Ring-Opening Reactions of Cyclic Sufinate Esters with a Phenolic Leaving Group

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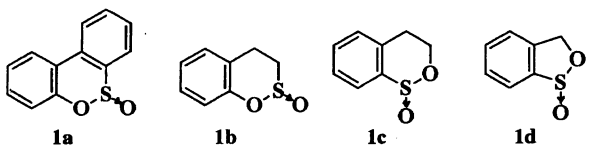
The reactions of dibenzo[1,2]oxathiin 6-oxide (**1a**) and 3,4-dihydro-1,2-benzoxathiin 2-oxide (**1b**) with a phenolic leaving group were examined in acid and buffer solutions. The substrate **1b** undergoes a ring opening in acid and at a higher pH, while **1a** is stable in acid with a reverse ring closure predominating. The ^{18}O-labeled **1a** undergoes an isotope exchange in acid through a ring opening-closure. Although the ring opening of **1a** and **1b** is accelerated by buffer bases, owing to nucleophilic catalysis, a similar reaction of 3*H*-2,1-benzoxathiole 1-oxide with a benzylic alcohol leaving group is independent of the buffer concentration, or is decelerated by some amines. The results are accommodated by a mechanism involving a hypervalent addition intermediate with a varying rate-determining step.

Nucleophilic substitutions at sulfur may proceed with or without a hypervalent intermediate (sulfurane) via a two-step addition-elimination mechanism or a concerted S_N2-like mechanism.[1] Substitution reactions of sulfinic acid derivatives usually occur with a predominant inversion of the configuration at the sulfur, and have often been interpreted by an addition–elimination mechanism involving sulfurane intermediates.[1] We have recently presented evidence for an intermediate in the acid hydrolysis of some sulfinamides,[2] while a single-step S_N2-like mechanism was suggested for the acid hyrolysis of alkyl sulfinate esters.[3] A similar conclusion was presented for the reaction of cyclic sulfinates[4] contrary to earlier suggestions.[5] We have, however, recently made interesting buffer catalysis observations on reactions of cyclic sulfinates with a phenolic leaving group, **1a** and **1b**, suggesting the possibility of the formation of a sulfurane intermediate in base-catalyzed hydrolysis.[6] We now present details concerning these results as well as the reaction behavior of these cyclic sulfinates in strong acids.

Cyclic sulfinate esters of aliphatic alcohols, 3,4-dihydro-2,1-benzoxathiin 1-oxide (**1c**) and 3*H*-2,1-benzoxathiole 1-oxide (**1d**), undergo ring opening in an aqueous alkaline solution, while a reverse ring closure predominates in an acidic solution (Chart 1).[4] Although dibenzo[1,2]oxathiin 6-oxide (**1a**) with a phenolic leaving group was found to behave similarly, undergoing an alkaline ring opening and acid ring closure, another phenolic cyclic sulfinate, 3,4-dihydro-1,2-benzoxathiin 2-oxide (**1b**), underwent a ring opening even in a strong acid as well as in an alkaline solution.

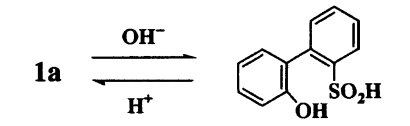


1a **1b** **1c** **1d**

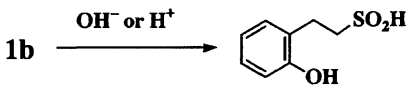
Chart 1.

