Studies on the Reaction of Benzo[X]quinoline *N*-Oxides (X=*f*, *h*, and *g*) with Methylsulfinyl Carbanion Using the Semi-empirical Molecular Orbital Method. Liberation of the *N*-Oxide Group

Hisao MATSUZAKI,*[,a] Isao TAKEUCHI,[b] and Yoshiki HAMADA[b]

Tohoku Pharmaceutical University,[a] 4–4–1 Komatsushima, Aoba-ku, Sendai 981–8558, Japan and Faculty of Pharmacy, Meijo University,[b] 150 Yagotoyama Tempaku-ku, Nagoya 468–8503, Japan.
Received October 18, 1999; accepted December 28, 1999

The mechanism of the liberation reaction of the *N*-oxide group has been studied and compared with the methylation reaction using a semi-empirical molecular orbital PM3 method. By comparing the calculated values of Gibbs free energy of activation, we can determine whether a liberation reaction or methylation reaction occurs.

Key words mechanism; transition state; quinoline; MO method; Gibbs free energy

The reaction of quinolines, isoquinolines,[1] and their *N*-Oxides[2] with methylsulfinyl carbanion (**6**) has been reported, the products all being methylated compounds. Hamada *et al*. also studied the reaction of 1,X-naphthyridine (X=5, 6, 7, 8),[3] benzo[*f*]- and benzo[*h*]quinoline, and their *N*-oxides[4] with **6**. They found that the *N*-oxides and **6** undergo a new type of reaction which eliminates the *N*-oxide group from the azaphenanthrene skeleton.[4] On the other hand, the reaction of benzo[*g*]quinoline with **6** produced only methylated compounds.[5] In the present work, we have theoretically studied the reaction of benzo[*f*]quinoline 4-oxide (**1**), benzo[*h*]quinoline 1-oxide (**2**), 4-methyl-benzo[*h*]quinoline 1-oxide (**3**), 2-methyl-benzo[*h*]quinoline 1-oxide (**4**), and benzo[*g*]quinoline 1-oxide (**5**) with **6**. We show the schemes of these reactions and the experimental yields of phenanthrene (**7**) for the reactions of **1** and **2**, the 4-methylphenanthrene (**8**), the 2-methylphenanthrene (**9**), and the 2-methylbenzo[*g*]quinoline 1-oxide (**10**) in Chart 1. We have focused our study on explaining whether liberation of the *N*-oxide group or methylation will occur. We calculated the heat of formation and the Gibbs free energies of formation of the molecules and ions involved in the reaction path at 70 °C. We regarded the energy difference between the transition state (TS) and the initial minimum energy state as the activation energy (Ea) of the reaction. We compared the calculated Ea of the liberation reaction of the *N*-oxide group with that of the methylation reaction of the *N*-oxide, and discuss which of these reactions will actually occur. We also compare the calculated Ea's with the yields of the corresponding products.

Results and Discussion

Hamada *et al*. have carried out the reaction of **2** with deuterated methylsulfinyl carbanion in an NMR sample tube to examine the reaction mechanism, then proposed a mechanism of the liberation of the *N*-oxide group.[6] As an example,

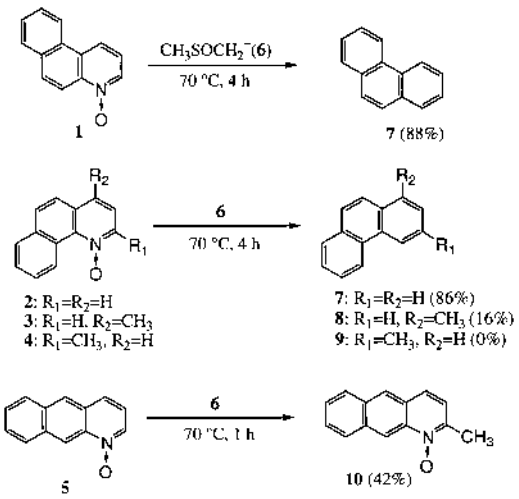

Chart 1

Table 1. Calculated Heat of Formation (ΔH) and Gibbs Free Energies of Formation (ΔG) at 70 °C in Unit of kcal/mol

