Effect of Ring Size on the Acid-Catalyzed Reduction of Cyclic Sulfoxides by Iodide Ion[1]

Seizo TAMAGAKI, Masao MIZUNO, Hiroshi YOSHIDA,
Hiroo HIROTA, and Shigeru OAE
Department of Applied Chemistry, Faculty of Engineering, Osaka City University, Sumiyoshi-ku, Osaka

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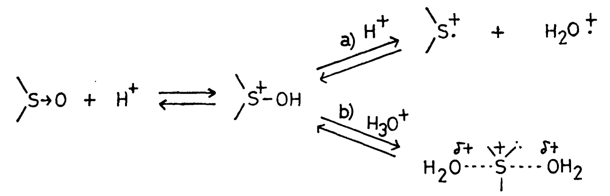
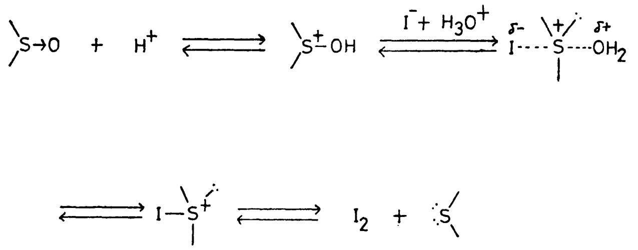
Acid-catalyzed reduction of various cyclic sulfoxides with iodide ion were kinetically investigated. The rates of reduction of thianthrene, phenoxathiin, dibenzothiophene oxides were found to be in a linear relation with their basicities, while those of alicyclic sulfoxides fall in the following sequence with a 700 fold range; 5->4->open>7->6- membered cyclic sulfoxides. This rate sequence seems to be correlated better by the steric effect than by basicity difference. For further information on the possible effect of steric hindrance, a few methyl alkyl sulfoxides were also subjected to the same reaction, but the results could not be explained by steric effect only.

The acid-catalyzed reduction of sulfoxide with iodide ion has been suggested to proceed by way of S_N2 type process on the sulfur atom.[2] Many similar S_N2 displacement reactions on the trivalent sulfur atom have been found. A distinct example[3] is oxygen exchange of diaryl sulfoxides with acetic anhydride or dilute sulfuric acid where the exchange leads to the inversion of configuration around the sulfur atom. Namely, the rate of oxygen exchange of diaryl sulfoxide is equal to that of racemization at a higher concentration (>80%) of sulfuric acid and the formation of radical cation intermediate was detected.[4] In the reactions at lower acid concentrations than 80% the mechanism changes from S_N1 (a) type to S_N2 (b) type displacement reaction shown below:



If the nucleophile in the above scheme, *i.e.*, H_2O, is replaced by such-reducing nucleophiles as iodide ion, the reaction does not lead to a reversible oxygen exchange but results in the predominant reduction illustrated below



By means of this reduction, we have investigated the nucleophilic displacement reaction on the trivalent sulfur atom of both aliphatic acyclic and cyclic sulfoxides. Although the structural effect on the reactivity of carbocyclic compounds has been examined by many workers and explanations have been given,[5] there is practically no investigation concerning the relation between the reactivity and the structure of heterocyclic compounds. We have therefore conducted a thorough kinetic study on the reduction of some simple alicyclic sulfoxides in order to disclose the effect of ring-size on the rates of the nucleophilic displacement reaction at the trivalent sulfur atom.

Experimental

Materials and kinetics: The boiling points or melting points of sulfoxides used are listed in Table 1.[6] The characterizations of reduction products of the acyclic sulfoxides were described[2] and the reduction of alicyclic sulfoxides such as five-, six- and seven- membered sulfoxides gave the corresponding sulfides in good yields of more than 80% under the kinetic conditions. However, in the case of the reduction of trimethylene sulfoxide, trimethylene sulfide was susceptible to decomposition to afford a polymer as white precipitates by the action of perchloric acid, although the sulfoxide itself was very stable to the same concentration of the acid. Special commercial grade 70%-perchloric acid was used for kinetics. Concentration of the acid was determined to be 11.83 mol/*l* with a standard solution of potassium hydroxide prepared by titrating with 0.200 mol/*l* potassium hydrogen phthalate. Water was distilled under nitrogen atmosphere and stored in a large nitrogen-flushed bottle. The aqueous solution of sodium iodide containing 0.50 mol/*l* was prepared and stored under nitrogen atmosphere. The reactor bottle was immersed in a thermostatted bath. Rate measurements were carried out by introducing a constant nitrogen stream into the reaction vessel in order to eliminate autoxidation of iodide ion to iodine which causes kinetic errors. The reaction was quenched by pouring the reaction mixture into a