Results and Discussion

Reactions in Acid. The reactions of cyclic sulfinate esters **1** were carried out in aqueous solutions at 25 °C and monitored spectrophotometrically. When **1** was dissolved in buffer solutions, the UV spectrum changed smoothly as the reaction proceeded, giving a ring-open hydroxy sulfinate ion (Figs. 1 and 2). The spectral change of **1b** in strong acid (>1 M[7]) $HClO_4$ or HCl) is similar to that observed at a higher pH in buffer solutions (Fig. 2), suggesting that the same ring-opening reaction occurs in acid. In contrast, the spectrum of **1a** was stable in an acid, as was observed for **1c** and **1d**.[4] On the contrary, when a ring-open sample of **1a** obtained in an aqueous NaOH solution was mixed in an acid, the spectrum of **1a** slowly developed, as can be seen in Fig. 1(b). The change is just opposite that for the ring opening observed in buffer solutions (a). The ring closure to form **1a** must take place in an acid. This behavior is closely similar to those observed for **1c** and **1d**.[4]



(1)



(2)

The pseudo-first-order rate constants (k_{obsd}) for the ring opening of **1b** and the ring closure to form **1a** were measured spectrophotometrically based on the absorbance changes at about 270 nm. In order to observe the ring closure, 0.1 mL of a solution of a ring-open sample of **1a** in 0.01 M NaOH was added to 3 mL of acid. The acid dependences of both

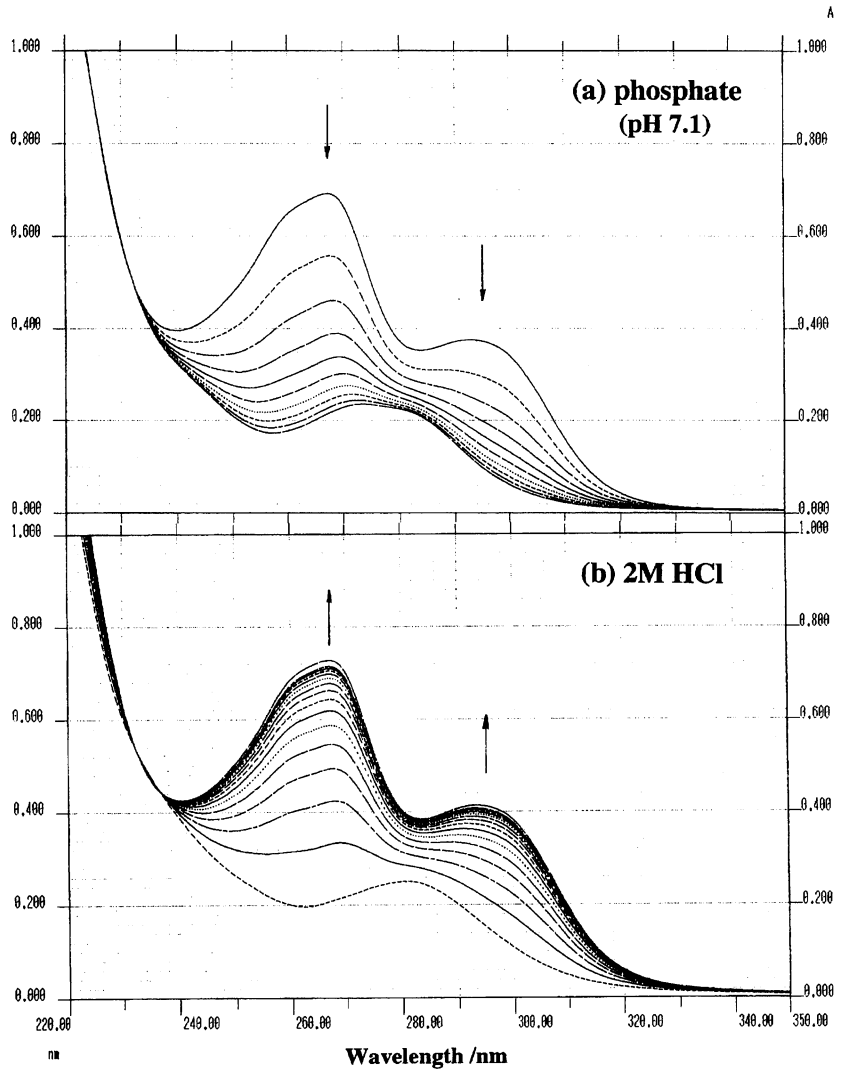


Fig. 1. UV Spectral changes for (a) the reaction of **1a** in a phosphate buffer at pH 7.1 (time interval of 3 min) and (b) the reaction of a ring-open sample of **1a** in 2 M HCl (time interval of 30 min).

