BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 47(1), 179—182 (1974)

Mechanism of the Oxygen Exchange Reaction of *n*-Butyl Methyl Sulfoxide in Sulfuric Acid[1)]

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(Received September 17, 1973)

Mechanistic investigations of the concurrent oxygen exchange and racemization reactions of ^{18}O-labeled and optically active *n*-butyl methyl sulfoxide in sulfuric acid of various concentrations have been carried out. The kinetic data were analyzed in the light of k_{ex}/k_{rac} values, activation parameters, correlations between the rates and acidity functions, *etc.* The results seem to suggest that the reaction proceeds through an A-1-like route to afford a cation radical ($-\overset{+\bullet}{S}-$) or a dication ($-\overset{++}{S}-$) intermediate, followed by a fast nucleophilic attack of water to give the starting sulfoxide.

Extensive investigations have been carried out on oxygen exchange reaction of sulfoxides in order to clarify the nature of the nucleophilic substitution on trivalent sulfur atom.[2–8)] The mechanisms of the concurrent oxygen exchange and racemizations reactions of phenyl *p*-tolyl sulfoxide (**2**) and methyl *p*-tolyl sulfoxide (**3**) in sulfuric acid were studied in detail.[9–12)]

We have carried out a detailed study of the oxygen exchange reaction of *n*-butyl methyl sulfoxide (**1**) in sulfuric acid, in order to clarify the mechanism and to elucidate the difference between the mechanisms of oxygen exchange of three typical sulfoxides such as **1**, **2**, and **3** and obtained interesting results that are quite different from those of **2** and **3**. This paper describes the oxygen exchange reaction of the dialkyl sulfoxide.

Results and Discussion

When *n*-butyl methyl sulfoxide (**1**) was dissolved in 96.8% sulfuric acid for two months at room temperature, the starting sulfoxide was recovered almost quantitatively upon dilution with excess water without any side reactions. Optically active and ^{18}O-labeled sulfoxide (**1**) was thus synthesized and subjected to kinetic experiments.

The rates of oxygen exchange and racemization of **1** in sulfuric acid in the concentration range 56.1—94.8% were determined at several temperatures. While the rate can be expressed as a function of the protonated sulfoxide $[\text{S}^+\text{-OH}]$,[13)] since the sulfoxide is significantly protonated in the range of acidity used in this work, it can be expressed by the equation.

$$\text{rate} = k_1[\text{S}^+\text{-OH}] \qquad k_1 = k_{\text{obs}}(h_A + K_{\text{SH}^+})/h_A$$

where k_{obsd} is the experimental rate coefficient and K_{SH^+} the thermodynamic ionization constant of sulfoxide. The thermodynamic constant, $\text{p}K_{\text{SH}^+}$ of **1**, evaluated on the basis of the Bunnett and Olsen equation, is -1.70,[14)] and the H_A acidity function can be used to describe the acid-base behavior of the sulfoxides with a good approximation, since plots of $\log([\text{S}^+\text{-OH}]/[\text{SO}])$ *vs.* $-H_A$ are linear with slopes of nearly one or above one.[12–15)]

The observed rate constants of oxygen exchange (k_{ex}) and racemization (k_{rac}) are given in Table 1.

Table 1. Rate constants for oxygen exchange and racemization of *n*-butyl methyl sulfoxide (**1**)[a)] in sulfuric acid

H_2SO_4 (wt%)	Temp. (°C)	10^4k_{rac} (s^{-1})	10^4k_{ex} (s^{-1})	k_{ex}/k_{rac}	H_0[b)]	H_A[c)]	Kinetic[d)] method
94.8	5.0	102	19.4	0.19	−9.82	−6.11[e)]	A
93.7	5.0	—	11.4	—	−9.62	−5.98[e)]	A
89.7	5.0	6.97	2.82	0.40	−8.87	−5.54	A
84.5	5.0	0.808	—	—	−8.06	−4.96	B
82.0	5.0	0.273	—	—	−7.66	−4.74	B
82.0	30.0	7.25	6.76	0.93	−7.66	−4.74	A
77.7	30.0	2.34	—	—	−6.98	−4.36	B
74.6	30.0	0.808	0.815	1.01	−6.49	−4.12	A
72.3	30.0	0.573	0.587	1.02	−6.14	−3.93	A
65.6	30.0	0.178	—	—	−5.15	−3.43	B
60.9	30.0	0.133	0.128	0.96	−4.56	−3.16	A
56.1	30.0	0.106	0.111	1.05	−3.94	−2.83	A

a) Sulfoxide: 0.1 mol/l.
b) Obtained from Ref. 16.
c) Obtained from Refs. 17 and 18.
d) See Experimental.
e) Extrapolated value.

