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Retro-Diels−Alder Reaction of 4*H*-1,2-Benzoxazines to Generate *o*-Quinone Methides: Involvement of Highly Polarized Transition States

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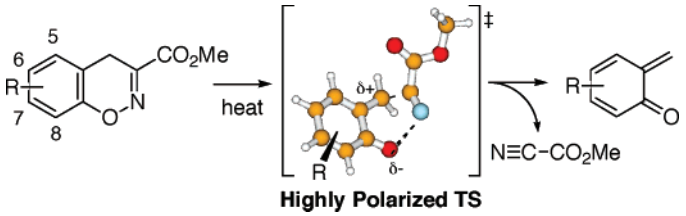

Here, we describe mechanistic studies of the retro-Diels−Alder reaction of 4*H*-1,2-benzoxazines bearing various substituents on the benzene ring. 4*H*-1,2-Benzoxazines are very simple, but quite new, heterocyclic compounds that afford substituted *o*-quinone methides (*o*-QMs) through retro-Diels−Alder reaction under mild thermal conditions. The resultant *o*-QMs undergo Diels−Alder reaction in situ with dienophiles to give phenol and chroman derivatives. The mechanism of the generation of *o*-QMs has been little studied. Our experimental and density functional theory (DFT) studies have yielded the following results. (1) The generation of *o*-QMs, i.e., the retro-hetero-Diels−Alder reaction of 4*H*-1,2-benzoxazines, is rate determining, rather than the subsequent Diels−Alder reaction of the resultant *o*-QM with dienophiles. (2) The reaction rate is strongly influenced by the electronic features of substituents and the polarity of the solvent. The reaction proceeds faster in a polar solvent such as dimethyl sulfoxide, probably because of stabilization of the electronically polarized TS structure. (3) The reactions show characteristic positional effects of substitution on the benzene ring. While an electron-withdrawing group such as CF_3 at C_5, C_6, or C_7 positions decelerates the reaction, the same substituent at C_8 accelerates the reaction, compared with the reaction of unsubstituted 4*H*-1,2-benzoxazine. In particular, substitution at C_5 significantly decelerates the reaction as compared with the unsubstituted case. This is due to the difference in the inductive effect of CF_3 at the different positions. Similar positional effects occur with a halogen (Cl) and a nitro group. All these data support the involvement of polarized TS structures, in which the O−N bond cleavage precedes the C−C bond cleavage.

Introduction

In spite of its limited popularity, the retro-Diels−Alder reaction has evolved as a useful protocol and remains the preferred method for the preparation of several reactive olefins or metastable molecular entities.[1,2] A few experimental and theoretical investigations of retro-Diels−Alder reactions have been reported,[3] but in most cases, the substrates have been confined to compounds containing bicyclo[2.2.1]heptane structures, which afford cyclopentadienes and olefins through the cleavage of two C−C bonds. Recently, however, *o*-quinone methides (*o*-QMs) bearing various substitutents on the benzene

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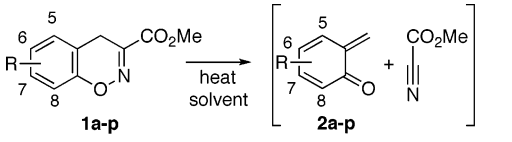
SCHEME 1. Generation of *o*-QMs from 4*H*-1,2-Benzoxazines



a : R = H **f** : R = 7-CO_2Me **k** : R = 6-CF_3 **p** : R = 8-NO_2
b : R = 7-Me **g** : R = 7-CF_3 **l** : R = 8-CF_3
c : R = 7-F **h** : R = 7-CN **m** : R = 5-Cl
d : R = 7-Cl **i** : R = 7-NO_2 **n** : R = 6-Cl
e : R = 7-Br **j** : R = 5-CF_3 **o** : R = 8-Cl

ring have been generated through the thermal retro-Diels−Alder reaction of 4*H*-1,2-benzoxazines (Scheme 1).[4,5]

o-QMs are highly reactive, short-lived intermediates. They undergo 1,4-conjugate addition with nucleophiles[6,7] and Diels−Alder cycloaddition with various dienophiles,[6,7] affording ortho-functionalized phenol and chroman derivatives with high chemo-, regio-, and stereoselectivities. This chemistry has been utilized for the synthesis of chroman structures found in several natural products.[7,8] Many thermal methods to generate *o*-QMs in situ from various precursors have been reported,[7] but most of them involve various disadvantages, including inaccessibility of precursors,[7] undesirably high reaction temperature,[7,9] long reaction time,[7,9,10] a need for additional catalysts,[7,11] and acidic[7,11] or basic conditions,[6m,7,12] and in all cases, side reactions can occur. In addition, there have been few studies of the generation and applications of *o*-QMs containing a variety of substituents attached at different positions. Recently, the aromatic substituent effect on the reactivity of *o*-QMs for 1,4-conjugate addition has been studied, and it turned out to be of potential significance.[6p] Rokita et al. have reported substituent effects on the rates of nucleophilic 1,4-conjugate addition of some substituted *o*-QMs, particularly at the C_6 and C_7 positions, and they showed that electronic perturbation of *o*-QMs by a substituent greatly influenced their stability and reactivity.[6p] It is possible that the electronic nature of substituents would similarly have a great influence on the Diels−Alder reaction of *o*-QMs.

In the present retro-Diels−Alder reaction of 4*H*-1,2-benzoxazine, a single C−C bond and a single O−N bond in the asymmetrical six-membered ring are broken, in contrast to the cleavage of two equivalent C−C bonds in the case of bicyclo-[2.2.1]heptane derivatives. While this retro-Diels−Alder reaction, which involves bond cleavage between heteroatoms, can generate O-containing reactive intermediates (*o*-QMs), the mechanism of this kind of asymmetric retro-hetero-Diels−Alder reactions is not well understood.[13] Herein, we show first that this retro-Diels−Alder reaction process, rather than the Diels−Alder reaction process of the resultant *o*-QMs with dienophiles, is the rate-determining step in the overall reaction, and second that there are significant impacts of the nature and position of the substituent and the polarity of the solvent on the retro-hetero-Diels−Alder reaction process of 4*H*-1,2-benzoxazines. We show that these features can be attributed to the polarized nature of the transition structures, on the basis of experimental kinetic studies and DFT calculations.