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[1] Paper XXXVII on Sulfoxides.

[2] F. Montanari, *Chem. Commum.*, **1969**, 3; S. Allenmark, *Acta Chem. Scand.*, **17**, 2715 (1963); D. Landini and F. Montanari, *Tetrahedron Lett.*, **1964**, 2691; J. H. Kruger, *Inorg. Chem.*, **5**, 132 (1966); S. Allenmark and H. Johnson, *Acta Chem. Scand.*, **21**, 1672 (1967); R. A. Strecker and K. K. Andersen, *J. Org. Chem.*, **33**, 2234 (1968); D. Landini, G. Modena, F. Montanari, and G. Scorrano, *J. Amer. Chem. Soc.*, **71**, 7168 (1970).

[3] S. Oae and N. Kunieda, This Bulletin, **41**, 696 (1968).

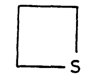
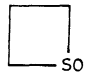
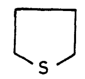
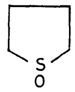
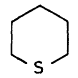
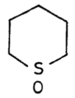
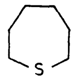
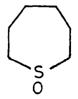
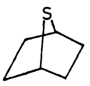
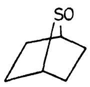
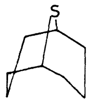
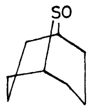
[4] S. Oae and N. Kunieda, *ibid.*, **42**, 1324 (1969).

[5] H. C. Brown and M. Borkowski, *J. Amer. Chem. Soc.*, **74**, 1894 (1952); H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).

[6] D. S. Tarbell and C. Weaver, *ibid.*, **63**, 2939 (1941); W. V. Whitehead, R. D. Dean, and F. A. Fidle, *ibid.*, **73**, 3632 (1951); G. G. Bennett and A. L. Hoak, *J. Chem. Soc.*, **1927**, 2456; E. A. Fehnell, S. Goodyear, and J. Berbowitz, *J. Amer. Chem. Soc.*, **73**, 4578 (1951).

mixed solution containing 5% of sodium iodide and 4 mol/*l* of AcONa·$3H_2O$ in 50 m*l*. Rate constants listed in Table 1 are the average of several runs.

Table 1. Boiling or melting point of sulfoxides

Sulfide	Bp, °C/mmHg (Mp, °C)	Sulfoxide	Bp, °C/mmHg (Mp, °C)
CH_3SCH_3	38	CH_3SOCH_3	86/25
$CH_3SC_2H_5$	65— 66	$CH_3SOC_2H_5$	72— 74/11
$CH_3S\text{-i-}C_3H_7$	83— 84	$CH_3SO\text{-i-}C_3H_7$	82— 83/13
$CH_3S\text{-sec-}C_4H_9$	111—112	$CH_3SO\text{-sec-}C_4H_9$	93/10
$CH_3S\text{-tert-}C_4H_9$	95— 97	$CH_3SO\text{-tert-}C_4H_9$	79— 82/10
$C_2H_5SC_2H_5$	91	$C_2H_5SOC_2H_5$	84/12
	95— 96		91/14
	119—120		113—114/14
	141—142		124—125/14
	170—171		144—145/14
	(120—123)		(205—8)
	(170—171)		(140/5)[a]

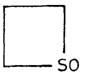
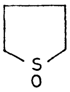
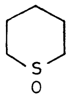
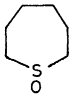
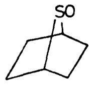
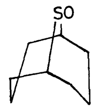
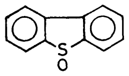
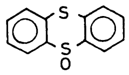
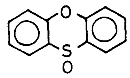
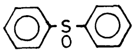
a) sublimed temp.

