# Studies on the 1,4-Oxazepine Ring Formation Reaction Using the Molecular Orbital Method

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**1,4-Oxazepine formation reactions of 1,8-naphthyridine derivatives (1—4) with peroxy acid have been studied using a semiempirical MO method (AM1) and an *ab initio* molecular orbital method (Gaussian 94). The energies of molecules involved in the reaction paths were calculated and the transition states related to experimental products were obtained. For the reactions of 1—3, the calculated energies of the transition states predicted the previously obtained products. However, the calculated values for the reaction of 4 suggested a different type of oxazepine compound, which was verified in further experiments.**

**Key words** mechanism; transition state; oxazepine; naphthyridine; MO method

Nitrogen-containing heterocyclic compounds have extensive pharmaceutical applications. Some chemical derivatives of these polyheterocyclic compounds express anticancer activity. Therefore, it is useful to examine the mechanism of known reactions in terms of energy along the reaction path, for the purpose of synthesizing new types of compounds. In previous papers, Takeuchi *et al*. reported the oxidation reactions of naphtho [2,1-b][1,8] naphthyridine (**1**) and naphtho [1,2-b][1,8] naphthyridine (**2**), and benzo[b] [1,8] naphthyridine (1,9-diazaanthracene) (**3**) with peracetic acid (**5**) and/or *m*-chloroperbenzoic acid (*m*-CPBA) (**6**),[1,2] producing compounds with a seven-membered 1,4-oxazepine ring moiety. In the present paper, we studied theoretically the 1,4-oxazepine ring formation reactions of **1**—**3** and naphtho [2,3-b][1,8] naphthyridine (**4**) and/or **5** and **6**, considering two routes to produce the 1,4-oxazepine ring[1] (Chart 1). For the reactions of **1**—**3**, the experiments and calculated results indicated one type of 1,4-oxazepine ring formation (P1 type). But the calculated result for the linear-type compound (**4**) suggested the formation of another type of 1,4-oxazepine ring (P2 type). To investigate the calculated result for the reaction of **4** experimentally, we performed new synthesis and oxidation of the compound (**4**) (Chart 2).

The following calculations were performed using the semiempirical molecular orbital AM1 method[3] in the MOPAC 93 program package.[4] The effect of solvent was not considered. All structure parameters were optimized. We assume that the reaction of **1** with **5** (reaction 1) proceeds as follows: The $C_5$-atom of the 1,8-naphthyridine skeleton in **1** has the maximum LUMO amplitude (0.4522). Then we can predict that the peracetate ion is added to the $C_5$-atom of **1**.[5] When the $O_{1'}$-atom of the peracetate ion approaches the $C_5$-atom of **1**, the minimum energy state ($C_5$–$O_{1'}$ distance= 3.04 Å and heat of formation [HF]=14.11 kcal/mol) is achieved. Then a new C–O bond is formed through the transition state (TS) ($C_5$–$O_{1'}$=2.159 Å and HF=23.76 kcal/mol). After attracting the $H^+$ ion without energy barriers, the intermediate state (Eq) ($C_5$–$O_{1'}$=1.474 Å and HF=35.50 kcal/mol) is achieved (Chart 1).

In the ring expansion process, we can assume two reaction paths (Chart 1).[1] In path 1, the product P1 will be formed through TS1 ($O_{1'}$–$O_{2'}$=1.866 Å, HF=79.71 kcal/mol), Eq1′ ($O_{1'}$–$O_{2'}$=3.977 Å, HF=57.09 kcal/mol), and TS1′ ($O_{1'}$–$O_{2'}$=3.716 Å, HF=61.87 kcal/mol). The $O_{2'}$-atom in TS1 or TS1′ has a large minus charge, but the LUMO density of the $C_5$-atom is very small (0.043) in TS1 and large (0.33) in TS1′. Therefore we may think that the $C_5$–$O_{2'}$ bond cannot be formed directly *via* TS1 but can be *via* TS1′. We performed the intrinsic reaction coordinate calculation and confirmed that Eq′ is actually produced from Eq *via* TS1 and P1 is produced from Eq′ *via* TS1′. In path 2, the product P2 is formed through TS2 ($O_{1'}$–$O_{2'}$=1.871 Å, HF=83.24 kcal/mol). Since the calculated value of TS1 energy is 3.53 kcal/mol lower than that of TS2, path 1 is preferred and product P1 is expected. The calculated structure of P1 coincides with the experimental product, the structure

