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"Two-Step" Mechanism in Single-Step Isomerizations. Kinetics in Highly Viscous Liquid Phase

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Abstract: The kinetic effects of pressure on the thermal *Z/E* isomerization of substituted azobenzenes and *N*-benzylideneanilines were studied in a viscous solvent, glycerol triacetate. In the lower pressure region ($P \leq 200$ MPa (=2000 bar)), the pressure effects observed were in accordance with the transition-state theory (TST). However, at higher pressures, all of the reactions studied were retarded relatively strongly by an increase in pressure, which increases the solvent viscosity. The observations were analyzed by assuming the existence of two steps in the reaction. In the first step, molecular arrangement in the solvated state is transformed during solvent diffusive fluctuations to form the intermediate state M; this step was considered to be slowed by the increase in viscosity. In the second step, the energy-barrier crossing toward the product surface takes place, and this process was assumed to be little influenced by the viscosity. In this two-step mechanism, the rate constant in the steady state can be given by $1/(k_{\mathrm{TST}}^{-1} + k_f^{-1})$, where k_{TST} is the TST-expected rate constant and k_f the fluctuation-limited one. The rate constants observed nicely fit this formula, where the k_f values thus obtained gave linear Arrhenius plots with a fractional-power-law dependence ($k_f \propto \eta^{-\beta}$, $0 < \beta < 1$) on the viscosity η. Compared at the same viscosity, the k_f values were almost independent of the reaction temperature in most of the reactions studied, suggesting that the steric transformations of the reactant generally remain minimal in the first step.

Introduction

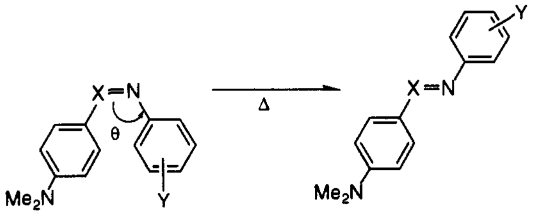
It has been long recognized that high-pressure kinetics can provide useful mechanistic information on chemical reactions. In such studies, activation volumes $\Delta V^{\ddagger}$ are calculated from pressure dependence of the rate constant according to the following equation.

$$\Delta V^{\ddagger} = -RT(\partial \ln k/\partial P) \qquad (1)$$

The sign and the magnitude of the parameter are interpreted in terms of molar volume changes caused by bond scission/formation and solvation/desolvation. This procedure assumes that the rate constant k can be expressed by eq 2, as predicted by the transition-state theory (TST).

$$k = \frac{\mathbf{k}T}{h} e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R} \qquad (2)$$

In almost all of the reactions studied so far, activation volumes thus obtained were satisfactorily correlated with known reaction mechanisms.[1] Compilation of a huge number of such studies[3–5] gave high pressure kineticists strong confidence in the use of activation volume as a mechanistic criterion. Recently, however, Asano and his co-workers[6] reported the failure of TST in thermal *Z/E* isomerization of 4-(dimethylamino)-4′-nitroazobenzene (DNAB) (eq 3). When the reaction was studied in common solvents, normal pressure effects were observed in the whole range of pressure studied ($P \leq 800$ MPa). However, unusual pressure-induced retardation was observed at high pressures when viscous liquids such as glycerol triacetate (GTA) were used as reaction media. In the present paper, the results of high-pressure kinetics in GTA for thermal *Z/E* isomerization of 4-(dimethylamino)-2′-methoxy-4′-nitroazobenzene (DMNAB), *N*-[4-(dimethylamino)benzylidene]-4-nitroaniline (DBNA), *N*-[4-(dimethylamino)-benzylidene]-4-ethoxycarbonylaniline (DBEA), *N*-[4-(dimethylamino)benzylidene]-4-bromoaniline (DBBA), and *N*-[4-(dimethylamino)benzylidene]-4-(dimethylamino)aniline (DBDA) are presented and the physical meaning of the observations is discussed.



(3)

X=N, Y=4-NO$_2$: DNAB
X=CH, Y=4-NO$_2$: DBNA
X=CH, Y=Br : DBBA
X=N, Y=2-MeO, 4-NO$_2$: DMNAB
X=CH, Y=4-COOEt : DBEA
X=CH, Y=4-NMe$_2$: DBDA

Experimental Section

Materials. DMNAB was prepared from *N,N*-dimethylaniline and 2-methoxy-4-nitroaniline. The preparation of *N*-benzylideneanilines was described previously.[7] All of the substrates gave satisfactory elementary analyses. The melting/decomposition points (in °C) are as follows:

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(1) Hamann[2] observed pressure-induced retardations in S$_N$2 reactions between ethyl bromide and various alkoxide ions at several gigapascals. The effect was attributed to the slow translational diffusion at highly viscous conditions.

(2) Hamann, S. D. *Trans. Faraday Soc.* **1958,** *54,* 507.

