these substituent effects, the barrier of the ring-opening reactions are reduced cumulatively.

A ring-opening reaction of oxazole derivative **1** into carbonyl nitrile ylide **3** is a key step of the transformation of an oxazole ring in the Cornforth rearrangement and some of non-Diels–Alder type cycloadditions (Figure 1).[1–4]



1 **2** **3**

Figure 1. Ring-opening reaction from oxazole **1** to nitrile ylide **3**.

Formation of nitrile ylide **3** was confirmed by trapping with dipolarophiles, and semiempirical molecular orbital calculations by Saalfrank et al.[3] and Fukushima et al.[4] in reactions of 4-cyano-5-methoxy-2-pyrrolidinooxazole ($R^1 = NR_2$, $R^2 = CN$, $R^3 = OR'$) and 5-alkoxy-2-aminooxazoles ($R^1 = NR_2$, $R^3 = OR'$). These oxazole derivatives **1** have both an amino group ($R^1 = NR_2$) and an alkoxy group ($R^3 = OR'$). Attempts to generate nitrile ylide **3** from oxazole derivatives which has only an amino group ($R^1 = NR_2$) or an alkoxy group ($R^3 = OR'$) were unsuccessful.[4] These experimental results indicate that the substituent effects by both the amino group (R^1) and the alkoxy group (R^3) are essential for the ring-opening reactions of the oxazole derivatives **1**. However, the mechanism of the substituent effects on the ring-opening reactions of the oxazoles **1** was not fully understood.

Recently, some groups reported that a reaction of formyl nitrile ylide (**3a**) to oxazole (**1a**) was theoretically categorized into a pseudopericyclic reaction which is a concerted reaction involving simultaneous interactions on two kinds of orthogonal π-systems (Figure 2).[5,8–10]

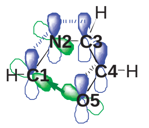


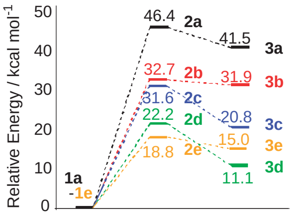
Figure 2. Electronic interactions in a vertical (blue) and a horizontal (green) π-systems at transition state (**2a**).

One of the π-systems consists of vertical π-orbitals on a nitrile ylide moiety and a carbonyl group, and is delocalized over the whole molecule at the transition state (depicted in blue, Figure 2). The other π-system consists of a horizontal π-orbital at C1–N2 in the nitrile ylide moiety and lone-pair electrons on carbonyl oxygen (depicted in green, Figure 2). The interaction in the latter π-system directly contribute to formation of a new C1–O5 σ-bond during ring-closure process.

In this paper, we will report density functional theory (DFT) calculations[11,12] and the natural bond orbital (NBO) analysis[13] of substituent effects on pseudopericyclic ring-opening reactions of oxazole derivatives **1**. The DFT calculations have revealed that an amino group ($R^1 = NR_2$) and an alkoxy group ($R^3 = OR'$) reduce barrier of the reactions through interaction with different π-systems at the transition states **2**.

Figure 3 shows calculated energy profiles of ring-opening reactions from oxazole **1** to nitrile ylide **3**. A ring-opening reaction from unsubstituted oxazole (**1a**) to formyl nitrile ylide (**3a**) was exothermic by 41.5 kcal mol^{-1}. Although the barrier for the reaction (46.4 kcal mol^{-1}) was rather high, introduction of an electron-donating group at R^1 and/or R^3 reduced it. In monosubstituted derivatives **1b** and **1c**, an effect of a dimethylamino group (R^1) and that of a methoxy group (R^3) reduced barriers to the reactions by more than 10 kcal mol^{-1}. Barriers for the reactions of di- and trisubstituted derivatives, **1d** and **1e**, which are model compounds of 5-alkoxy-2-aminooxazoles and 4-cyano-5-methoxy-2-pyrrolidinooxazole, were cumulatively reduced by both the dimethylamino group (R^1) and the methoxy group (R^3). The calculated low barriers (22.2 and 18.8 kcal mol^{-1}) are consistent with experimentally observed easy generation of nitrile ylide **3**.[3,4]

Figure 4 illustrates optimized geometries, the lowest frequencies, and the summary of the NBO analysis[13] of transition states **2b** ($R^1 = N(CH_3)_2$) and **2c** ($R^3 = OCH_3$).[14] It shows two different types of substituent effect. At the transition state **2b**, C1 became electron-deficient with breaking of a C1–O5 bond. Electron-donation from lone-pair electrons of a dimethylamino group (R^1) to the electron-deficient orbital on C1 stabilized **2b**. The interaction was strong enough to be represented



	R^1	R^2	R^3
a	H	H	H
b	$N(CH_3)_2$	H	H
c	H	H	OCH_3
d	$N(CH_3)_2$	H	OCH_3
e	$N(CH_3)_2$	$COOCH_3$	OCH_3

Figure 3. Energy profile of ring-opening reaction from oxazole **1** to nitrile ylide **3** calculated at the B3LYP/6-31+G(d) level of theory. Energies are relative to those of oxazole (**1**).