Results and Discussion

Effect of Basicity on Rate. The acid-dependency of this reaction was studied and the rates were shown to be in linear relationships with the Hammett acidity-function (ho) in perchloric acid but the slope was found to vary from one sulfoxide to an other.[7] However, the effect of basicity on the overall rate of reduction of the sulfinyl group has not been examined. First we reexamined the basicities of several sulfoxides. Tamres and Seales[8] investigated the hydrogen-bonding ability of cyclic sulfoxides and concluded that the basicities of the cyclic sulfoxides fall in the following sequence assuming the parallelism[9] between the basicity and hydrogen-bonding ability with methanol.

$$6\text{-} \geq 5\text{-} > 4\text{-membered ring sulfoxides}$$

Table 2. $\Delta\nu_{OH}$[a] for various sulfoxides in CCl_4

Compound	$\Delta\nu_{OH}$	$\Delta\nu_{OH}$[8]
	295	—
	375	161
	349	155
	357	—
	340	—
	346	—
CH_3SOCH_3	350	158
EtSOEt	355	167
n-BuSOBu-*n*	370	—
	286	—
	220	—
	270	—
	264	—

a) unit in cm^{-1}

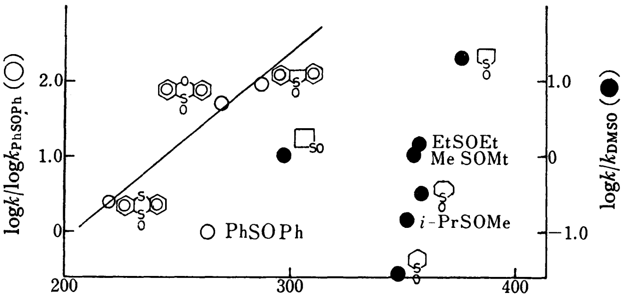


Fig. 1. Plot of log k_{rel} against $\Delta\nu_{OH}$

We measured the hydrogen-bonding abilities of sulfoxides with more acidic substrate, *i.e.*, phenol and found that the basicity sequence is not in complete agreement with that found in literature. The hydrogen-bonding abilities of several other acyclic and cyclic sulfoxides are listed in Table 2 and the plot of the rate constants against the differences of O–H stretching frequencies relative to the free phenol OH stretching frequency is shown in Fig. 1. Thus, the basicities newly determined fall in the following sequence:

$$5\text{-} > \text{Et-SO-Et} > 7\text{-} > \text{DMSO} > 6\text{-} >$$
$$(3.3.1) > (2.2.1) > 4\text{-membered sulfoxides}$$

The kinetic results of the reductions are also summarized

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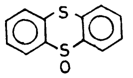
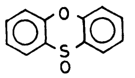
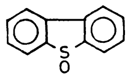
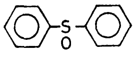
[7] D. Landini, F. Montanari, H. Hogeveen, G. Maccagnani, *Tetrahedron Lett.*, **1964**, 2691; *ibid.*, **1966**, 3309; *Chem. Commum.*, **1968**, 86; J. H. Kruger, *Inorg. Chem.*, **5**, 132 (1966).

[8] M. Tamres and S. Seales, Jr., *J. Amer. Chem. Soc.*, **81**, 2100 (1959).

[9] D. Landini, G. Modena, G. Scorrano, and F. Taddei, *ibid.*, **91**, 6703 (1969).

TABLE 3. REACTION RATE OF DIBENZO DERIVATIVES AT 298°K

Compound	$HClO_4$,M	H_0	$k \times 10^{-5}$ sec^{-1}	25° k_{rel} ($\log k_{rel}$)
	5.82	−2.71	9.11	2.4 (0.38)
 a)	5.82	−2.71	194	51.0 (1.71)
	2.85 (5.82)	−1.17 (−2.71)	25.0 (725)	91.0 (1.96)[b]
	5.44 (5.82) 6.75	−2.49 (−2.71) −3.39	2.07 (3.78) 24.1	 (1.0)[b] (0.0)

a) Slope *vs* H_0: 0.95.
b) Numerals in parenthesis indicate the interpolated values.