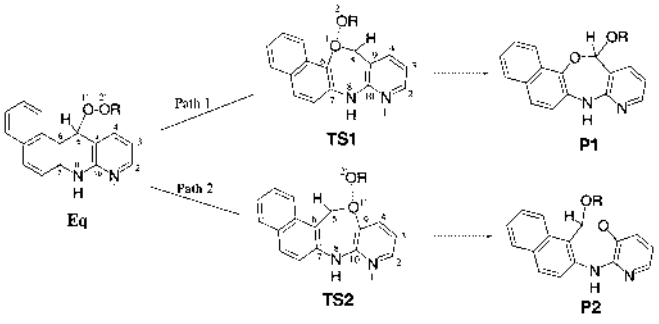


Chart 1. Reaction Paths for the Ring Expansion Process for Reactions 1 (R=$COCH_3$) and 3 (R=$COC_6H_4Cl$)

Table 1. Calculated Energies (kcal/mol) for the Ring Expansion Process and the Corresponding Experimental Yields (%)

| Reaction | Reactant | E0[a] | TS1 | TS2 | ΔE | ΔE(G94)[b] | Ea | Yield[c] | Temp., Time |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1**+**5** | 37.69 | 79.71 | 83.24 | 3.53 | 11.43 | 42.02 | 56 | 60—65 °C, 4 h |
| 2 | **2**+**5** | 36.72 | 81.20 | 84.03 | 2.83 | 8.89 | 44.48 | 19 | 60—65 °C, 4 h |
| 3 | **1**+**6** | 66.61 | 106.16 | 109.55 | 3.39 | 10.74 | 39.55 | 22 | r.t., 2 h |
| 4 | **2**+**6** | 65.64 | 107.70 | 110.37 | 2.67 | 8.52 | 42.06 | 1 | r.t., 15 h |
| 5 | **3**+**6** | 51.41 | 90.53 | 90.53 | 0.00 | 1.63 | 39.12 | 71 | 20 °C, 3 h |
| 6 | **4**+**6** | 75.56 | 111.39 | 109.78 | −1.61 | −0.45 | 34.22 | 16[d] | 20 °C, 10 min |

Energies are expressed in terms of the heat of formation calculated using the AM1 method except for ΔE(G94). ΔE denotes the energy difference between TS1 and TS2. *a*) Sum of energies of the reactants. *b*) Energy difference between TS1 and TS2 calculated using Gaussian 94 with RHF/3-21G.[6] *c*) Yield denotes the sum of the experimental yields of the products with a 1,4-oxazepine ring.[7] *d*) Yield of product (**10**) with a 1,4-oxazepine ring of the P2 type (see Chart 1).

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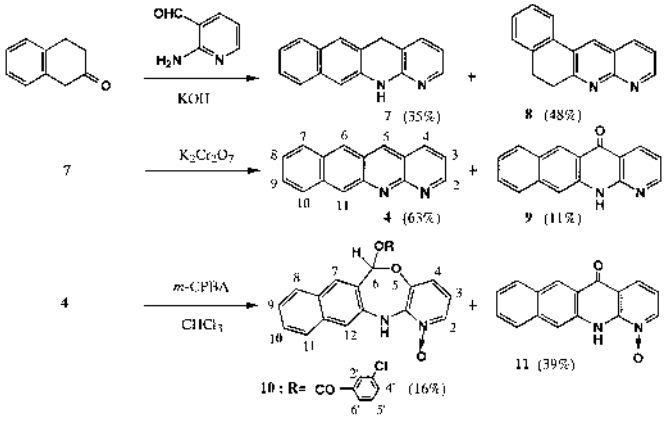


Chart 2

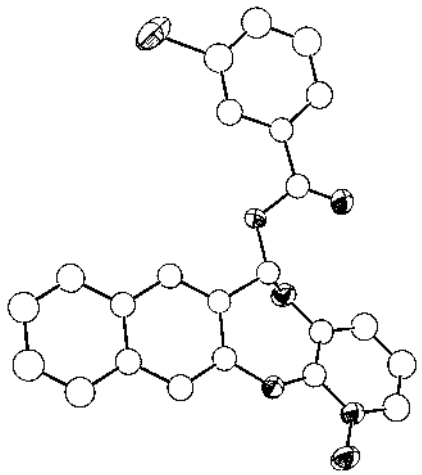

Fig. 1. A Perspective View of the Molecular Structure of **10** Determined Using X-ray Crystallography

of which was determined using X-ray crystallography.[1)] The root mean square error of these structures is 0.05 Å for 19 heavy atoms in the four rings when the structure of P1 is re-optimized using the restricted Hartree-Fock (RHF) method in the Gaussian 94 program package with the 3-21G basis set (RHF/3-21G).[6)]