the ring opening and closure are similar to those observed for **1c** and **1d**.[4] The reactions are faster in HBr and HCl than in $HClO_4$. The rate constants at about 2 M acid are summarized in Table 1 together with data for **1c**.[4]

In an ^{18}O-enriched acid solution, isotope labeling at the sulfinyl oxygen took place with a complete recovery of ^{18}O-labeled **1a**. The isotope content could be determined by mass spectrometry. A reverse isotope loss was observed when the labeled **1a** was added to a strong acid. The loss of the isotope determined by mass spectrometry followed pseudo-first-order kinetics, and the rate constants for the isotope exchange were calculated from the isotope loss, as given in Table 1. Isotope exchange must occur through a reversible ring opening and closure with the opening as the slow step, as previously described for **1c** and **1d**.[4] That is, the rate constant for the ring opening (k_{open}) is equal to two times that for the exchange (k_{ex}). The equilibrium constant for the ring closure ($K_c=k_{clos}/k_{open}$) can be calculated as listed in Table 1. The constant K_c is dependent on acidity, or is affected by salts, as discussed previously for **1c**.[4]

Table 1. Rate Constants for Reactions of **1** in Acids at 25 °C

Acid	**1a**[a]	**1b**	**1c**[b]
Ring closure ($10^5 k_{obsd}/s^{-1}$)			
1.82 M $HClO_4$	2.01		5.60
1.82 M HCl	14.9		37.7
1.82 M HBr	74.7		170
^{18}O exchange or ring opening ($10^6 k_{obsd}/s^{-1}$)			
1.95 M $HClO_4$	0.373	69.4	1.57
1.95 M HCl	4.28	992	17.9
1.95 M HBr	5.87		53.1
Equilibrium constant for ring closure (K_c)			
1.95 M $HClO_4$	30	0	20

a) The ^{18}O content of the sample used for isotope exchange was 24.6%. b) Data are taken from Ref. 4.