(3) le Noble, W. J. *Prog. Phys. Org. Chem.* **1967,** *5,* 207.

(4) Asano, T.; le Noble, W. J. *Chem. Rev.* **1978,** *78,* 407.

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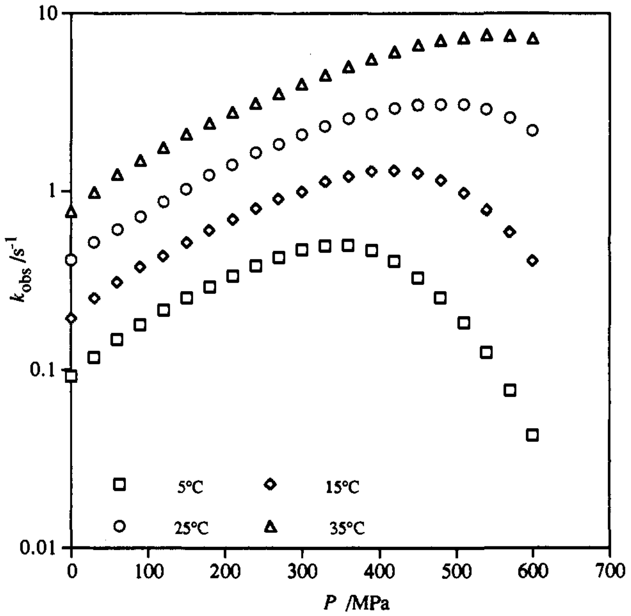


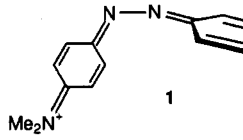
Figure 1. Pressure effects on the thermal *Z/E* isomerization of DMNAB at various temperatures.

DMNAB, 176–7.5; DBNA, 208.5–9.5 (207[8]); DBEA, 120–2 (121[9]); DBBA, 161–2 (162[9]); DBDA, 238–9 (239–40[10]). The structure of DMNAB was confirmed by ^{1}H NMR (270 MHz CDCl$_3$) (δ 3.11 (6H, s), 4.08 (3H, s), 6.74 (2H, d, J = 9.6 Hz), 7.68 (1H, d, J = 7.7 Hz), 7.86–7.92 (4H, m)) and ^{13}C NMR (67.8 MHz, CDCl$_3$) (δ 40.2, 56.7, 107.7, 111.4, 116.5, 117.4, 126.1, 144.4, 146.9, 148.2, 153.2, 155.6) spectra. Glycerol triacetate (Wako Pure Chemical Ind.) was used after distillation (140 °C/12 mmHg).

Kinetic Measurements. The unstable *Z*-isomer was formed by irradiation from a xenon flash lamp, and its decay was followed spectrophotometrically. The details of the kinetic measurements were described in the literature.[11]

Results and Discussion

Isomerization of DMNAB. Azobenzenes with push–pull substituents isomerize *via* rotation after heterolytic scission of the nitrogen–nitrogen π bond (transition state **1**).[12] DMNAB isomerizes slightly more slowly than DNAB because of the electron donation by the 2-methoxy group: the rate constants at 25 °C and 0.1 MPa (=1 bar) were 0.412 and 1.29 s^{-1} for DMNAB and DNAB, respectively. The pressure dependence of the isomerization rate of DMNAB was studied at four different temperatures in the range 0.1–600 MPa. The results are illustrated in Figure 1. Stronger electrostriction in the transition state causes a volume decrease during the activation, and it should result in acceleration by an increase in pressure. This expectation was met at the beginning of pressurization. However, at higher pressures, the reaction was strongly suppressed by an increase in pressure, as observed for DNAB.



1

Isomerization of *N*-Benzylideneanilines. Despite the apparent structural similarities in azobenzene and *N*-benzylideneaniline, the latter does not isomerize *via* rotation even in the presence of strongly electron-donating and electron-attracting substituents.[7,13] The isomerization is effected by inversion of the nitrogen atom; that is, the nitrogen is rehybridized (sp^2 → sp) while the bond angle θ increases (transition state **2**). In this mechanism, a large volume change will not take place during the activation because neither bond scission/formation nor charge separation/neutralization takes place. There might be a small volume increase caused by a slight polarity decrease in the nitrogen rehybridization.[14] A small volume decrease may also be possible if the rotation of the *N*-phenyl group becomes more restricted by stronger conjugation of the nitrogen lone pair with the phenyl group in the transition state.[7] These two effects will offset each other, and as a result, very small kinetic effects of pressure will be observed under TST-applicable circumstances. Figure 2 presents the results for DBEA at various temperatures, and Figure 3 shows the results at 25 °C for various anils. The reaction was slightly suppressed by an increase in pressure ($\Delta V^{\ddagger}$ = 0.0–2.6 cm^3 mol^{-1}) at lower pressures. As can be seen clearly from the figures, however, much stronger pressure-induced retardations were observed at the later stage of pressurization.