Results and Discussion

Generation of *o*-QMs from 4*H*-1,2-Benzoxazines. In general, *o*-QMs are too unstable to be isolated and observed spectroscopically, unless they are trapped with metals such as Cp*Ir.[6c,k,q] In all reported thermal methods, *o*-QMs were generated in situ, and underwent 1,4-conjugate addition with nucleophiles or Diels−Alder cycloadditions with dienophiles.[6,7] In this study, we used vinyloxycyclohexane as a Diels−Alder dienophile, because of the reverse-electron demanding nature of the Diels−Alder reaction of *o*-QMs (Scheme 2). That is, *o*-QMs require a highly electron-rich dienophile, such as vinyl ether.[4] In addition, vinyloxycyclohexane has a high boiling point among vinyl ethers, and its less volatile nature enabled us to control the reaction conditions precisely.

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SCHEME 2

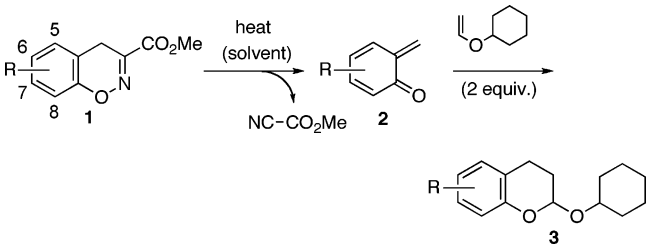

TABLE 1. Sequential Reactions Involving the Retro-Diels−Alder Reaction of 4*H*-1,2-Benzoxazine and the Diels−Alder Reaction of the Resultant *o*-QM with Vinyloxycyclohexane

R	solvent	T (°C)[a]	time (h)	yield (%)[b]
H (**1a**)	toluene	90	0.5	56
	toluene	90	3	100
	acetonitrile	90	0.5	97
	acetonitrile	70	1	51
	acetonitrile	70	6	92
	dimethyl sulfoxide	90	0.5	91
	dimethyl sulfoxide	70	1	50
	dimethyl sulfoxide	70	6	91
5-CF_3 (**1j**)	toluene	100	1	30
	toluene	100	12	98
7-CF_3 (**1g**)	toluene	100	1	48
	toluene	100	12	100
8-CF_3 (**1*l***)	toluene	100	0.5	93
5-Cl (**1m**)	toluene	90	1	22
	toluene	90	12	92
7-Cl (**1d**)	toluene	90	1	82
	toluene	90	3	96
8-Cl (**1o**)	toluene	90	0.5	95
7-NO_2 (**1i**)	toluene	100	1	35
	toluene	100	12	98
8-NO_2 (**1p**)	toluene	90	1	90

[a] Temperature was controlled within ±0.1 °C. [b] Isolated yield.

Heating of a solution of 4*H*-1,2-benzoxazines (**1**) bearing various substituents on the benzene ring in the presence of vinyloxycyclohexane afforded the chroman derivatives (**3**) in high yields under optimal reaction conditions (temperature and time) (Table 1). The high-yield formation of the chroman derivatives is indicative of quantitative in situ generation of *o*-QMs (**2**) from the corresponding 4*H*-1,2-benzoxazines. The overall reaction includes two steps (the retro-Diels−Alder reaction of the 4*H*-1,2-benzoxazine to generate the *o*-QM, and the Diels−Alder reaction of the resultant *o*-QM with the vinyl ether) (see Scheme 2). Our kinetic studies of unsubstituted 4*H*-1,2-benzoxazine (**1a**) revealed that the former step, i.e., the retro-Diels−Alder reaction, is rate-determining (Figure S1, Supporting Information). That is, the orders of the reagent concentration dependency of the rate of appearance of the chroman product were 1.06 and 0.02 for **1a** and the vinyl ether, respectively. Therefore, the overall reaction rate is independent of the concentration of the vinyl ether, and represents the rate of the retro-Diels−Alder reaction of 4*H*-1,2-benzoxazines (**1**), not that of the Diels−Alder reaction of *o*-QMs (**2**).

To gain insight into the reaction mechanism of the rate-determining retro-Diels−Alder reaction, we have carried out a detailed investigation of the reaction profile by means of experimental kinetic studies and theoretical DFT calculations.

Theoretical Mechanistic Insight into Retro-Diels−Alder Reaction of Unsubstituted 4*H*-1,2-Benzoxazine. First, the retro-Diels−Alder reaction of unsubstituted 4*H*-1,2-benzoxazine (**1a**) was studied in detail by means of DFT calculations. The calculated activation energy and selected geometrical parameters are shown in Table 2. The geometry of the transition structure suggested that this retro-Diels−Alder reaction proceeds in a concerted manner, but the bond cleavage occurs asynchronously (Table 2 and Figure 1). The elongation of the O_1-N_2 bond of the transition structure (2.458 Å, 177% elongation as compared with the corresponding bond length in the reactant) was much larger than that of the C_3-C_4 bond (1.887 Å, 125% elongation).

This is consistent with the notion that the O_1-N_2 bond of 4*H*-1,2-benzoxazine is weaker and more unstable than the C_3-C_4 bond. The change of the lengths of the C_3-C_4 bond and the O_1-N_2 bond along the reaction coordinate of the retro-Diels−Alder reaction of unsubstituted 4*H*-1,2-benzoxazine (**1a**) is shown in Figure 2. In the vicinity of the transition state, the C_3-C_4 bond continues to elongate consistently, while the elongation of the O_1-N_2 bond levels off. This is also consistent with the foregoing idea that cleavage of the O_1-N_2 bond occurs prior to that of the C_3-C_4 bond. In this case there is a possibility of the system including a biradical character. However, the process of the singlet biradical formation that involves homolytic cleavage of the N−O bond of unsubstituted 4*H*-1,2-benzoxazine (**1a**) demanded energy larger than the proposed asynchronous concerted process did.[14] This excludes the contribution of the putative biradical process in the present case.

In addition, the frequency calculation of the transition state showed the presence of a single imaginary frequency (387.4*i* cm^{-1}), which corresponds predominantly to stretching of the C_3-C_4 bond. These results suggested that the degree of cleavage of the C_3-C_4 bond has a greater influence on the reactivity in this retro-Diels−Alder reaction.