The ratio of k_{ex}/k_{rac} is found to be unity except in higher concentrated sulfuric acid where the ratio is smaller than unity. This differs from the case of diaryl sulfoxide (**2**) and alkyl aryl sulfoxide (**3**), in which the ratio of k_{ex}/k_{rac} gradually changes from 0.5 to 1 with an increase in acid concentration accompanied by a change of mechanism from S_N2 type to an A-1-like route.[11,12)]

Since the reaction appeared to be acid-catalyzed, the values of $\log k_1$ of oxygen exchange and racemization in sulfuric acid in the concentration range 56.1—94.8% were plotted against acidity function H_A (or H_0). There is a curvature below 70% sulfuric acid and a straight line with a slope of $+1.38$ (or $+0.82$ *vs.* H_0) above 70% sulfuric acid for both oxygen exchange and racemization reactions. However, the racemization above 85% acid only deviated upward from the line (slope $+1.38$) to give a straight line with a slope $+1.83$ (or $+1.21$ *vs.* H_0) (Fig. 1).

From the linear correlation with acidity function the reaction above 70% acid would involve the monoprotonated species which picks up another proton before reaching the transition state of the reaction, indicating

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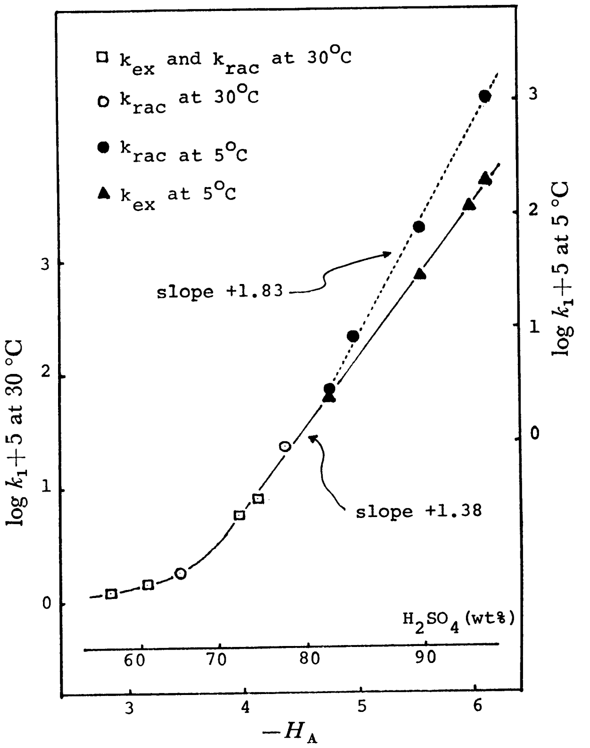


Fig. 1. Correlation between rate constant and acidity function H_A.

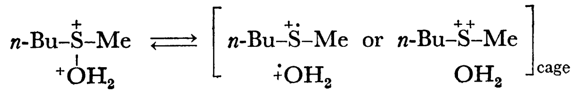
that the reaction is of the A-1-like mechanism according to the Zucker-Hammett hypothesis.[19] The energy and entropy of activation for the racemization in 82% acid are found to be 21.8 kcal/mol and −2.68 e.u., respectively (Table 2). The small negative value of entropy of activation also favors the rate-determining A-1-like S–O bond cleavage of sulfoxide.

