Isotope Effects in the Reaction of Benzo[*h*]quinoline *N*-Oxides with Methylsulfinyl Carbanion Examined by *ab Initio* Molecular Orbital Methods

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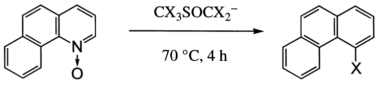
The reactions of benzo[*h*]quinoline *N*-oxide with methylsulfinyl carbanion and deuterated methylsulfinyl carbanion, respectively, were studied theoretically. Differences in yield between these reactions were explained using *ab initio* molecular orbital methods by considering the zero-point energy correction and the barrier penetration effect. In these reactions, two transition states affected the total reaction rate. The hydrogen- or deuterium-transfer step played a significant role, accounting for the difference in reaction rates.

Key words benzo[*h*]quinoline; zero-point energy; tunneling effect; transition state; reaction mechanism; *ab initio* molecular orbital method

The mechanism of the *N*-oxide-liberating reaction of substituted benzo[*f* or *h*]quinoline *N*-oxides with the methylsulfinyl carbanion[1)] has been studied experimentally using deuterated carbanions.[2)] This mechanism has also been studied theoretically using semiempirical molecular orbital (MO) methods,[3)] but the difference in the reaction rate between the reactions with the carbanion and with the deuterated carbanion was not examined (Chart 1).

In the present investigation, we studied the difference in reaction rate (or yield of adduct) between the following two reactions using *ab initio* MO methods: the reaction of benzo[*h*]quinoline *N*-oxide (**1**) with the methylsulfinyl carbanion (**2**) liberating the *N*-oxide group and producing phenanthrene (**4**) (hereafter we refer to this reaction as entry 1) and the reaction of **1** with the deuterated methylsulfinyl carbanion (**3**) producing deuterated phenanthrene (**5**) (entry 2). We assumed that these reactions proceeded as described by Hamada *et al.*[2)] and optimized the structures of the initial state, transition states (TS1—TS4), and intermediate states (Eq1—Eq5) using Gaussian 98 at the HF/6-311++G(d, p) level.[4)] The calculated energy diagram is shown in Fig. 1. Because ordinary MO methods employing the Born–Oppenheimer approximation give the same energies regardless of isotope mass, we took into account corrections due to zero-point oscillation and transmission through the potential barrier (the tunneling effect) to study the isotope effect.

Zero-Point Correction Since a deuterium (D) atom has twice the mass of a hydrogen (H) atom, the vibrational frequency of the C–D bond is about $1/\sqrt{2}$ times that of the C–H bond. The ground state energy of a molecule includes the energies of all zero-point oscillations, but a transition state has an imaginary vibrational frequency, which does not contribute to the zero-point energy (ZPE). Therefore, if a TS is involved in the transfer of a H or D atom, its energy is subject to a zero-point correction of which the value depends on the mass of the transferred atom (Figs. 2 and 3).



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4: X=H (86%)
5: X=D (50%)

Chart 1

We performed vibrational calculations and estimated the ZPE correction for the initial state, Eq2, TS3, and TS4 by including the scale factor 0.9248.[5)] We also calculated activation energies (*Ea*) as differences in energy between each TS and Eq2. These results are shown in Table 1. The corrected

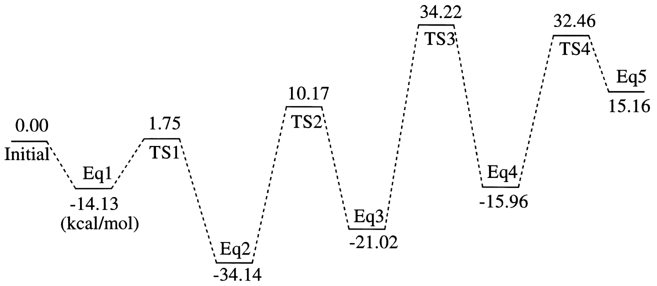

Fig. 1. Energy Diagram Optimized at RHF/6-311++G(d, p) Level (before Corrections)