Reactant		Eq2	Eq3	TS4	TS7	Ea(L)	Ea(M)
1	ΔG	−52.98	−53.05	−3.53	5.54	49.52	58.59
	ΔH	−3.82	−2.23	46.47	53.88	50.29	57.70
2	ΔG	−50.54	−48.97	0.39	3.38	50.93	53.92
	ΔH	−1.77	1.73	50.69	53.77	52.46	55.54
3	ΔG	−62.60	−58.10	−10.57	−6.91	52.03	55.69
	ΔH	−11.81	−3.85	42.72	46.73	54.53	58.54
4	ΔG	−54.77	−60.99	−4.77	—	56.22	—
	ΔH	−5.63	−6.42	45.47	—	51.89	—
5	ΔG	−45.75	−46.96	15.69	8.14	62.65	53.89
	ΔH	2.09	5.35	64.39	58.98	62.30	56.89

The activation energies are also shown. Here, L and M in parentheses denote the liberation of an *N*-oxide group and the methylation process, respectively.

* To whom correspondence should be addressed.

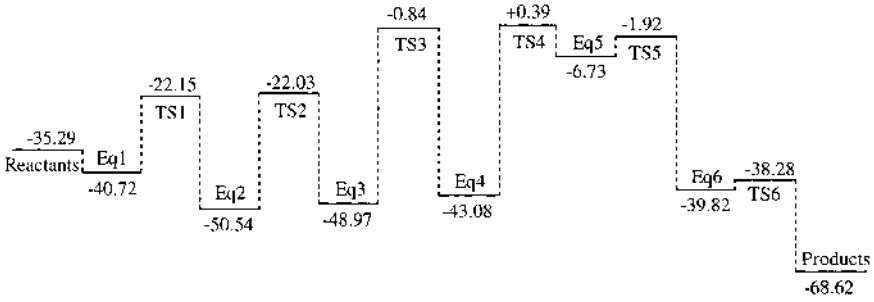

Fig. 1. Energy Diagram along the Path for the Liberation Reaction of the *N*-Oxide Group for the Reaction of **2** with **6**

Numerical values are the Gibbs free energies of formation in kcal/mol of the optimized states.

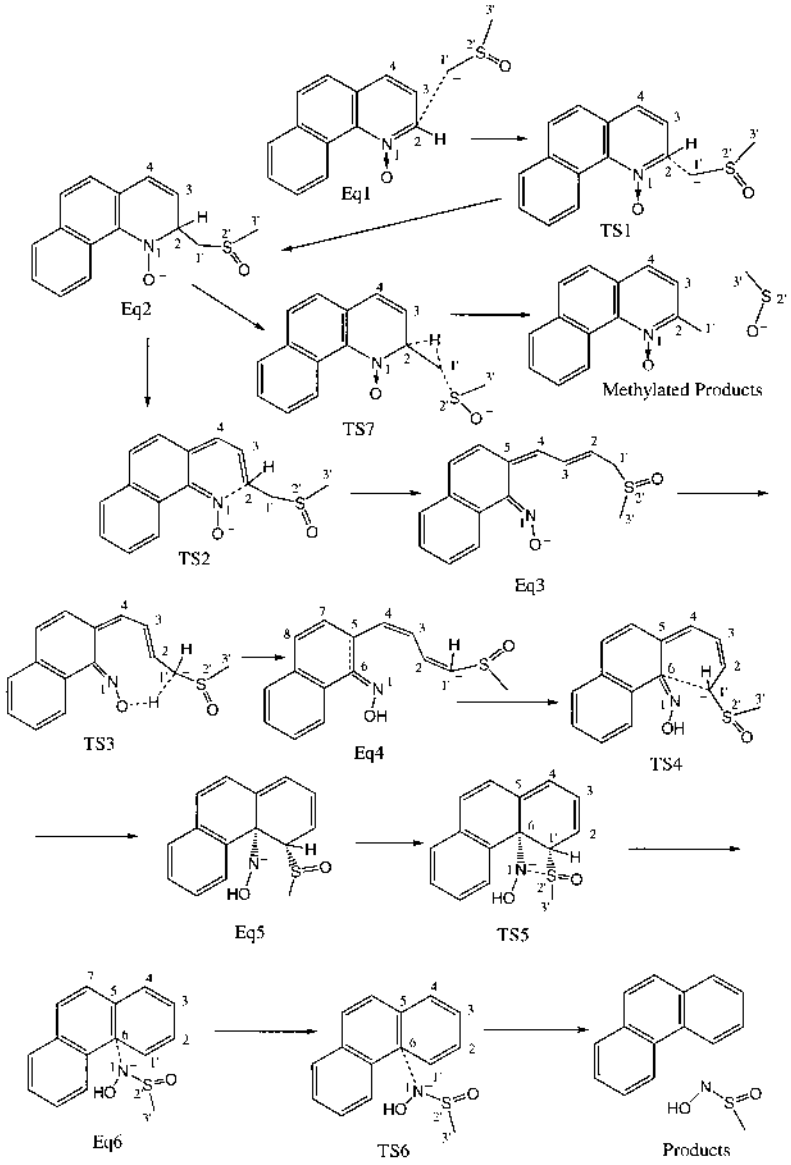

Fig. 2. Schematic View of the Optimized Structures for the Reaction of **2** with **6**