TABLE 2. ACTIVATION PARAMETERS FOR RACEMIZATION OF (+)-n-BUTYL METHYL SULFOXIDE (**1**) IN SULFURIC ACID

H_2SO_4 (wt%)	E_a (kcal/mol)	$\Delta S^{\neq}$ (e.u.)
89.7	17.3	−13.8
82.0	21.8	− 2.68
65.6	21.4	−11.7
56.1	16.7	−28.0

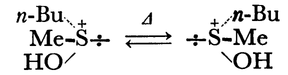
However, above 85% sulfuric acid, the racemization would be caused by both an A-1-like reaction and some other reaction without oxygen exchange. The following possibilities are considered for the racemization without oxygen exchange: 1) formation of an intimate ion pair produced by S–O bond fission of protonated sulfoxide followed by a fast internal return in solvent cage to afford the racemized sulfoxide; 2) a thermal racemization of protonated sulfoxide caused by a pyramidal inversion process; 3) a fast equilibrium of protonated sulfoxide and the corresponding ylide produced by abstraction of α-hydrogen of the protonated sulfoxide.

(1) Intimate ion-pair in solvent cage



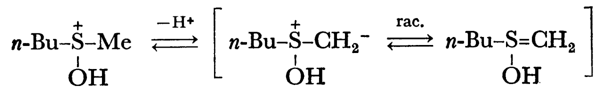
$$n\text{-Bu-}\underset{{}^{+}\text{OH}_2}{\overset{+}{S}}\text{-Me} \rightleftarrows \left[n\text{-Bu-}\overset{+\cdot}{S}\text{-Me} \quad \dot{+}\text{OH}_2 \ \text{ or } \ n\text{-Bu-}\overset{++}{S}\text{-Me} \quad \text{OH}_2 \right]_{\text{cage}}$$

(2) Pyramidal inversion



$$\text{Me-}\overset{+}{S}(n\text{-Bu})(\text{HO}) \overset{\Delta}{\rightleftarrows} (n\text{-Bu})(\text{OH})\overset{+}{S}\text{-Me}$$

(3) Ylide-ylene intermediate



$$n\text{-Bu-}\underset{\text{OH}}{\overset{+}{S}}\text{-Me} \overset{-H^+}{\rightleftarrows} \left[n\text{-Bu-}\underset{\text{OH}}{\overset{+}{S}}\text{-CH}_2^- \overset{\text{rac.}}{\rightleftarrows} n\text{-Bu-}\underset{\text{OH}}{S}\text{=CH}_2 \right]$$

However, since the rate of racemization is so fast in concentrated sulfuric acid of around 95%, in which racemization without oxygen exchange takes place almost predominantly, its mechanism can not be visualized on the basis of kinetic observation alone.

The third possibility may be readily tested by using α-deuterium labeled sulfoxide. When n-butyl trideuteriomethyl sulfoxide (**1**—d_3) was dissolved in an excess non-labeled sulfuric acid, no detectable amount of H–D exchange was observed under both normal and drastic reaction conditions (See Experimental). It can thus be ruled out.

It is well known that a pyramidal inversion of an optically active trialkyl substituted sulfonium salt takes place slowly only on being heated around 50 °C,[20–22] while there is no thermal racemization without any oxygen exchange reaction of sulfoxides for both alkyl aryl and diaryl sulfoxides in the concentrated sulfuric acid.[10–12] Therefore the second possibility would not be significant.

Thus, the first possibility seems to be most favorable in view of the fact[23] that a highly concentrated sulfuric acid should have a larger solvent cage effect, because of the higher viscosity and a lower nucleophilicity of water molecules.

In order to clarify the mechanism, we have analyzed the data on the basis of the Φ parameter.[24] This is taken from the slope of the plots of log $[k_1+H_0]$ *vs.* $[H_0+\log[H^+]]$ and is an indication of the change in solvation from the initial to the transition states; namely, if Φ value is larger than 0.58, water is involved as a proton transfer agent in the rate-determining step; in the Φ range 0.22—0.56, water is involved as a nucleophile in the rate-determining step; while if the Φ value is smaller than zero, water is not involved in the rate-determining step.