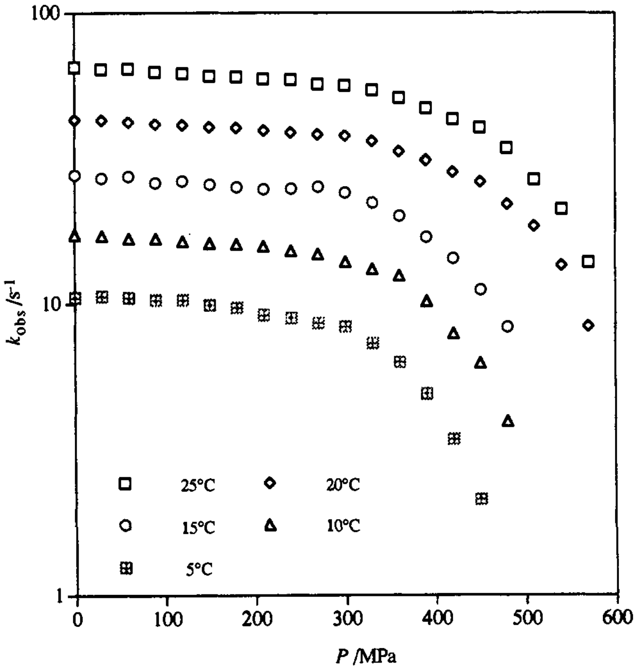
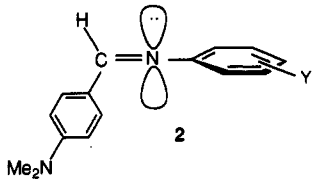


Figure 2. Pressure effects on the thermal *Z/E* isomerization of DBEA at various temperatures.



2

Existence of Two Steps at Fluctuation-Controlled Conditions. The observed strong pressure-induced retardation cannot be rationalized by assuming the existence of two competing reaction routes because a reaction with a positive activation volume has no chance to become predominant at high pressures. The fact that such pressure-induced retardation was observed only in viscous liquids strongly suggests that these thermal unimolecular reactions became solvent-fluctuation-controlled at high pressures

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(8) Eley, D. D.; Newman, O. M. G. *Trans. Faraday Soc.* **1970**, *66*, 1106.

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(12) Asano, T.; Okada, T. *J. Org. Chem.* **1986**, *51*, 4454.

(13) Asano, T.; Okada, T.; Herkstroeter, W. G. *J. Org. Chem.* **1989**, *54*, 379.

(14) Haberfield, P.; Block, P. M.; Lux, M. S. *J. Am. Chem. Soc.* **1975**, *97*, 5804.

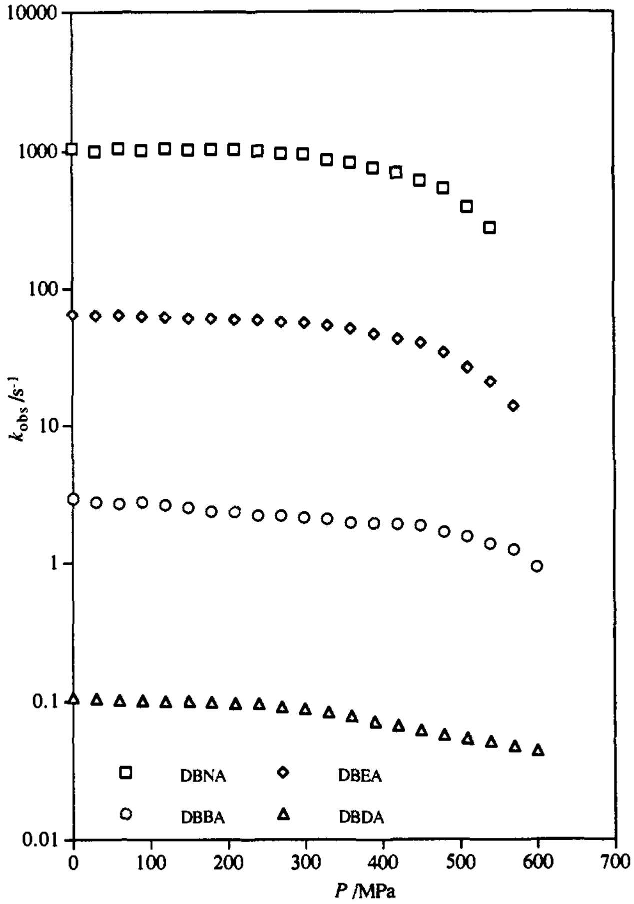

Figure 3. Pressure effects on the thermal Z/E isomerization of several N-benzylideneanilines at 25 °C.