The methylated product through TS7 was not experimentally obtained for this reaction. The double bonds and the minus charge in the molecules are drawn based on the calculated values of the bond order and the charge, respectively.[7] The calculated relevant interatomic distances are as follows: $C_2C_{1'}$=4.86 Å (Eq1), $C_2C_{1'}$=2.364 Å (TS1), N_1C_2=2.031 Å (TS2), OH=1.295 Å (TS3), $C_{1'}H$=1.491 Å (TS3), $C_6C_{1'}$=2.043 Å (TS4), $N_1S_{2'}$=2.194 Å (TS5), N_1C_6=1.613 Å (Eq6), N_1C_6=1.975 Å (TS6).

we show the reaction path of **2** with **6** in detail following the proposal. We assume that the reaction proceeds through the following steps. When the reactants **2** and **6** are separated an infinite distance, the system has the electric charge −1 and Gibbs free energy of formation (ΔG)=−35.29 kcal/mol. When **2** and **6** mutually interact by the intermolecular interaction, an equilibrium state (Eq1, ΔG=−40.72 kcal/mol) is realized. Step 1: **6** is added to the 2-position of **1** and an in-

termediate product (Eq2, $\Delta G = -50.54$ kcal/mol) is formed through TS1 ($\Delta G = -22.15$ kcal/mol). We show the heat of formation and Gibbs free energy of formation calculated at 70 °C in Table 1. We also display an energy diagram along the reaction path for the liberation of an *N*-oxide group in Fig. 1 and the schematic view of the optimized structures in Fig. 2. In experiments, the NMR signal of starting compounds disappeared soon after the beginning of the reaction.[6] Eq2 is the lowest state in energy and the energy of TS1 is low (Fig. 1). Therefore, we consider that the majority of reactants exist in the form of Eq2 and the activation energy must be measured from Eq2.

Step 2: The N_1–C_2 bond of Eq2 is broken, ring opening occurs, and the intermediate state Eq3 ($\Delta G = -48.97$ kcal/mol) is formed *via* TS2 ($\Delta G = -22.03$ kcal/mol). Step 3: A hydrogen atom attached to the $C_{1'}$ atom of Eq3 transfers to the oxygen atom in the *N*-oxide group and Eq4 ($\Delta G = -43.08$ kcal/mol) is formed *via* TS3 ($\Delta G = -0.84$ kcal/mol). Since the H atom has been removed from the $C_{1'}$ atom, the double bonds at the C_2–C_3 and C_4–C_5 positions in Eq3 move to the $C_{1'}$–C_2 and C_3–C_4 positions in Eq4, respectively.[7] Step 4: After the O–H bond is formed, through TS4 ($\Delta G = +0.39$ kcal/mol), a new C_6–$C_{1'}$ bond and a new 6-membered ring are formed, making Eq5 ($\Delta G = -6.73$ kcal/mol). The 3-dimensional view of TS4 is shown in Fig. 3. TS4 for this ring-closure process is the highest state in energy over the whole process of this liberation reaction of *N*-oxide. We consider that this reaction proceeds while maintaining equilibrium between Eq2, Eq3, and Eq4 states. Consequently, the Gibbs free energy of activation of this *N*-oxide liberation process is obtained from the energy difference between TS4 and Eq2 and has a value of 50.93 kcal/mol (Table 1). Step 5: N_1 and $S_{2'}$ atoms of Eq5 approach each other, *via* TS5 ($\Delta G = -1.92$ kcal/mol), a new N_1–$S_{2'}$ bond is formed, and the $C_{1'}$–$S_{2'}$ bond breaks, making Eq6 ($\Delta G = -39.82$ kcal/mol). The N_1–C_6 bond of Eq6 is weak (the calculated bond-order is 0.751 and the force constant is 1.49 mdyn/Å). The Gibbs free energy of activation required to break this N_1–C_6 bond is only 1.5 kcal/mol, as is seen in the next step. Step 6: Finally, the N_1–C_6 bond of Eq6 is broken and, *via* TS6 ($\Delta G = -38.28$ kcal/mol), products including **7** ($\Delta G = -68.62$ kcal/mol) are formed (Fig. 2).