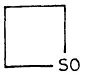
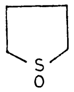
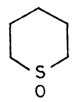
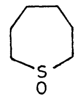
in Tables 3 and 4.

We see that the sequence of the hydrogen-bonding abilities is not always identical with that for the reduction, although the five-membered sulfoxide reacts remarkably fast as expected from its hydrogen-bonding ability. Thus, we may conclude that the overall rate of reduction may not entirely be controlled by the basicity of the sulfinyl groups.

Another illustration for the effect of basicity can be made with the dibenzo derivatives of a few heterocyclic sulfoxides (Table 3). The plot of the rate constants against the hydrogen bonding abilities is shown in Fig. 1, which indicates an approximate linearity between the rate constants and the hydrogen-bonding abilities. While diphenyl sulfoxide deviates far below the line, this phenomenon is easily accounted for by the steric hindrance caused by the four ortho hydrogens on the two phenyl rings. However, there is no further information as to what extent the protonation step influences the over-all rate of the reduction of these sulfoxides.

Activation Parameters. We see from Table 4 that the range of rates from the lowest one for the six-membered sulfoxide to that of the highest for the five-membered ring sulfoxide is 700 fold and the relative rates of the sulfoxides fall in the following decreasing order: 5->4->DMSO>7->6- membered cyclic sulfoxides. The nucleophilic substitution reaction of carbocyclic compounds[10] involving the rehybridization of reaction

TABLE 4. REDUCTION OF ALIPHATIC SULFOXIDES

Compound	Temp, °C	Pseudo-lst-order rate const, sec^{-1}	Activation enthalpy (kcal/mol)	entropy (e.u.)	$k_{rel}^{25°}$
	15	$3.78+0.07 \times 10^{-4}$	20.0	−6.7	34.7
	20	$7.13+0.13 \times 10^{-4}$			
	25	$12.6+0.078 \times 10^{-4}$			
	15	$0.98+0.14 \times 10^{-2}$	15.7	−15.1	717
	20	$1.60+0.10 \times 10^{-2}$			
	25	$2.55+0.10 \times 10^{-2}$			
	25	$3.55+0.16 \times 10^{-5}$	17.6	−21.6	1.00
	30	$6.16+0.07 \times 10^{-5}$			
	35	$9.65+0.25 \times 10^{-5}$			
	20	$2.16+0.11 \times 10^{-4}$	16.1	−22.2	9.9
	25	$3.51+0.10 \times 10^{-4}$			
	30	$5.57+0.05 \times 10^{-4}$			
DMSO	15	$4.56+0.09 \times 10^{-4}$	17.4	−15.2	32.6
	20	$7.57+0.09 \times 10^{-4}$			
	25	$13.1+0.3 \times 10^{-4}$			
CH_3SOEt	15	$5.07+0.09 \times 10^{-4}$	17.0	−16.5	4.00
	20	$8.04+0.13 \times 10^{-4}$			
	25	$14.22+0.66 \times 10^{-4}$			
EtSOEt	15	$6.38+0.22 \times 10^{-4}$	17.3	−15.1	51.2
	20	$10.28+0.22 \times 10^{-4}$			
	25	$18.2 +0.08 \times 10^{-4}$			
$CH_3SO\text{-}iC_3H_7$	20	$1.02+0.02 \times 10^{-4}$	18.1	−17.0	5.3
	25	$1.88+0.02 \times 10^{-4}$			
	30	$2.94+0.03 \times 10^{-4}$			
CH_3SO-t-Bu		too slow			
(3.3.1)[a]		too slow			
(2.2.1)[b]		too slow			

a) 9-thia-monoxybicyclo(3.3.1)octane
b) 7-thia-monoxybicyclo(2.2.1)heptane

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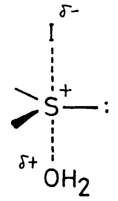
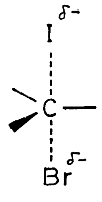
[10] P. J. C. Fierens and P. Verschelden, *Bull. Soc. Chim. Belges*, **61**, 427, 609 (1952); *ibid.*, **68**, 580 (1958).

center from sp^3 to sp^2 shows a similar tendency, namely, 5- > open > 7- > 6- > 4- membered ring sulfoxides except the four-membered ring compound which is known to undergo solvolysis through a different course.