Furthermore, a comparison of the natural population analysis (NPA) charges between the reactant (**1a**) and the transition structure (**1a-TS**) provides useful information about the redistribution of electrons in the reaction. While the electron densities of the O_1, N_2, and C_3 atoms increased (−0.357 to −0.510, −0.047 to −0.180, and +0.113 to +0.079, respectively), the positive charge of the C_4 atom increased (+0.040 to +0.139). This coincides with the shift of the electron densities of the O_1-N_2 bonding electrons to the O_1 atom, and of the C_3-C_4 bonding electrons to the N_2-C_3 bond (Figure 3). As a result, in this retro-Diels−Alder reaction, the C_4 atom will be relatively electron-deficient and the O_1 atom will be electron-rich in the transition structure (**1a-TS**) (Figure 3).

Solvent Effect on the Retro-Diels−Alder Reaction of Unsubstituted 4*H*-1,2-Benzoxazines. The present retro-Diels−Alder reaction of **1a** proceeded efficiently in various solvents, including toluene ($\epsilon = 2.4$), acetonitrile ($\epsilon = 37.5$), and dimethyl sulfoxide ($\epsilon = 46.7$) (Table 1). Judging from the yields under similar conditions (90 °C, 0.5 h) (Table 1), the reaction rate seems to depend on the polarity of the solvents: as the polarity of the solvent increases, the yield is increased. The experimental reaction rates in the individual solvents and the thermodynamic

(14) While probably due to the shallow potential energy surface, it was difficult to find the transition structure for the homolytic cleavage of the N−O bond of **1a**; we obtained the biradical structure of **1a** in UB3LYP/6−31+G(d,p) calculations, which involved homolytic cleavage of the N−O bond. Formation of the biradical intermediate was endothermic, and the energy difference from **1a** is 39.6 kcal/mol (UB3LYP/6-311+G(d,p)//UB3LYP/6-31+G(d,p)). This result suggests that the activation energy for the putative biradical formation process, the rate-determining step in the singlet biradical pathway, will be highly energetic as compared with the asynchronous concerted process (30.0 kcal/mol, B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d,p)) (see Figure S4, Supporting Information).

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TABLE 2. Calculated Thermodynamic and Selected Geometric Parameters, and NPA Atomic Charges in the Retro-Diels−Alder Reaction of Unsubstituted 4*H*-1,2-Benzoxazine (1a)[a]

species	$\Delta E_{0,calcd}$ (kcal/mol)[b]	O_1-N_2 (Å)	C_3-C_4 (Å)	$\angle C_{8a}O_1N_2$ (deg)	$\angle C_{4a}C_4C_3$ (deg)	$q(O_1)$	$q(N_2)$	$q(C_3)$	$q(C_4)$[c]	$P(O_1-N_2)$ (%)[d]	$P(C_3-C_4)$ (%)[d]
7-H reactant (**1a**)		1.389	1.507	120.2	110.1	−0.357	−0.047	0.113	0.040	-	
7-H TS (**1a-TS**)	30.0	2.458	1.887	101.2	105.1	−0.510	−0.180	0.079	0.139	76.9	25.2

[a] All structures were obtained at the B3LYP/6-31+G(d,p) level. [b] $\Delta E_{0,calcd}$ was calculated at the B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d,p) level with inclusion of ZPE correction. [c] Total charge of the CH_2 group at C4, i.e., summation of charges of C4 and the two bearing hydrogen atoms. [d] Also given is the relative lengthening of the bonds on going from the stable conformer of the reactant to the transition state (expressed in percent): $P(l) = (l_{TS} - l_{reactant})/(l_{reactant}) \times 100$ (%).

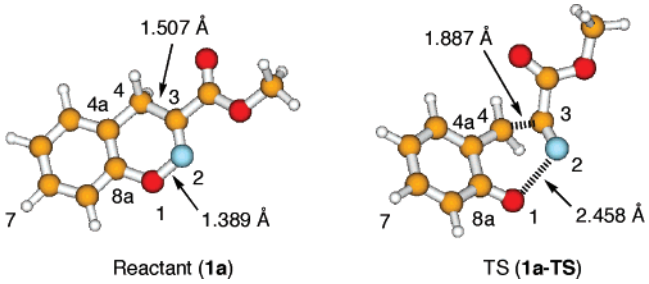

FIGURE 1. Calculated structures of reactant and transition state in the retro-Diels−Alder reaction of unsubstituted 4*H*-1,2-benzoxazine (**1a**).

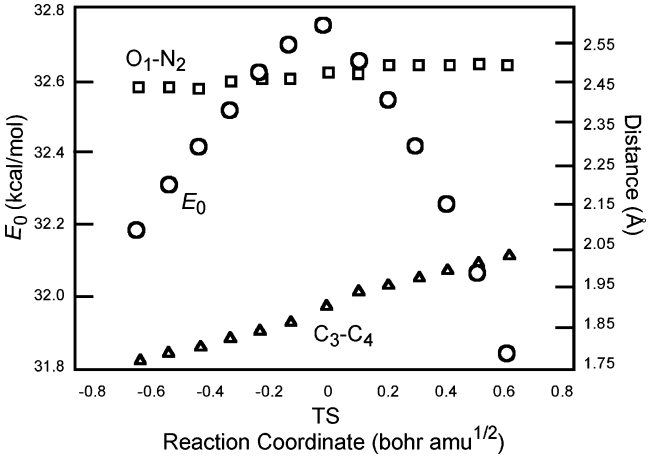

FIGURE 2. Increases of C_3-C_4 and O_1-N_2 bond lengths in the vicinity of the transition state (B3LYP/6-31+G(d,p) level).