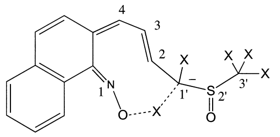

Fig. 2. Schematic View of TS3: X=H or X=D

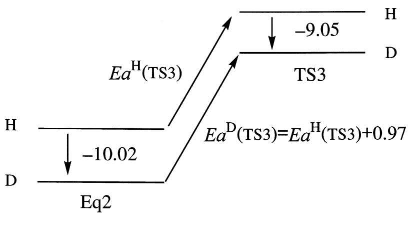

Fig. 3. Energy Diagram (kcal/mol) of Eq2 and TS3 after ZPE Correction

The value 0.97 kcal/mol can also be read from Table 1 as a difference 64.90—63.93 in *Ea*(TS3) after ZPE correction.

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Table 1. Energies (kcal/mol) of Eq2, TS3, Eq4 and TS4 after Corrections for ZPE and Barrier Penetration

	HF	ZPE correction only		ZPE+Tunneling	
		(Entry 1)	(Entry 2)	(Entry 1)	(Entry 2)
Initial	0.0	0.0	0.0	0.0	0.0
Eq2	−34.14	−31.26	−31.89	−31.26	−31.89
TS3	34.22	32.67	33.01	31.65	32.59
Ea(TS3)[a]		(63.93)	(64.90)	(62.91)	(64.48)
Eq4	−15.96	−14.38	−14.95	−14.38	−14.95
TS4	32.46	33.40	32.84	33.32	32.76
Ea(TS4)[b]		(64.66)	(64.73)	(64.58)	(64.65)

Energies were calculated at the RHF/6-311++G(d, p) level and normalized to the initial state. *a*) *E*(TS3)−*E*(Eq2). *b*) *E*(TS4)−*E*(Eq2).

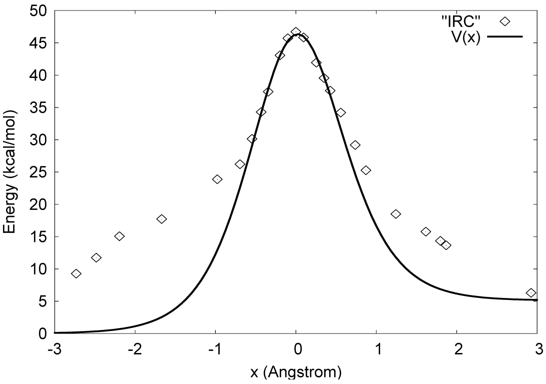

Fig. 4. Potential Energy Surface around TS3 Calculated Using PM3 Method

The horizontal axis (x) stands for the distance of the H(D) atom from its position at TS3. The diamonds denote the values obtained from IRC calculations and the solid line denotes the Eckart potential (A=5.11 kcal/mol, B=175.0 kcal/mol, L=2.48 Å) fitted to IRC data within $x=\pm 0.5$ Å.

value for the *Ea* of TS3 in entry 2 was 0.97 kcal/mol larger than that in entry 1, but this difference was very small for the *Ea* values of TS4.

Effect of Barrier Penetration The tunneling effect had a significant influence only on TS3, which involves H or D transfer, because the effect becomes larger as the mass of the barrier-penetrating particle becomes smaller. We calculated the potential energy surface along the reaction coordinates around TS3 using the PM3 method[6)] to save computational time. For this purpose, we reoptimized the structures of TS3 and performed vibrational and intrinsic reaction coordinate calculations. Subsequently, we obtained the potential energy in the vicinity of TS3 *versus* distance between the current position of H (or D) and that at TS3, as shown in Fig. 4.