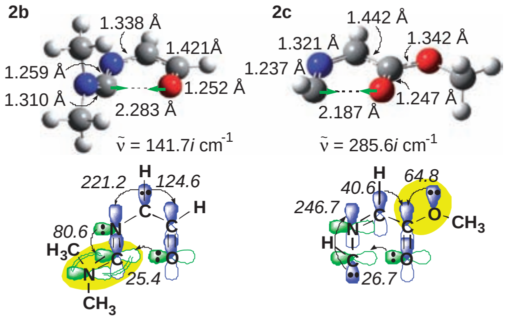


Figure 4. Optimized geometries and the lowest frequencies (top), and the second-order perturbative energy-lowering (kcal mol^{-1}) between donor/acceptor NBOs (bottom) at transition states **2b** and **2c**.

as a C=N double bond, which was conjugated with lone-pair electrons on N2 (nN2), by the NBO analysis. The conjugated π-bond character was confirmed by geometrical features of **2b**; a 1.310 Å of $(H_3C)_2N$–C1 distance, which is slightly shorter than that of an imidazole (1.333 Å), and almost orthogonal dihedral angles (80.4 and 88.3°) between H_3C–N bonds and an N2–C3 bond, which allowed effective overlap between the πC1–N(R^1) and the nN2 within a horizontal mean molecular plane. The transition state **2c** was almost planar except for some hydrogen atoms. The NBO analysis showed that vertical π-orbitals in a nitrile ylide moiety and a carbonyl group were conjugated over the whole molecule. Lone-pair electrons on a methoxy group [nO(R^3)] interacted with the vertical π-system, which stabilized the transition state **2c**.

Table 1 lists the second-order perturbative energy-lowerings through electron-donating interaction from nO(R^3) to π^*C4–O5 at **2c**–**2e**. Figure 5 illustrates the interactions between donor and accepter NBOs at **2d** and **2e**. In these transition states, **2c** has only a methoxy group (R^3), while **2d** and **2e** have both a dimethylamino group (R^1) and the methoxy group (R^3). The data in Table 1 indicated that there was little influence of R^1 on the magnitude of the electron-donating interaction between R^3 and π^*C4–O5 orbital at **2d** and **2e**. Table 1 and Figure 5 show that the electron-donating interactions from R^1 and those of R^3 are orthogonal in **2d** and **2e**, and are substantially independent to each other.

Table 1. The second-order perturbative energy-lowerings (kcal mol^{-1}) through electron-donating interaction from nO(R^3) to π^*C4–O5 at **2c**–**2e**.

2c	**2d**	**2e**
64.8	56.8	69.3

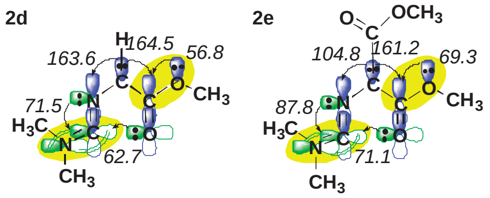


Figure 5. The second-order perturbative energy-lowering (kcal mol^{-1}) between donor/acceptor NBOs at transition states **2d** and **2e**.

A substituent (R^1 or R^3) on oxazole ring reduced barrier of the reaction by about 10 kcal mol^{-1} as shown in Figure 3. Multiple substituents (R^1 and R^3) stabilized the transition states (**2d** and **2e**) by about 20 kcal mol^{-1}. Thus, the effects of the R^1 and R^3 cumulatively reduce the barriers of the reactions.

In conclusion, a dimethylamino group (R^1) and a methoxy group (R^3) independently interact with a horizontal and a vertical π-systems in transition states of pseudopericyclic ring-opening reactions of oxazole derivatives **1**. The cumulative reductions of the energy-barriers through these interactions are essential for the experimentally observed formation of nitrile ylide **3** from oxazole derivatives **1**.

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