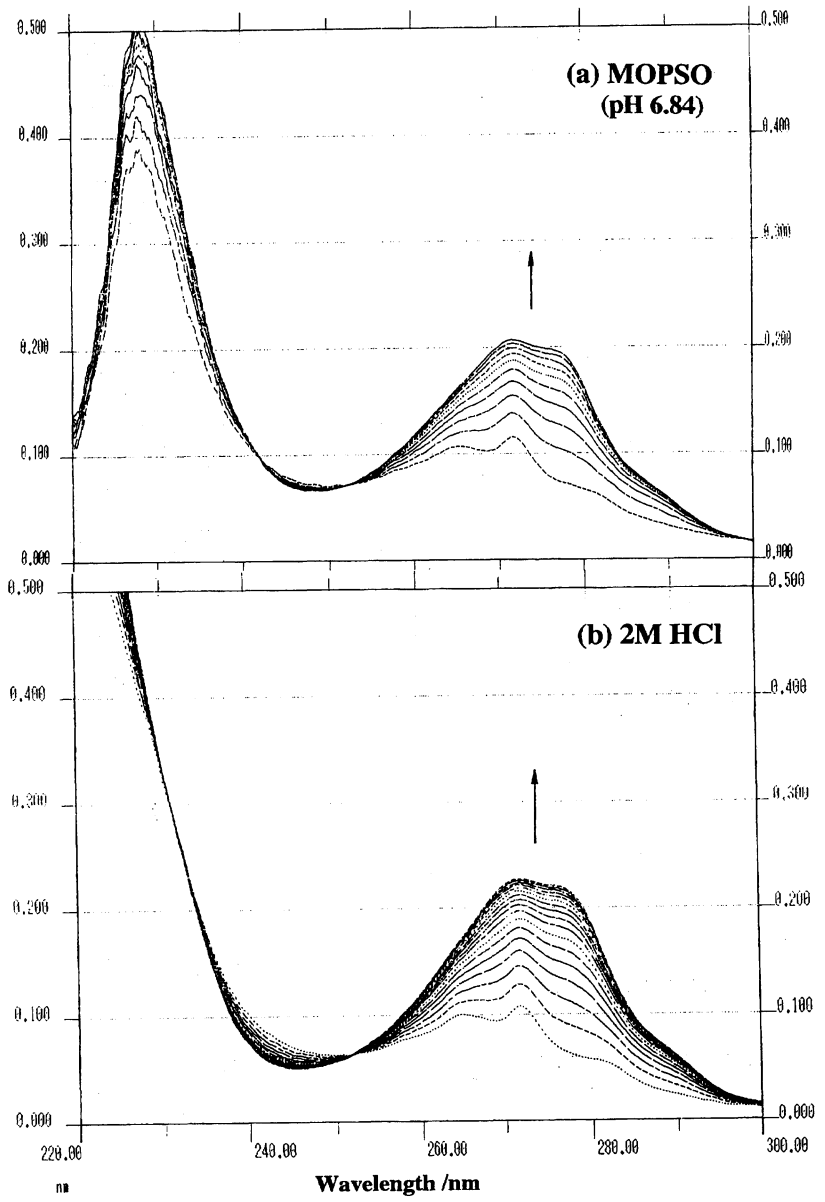
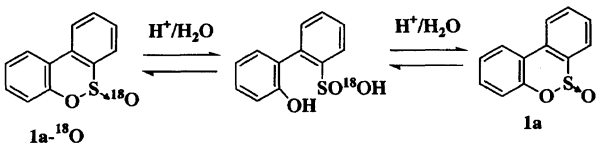


Fig. 2. UV spectral changes for the reaction of **1b** in (a) an MOPSO buffer at pH 6.84 (time interval of 2 min) and (b) 2 M HCl (time interval of 3 min).



(3)

Reaction in Buffer Solutions. Ring-opening reactions of both **1a** and **1b** are strongly buffer dependent. The spectral changes always excellently follow pseudo-first-order kinetics, and no symptom of the accumulation of an intermediate or the formation of any other nucleophilic products was found. These observations indicate that the buffer operates as a catalyst. Typical buffer dependences of the reaction of **1a** are shown for 3-morpholinopropanesulfonate (MOPS) buffers around pH 7 in Fig. 3. The observed rate constants (k_{obsd}) are linearly dependent on the total buffer concentration ($[B]_t$): $k_{obsd}=k_0+k_B[B]_t$. The rate constants obtained for **1a** and **1b** are summarized in Tables 2 and 3, respectively. The rate constants (k_0) extrapolated to zero buffer concentration increased with the pH. The hydroxide-dependent rate constants (k_{OH}) were calculated to be 7.0×10^3 and 2.8×10^4 $M^{-1}\,s^{-1}$ for **1a** and **1b**, respectively, by assuming $pK_w=14$ in spite of the ionic strength of 0.1 employed.

The buffer-dependent second-order rate constants (k_B) are plotted against the base fraction in the inset of Fig. 3, indicating that only the conjugate base of the buffer acts as a catalyst. The catalytic constants (k_{Nu}), which are dependent on the base component, were evaluated from the k_B obtained at a buffer ratio of unity ([conjugate base]=[acid]): $k_{Nu}=2k_B$. The catalytic constants k_{Nu} are plotted against pK_a