We also assume that the other reactions of **1**, **2**, **3**, and **4** with **5** and/or **6** (reactions 2 to 6) proceed in the same way. We summarize the calculated energies for the ring expansion process in Table 1, together with the experimental yields of products with a 1,4-oxazepine ring.[7)] To confirm the results of the AM1 method, we optimized the structures of TS1 and TS2 using RHF/3-21G. The structures of TS1 and TS2 optimized using RHF/3-21G are almost the same as those optimized using the AM1 method. The differences in these TS1 and TS2 energies obtained by RHF/3-21G are also shown in Table 1. For reactions 1 to 5, the calculated energies of TS1 are lower than those of TS2. Therefore the ring expansion process occurs through path 1 and products corresponding to P1 are produced. In experiments, P1-type products with a 1,4-oxazepine ring *via* TS1 were synthesized, but compounds *via* TS2 were not obtained.[1,2)]

On the other hand, in the reaction of **4** with **6** (reaction 6), the calculated energy of TS1 is greater than that of TS2 (see Table 1). Therefore it is anticipated that a product with another type of oxazepine moiety *via* TS2 will be obtained in reaction 6 (Chart 1). To verify the calculated result for reaction 6, we performed the following experiments (Chart 2): We produced dihydro compounds (**7** and **8**) using the condensation of $\beta$-tetralone and 2-aminonicotinaldehyde and obtained the desired linear compound (**4**)[8)] with oxidation of compound (**7**). Compound (**4**) was treated with *m*-CPBA at 20 °C for 10 min, producing the expected 1,4-oxazepine compound (**10**,[9)] 16%) and another compound (**11**, 39%). The molecular structure of **10** was determined using X-ray crystallography. A perspective view of product (**10**) is shown in Fig. 1. The 1,4-oxazepine ring of **10** has the same structure (P2 type) as predicted from the calculated energies of TS1 and TS2 for reaction 6.

The activation energy (Ea) of the reaction is estimated from the difference between TS1 energy (TS2 for reaction 6) and the energy of reactants. The values of Ea are shown in Table 1.

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7) We take a sum of the yields of products with a 1,4-oxazepine ring as the experimental yield in reactions 1—3, and 5 (see refs. 1 and 2).
8) Selected data for **4**: mp 238—240 °C (dec.) (AcOEt). FAB-MS *m*/*z*: 231 ($M^+$+1). $^1$H-NMR (270 MHz, $CDCl_3$) $\delta$: 7.40 (1H, dd, $J$=8.5, 3.9 Hz, H-3), 7.49 (1H, m, H-8), 7.53, (1H, m, H-9), 8.04 (1H, m, H-7), 8.13 (1H, m, H-10), 8.36 (1H, dd, $J$=8.5, 3.9 Hz, H-4), 8.68 (1H, s, H-6), 9.03 (1H, s, H-11), 9.06 (1H, s, H-5), 9.29 (1H, dd, $J$=3.9, 2.0 Hz, H-2). *Anal*. Calcd for $C_{16}H_{10}N_2$: C, 83.46; H, 4.38; N, 12.17. Found: C, 83.35; H, 4.42; N, 12.09.
9) Selected data for **10**: mp 203—205 °C (dec.) (AcOEt). FAB-MS *m*/*z*: 419 ($M^+$+1). $^1$H-NMR (270 MHz, $CDCl_3$) $\delta$: 6.71 (1H, dd, $J$=8.3, 6.3 Hz, H-3), 7.27 (1H, dd, $J$=8.3, 1.0 Hz, H-4), 7.29, (1H, s, H-12), 7.32 (1H, t, $J$=8.0 Hz, H-5′), 7.34 (1H, m, H-9), 7.40 (1H, s, H-6), 7.47 (1H, m, H-10), 7.52 (1H, m, H-4′), 7.65 (1H, br, s, NH), 7.68 (1H, m, H-11), 7.78 (1H, m, H-8), 7.81 (1H, m, H-6′), 7.89 (1H, s, H-7), 7.92 (1H, d, $J$=2.4 Hz, H-2′), 7.97 (1H, dd, $J$=6.3, 1.0 Hz, H-2). *Anal*. Calcd for $C_{23}H_{15}ClN_2O_4$: C, 65.96; H, 3.61; N, 6.69. Found: C, 65.92; H, 3.80; N, 6.57.