because of the extremely high viscosity of the reaction medium. For example, the viscosity of GTA[6,15] at 25 °C and 600 MPa is estimated to be 4580 Pa s, which is 4850 times as large as that of glycerol at 25 °C and 0.1 MPa. At higher temperatures, the solvent viscosity is lower and higher pressures will be required to realize solvent-fluctuation control. Figures 1 and 2 are in accordance with this expectation. The solvent-fluctuation control of the unimolecular reactions can be understood by assuming a two-step mechanism[18] shown below, where Z and E denote the two isomers and M denotes the intermediate state.

$$Z \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} M \xrightarrow{k_2} E \qquad (4)$$

The first step, with rate constants k_1 and k_{-1}, depicts rearrangement of the solvent molecules around the reactant during solvent diffusive fluctuations whose speed depends on the solvent viscosity. The reactant still remains on the energy surface of the initial species at M. The second step, with a rate constant k_2, is the energy-barrier crossing from M toward the product surface due to thermal intramolecular vibrations of the reactant which are not suppressed by an increase in the solvent viscosity. When the solvent fluctuations are fast enough, i.e., in low-viscosity solvents, Z and M are in equilibrium and the observed rate constant must be the one predicted by TST, whose value is given by k_1k_2/k_{-1}, where k_1/k_{-1} equals the equilibrium constant for M relative to Z.

$$k_{obs} = k_{TST} = k_1k_2/k_{-1} \qquad (5)$$

On the other hand, in extremely viscous media, the first step will be much slower than the vibration-induced second step. Then, the reaction becomes solvent-fluctuation-controlled, and the observed rate constant should tend to the fluctuation-limited rate constant k_f given by k_1.

$$k_{obs} = k_f = k_1 \qquad (6)$$

In the intermediate viscosity region, the observed rate constant will be correlated to the TST-expected and the fluctuation-limited rate constants by eq 7, which can be obtained by assuming the steady state in the two-step mechanism of eq 4, as shown in the Appendix.

$$1/k_{obs} = 1/k_{TST} + 1/k_f \qquad (7)$$

TST-expected rate constants at higher pressures can be estimated by extrapolating the results at TST-applicable pressures. In the N-benzylideneanilines, this extrapolation is relatively simple because the pressure effects are small and the free energy of activation can be assumed to be linearly correlated with pressure. In the azobenzenes, the TST-expected pressure effect is relatively large and it is nonlinearly correlated with the pressure. In such cases, eqs 8 and 9 had been proved to be suitable for extrapolations, where k_P and k_0 are the rate constants at pressure P and atmospheric pressure, respectively, and a, b, and c are the adjustable parameters.[11,15]

$$\ln(k_P/k_0) = aP + b\ln(1 + cP) \qquad (8)$$

$$\ln(k_P/k_0) = aP + bP/(1 + cP) \qquad (9)$$

Both of these equations are almost equally effective to reproduce relatively large kinetic effects of pressure, and eq 9 was adopted in order to extrapolate the results for DMNAB because it resulted in slightly better fittings for lower pressure data.

Figures 4 and 5 show examples of the extrapolations and the fluctuation-limited rate constants derived on the basis of eq 7. If eq 4 describes the reaction correctly, k_f values are expected to give linear Arrhenius plots because the solvent fluctuations require thermal activation and the reactant may climb up the energy surface during the first step. This expectation was met, as exemplified by Figure 6. In all of the compounds studied, no systematic deviation from the expected linear correlation between ln k_f and $1/T$ was observed. The validity of the two-step mechanism can be further tested by examining the viscosity dependence of the fluctuation-limited rate constant k_f. Rate constants observed in many fast unimolecular reactions such as photo-induced Z/E isomerization of stilbene[19] have been shown to have a fractional-power dependence on the inverse of the solvent viscosity η as $k_{obs} \propto \eta^{-\beta}$ with $0.2 < \beta < 1$. Similar dependence on η may be expected for our k_f values since k_{obs} in these fast reactions tends to k_f in eq 7 because they may be considered to be in the fluctuation-controlled regime ($k_f \ll k_{TST}$). This expectation was also met as

$$k_f = B\eta^{-\beta} \quad (0.5 \le \beta \le 0.8) \qquad (10)$$

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[15] Pressure dependence of the solvent viscosity η was measured at five different temperatures in the pressure range 0.1–415 MPa, and the results were fitted to the following equation,[16] where η and η_0 are the viscosities at pressure P and atmospheric pressure, respectively.

$$\eta = \eta_0 \exp(\alpha P)$$

Since the pressure usually ranges up to several hundred megapascals, the atmospheric pressure is assumed to be 0 in this and other empirical functions describing pressure effects. The pressure–viscosity coefficient α at the reaction temperature was estimated by the empirical linear correlation[17] between α and the logarithm of the atmospheric kinematic viscosity.

[16] Barns, C. *Am. J. Sci.* **1893**, *45*, 87.

[17] Wu, C. S.; Klaus, E. E.; Duda, J. L. *Trans. ASME, J. Tribol.* **1989**, *111*, 121.