We approximated this potential energy surface using the following Eckart potential[7)] (A=5.11 kcal/mol, B=175.0 kcal/mol, L=2.48 Å), shown in Fig. 4 by a solid line:

$$V(x) = \frac{Au}{1+u} + \frac{Bu}{(1+u)^2}, \quad u = \exp(-2\pi x/L) \tag{1}$$

Since an analytical expression exists for the transmission coefficient as a function of particle energy E, $\kappa(E)$, for the Eckart potential, we can express the ratio (R) of the quantum rate constant to the classic rate constant by averaging this coefficient with the Boltzmann distribution[8,9)]:

$$R = e^{E^*/k_B T} \int_0^\infty \kappa(E) e^{-E/k_B T} d(E/k_B T) \tag{2}$$

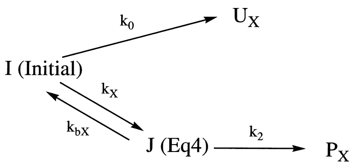

Fig. 5. Schematic Model of the Reactions: X=H or X=D

Here E^* and k_B denote the classic activation energy and the Boltzmann constant, respectively. Performing this integral numerically at the experimental temperature (70 °C),[1)] we obtained R=4.48 for H transfer and R=1.86 for D transfer. These values can be converted to a change in activation energy of −1.02 and −0.42 kcal/mol, respectively. The tunneling effect for TS4 was calculated using the Wigner expression.[10,11)] The correction for the activation energy of TS4 was −0.08 kcal/mol for both reactions. These results are summarized in Table 1.

Schematic Model of the Reaction Since the difference in activation energy between TS3 and TS4 was small after zero-point and tunneling corrections, as shown in Table 1, both transition states will contribute to the rate constant. Since Eq2 is the lowest-energy state, and the energy of TS1 is not large, we assumed that the majority of reactants exist in the form of Eq2, from which the reaction starts. Taking into account miscellaneous sidereactions in addition to the main reaction (Chart 1), we propose the simple reaction model shown in Fig. 5.

In Fig. 5, P and U denote the final compound and byproduct, respectively. k_X is the rate constant of the reaction forming Eq4 *via* TS3, and k_{bX} is that of the reverse reaction, where the suffix X stands for H or D. k_2 is the rate constant of the reaction forming the product P (**4** or **5**) from Eq4 *via* TS4. These rate constants are expressed by the following Arrhenius equations:

$$k_X = A_f \exp(-(E_X(\mathrm{TS3}) - E_X(\mathrm{Eq2}))/RT) \tag{3a}$$

$$k_{bX} = A_f \exp(-(E_X(\mathrm{TS3}) - E_X(\mathrm{Eq4}))/RT) \tag{3b}$$

$$k_2 = A_f \exp(-(E_X(\mathrm{TS4}) - E_X(\mathrm{Eq4}))/RT) \tag{3c}$$

Here A_f denotes a frequency factor and was assumed to have the same value for k_X, k_{bX}, and k_2. Using the corrected values of E_X in Table 1, we obtained the following ratios of rate constants:

$$\frac{k_H}{k_D} = 10.0, \quad \frac{k_{bH}}{k_2} = 11.6, \quad \frac{k_{bD}}{k_2} = 1.28 \tag{4}$$

The rate constant of the unidentified sidereaction forming U is k_0. We assumed that k_2 and k_0 had the same value for X=H or D.

For simplicity, we express the amounts of the reactant and Eq4 as $[I]$ and $[J]$, respectively. If we assume that the reactions in Fig. 5 are all first order, the rate of change in concentration for each compound is expressed as:

$$\frac{d[I]}{dt} = -(k_0 + k_X)[I] + k_{bX}[J], \quad \frac{d[J]}{dt} = k_X[I] - (k_{bX} + k_2)[J] \tag{5a}$$

$$\frac{d[U]}{dt} = k_0[I], \quad \frac{d[P]}{dt} = k_2[J] \tag{5b}$$

Here, if we put $[I]=[I_0]$, $[J]=[U]=[P]=0$ at the beginning of the reaction (t=0), we obtain the following expression at

$t \rightarrow \infty$:

$$\frac{[P_X]}{[U_X]} = \frac{k_X k_2}{k_0(k_{bX}+k_2)} \qquad (6)$$

Since we did not identify the side reaction, we cannot theoretically calculate the value of k_0. We therefore extract the value of k_0 using the measured yield of entry 1, estimate the yield of adduct in entry 2, and compare the value with the measured yield.