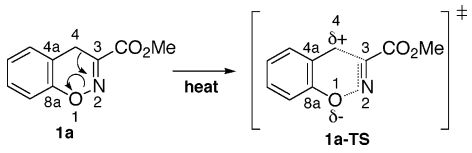

FIGURE 3. Electron shifts in the retro-Diels−Alder reaction of 4*H*-1,2-benzoxazine (**1a**).

parameters of the retro-Diels−Alder reaction of unsubstituted 4*H*-1,2-benzoxazine (**1a**) are shown in Table 3, together with the DFT calculated activation energies. While the calculated activation energies ΔE_{calcd} are consistently overestimated as compared with the experimental activation energies $E_{a,exp}$, the relative magnitudes of the $E_{a,exp}$ and ΔE_{calcd} values agree well. It is apparent that the reactions are more rapid in polar solvents, such as acetonitrile or dimethyl sulfoxide. The experimental activation energies $E_{a,exp}$ were 27.3 ± 0.7 kcal/mol in dimethyl sulfoxide and 28.8 ± 0.4 kcal/mol in toluene, the difference being 1.5 kcal/mol. The SCIPCM calculated activation energy

TABLE 3. Experimental and Calculated Thermodynamic Parameters for the Retro-Diels−Alder Reaction of 4*H*-1,2-Benzoxazine 1a in Several Solvents

solvent	ϵ	T (°C)[a]	10^4k (s^{-1}) at T (°C)	$E_{a,exp}$ (kcal/mol)[b]	ΔE_{calcd} (kcal/mol)[c]
toluene	2.4	80.0	1.47 ± 0.02	28.8 ± 0.4	31.6
		90.0	4.72 ± 0.14		
		100.0	14.1 ± 0.25		
		110.0	36.2 ± 1.02		
acetonitrile	37.5	60.0	0.533 ± 0.05	27.9 ± 1.0	30.0
		70.0	2.01 ± 0.02		
		80.0	5.40 ± 0.35		
		90.0	18.5 ± 1.55		
dimethyl sulfoxide	46.7	60.0	0.483 ± 0.06	27.3 ± 0.7	29.9
		70.0	1.94 ± 0.07		
		80.0	5.46 ± 0.27		
		90.0	14.5 ± 0.78		

[a] Temperature was controlled within ±0.1 °C. [b] $E_{a,exp}$ is the experimental activation energy and k is the reaction rate constant of the retro-Diels−Alder reaction in each solvent at each temperature. [c] ΔE_{calcd} is the calculated activation energy in the presence of dielectric medium, using the SCIPCM model at the B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d,p) level.

ΔE_{calcd} in dimethyl sulfoxide was also 1.7 kcal/mol lower than that in toluene, this value being very close to the experimental difference (1.5 kcal/mol). The acceleration of the reactions in polar solvents was assumed to be due to the polar nature of the transition structure, arising from the N−O bond cleavage. In fact, unsubstituted 4*H*-1,2-benzoxazine (**1a**) generated *o*-QM (**2a**) in dimethyl sulfoxide upon quite mild heating (at 50 °C, though the reaction was slow) without any additional catalyst. This is one of the mildest conditions known for the generation of *o*-QMs. In the cases of the bicyclo[2.2.1]heptane derivatives, solvent effects have also been reported.[3b−d] This is consistent with the involvement of a slightly polarized TS, which is more stabilized than the initial state in a polar solvent.

Kinetic Studies of Retro-Diels−Alder Reaction of 4*H*-1,2-Benzoxazines Bearing Various Substituents at C_7: Substituent Effect. The yield of the chroman product also seemed to be dependent on the nature of the substituent, for example, at the C_7 position, judging from the yields obtained under similar conditions (Table 1 and Scheme 1). For example, the reactions of 4*H*-1,2-benzoxazines bearing an electron-withdrawing group, such as CF_3 (**1g**) and NO_2 (**1i**), at C_7 were apparently slower than that of unsubstituted 4*H*-1,2-benzoxazine (**1a**).

To get more quantitative information about the substituent effect, we carried out kinetic measurements of the reactions of 7-substituted 4*H*-1,2-benzoxazines (**1a**−**i**, Scheme 1) in a nonpolar solvent, toluene, where the retro-Diels−Alder reaction is slow. When the reaction was carried out in a polar solvent, such as dimethyl sulfoxide, it was difficult to obtain accurate kinetic data, because the reaction was too rapid at high temperature. The 4*H*-1,2-benzoxazines (**1b**−**i**) bearing various substituents at C_7 were prepared and the reaction rates were measured. All the substrates showed first-order kinetics with

TABLE 4. Experimental Thermodynamic Parameters of the Retro-Diels−Alder Reaction

substituent	σ_p	T (°C)[a]	10^4k (s^{-1}) at T (°C)	$E_{a,exp}$ (kcal/mol)[b]	substituent	σ_p	T (°C)[a]	10^4k (s^{-1}) at T (°C)	$E_{a,exp}$ (kcal/mol)[b]
7-H (**1a**)	0	80.0	1.47 ± 0.02	28.8 ± 0.4	7-CO_2Me (**1f**)	0.45	100.0	3.08 ± 0.02	30.2 ± 0.6
		90.0	4.72 ± 0.14				110.0	9.24 ± 0.29	
		100.0	14.1 ± 0.25				120.0	24.5 ± 0.29	
		110.0	36.2 ± 1.02		7-CF_3 (**1g**)	0.54	100.0	2.03 ± 0.01	30.6 ± 0.6
7-Me (**1b**)	−0.17	80.0	4.38 ± 0.11	27.9 ± 0.5			110.0	6.20 ± 0.20	
		90.0	12.7 ± 0.38				120.0	16.7 ± 0.21	
		100.0	37.0 ± 1.01		7-CN (**1h**)	0.66	100.0	1.55 ± 0.02	30.7 ± 0.2
		110.0	68.2 ± 0.67				110.0	4.62 ± 0.17	
7-F (**1c**)	0.06	90.0	9.01 ± 0.24	27.6 ± 0.5			120.0	12.7 ± 0.17	
		100.0	24.3 ± 0.87		7-NO_2 (**1i**)	0.78	100.0	1.16 ± 0.04	31.0 ± 1.5
		110.0	66.5 ± 0.44				110.0	3.77 ± 0.16	
7-Cl (**1d**)	0.22	80.0	1.60 ± 0.04	28.5 ± 0.8			120.0	9.68 ± 0.92	
		90.0	5.17 ± 0.09						
		100.0	14.1 ± 0.06						
		110.0	33.8 ± 1.61						
7-Br (**1e**)	0.23	80.0	1.58 ± 0.52	28.4 ± 0.6					
		90.0	4.49 ± 0.12						
		100.0	13.9 ± 0.23						
		110.0	34.7 ± 0.98						

[a] Temperature was controlled within ±0.1 °C. [b] $E_{a,exp}$ is the experimental activation energy and k is the reaction rate constant of the retro-Diels−Alder reaction in toluene at each temperature.