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[19] Waldeck, D. H. *Chem. Rev.* **1991**, *91*, 415.

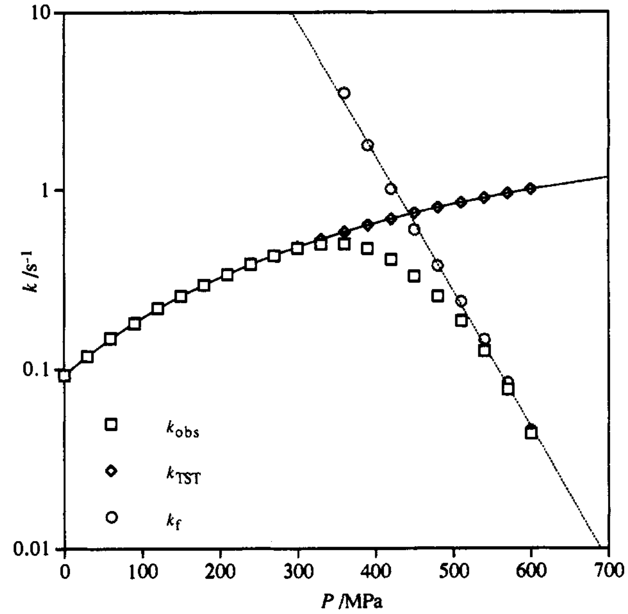

Figure 4. Analysis of the results for DMNAB at 5 °C.

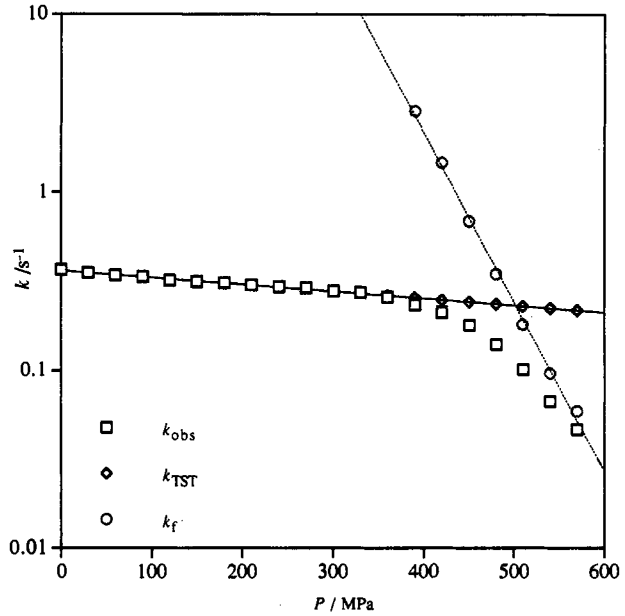

Figure 5. Analysis of the results for DBBA at 5 °C.

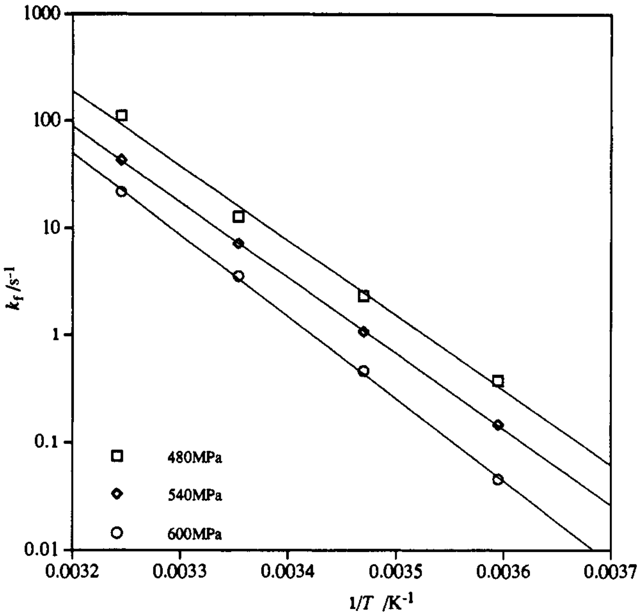

Figure 6. Arrhenius plots for the fluctuation-limited rate constant in the thermal Z/E isomerization of DMNAB at various pressures.

Table 1. Viscosity Coefficients β for the Fluctuation-Limited Rate Constants in the Thermal Z/E Isomerization of Azobenzenes and *N*-Benzylideneanilines in GTA

T/°C	DNAB[a]	DMNAB	DBNA	DBEA	DBBA	DBDA
5	0.589	0.561	0.648	0.632	0.705	
10			0.670	0.686	0.759	
15	0.629	0.519	0.739	0.764	0.833	
20			0.904	0.671	0.830	0.217
25	0.728	0.511	0.682	0.779		0.265
30						0.360
35						0.351
40	0.737					

[a] Calculated from the results in ref 6.