From the measured value:

$$\frac{[P_H]}{[U_H]+[P_H]} = 0.86 \text{ (Chart 1)}$$

we obtain:

$$\frac{[P_H]}{[U_H]} = \frac{k_H/k_0}{1+k_{bH}/k_2} = 6.14$$

Combining this and the values in Eq. 6, we obtain the following ratios of rate constants:

$$\frac{k_H}{k_0} = 77.3, \quad \frac{k_D}{k_0} = 7.73 \qquad (7)$$

Using the values in Eqs. 6 and 7, we can calculate the yield of the reaction involving D transfer (entry 2):

$$\frac{[P_D]}{[U_D]+[P_D]} = \frac{k_D/k_0}{1+k_D/k_0+k_{bD}/k_2} = 0.77 \qquad (8)$$

Although this value is somewhat greater than the measured value of 0.50, we can qualitatively explain why the yield of adduct in entry 2, involving D transfer, was smaller than that in entry 1, involving H atom transfer.

We were able to explain qualitatively the difference in reaction rate (or yield of adduct) between entries 1 and 2, involving H or D atom transfer, respectively, by calculating the optimized energies of relevant transition states and intermediate states using *ab initio* MO methods. This was achieved by adding the ZPE correction and estimating the barrier penetration effect around TS3, and by constructing a simplified reaction model. The tunneling effect in TS4 was small and equal for both reactions since the reduced masses of vibration (having an imaginary frequency) at TS4 are large and nearly equal. It is interesting to note that the ratio of rate constants (k_H/k_D) for forming Eq4 *via* TS3 was 10.0 (calculated value) but the final ratio of yields was only 1.72 (measured value). This is because *Ea* (TS3, H) is significantly smaller than *Ea* (TS3, D) and the rate-determining step involves not TS3 but TS4. Therefore the ratio of rate constants for the reverse reaction (k_{bH}/k_{bD}) *via* TS3 is also large (9.17, calculated) and the ratio of product yields is understandably not as large.

References

1) Hamada Y., Takeuchi I., *J. Org. Chem.*, **42**, 4209—4213 (1977).
2) Hamada Y., Morishita Y., Ozawa I., Takeuchi I., Hirota M., *Chem. Pharm. Bull.*, **27**, 1535—1543 (1979).
3) Matsuzaki H., Takeuchi I., Hamada Y., *Chem. Pharm. Bull.*, **48**, 525—528 (2000).
4) Gaussian 98, Revision A.11.3, Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Zakrzewski V. G., Montgomery J. A., Jr., Stratmann R. E., Burant J. C., Dapprich S., Millam J. M., Daniels A. D., Kudin K. N., Strain M. C., Farkas O., Tomasi J., Barone V., Cossi M., Cammi R., Mennucci B., Pomelli C., Adamo C., Clifford S., Ochterski J., Petersson G. A., Ayala P. Y., Cui Q., Morokuma K., Rega N., Salvador P., Dannenberg J. J., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Cioslowski J., Ortiz J. V., Baboul A. G., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Gomperts R., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Andres J. L., Gonzalez C., Head-Gordon M., Replogle E. S., Pople J. A., Gaussian, Inc., Pittsburgh PA, 2002.
5) Scott A. P., Radom L., *J. Phys. Chem.*, **100**, 16502—16513 (1996).
6) MOPAC 2000, Stewart J. J. P., Fujitsu Limited, Tokyo, Japan, 1999.
7) Eckart C., *Phys. Rev.*, **35**, 1303—1309 (1930).
8) Johnston H. S., Rapp D., *J. Am. Chem. Soc.*, **83**, 1—9 (1961).
9) Johnston H. S., Heicklen J., *J. Phys. Chem.*, **66**, 532—533 (1962).
10) Wigner E., *Z. Phys. Chem.*, **B19**, 203—216 (1932).
11) Bell R. P., *Trans. Faraday Soc.*, **55**, 1—4 (1959).