TABLE 5. Experimental Thermodynamic Parameters for the Retro-Diels−Alder Reaction of 4*H*-1,2-Benzoxazine Bearing CF_3 or Cl at C_5−C_8 and NO_2 at C_7−C_8

substituent	T (°C)[a]	10^4k (s^{-1}) at T (°C)	$E_{a,exp}$ (kcal/mol)[b]	substituent	T (°C)[a]	10^4k (s^{-1}) at T (°C)	$E_{a,exp}$ (kcal/mol)[b]
5-CF_3 (**1j**)	100.0	1.08 ± 0.02	30.6 ± 0.8	5-Cl (**1m**)	90.0	0.786 ± 0.02	30.2 ± 0.2
	110.0	3.03 ± 0.06			100.0	2.39 ± 0.10	
	120.0	8.86 ± 0.24			110.0	6.98 ± 0.05	
6-CF_3 (**1k**)	100.0	1.42 ± 0.02	30.4 ± 0.4	6-Cl (**1n**)	80.0	2.54 ± 0.02	28.0 ± 0.5
	110.0	4.04 ± 0.04			90.0	8.00 ± 0.10	
	120.0	11.5 ± 0.25			100.0	23.1 ± 0.60	
7-CF_3 (**1g**)	100.0	2.03 ± 0.01	30.6 ± 0.6		110.0	57.7 ± 3.88	
	110.0	6.20 ± 0.20		7-Cl (**1d**)	80.0	1.60 ± 0.04	28.5 ± 0.8
	120.0	16.7 ± 0.21			90.0	5.17 ± 0.09	
8-CF_3 (**1l**)	80.0	1.87 ± 0.93	27.7 ± 1.4		100.0	14.1 ± 0.06	
	90.0	5.07 ± 0.08			110.0	33.8 ± 1.61	
	100.0	35.8 ± 1.07		8-Cl (**1o**)	60.0	0.734 ± 0.01	27.2 ± 0.5
					70.0	2.52 ± 0.01	
					80.0	7.52 ± 0.09	
				7-NO_2 (**1i**)	100.0	1.16 ± 0.04	31.0 ± 1.5
					110.0	3.77 ± 0.16	
					120.0	9.68 ± 0.92	
				8- NO_2 (**1p**)	90.0	5.87 ± 0.23	27.1 ± 0.6
					100.0	15.5 ± 0.53	
					110.0	41.9 ± 1.40	

[a] Temperature was controlled within ±0.1 °C. [b] $E_{a,exp}$ stands for the activation energy and k for the reaction rate constant of the retro-Diels−Alder reaction in toluene at each temperature.

respect to the substrate concentration. The experimental and calculated thermodynamic parameters of the retro-Diels−Alder reactions of 4*H*-1,2-benzoxazines (**1b**−**i**) bearing various substituents at C_7 are shown in Tables 4 and 5, respectively.

The 4*H*-1,2-benzoxazines (**1f**−**i**) bearing a strong electron-withdrawing substituent (in terms of σ_p) on the benzene ring had larger $E_{a,exp}$ values than that of the unsubstituted substrate (**1a**) (Table 4). The electron-donating methyl group (**1b**) reduced the activation energy as compared with that of **1a**. For example, $E_{a,exp}$ of 4*H*-1,2-benzoxazine (**1i**, R = NO_2) bearing a NO_2 group at C_7 was 31.0 kcal/mol, and that of 4*H*-1,2-benzoxazine (**1b**, R = CH_3) bearing a methyl group at C_7 was 27.9 kcal/mol, while that of the unsubstituted compound (**1a**, R = H) was 28.8 kcal/mol. In fact, the rate constant k_{100} at 100 °C of **1b** (37.0×10^4) was approximately 30 times that of **1i** (1.16×10^4). This indicates that the electron-withdrawing substituent at the C_7 position retarded the reaction. This tendency is consistent with the magnitudes of the DFT-calculated activation energies, corrected for the zero-point energies (ZPE) (Table S1, Supporting Information). The calculated activation energy $\Delta E_{0,calcd}$ of **1i** (R = 7-NO_2, 31.3 kcal/mol) was 2.2 kcal/mol higher than that of **1b** (R = 7-Me, 29.1 kcal/mol).

A Hammett plot of the experimental relative reaction rates at 110 °C, $\log(k_{110,R}/k_{110,H})$, against σ_p values is shown in Figure 4. A plot of the relative rates (logarithmic) against σ_p rather than σ_m showed a better linear correlation (regression coefficient $r = 0.993$, excluding halogen atoms (see below); see also Figure S3 in the Supporting Information). This is consistent with the calculated TS structures, in which the electronic nature of the C_3−C_4 bond located at the para position with respect to the 7-substituent seemed to have a great influence on the reactivity. The negative slope of the relationship ($\rho = -1.33$, excluding halogen atoms, see below) is indicative of the creation of the electron-deficient reaction center, which might be assigned to

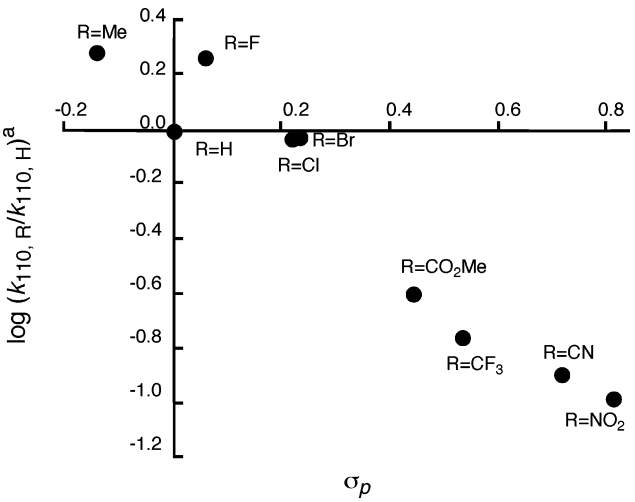

FIGURE 4. Correlation between the relative reaction rate constants (k_{110}, the reaction rate constant of the retro-Diels−Alder reaction in toluene at 110 °C) and Hammett σ_p.[15]

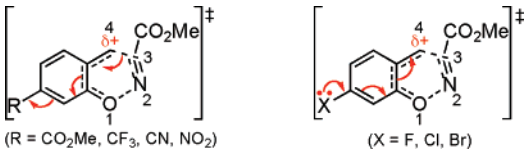

FIGURE 5. Resonance destabilization (left)/stabilization (right) of the transition state arising from the substituent at C_7.