At step 2, when the hydrogen atom at the 2-position of Eq2 approaches the $C_{1'}$ atom of the attached carbanion group, the $C_{1'}$–$S_{2'}$ bond becomes longer, and a methyl group will be formed at the 2-position *via* TS7 ($\Delta G = 3.38$ kcal/mol). The Gibbs free energy of activation of this methylation process is 53.92 kcal/mol, which is much greater than that of the ring-closure process (50.93 kcal/mol). The calculated heat of formation shows the same tendency (Table 1). This fact coincides with the experimental result that phenanthrene was obtained but no methylated *N*-oxide was obtained in this reaction (see Table 2).

We can also assume that the reactions of **1**, **3**, and **4** with **6** proceed in a similar manner. We show the calculated heat of formation and Gibbs free energy of formation in Table 1. For the reaction of **1**, Eq3 is the lowest state in Gibbs free energy and the Gibbs free energy of activation for the liberation process is obtained from TS4 and Eq3. Of course, Gibbs free energy of activation for the methylation is obtained from TS7 and Eq2. The circumstances are the same for the reaction of **4**. The calculated Gibbs free energies of activation and the experimental yields of the products are summarized in Table 2. For the reactions of **1** and **3**, the calculated Gibbs free energy of activation of the *N*-oxide liberation process is lower than that of the methylation process in each case. These results are consistent with the fact that **7** and **8** have been obtained, but the methylated compounds have not been obtained experimentally for the reactions of **1** and **3**. We suppose that **9** has not been obtained experimentally, since the Gibbs free energy of activation for the reaction of **4** is large. On the other hand, the heat of formation of activation for the reaction of **4** is too small to explain the experiments. For reactants **1**, **2**, **3**, and **4**, the Gibbs free energies of activation of the liberation reaction of the *N*-oxide group correlate well with the experimental yields of the related products.

We have also studied the reaction path of **5** with **6** in a similar way. Here, Eq3 is the lowest state in Gibbs free energy and the Gibbs free energy of activation for the liberation process is obtained from TS4 and Eq3 (Table 1). The Gibbs free energy of activation for the methylation process is obtained from TS7 ($\Delta G = 8.14$ kcal/mol, see Table 1) and Eq2. The 3-dimensional view of TS7 is shown in Fig. 4. As shown

Table 2. Calculated Gibbs Free Energy of Activation and Experimental Yield of Adduct

Reactant	Ea(L) (kcal/mol)	Ea(M) (kcal/mol)	Yield(L) (%)	Yield(M) (%)	Temperature and time
1	49.52	58.59	88	—	70 °C, 4h
2	50.93	53.92	86	—	70 °C, 4h
3	52.03	55.69	16	—	70 °C, 4h
4	56.22	—	—	—	70 °C, 4h
5	62.65	53.89	—	42	70 °C, 1h

Here, L and M in parentheses indicate the liberation of an *N*-oxide group and the methylation, respectively.

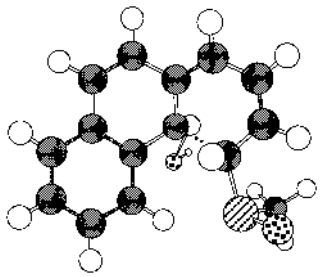

Fig. 3. 3-Dimensional View of TS4 for the Reaction of **2** with **6**, Drawn Using CSC Chem3D Routine

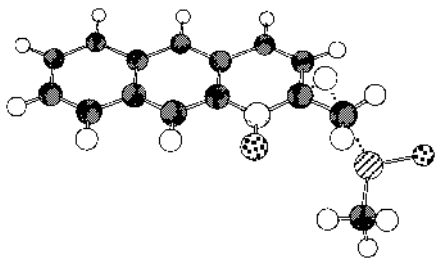

Fig. 4. 3-Dimensional View of TS7 for the Reaction of **5** with **6**, Drawn Using CSC Chem3D Routine

The calculated relevant interatomic distances are: $C_2H = 1.588$ Å, $C_{1'}H = 1.429$ Å, and $C_{1'}S_{2'} = 2.168$ Å. The quoted numbers of atoms are identical with those of TS7 in Fig. 2.

in Tables 1 and 2, the calculated Gibbs free energy of activation for *ortho*-methylation is 53.89 kcal/mol, which is much smaller than that for the liberation reaction of the *N*-oxide group (62.65 kcal/mol). This fact coincides with the experimental result that the *ortho*-methylated compound **10** was obtained, while the anthracene was not obtained experimentally in this reaction. In terms of heat of formation, it seems that the calculated activation energy for the *ortho*-methylation for the reaction of **5** with **6** is too large (Table 1).