The β values are given in Table 1. The fractionality of the viscosity dependence may be understood by considering that M is not a single state but is distributed on the reactant surface along which diffusive fluctuations of molecular arrangement take place.[18] Judging from these results, it may be safely concluded that the two-step mechanism is valid in highly viscous media for the present thermal isomerizations, which can be considered to proceed in a single step at normal conditions.[20]

Activation energies Ea_{TST} and Ea_f calculated from the temperature dependence of the isopiestic k_{TST} and k_f values are listed in Tables 2 and 3, respectively. Although k_f values were larger in the reactions with larger k_{TST} values, no clear correlation between Ea_{TST} and Ea_f was found. This fact seems consistent also with eq 10, where Ea_f is determined not only by the temperature dependence of B but also by that of η^{-1}, which shows usually a thermally activated temperature dependence. On the other hand, Ea_{TST} is determined simply by the energy of the transition state, which is usually independent of the solvent viscosity.

The temperature dependence of B in eq 10 should be determined by the energy of the M state. In this context, it is interesting to note that, compared at the same viscosity, the fluctuation-limited rate constant k_f shows only nominal temperature dependence except in DBDA. An example is illustrated in Figure 7. This fact suggests strongly that the energy of the reactant itself remains almost unchanged during the first step. Therefore, the activation energy for the first step is mainly determined by that of η^{-1}, which is required to activate solvent fluctuations. We consider that suitable solvent orientations, probably larger cavities, must be formed prior to the isomerization as the first step in the two-step mechanism of eq 4. The activation volumes[22] calculated from the pressure dependence of k_f in Table 4 might be taken to give the magnitude of the volume increase at the first step. DBDA was an exception. As shown in Figure 8, k_f values at the same viscosity were dependent on the temperature in this anil. It seems, therefore, that the energy of the reactant increases during the first step in DBDA. In other words, solvent fluctuations and a part of the steric transformations of the reactant are interlocked in this compound. If a conformational change such as rotation of a phenyl group is required prior to an increase in the bond angle θ, the rotation may be slowed down with an increase in the solvent viscosity. Smaller activation volumes (Table 4) in this compound are in accordance with this interpretation. The

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[20] Whalley and his co-workers[21] reported pressure-induced retardations of some solvolyses in the gigapascal region. The results were rationalized on the basis of TST. In the light of the present results, however, their observations may be understood by assuming solvent-fluctuation-control prior to the heterolytic cleavage of the carbon–halogen bond.

[21] Cameron, C.; Saluja, P. P. S.; Floriano, M. A.; Whalley, E. *J. Phys. Chem.* **1988**, *92*, 3417.

[22] A linear correlation, $\ln k_f = a + bP$, was assumed in the calculations.

Table 2. Frequency Factors (A_{TST}/s^{-1}) and Activation Energies (Ea_{TST}/kJ mol^{-1}) Calculated from k_{TST} Values for the Thermal *Z/E* Isomerization of Azobenzenes and *N*-Benzylideneanilines

	DNAB[a]		DMNAB		DBNA		DBEA		DBBA		DBDA	
P/MPa	A_{TST}	Ea_{TST}	A_{TST}	Ea_{TST}	A_{TST}	Ea_{TST}	A_{TST}	Ea_{TST}	A_{TST}	Ea_{TST}	A_{TST}	Ea_{TST}
0.1	6.2×10^8	49.5	3.2×10^8	50.8	2.4×10^{12}	53.5	6.1×10^{12}	62.6	8.7×10^{12}	71.3	1.7×10^{12}	75.4
60	1.6×10^9	51.0[b]	4.0×10^8	50.3	3.2×10^{12}	54.2	5.7×10^{12}	62.5	5.9×10^{12}	70.5	1.1×10^{12}	74.3
120	3.2×10^9	51.4[c]	4.5×10^8	49.7	3.0×10^{12}	54.0	4.5×10^{12}	62.0	9.3×10^{12}	71.7	7.7×10^{11}	73.6
180	3.3×10^9	50.9[d]	7.0×10^8	50.0	1.4×10^{12}	52.3	3.6×10^{12}	61.5	4.3×10^{12}	70.0	6.9×10^{11}	73.4

[a] Calculated from the k_{TST} values in ref 6. [b] At 50 MPa. [c] At 150 MPa. [d] At 200 MPa.