C_4, in the transition structure. This is consistent with the calculated charge distribution shown in Figure 3.

In this Hammett plot (Figure 4), halogen substituents are located slightly above the line. This indicates that halogen atoms accelerated the reaction, probably because the electron deficiency of the reaction center in the transition state could be stabilized by the lone pair electrons of halogen atoms (Figure 5).[16]

In all cases of calculated TS (**1b-TS** to **1i-TS**), the reactions appeared to proceed in an asynchronous and concerted manner, as in the case of unsubstituted 4*H*-1,2-benzoxazine (**1a**). Irrespective of the substituents of the 4*H*-1,2-benzoxazines, the elongation of the O_1-N_2 bond was more significant than that of the C_3-C_4 bond in the transition structures (see Table S1, Supporting Information). This suggested that the electron flow in the retro-Diels−Alder reactions of 4*H*-1,2-benzoxazines (**1c**−**i**) that bear any substituent at the C_7 position is essentially as shown in Figure 3.

The destabilization of C_4 by the inductive/resonance effect of the electron-withdrawing substituents would decelerate this retro-Diels−Alder reaction, and the stabilization of C_4 owing to the resonance effect of the lone-pair electrons would accelerate the reaction. In fact, as compared with the calculated charges of the CH_2 group at C_4 in the transition structures, the CH_2 group at C_4 of the compounds with electron-withdrawing groups (**1g**: CF_3, **1h**: CN and **1i**: NO_2) was more positively charged (+0.154, +0.159, and +0.163, respectively) than in the halogen compounds (**1c**: F, +0.144; **1d**: Cl, +0.146; and **1e**: Br, +0.146) (Table S1, Supporting Information). The halogen atoms might also block the reaction through their inductive effects. The results, however, suggested that the stabilization of transition state was dominant over the destabilizing inductive effect.

Such a substituent effect on the retro-Diels−Alder reactions is also consistent with the changes in the NPA charges from the reactants to the TSs (Table S1, Supporting Information). In the cases of truly electron-withdrawing substituents (**1f**−**i**), such as CF_3, CN, and NO_2, the positive charge of the CH_2 group at C_4 increased along the reaction path, the increase being larger than that of the unsubstituted compound (**1a**), probably because of the electron-withdrawing inductive/resonance effect of the substituent. The NPA charge of the CH_2 group at C_4 of 4*H*-1,2-benzoxazine bearing an NO_2 group changed from the comparable positive value (reactant: +0.047) to the most positive value (TS: +0.163) along the reaction path. The inductive/resonance effect of an electron-withdrawing substituent reduced the availability of the bonding electrons of the C_3-C_4 bond, resulting in retardation of the reaction (Figure 5). In the case of the electron-donating substituent (**1b**: Me), the increase of the charge of the CH_2 group at C_4 in the transition from the reactant to the TS (+0.093) is smaller than that in the unsubstituted compound (**1a**: +0.099).

Positional Effect of Substitution in Retro-Diels−Alder Reactions of 4*H*-1,2-Benzoxazines. Positional effects of substitution on the reactivities of 4*H*-1,2-benzoxazines were also examined. 4*H*-1,2-Benzoxazines with a CF_3 group at C_5 (**1j**), C_6 (**1k**), C_7 (**1g**), or C_8 (**1*l***), a Cl group at C_5 (**1m**), C_6 (**1n**), C_7 (**1d**), or C_8 (**1o**), or a NO_2 group at C_7 (**1i**) or C_8 (**1p**) were prepared.[17] The experimental and calculated thermodynamic parameters for the retro-Diels−Alder reactions of 4*H*-1,2-benzoxazines bearing CF_3 (**1j**,**1k**, **1g** and **1*l***) or Cl at C_5-C_8 (**1m**, **1n**, **1d**, and **1o**) are shown in Table 5. The magnitude of the experimental activation energies ($E_{a,exp}$) varied significantly, depending upon the position of the given substituent, i.e., CF_3, Cl, or NO_2 (Table 5).

To our surprise, while the reactions of 4*H*-1,2-benzoxazines bearing CF_3 or Cl at C_5 (**1j**/**1m**), C_6 (**1k**/**1n**), or C_7 (**1g**/**1d**) were much slower than that of unsubstituted 4*H*-1,2-benzoxazine (**1a**), those of 4*H*-1,2-benzoxazines bearing the substituent at C_8 (**1*l***/**1o**) were much faster than in the case of **1a**. Thus, it is not appropriate to generalize that an electron-withdrawing group or halogen atom on the benzene ring of 4*H*-1,2-benzoxazines decelerates the retro-Diels−Alder reaction. Acceleration or deceleration of the reaction depends significantly on the position of the substitution.

The activation energy ($E_{a,exp}$) of 4*H*-1,2-benzoxazine bearing CF_3 at C_8 (**1*l***) (27.7 kcal/mol) was found to be smaller than those of 4*H*-1,2-benzoxazines bearing CF_3 at C_5 (**1j**), C_6 (**1k**), and C_7 (**1g**) (30.6, 30.4, and 30.6 kcal/mol, respectively). Correspondingly, the reaction rate (k), for example at 100 °C, of 4*H*-1,2-benzoxazine bearing CF_3 at C_8 (**1*l***) was larger than those of the compounds with CF_3 at C_5 (**1j**), C_6 (**1k**), and C_7 (**1g**). A similar acceleration owing to substitution at C_8 was also observed in the case of a Cl substituent. That is, the activation energy ($E_{a,exp}$) of 4*H*-1,2-benzoxazine bearing Cl at C_8 **1o** was the smallest (27.2 kcal/mol), while that of 4*H*-1,2-benzoxazine bearing Cl at C_5 **1m** was the largest (30.2 kcal/mol) among the regioisomers **1m**, **1n**, **1d**, and **1o**. The $E_{a,exp}$ values of 4*H*-1,2-benzoxazines bearing Cl at C_6 (**1n**) and C_7 (**1d**) were similar in

(16) Brown, H. C.; Okamoto, Y.; Ham, G. *J. Am. Chem. Soc.* **1957**, *79*, 1906−1909.