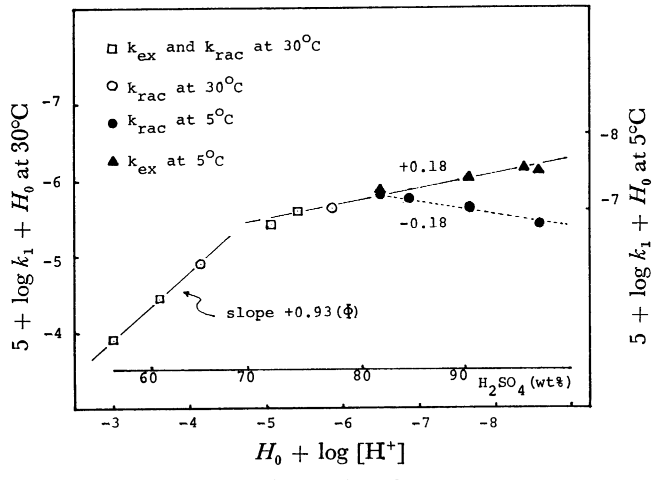
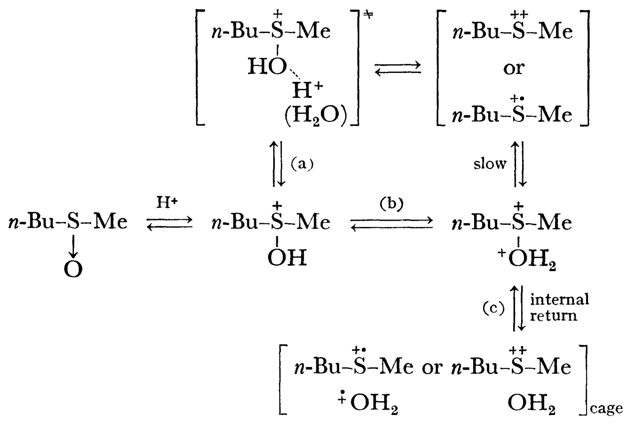


Fig. 2. Bunnett-Olsen plot of rate constant.

The plot, in which straight lines with slopes (Φ values) of +0.93 and +0.18 were obtained for below 70% and above 70% sulfuric acids, respectively, is shown in Fig. 2.

Thus, the oxygen exchange reaction below 70% sulfuric acid would proceed through the rate-determining A-1-like S–O bond cleavage in which water is involved as a proton transfer agent and the solvation in the transition state is markedly high from the data of Φ value. The unity of k_{ex}/k_{rac} and a large negative activation entropy ($\Delta S^{\neq}=-28.0$ e.u.) for racemization in 56.8% sulfuric acid also supported this (Tables 1 and 2). A similar mechanism was proposed in the A-1-like oxygen exchange reaction of sulfoxide with acetic acid and chloroacetic acids,[5] in which acetic acid acts as an acid-catalyst and the solvation is remarkably high at the transition state ($k_{ex}/k_{rac}=1.01$, $\Delta S^{\neq}=-23.4$—-32.9 e.u.).

An overall scheme for the oxygen exchange and racemization of *n*-butyl methyl sulfoxide (**1**) might be schematically drawn as shown below.



The reaction seems to proceed through path (a) below 70% acid, path (b) above 70% acid and paths (b) and (c) above 85% acid to afford the symmetrical dication ($-\overset{++}{S}-$) or cation radical ($-\overset{+\cdot}{S}-$) intermediate, while the subsequent attack of water should be very fast.

The labile symmetrical intermediate should be detected by the following ^{18}O tracer experiment by quenching the solution of the non-labeled sulfoxide with ^{18}O-enriched water. A small amount of incorporation of ^{18}O into the sulfinyl function of the recovered sulfoxide was observed by quenching the non-labeled sulfuric acid solution containing non-labeled sulfoxide (**1**) with a large amount of cold ^{18}O-labeled water (See Experimental).

Experimental

Materials. *Optically Active (+)n-Butyl Methyl Sulfoxide, (+)-**1**,* was prepared from the reaction of (−)menthyl (−)*n*-butanesulfinate with methylmagnesium iodide in ether according to the method of Andersen.[25] The optically active sulfoxide thus obtained was purified by the method of Mislow *et al.*[26] $[\alpha]_D$ +33.0° (*c* 1.20, $CHCl_3$) (lit,[27] +112° (*c* 1.02, isooctane, 94% optically pure)).