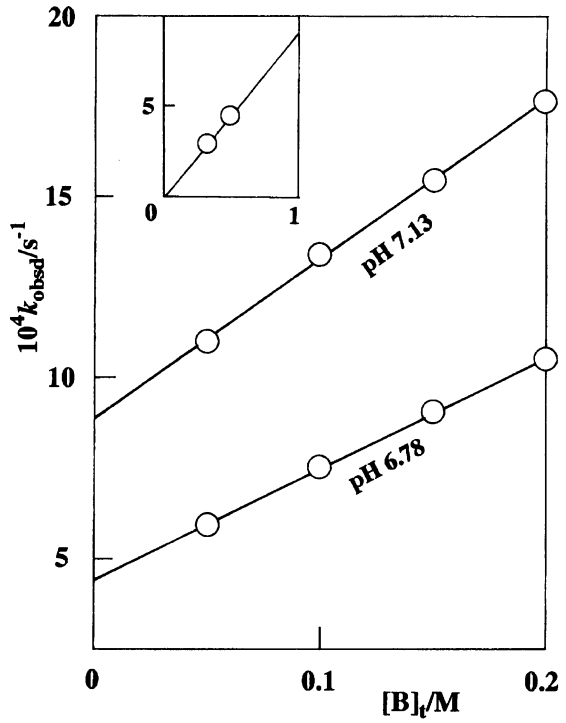


Fig. 3. Dependences of rate constants for ring opening of **1a** on MOPS buffer concentrations at 25 °C and the ionic strength of 0.10 ($NaClO_4$). The inset shows dependence of $10^3 k_B/M^{-1}\,s^{-1}$ (ordinate) on base fraction (abscissa).

of the conjugate acid of the catalyst in Fig. 4. Although the points are considerably scattered, they fall in the vicinity of lines having a slope β of unity. The scattering and the large

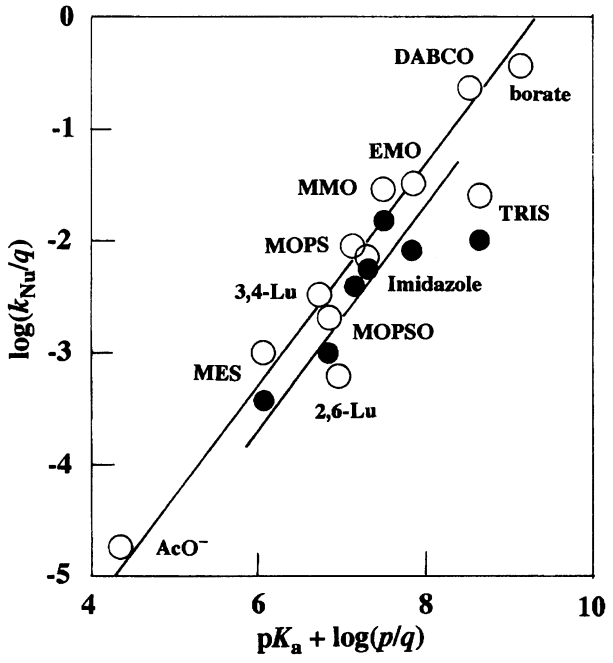


Fig. 4. The Bronsted plots for catalytic constants in ring openings of **1a** (○) and **1b** (●). Numbers, p and q, are that of ionizable protons in the acid and that of protonation sites in the conjugate base, respectively.

Table 2. Rate Constants for the Ring Opening of **1a** in Buffer Solutions[a)]

Buffer base[b)]	Buffer ratio[c)]	pH	$10^3 k_0/s^{-1}$	$10^2 k_B/M^{-1}s^{-1}$
DABCO	1	8.85	30.5	22.8
EMO	1	7.85	3.86	1.60
MMO	1	7.51	2.00	1.42
MOPS	1	7.13	0.876	0.448
MOPS	2	6.78	0.438	0.313
MOPSO	1	6.84	0.470	0.100
MES	1	6.06	0.100	0.050
Imidazole	1	7.01	0.700	0.350
TRIS	1	8.18	7.55	1.25
2,6-Lutidine	1	6.67	0.396	0.030
3,4-Lutidine	1	6.44	0.228	0.161
Acetate	1	4.64	0.003	0.0018
Borate	1	9.16	82	36

a) Determined at 25 °C and the ionic strength of 0.10 ($NaClO_4$). Rate constants are estimated to be accurate to within ±10%. b) DABCO = 1, 4- diazabicyclo[2.2.2]octane, EMO = *N*- ethylmorpholine, MMO=*N*-methylmorpholine, MOPS=3-morpholinopropanesulfonate, MOPSO=3-morpholino-2-hydroxypropanesulfonate, MES=2-morpholinoethanesulfonate, TRIS=tris(hydroxymethyl)methylamine. c) [conjugate acid]/[base].