(17) CF_3 and Cl groups were selected because they could be introduced at any position on the benzene ring. In fact, for example, 4*H*-1,2-benzoxazine bearing an NO_2 group at C_5 was not able to be prepared.

magnitude (28.0 and 28.5 kcal/mol, respectively). The retarding effect of the substituent at C_5 was more apparent in the case of Cl (**1m**) than CF_3 (**1j**). These tendencies are consistent with the relative magnitude of the DFT-calculated activation energies, corrected for the zero-point energies (ZPE) (see Table S2, Supporting Information). The calculated activation energy $\Delta E_{0,calcd}$ of **1*l*** (R = 8-CF_3, 29.0 kcal/mol) was smaller than those of **1j**, **1k**, and **1g** (30.4, 30.3, and 30.5 kcal/mol, respectively). A similar trend was found in the Cl substituent (Table S2, Supporting Information). The retro-Diels−Alder reactions of 4*H*-1,2-benzoxazine bearing CF_3 or Cl at any position appeared to proceed asynchronously and concertedly, judging from the vibration mode of a single imaginary frequency and the elongation of the O_1-N_2 bond in the calculated transition states. The bond angles of $\angle C_{8a}O_1N_2$ and $\angle C_{4a}C_4C_3$ in the transition state structures of the 4*H*-1,2-benzoxazines were comparable in magnitude among all the positional isomers of substitution (C_5-C_8) in both CF_3 and Cl substituted compounds (Table S2 and Scheme 1). The geometrical similarity of these TS structures indicated that the differences in the reaction rates among the 4*H*-1,2-benzoxazines (for CF_3, **1g** and **1j**−***l***; for Cl, **1d** and **1m**−**o**) bearing the same substituent at different positions are not due to steric factors, but rather are mainly due to electronic effects arising from the subtituent at the individual position. The length of the C_3-C_4 bond in the transition structure (**1*l*-TS**) of 4*H*-1,2-benzoxazine bearing CF_3 at C_8 was the shortest (1.887 Å) and **1*l*** gave the smallest $\Delta E_{0,elec}$. That of the isomer bearing CF_3 at C_5 (**1j**), which gave higher $\Delta E_{0,elec}$, was the longest (1.911 Å). This result indicates that the earlier the transition state with respect to the C_3-C_4 bond cleavage (i.e., the less the bond cleavage proceeds), the lower the reaction barrier. In this context, the C_3-C_4 bond length can be considered as an indicator of the reaction progress. A similar trend was observed in the case of the Cl group. The transition state structure (**1m-TS**) of 4*H*-1,2-benzoxazine bearing Cl at C_5 suggested the involvement of a later transition state (i.e., the bond cleavage proceeded to greater extent) with respect to the C_3-C_4 bond (1.899 Å), as compared with that of 4*H*-1,2-benzoxazine bearing Cl at C_7 (**1d-TS**, 1.875 Å). On the other hand, the C_3-C_4 bond length in the transition state structure (**1o-TS**) of 4*H*-1,2-benzoxazine bearing Cl at C_8 is exceptional. The C_3-C_4 bond length of **1o-TS** was 1.884 Å, which is longer than that of **1d-TS** (Cl at C_7), while **1o-TS** was more stabilized than **1d-TS**. The reason for this is not clear, but an alternative stabilization effect may be involved.[18]

These positional effects of the substituents can be explained by postulating that an electron-withdrawing substituent at C_5 predominantly has an inductive effect on the C_3-C_4 bond, and the same substituent at C_8 has an inductive effect on the O_1-N_2 bond; this view is supported by the results of NPA analysis (Figure 6).[19]

The effect of a nitro group at C_8 was also studied in the retro-Diels−Alder reaction of 4*H*-1,2-benzoxazine. The experimental thermodynamic parameters for the retro-Diels−Alder reaction of 4*H*-1,2-benzoxazine bearing NO_2 at C_8 (**1p**) are shown in Table 5. As expected, $E_{a,exp}$ of 4*H*-1,2-benzoxazine bearing NO_2 at C_8 (**1p**) (27.1 kcal/mol) was smaller than that of unsubstituted 4*H*-1,2-benzoxazine (**1a**, 28.8 kcal/mol) and also smaller than that of 4*H*-1,2-benzoxazine bearing NO_2 at C_7 (**1i**, 31.0 kcal/mol). This apparent positional acceleration/deceleration effect is consistent with the highly polarized transition structure of the retro-Diels−Alder reaction.

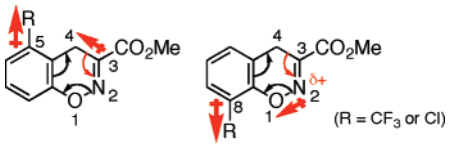

FIGURE 6. Deceleration (left) and acceleration (right) of C_3-C_4 bond cleavage.

Conclusion

In this paper we present a mechanistic study of the retro-Diels−Alder reaction of 4*H*-1,2-benzoxazines with various substituents on the benzene ring. This reaction provides substituted *o*-QMs under mild thermal conditions, and is useful in synthetic chemistry. The results of DFT calculations are consistent with the experimental kinetic and thermodynamic data. The reaction proceeded in an asynchronous and concerted manner. As a result, the reaction rates were greatly affected by the electronic nature and positions of substituents, and by the polarity of the solvent. The reaction proceeded faster in a polar solvent, such as dimethyl sulfoxide, because the transition state is significantly polarized by asymmetrical bond cleavage. Comparison of the bond lengths and frequency analysis of the transition state showed that the O_1-N_2 bond is cleaved significantly, and the bonding nature of the remaining C_3-C_4 bond has a great influence on the reaction rate. The effect of substituent position was found to be significant. The reaction of 4*H*-1,2-benzoxazine bearing an electron-withdrawing group such as CF_3 at C_5 (**1j**), C_6 (**1k**), or C_7 (**1g**) was slower than that of unsubstituted 4*H*-1,2-benzoxazine (**1a**), while that of 4*H*-1,2-benzoxazine bearing CF_3 at C_8 (**1*l***) was faster than that of **1a**. This tendency was also seen in the case of Cl and NO_2 groups. The present detailed study has uncovered characteristic effects of substitution position and solvent polarity on the retro-hetero-Diels−Alder reactions to generate *o*-QMs.