Table 3. Frequency Factors (A_f/s^{-1}) and Activation Energies (Ea_f/kJ mol^{-1}) Calculated from k_f Values for the Thermal *Z/E* Isomerization of Azobenzenes and *N*-Benzylideneanilines

	DNAB[a]		DMNAB		DBNA		DBEA		DBBA		DBDA	
P/MPa	A_f	Ea_f	A_f	Ea_f	A_f	Ea_f	A_f	Ea_f	A_f	Ea_f	A_f	Ea_f
330					3.7×10^{30}	150						
360					9.9×10^{28}	142	9.8×10^{23}	121				
390					2.7×10^{28}	141	1.7×10^{24}	123				
420					4.4×10^{25}	127	1.7×10^{25}	130				
450	3.9×10^{22}	118			1.6×10^{27}	137	3.5×10^{27}	144	6.0×10^{28}	154		
480			4.2×10^{24}	134			1.1×10^{27}	143	6.8×10^{28}	156	3.2×10^{22}	132
510	9.8×10^{22}	122[b]	2.5×10^{24}	133					3.9×10^{28}	156	1.1×10^{27}	159
540	5.2×10^{23}	128[c]	3.7×10^{24}	135					9.3×10^{27}	154	6.0×10^{25}	152
570			1.5×10^{25}	140					2.5×10^{28}	158	4.6×10^{23}	140
600	7.5×10^{25}	142	1.5×10^{26}	146					3.4×10^{26}	149	2.1×10^{23}	139

[a] Calculated from the k_{dif} values in ref 6. [b] At 500 MPa. [c] At 550 MPa.

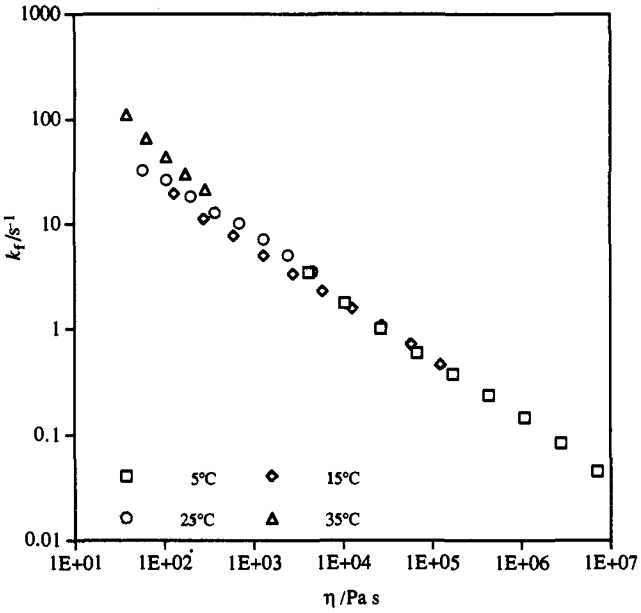

Figure 7. Relation between the fluctuation-limited rate constant and the solvent viscosity in the thermal *Z/E* isomerization of DMNAB.

Table 4. Activation Volumes ($\Delta V^{\ddagger}_f$/cm^3 mol^{-1}) for the Fluctuation-Limited Rate Process in the Thermal *Z/E* Isomerization of Azobenzenes and *N*-Benzylideneanilines

	T/°C							
reactant	5	10	15	20	25	30	35	40
DNAB[a]	42		38		39			30
DMNAB	40		32		26		35	
DBNA	47	44	47	51	35			
DBEA	45	46	53	38	40			
DBBA	51	50	51	47	52			
DBDA				12	12	17	15	34

[a] Calculated from the results in ref 6.

geometrical changes in the second step will be less extensive, and smaller cavities will suffice for such transformations. The reasons behind this peculiar behavior of DBDA are not clear enough at this moment. Similar measurements in other solvents and on other compounds are in progress. The results will be reported when they are completed.

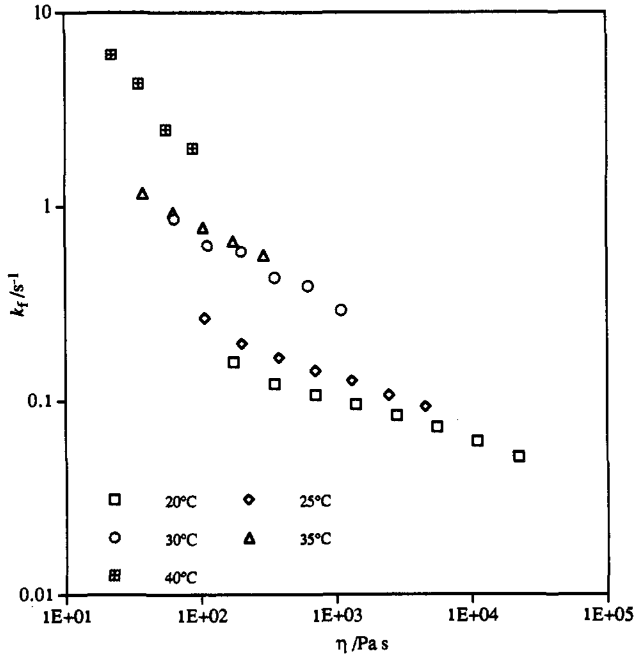

Figure 8. Relation between the fluctuation-limited rate constant and the solvent viscosity in the thermal *Z/E* isomerization of DBDA.