Table 3. Rate Constants for the Ring Opening of **1b** in Buffer Solutions[a)]

Buffer base[b)]	Buffer ratio[b)]	pH	$10^3 k_0/s^{-1}$	$10^3 k_B/M^{-1}s^{-1}$
EMO	1	7.85	14.9	4.3
MMO	1	7.51	7.16	7.8
MOPS	1	7.13	3.65	1.95
MOPS	2	6.78	1.90	1.15
MOPSO	1	6.84	2.06	0.49
MES	1	6.06	0.36	0.18
Imidazole	1	7.01	3.0	2.9
TRIS	1	8.18	28	5.0

a) Determined at 25 °C and the ionic strength of 0.10 ($NaClO_4$). Rate constants are estimated to be accurate to within ±10%. b) See footnotes for Table 2.

β value suggest that the conjugate bases are operating as nucleophilic catalysts. The points for tris(hydroxymethyl)-methylamine (TRIS) and 2,6-lutidine (Lu) fall considerably below the line, probably due to steric effects against a nucleophilic attack. It may be also worthwhile pointing out that the point for acetate falls closely on the line for **1a**. This is in contrast to observations that carboxylates are very efficient catalysts in the hydrolysis of phenyl benzenesulfinate, an acyclic analog.[8)]

The reactions of the esters of aliphatic alcohol, **1c** and **1d**, were also examined in buffer solutions for the sake of a comparison. The reaction of the six-membered analog **1c** is too slow to be examined at a lower pH, and only limited buffers were used. The results are illustrated in Figs. 5 and 6. The dependences of the rates on the buffer concentrations are rather small, in contrast to observations with the phenolic analogs, **1a** and **1b**. The buffer effects observed for **1d** (and **1c**) were: (1) Negligible effects of the buffer concentration were observed for 1,4-diazabicyclo[2.2.2]octane (DABCO),

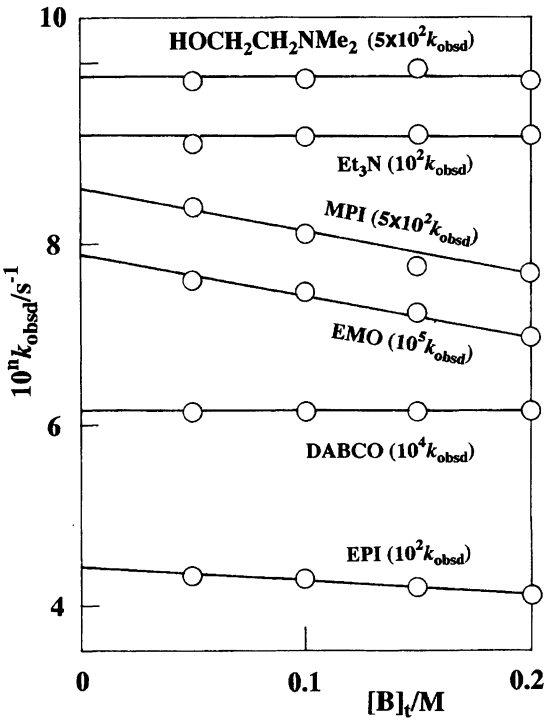


Fig. 5. Buffer dependences of ring opening of **1d** at 25 °C and the ionic strength of 0.10 ($NaClO_4$). 2-(Dimethylamino)ethanol, pH=9.40; triethylamine, pH=11.25; MPI, pH=10.47; EMO, pH=7.85; DABCO, pH=8.85; EPI, pH=10.88.