Experimental Section

Diels−Alder Reactions of *o*-Quinone Methides Generated from 4*H*-1,2-Benzoxazines with Vinyloxycyclohexane (3a−p): Typical Procedure for 2-Cyclohexyloxychroman (3a). A solution of **1a** (180 mg, 0.940 mmol) and vinyloxycyclohexane (252 mg, 2.00 mmol, 2.1 equiv) in dry toluene (15 mL) was heated at 90 °C with stirring for 3 h. Then the solvent was evaporated under reduced pressure to give a residue, which was column-chromatographed on

(18) The geometrical distortion, i.e., bending of the Cl atom toward the O−N bond moiety of the heterocycle in the TS structure (**1o-TS**), suggested involvement of a different stabilization arising from orbital interaction between the non-bonding orbital of the 8-Cl atom and the O_1-N_2 σ^*-orbital (see Table S3 and Figure S5 in the Supporting Information).

(19) Acceleration of the retro-Diels−Alder reaction of 4*H*-1,2-benzoxazine bearing CF_3 at C_8 (**1*l***) might be related to the fact that the negative charge of N_2 in the reactant **1*l*** (−0.043) is the smallest among the isomers (**1g** and **1j**−***l***) (see Table S2, Supporting Information). This small negative charge of N_2 of **1*l*** can be interpreted in terms of the inductive effect of CF_3 at C_8, which polarizes the electron density of the O_1-N_2 bond toward the O_1 atom. Consequently, the electron-deficient N_2 promotes redistribution of the electrons of the C_3-C_4 bond into the N_2-C_3 bond (Figure 6). The NPA charge also showed the negative charge of C_4 was the highest in **1j** among the isomers bearing CF_3 at C_5 (**1j**), C_6 (**1k**), C_7 (**1g**), or C_8 (**1*l***). This might mean that the inductive effect of the 5-CF_3 group on the C_3-C_4 bond is the strongest in the case of **1j**. This effect retarded the cleavage of the C_3-C_4 bond, as depicted in Figure 6, and thus the substrate bearing CF_3 at C_5 (**1j**) showed the smallest reaction rate among the isomers (**1g** and **1j**−***l***) (Table 5).

silica gel (eluent: *n*-hexane-ethyl acetate (10:1)) to afford 2-cyclohexyloxychroman **3a** as a colorless oil (216 mg, 0.874 mmol, 100% yield).

Kinetic Studies: Order Dependencies on 4*H*-1,2-Benzoxazine (1a) and Vinyl Ether. Initial kinetics was measured in toluene-d_8 at 90 °C by ^{1}H NMR, with various concentrations of 4*H*-1,2-benzoxazine (**1a**) and vinyl ether. Magnetic field locking and external standard peaks were obtained by using a capillary tube filled with acetic acid/toluene-d_8. The order dependency on each component was determined by the slope of ln k−ln [component] relationships (Figure S1, Supporting Information). The order dependencies on 4*H*-1,2-benzoxazine (**1a**) and vinyl ether were found to be 1.06 and 0.02, respectively.

Determination of Activation Energy E_a of Retro-Diels−Alder Reactions: Typical Procedure. The substrate 4*H*-1,2-benzoxazine (**1a**−**p**) (0.075 mmol) and vinyloxycyclohexane (0.15 mmol, 2 equiv to **1a**−**p**) were dissolved in 1.5 mL of toluene-d_8. The mixture was transferred into a NMR tube under an Ar atmosphere. The tube was placed in a temperature-controlled oil bath preheated to the desired temperature (±0.1 °C). At different time intervals the tubes were removed from the bath and cooled to 0 °C, and the progress of the reaction in each case was followed by ^{1}H NMR spectroscopy. Magnetic field locking and external standard peaks were obtained by using a capillary tube filled with acetic acid/toluene-d_8. The concentration of the substrate in the mixture was obtained by comparing the integration values of the substrate and external standard. The ratios of disappearance of the starting substrate against time were plotted to give first-order kinetics (regression coefficient $r > 0.99$). Activation energies $E_{a,exp}$ were calculated by Arrhenius equation. Arrhenius plots were shown in Figure S2 in the Supporting Information.

Computational Methods. Ab initio calculations were performed with the Gaussian 03 suite of programs.[20] Geometry optimizations were performed by using the B3LYP/6-31+G(d,p) method. Single-point energies were calculated at the B3LYP/6-311+G(d,p) level. For compounds that have multiple conformations, the conformation with the lowest energy was chosen for the present study. Frequency calculations were carried out at the B3LYP/6-31+G(d,p) level and performed on all of the species to confirm convergence to appropriate local minima or saddle points on the energy surface. In all instances, transition state structures gave one significant imaginary frequency, while no imaginary frequencies were observed for the minimum-energy species. Corrections of the energies were made from the frequency calculations, including zero-point energy corrections at the B3LYP/6-31+G(d,p) level, which was scaled by the factor of 0.9614.[21] Natural charge analysis with NBOs[22] was performed at the B3LYP/6-31+G(d,p) level. Effects of dielectric solvent were simulated by using the SCIPCM model[23] as implemented in Gaussian 03. SCIPCM calculations were single-point calculations; i.e., geometry was taken from the gas-phase calculations and was not reoptimized using the dielectric model. The performance of the B3LYP method with the 6-31+G(d,p) basis set is known as a reliable method to calculate the Diels−Alder reaction of *o*-QMs.[24]

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Supporting Information Available: Spectroscopic and analytical data, experimental procedures, Cartesian coordinates, and energetic and geometrical values of calculated species. This material is available free of charge via the Internet at http://pubs.acs.org.

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