Conclusions

Thermal isomerizations with appreciable activation energies became solvent-fluctuation-controlled when they were run in highly viscous conditions. The results could be analyzed on the basis of a two-step mechanism. Rearrangement of the solvent molecules to form cavities during solvent diffusive fluctuations seems to be required before the actual steric transformations.

Appendix

The steady state can be realized in two ways in the two-step mechanism of eq 4. When Z is supplied with an appropriate rate, populations at the Z and M states, written as [Z] and [M] respectively, can be maintained time-independent in the steady state. In this case, incoming and outgoing rates of populations balance each other at each state. Therefore,

$$\left.\begin{array}{l} k_s[\mathrm{Z}] - k_1[\mathrm{Z}] + k_{-1}[\mathrm{M}] = 0 \\ k_1[\mathrm{Z}] - (k_{-1} + k_2)[\mathrm{M}] = 0 \end{array}\right\} \quad (\text{A-1})$$

is satisfied, where $k_s[\mathrm{Z}]$ represents the supply rate of Z with a rate constant k_s. Eliminating [M] from eq A-1, we can easily obtain k_s given by

$$k_s = \frac{k_{\mathrm{TST}} k_f}{k_{\mathrm{TST}} + k_f} \quad (\text{A-2})$$

with $k_{\mathrm{TST}} = k_1 k_2 / k_{-1}$ and $k_f = k_1$, in agreement with eq 7 in the text.

In the present experiment, however, Z is not supplied during the reaction except at the initial moment when Z is produced by photoexcitation. In this situation, [Z] decays with time t. Time evolution of [Z] and [M] is described by coupled rate equations

$$\left.\begin{array}{l} \mathrm{d}[\mathrm{Z}]/\mathrm{d}t = -k_1[\mathrm{Z}] + k_{-1}[\mathrm{M}] \\ \mathrm{d}[\mathrm{M}]/\mathrm{d}t = k_1[\mathrm{Z}] - (k_{-1} + k_2)[\mathrm{M}] \end{array}\right\} \quad (\text{A-3})$$

In the steady state, both [Z] and [M] show a single-exponential decay, whose rate constant is also written as k_s. Then $\mathrm{d}[\mathrm{Z}]/\mathrm{d}t$ and $\mathrm{d}[\mathrm{M}]/\mathrm{d}t$ are equal respectively to $-k_s[\mathrm{Z}]$ and $-k_s[\mathrm{M}]$. With this correspondency, the first equation of A-3 tends to that of A-1, but the second equation of A-3 does not tend to that of A-1. In order for eq A-3 to tend to eq A-1, therefore, $\mathrm{d}[\mathrm{M}]/\mathrm{d}t$ ($= -k_s[\mathrm{M}]$) must be much smaller than both $k_1[\mathrm{Z}]$ and $(k_{-1} + k_2)[\mathrm{M}]$ in the second equation of A-3. This is satisfied by $k_1[\mathrm{Z}] = (k_{-1} + k_2)[\mathrm{M}]$ and $k_s \ll k_{-1} + k_2$, the former of which gives the second equation of A-1, while the latter gives the condition under which the steady state is realized.

When the steady state is not realized, however, we cannot obtain the rate constant unambiguously. Even in this case, eq A-2 can be obtained so long as k_s is redefined as an average rate constant given by the inverse of the mean lifetime of Z, as

$$k_s = \frac{1}{\int_0^\infty t\left(-\frac{\mathrm{d}[\mathrm{Z}]}{\mathrm{d}t}\right)\mathrm{d}t} = \frac{1}{\int_0^\infty [\mathrm{Z}]\,\mathrm{d}t} \quad (\text{A-4})$$

under the initial normalization of $[\mathrm{Z}] = 1$ at $t = 0$, where $\mathrm{d}[\mathrm{Z}]/\mathrm{d}t$ represents the probability of Z lost at time t and the second equality is obtained by partial integration with $t[\mathrm{Z}] = 0$ at $t = \infty$. In fact, when both sides of eq A-3 are integrated in time t from 0 to ∞, the integral of $\mathrm{d}[\mathrm{M}]/\mathrm{d}t$ vanishes since $[\mathrm{M}] = 0$ both at $t = 0$ and ∞, while that of $\mathrm{d}[\mathrm{Z}]/\mathrm{d}t$ gives -1. Then eliminating the integral of [M] from eq A-3 integrated as above, we can derive eq A-2 for k_s defined by eq A-4. Therefore, eq A-3 is ensured to hold as long as the observed time decay of [Z] is approximated by a single-exponential decay proportional to $\exp(-k_s t)$, where k_s can be derived from the time integration of [Z] by eq A-4.

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Supplementary Material Available: The observed and the fluctuation-limited rate constants for DMNAB, DBNA, DBEA, DBBA, and DBDA in GTA at various temperatures and pressures (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.