The apparent parallelism in reaction sequence between the two series of reactions undergoing displacement reaction on the two different atoms may be made clear by assuming both reactions to proceed through similar transition states. That is, in the case of sulfoxides the formation of trigonal bipyramidal structure such as (A) might be involved as in the S_N2 process on the carbon atom (B).



(A)

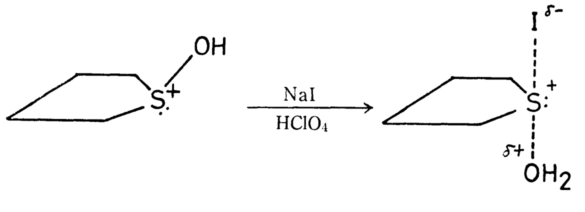


(B)

Further evidence for the S_N2 like displacement at the sulfur atom may be the large negative activation entropy, −15 e.u., which is comparable to that of a typical S_N2 reaction on the carbon atom.

We have extended the study of this reduction to the series of methyl alkyl sulfoxides in order to re-examine the steric nature of this reaction. Strecker and Andersen[11] reported the importance of steric effect in a similar reduction of phenyl alkyl sulfoxides in which the rate constants decreased monotopically with increasing bulkiness of the alkyl group. However, there is a small rate acceleration by substitution of the ethyl group suggesting that in this series of methyl alkyl sulfoxides the ethyl group acts as an electron-donating group to facilitate the initial protonation step rather than as a steric hindrance group toward the incoming nucleophile at the second step. Likewise, the rate of reaction of diethyl sulfoxide is also about 30% faster than that of dimethyl sulfoxide. This seems to indicate that the steric inhibition is more important in the reaction of phenyl alkyl sulfoxides, perhaps due to the fact that the presence of a bulkier phenyl group makes the reaction center more sensitive to steric hindrance while in the series of methyl alkyl sulfoxides, the small methyl group can easily tolerate the steric inhibition of another primary alkyl group.

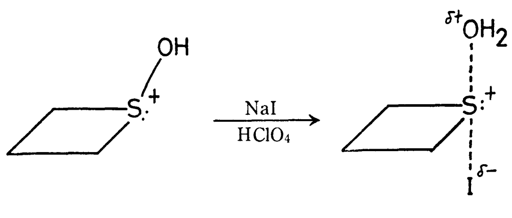
In view of thermodynamic parameters it is clear that the difference in reactivities of cyclic sulfoxides is mainly caused by the change in activation entropy. The activation entropy obviously decreases with increasing ring size and takes more negative value in the reaction of six- and seven- membered cyclic compounds and becomes less negative in reactions of four- and five-membered cyclic sulfoxides. The results can be best rationalized in terms of rigidity of the transition complex; namely, the less negative activation entropy for the five-membered cyclic sulfoxide indicates the transition state to have a similar rigidity to the ground state, and no reorganization of the molecular geometry along the reaction coordinate might be required. In other words, molecules which have already built-in ordered structure at the ground-state can reach the transition state without much loss of entropy to disturb the molecular motions. This gain of activation entropy would decrease the free energy of activation. For the enthalpy of activation, the five membered cyclic compound is so constrained already at the ground state that far less energy is required to reach the transition state, thus resulting in the lowest energy of activation among the aliphatic sulfoxides.



This is confirmed by an examination of the reaction of dibenzothiophene oxide which is very rigid due to the two benzo groups on both sides of thiophene molecule.