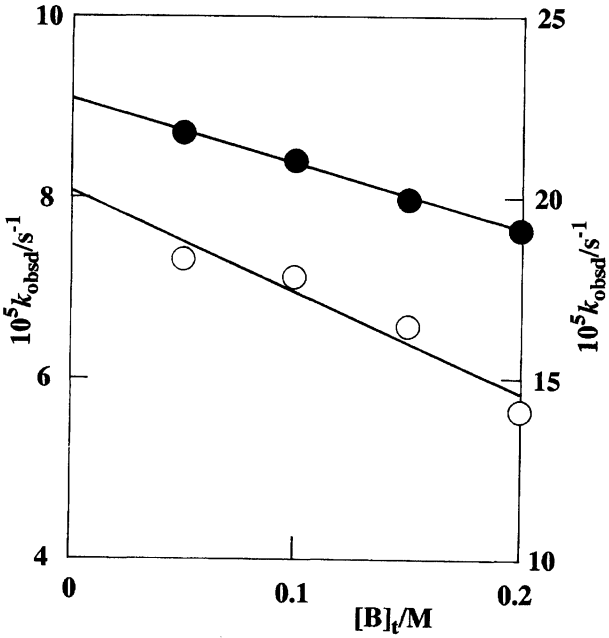


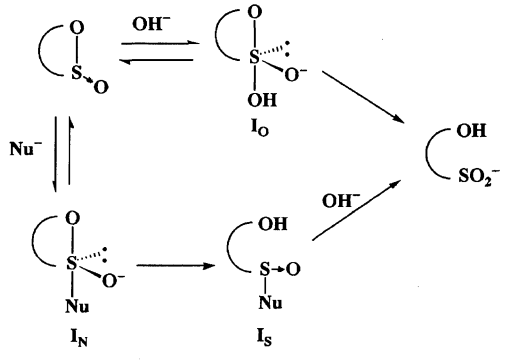
Fig. 6. Buffer dependences of ring opening of **1c** at 25 °C and the ionic strength of 0.10 ($NaClO_4$). ●: MPI buffer at pH 10.47 (left ordinate). ○: EPI buffer at pH 10.82 (right ordinate).

2-(dimethylamino)ethanol, and triethylamine. (2) Small negative effects were apparent with *N*-ethylmorpholine (EMO), *N*-methylpiperidine (MPI), and *N*-ethylpiperidine (EPI).

Reaction Mechanism. The observed nucleophilic catalysis of the reaction at the sulfinyl sulfur may be accommodated by a concerted S_N2-like mechanism with a sylfinyl intermediate ($\mathbf{I_S}$) or by a stepwise addition-elimination mechanism with two intermediates of a hypervalent and sulfinyl forms ($\mathbf{I_N}$ and $\mathbf{I_S}$ in Scheme 1). The contrasting behavior of the two groups of cyclic sulfinate esters toward a buffer catalysis must arise from the different nature of the transition state for the reactions of these sulfinates, and may be best accounted for by the latter mechanism involving a hypervalent addition intermediate ($\mathbf{I_O}$ or $\mathbf{I_N}$) with a different rate-determining step for the different classes of substrates. The hydrolysis of **1a** and **1b** may proceed with a rate-determining formation of the intermediate, owing to the high nucleofugality of phenolate (fast decay of the intermediate), while that of **1c** and **1d** may take place along with a fast equilibrium formation of the intermediate followed by its slow decay (departure of the poor aliphatic nucleofuge). The nucleofugality decreases in the following order: R_3N, $RCOO^-$ (catalytic nucleophile) $>ArO^->HO^-$, RO^-.