To summarize, the reactions of **1**, **2**, and **3** with **6** lead to the liberation of an *N*-oxide group, whereas the reaction of **5** with **6** leads to *ortho*-methylation, on the basis of the reaction path and the calculated Gibbs free energies of activation. The reaction of **4** with **6** cannot occur, since the calculated Gibbs free energies of activation is too large. For reactants **1**, **2**, and **3**, the Gibbs free energies of activation of the liberation reaction of the *N*-oxide group correlate well with the experimental yields of the corresponding products.

Calculation

We calculated the energies of molecules and ions using the semi-empirical molecular orbital PM3 method[8] in the MOPAC 93/97 computational package.[9] All calculations were performed on an IBM RS/6000 model 590 and SGI (Silicon Graphics, Inc.) Indigo2 computers. A graphic interface, MOL-GRAPH,[10] was used for preparing input data for MOPAC 93/97 and for visualizing the resulting structures. The energies of the ground state and transition states were optimized until gradient norms of less than 0.05 kcal/mol/Å were achieved. All structure parameters were optimized. The effect of a solvent was not considered. After optimizing the TS structures, we carried out the vibrational calculation and confirmed that the TS had exactly one imaginary vibrational frequency. We used FORCE and THERMO options and calculated the heat of formation (ΔH) and entropy (S)[11, 12] of the molecules and ions at 70 °C using harmonic oscillator approximation, since the experiments were performed at 70 °C. Then, we calculated the Gibbs free energy of formation (ΔG) by

$$\Delta G = \Delta H - TS$$

Here, T denotes the absolute temperature. Exactly speaking, we must subtract $\Delta H - TS$ for the reference state from above ΔG.[11] When we calculate the Gibbs free energy of activation, these contributions are compensated for. We also performed intrinsic reaction coordinate (IRC) calculations to make sure that the TS connects the initial with the intended final state.

References and Notes

1) Russell G. A., Weiner S. A., *J. Org. Chem*., **31**, 248—251 (1966).
2) Kobayashi Y., Kumadaki I., Sato H., Yokoo C., Miura T., *Chem. Pharm. Bull*., **21**, 2066—2067 (1973).
3) *a*) Hamada Y., Takeuchi I., Hirota M., *Chem. Pharm. Bull*., **19**, 1751—1755 (1971); *b*) Takeuchi I., Hamada Y., *ibid*., **24**, 1813—1821 (1976).
4) Hamada Y., Takeuchi I., *J. Org. Chem*., **42**, 4209—4213 (1977).
5) Takeuchi I., Uchida M., Hamada Y., Yuzuri T., Suezawa H., Hirota M., *Heterocycles*, **41**, 2221—2231 (1995).
6) Hamada Y., Morishita Y., Ozawa I., Takeuchi I., Hirota M., *Chem. Pharm. Bull*., **27**, 1535—1543 (1979).
7) Judging from the calculated values of the bond order, the C_4–C_5, C_5–C_6, and C_5–C_7 bonds in Eq4 have an intermediate nature between the surrounding single and double bonds. We display the C_5–C_6 bond in Eq4 with solid and dotted lines in Fig. 2.
8) Stewart J. J. P., *J. Comput. Chem*., **10**, 209—220; 221—264 (1989).
9) MOPAC 93 release 2, Stewart J. J. P., Fujitsu Limited, Tokyo, Japan (1994); MOPAC 97, Stewart J. J. P., Fujitsu Limited, Tokyo, Japan (1997).
10) MOL-MOLIS/CRYS version 2.4, Daikin Industries, Ltd., Tokyo, Japan (1995).
11) MOPAC 93.00 Manual, Stewart J. J. P., Fujitsu Limited, Tokyo, Japan (1993).
12) In the MOPAC program package, contributions from the vibrational states which have wave numbers lower than 100 cm^{-1} are excluded. Here, we calibrated the above contributions with the excluded vibrational frequencies.