As anticipated, dibenzothiophene oxide has a less negative entropy of activation and a much lower enthalpy of activation, *i.e.*, $\Delta S^{\neq}=-10.4$ e.u. and $\Delta H^{\neq}=18.5$ kcal/mol than $\Delta S^{\neq}=-15.1$ e.u. for tetramethylene sulfoxide and $\Delta H^{\neq}=20.0$ kcal/mol for diphenyl sulfoxides.

Consideration of rigidity can be extended also to the four-membered sulfoxide system where the angle strain due to the smaller C–S–C angle and the molecular rigidity is evident. Thus, the four-membered cyclic sulfoxide is expected to have a large value of enthalpy and a less negative value of entropy of activation and hence to be highly reactive. This was the case for the highly strained four-membered cyclic sulfoxide. The observed large activation enthalpy amounting to 20 kcal/mol is in line with the relatively large energy required to overcome the accompanying unusual angle strain, while the less negative value of entropy of activation supports the view that the molecular shape is relatively unchanged in reaching the transition state.



However, in this case, from the consideration of less negative entropy of activation of −6.7 e.u., there is a possibility that the direct nucleophilic attack of iodide ion on the sulfur or carbon atom provides the ring-opening product instead of the corresponding normal reduction product, *i.e.*, trimethylene sulfide. Because of the instability of trimethylene sulfide which decomposed to form a polymer in the highly acidic condition we chose for the kinetic study, we can give no plausible mechanism.

When the ring size becomes larger than five, the sulfoxides should display entirely different patterns in

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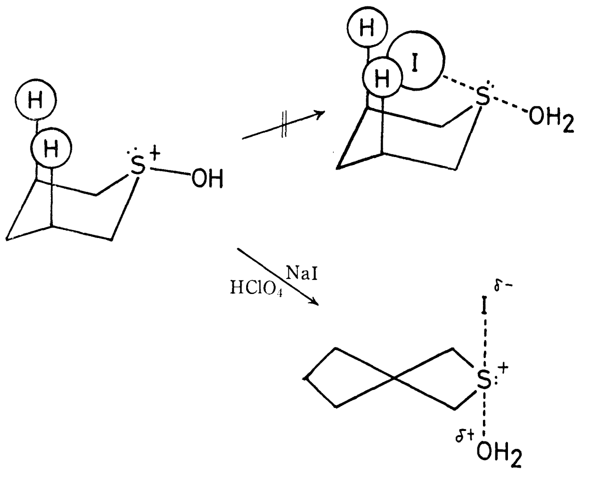
[11] R. A. Strecker and K. K. Andersen, *J. Org. Chem.*, **33**, 2234 (1968).

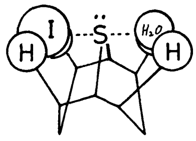
the thermodynamic parameters from those of tetramethylene sulfoxide, since the molecules are no longer rigid.

Entropies of activation for the reduction of pentamethylene and hexamethylene sylfoxides are smaller by 6 e.u. than that of tetramethylene sulfoxide. Although these reactions may not be of a simple elementary process, a possible structure for the transition state may be obtained from a consideration of the activation parameters.

If the reaction proceeds keeping the molecular shape unchanged all through the process, the attack of iodide ion at the sulfur atom should be hindered by the presence of the axial hydrogens on β-carbon atoms of pentamethylene sulfoxide and the rate depressed. However, since the molecule is not rigid it can avoid such a steric strain by distorting or twisting the ring into a half-chair form.[12] This idea of half-chair form at the transition state does not violate the microscopic reversibility principle and both the entering and leaving groups have to occupy equivalent positions.



The same idea may be applied to the reaction of the seven-membered cyclic compound. The extremely slow rate of reduction of the bicyclic (3.3.1)-9-sulfoxide also may serve to support the above mentioned argument. Such a rigid compound which has built-in two chair forms should be in a much more unfavorable situation in the process of the relief of steric strain as compared with the case of the six-membered sulfoxide. The molecule is so rigid that it cannot bend the bonds to assume the energetically favorable conformation to allow an attack of nucleophile to come close to the reaction center.



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[12] J. C. Martin and J. J. Uebel, *J. Amer. Chem. Soc.*, **86**, 2937 (1964).