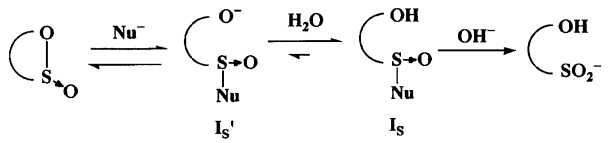
In the reaction of **1a** and **1b**, the buffer nucleophile can act as a catalyst, since it can compete with hydroxide ion to form a hypervalent intermediate $\mathbf{I_N}$, which then rapidly gives the sulfinyl intermediate $\mathbf{I_S}$ (Scheme 1). The nucleofugality of the catalytic nucleophile of the intermediate $\mathbf{I_S}$ must be still better than the phenolate, and neither of the hypervalent or sulfinyl intermediate can accumulate during the reaction. In contrast, in the reaction of aliphatic analog **1d** (**1c**) the added nucleophile of $\mathbf{I_N}$ is a much better leaving group than the alcoholic group. Since the reverse of the addition of the nucleophilic catalyst is much faster than the decay of the addition intermediate $\mathbf{I_N}$, the participation of this intermediate cannot be significant in the kinetic processes. Only the hydroxide ion is a reactive nucleophile of this reaction. That is, the reaction undergoes essentially a specific hydroxide catalysis, and general nucleophiles are not effective. Although the reasons for the retarding effects of some amines are not clear at this moment, the solvent effects[9] or an accumulation of the intermediate $\mathbf{I_N}$ may result in apparent inverse effects of the added amines.

Could a change in the rate-determining step accommodate the observed contrasting behavior if the sulfinyl intermediate $\mathbf{I_S}$ is the sole intermediate of the reaction pathway via the S_N2-like mechanism? The controling factor to determine



Scheme 1.

which step of the formation or decay of the intermediate $\mathbf{I_N}$ may be rate limiting is the relative leaving abilities of alkoxide/phenoxide and nucleophile Nu^- from $\mathbf{I_N}$, while that for the intermediate $\mathbf{I_S}$ is the relative nucleophilicities of the internal hydroxy group and solvent hydroxide toward $\mathbf{I_S}$. The leaving ability of phenolate is no doubt better than alkoxide, as discussed above, and the mechanism involving $\mathbf{I_N}$ seems to be compatible with the observations. However, the sulfinyl intermediate is present in the rapid proton-transfer equilibrium (Eq. 4) and the predominant form is neutral ($\mathbf{I_S}$) under the reaction conditions.



(4)

A ring closure should occur through the anionic form ($\mathbf{I_S}'$) as a microscopic reverse. Since the equilibrium fraction of the anionic form ($\mathbf{I_S}'$) is more favored for the phenolic analog (**1a** and **1b**), compared with the alcoholic ones (**1c** and **1d**), the reverse step of the formation of $\mathbf{I_S}$ for the former group could be more favored than that for the latter. That is, a possibility of the rate-determining formation of $\mathbf{I_S}$ cannot be greater for the former than for the latter in the S_N2-like mechanism. The S_N2-like mechanism is thus reasonably excluded for the nucleophilic reaction of cyclic sulfinate esters.

In conclusion, the contrasting observations of buffer effects in the ring-opening reaction of cyclic sulfinates of the phenolic and aliphatic leaving groups are taken as evidence for the addition–elimination mechanism involving the hypervalent intermediate.

Experimental

Materials. Dibenzo[1,2]oxathiin 6-oxide (**1a**)[10] and 3,4-dihydro-1,2-benzoxathiin 2-oxide (**1b**)[11] were prepared according to the literature.[12] The ^{18}O-labeled substrate of **1a** was obtained as described previously.[12] The samples of **1c** and **1d** were obtained previously.[4] The salts and solid amines used for buffer preparations were of the best grade commercially available. Liquid amines were distilled from potassium hydroxide immediately before use.

Reactions and Kinetic Measurements. The reactions of **1** were carried out in the same way as described previously,[4] and were followed spectrophotometrically on a Shimadzu UV 2200 spectrophotometer. The ^{18}O isotope content of **1a** was determined on a JMS DX303 mass spectrometer.[4]

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