*^{18}O-Labeled n-Butyl Methyl Sulfoxide, **1**,* was prepared by the oxidation of *n*-butyl methyl sulfide with bromine in the presence of pyridine in acetic acid and $H_2{}^{18}O$, according to the usual procedure.[28] ^{18}O-Content was 1.70 atom %.

*n-Butyl Trideuteriomethyl Sulfoxide, **1-d**$_3$,* was prepared by treating *n*-butyl methyl sulfoxide with NaOD–D_2O at 60 °C for 14 hr. The deuterium content was determined by NMR measurement and the D content was found to be above 95%.

Sulfuric Acid. Concentrations of sulfuric acid were determined by titration with a standard alkali solution. H_A values are taken from reported tables[17,18] and H_0 values from the table prepared by Johnson *et al.*[16]

*Test for H–D Exchange of Sulfoxide, **1-d**$_3$, with Sulfuric Acid.* Deuterium labeled sulfoxide, **1**-d_3, (*ca.* 50 mg) was dissolved in 0.5 ml sulfuric acid and the sulfuric acid solution was introduced into an NMR tube. After being kept standing under three different conditions, *i.e.*, i) 92% sulfuric acid at room temperature for 240 hr; ii) 72.3% acid at room temperature for 50 hr; iii) 56.1% acid at 50 °C for 58 hr, ^1H-NMR spectra of the sulfoxide solution were measured. However, no detectable peak of methyl proton (CH_3SO; 3.3 ppm) appeared.

Trapping of the Dication or Cation Radical Intermediate by Quenching with $H_2{}^{18}O$. Non-labeled sulfoxide (**1**) was dissolved in non-labeled sulfuric acid and kept standing under appropriate conditions and then the sulfuric acid solution was quenched with a large excess of cold $H_2{}^{18}O$. The sulfoxide was recovered according to the procedure described below, and subjected to ^{18}O-analysis. The result is given in Table 3.

TABLE 3. ^{18}O-CONTENTS OF SULFOXIDE (**1**) RECOVERED BY QUENCHING WITH $H_2{}^{18}O$ [a,b)]

H_2SO_4 (wt%)	Time (hr)	Temperature (°C)	^{18}O-Content (atom%)[c)]
56.1	24	30	0.204
72.3	1.5	30	0.214
96.8	0.7	25	0.244

a) Sulfoxide: 0.1 mol/l.
b) ^{18}O-Content of water used is 1.67 atom%.
c) Natural abundance: 0.204, accuracy of analysis of mass spectrum: ±0.005 atom%.

Kinetic Procedure. The rates of oxygen exchange and racemization were measured by the following two methods with a Yanagimoto OR-10 type polarimeter and a Hitachi RMU-6E mass spectrometer.

Method A (for Both Oxygen Exchange and Racemization). In order to compare the rate constants, both oxygen exchange and racemization reactions were carried out under identical conditions. An ^{18}O-labeled or optically active sulfoxide was dissolved in a sulfuric acid in such a way as to maintain the concentration of the sulfoxide at just about 0.1 mol/l at a given temperature. Five aliquot portions of the solution were removed from the constant temperature bath at appropriate time intervals and quenched with a large amount of ice-water. The sulfoxide was extracted from the solution with chloroform or dichloromethane by the salting-out technique, and the extract was washed with a 5% aqueous solution of sodium carbonate and water containing salt, and then dried over anhydrous sodium sulfate after which the solvent was distilled off. The resulting sulfoxide was subjected to both ^{18}O-analysis and specific rotation measurement. The ^{18}O-atom % was calculated from the mass peak heights of 44 and 46 according to the method of Samuel.[29]

Method B (for Racemization). A sulfuric acid solution containing an optically active sulfoxide of a set mol was placed in a square cell (5 cm). The rate was measured directly by checking the rotation α of the polarimeter, which was connected with a constant temperature bath at the desired temperature.

Calculation of Pseudo first-order Rate Constant. For racemization, $\log[\alpha_0]-\log[\alpha_t]=kt/2.303$, where α_0 and α_t are the rotations at times 0 and t, respectively; and for oxygen exchange, $\log[\beta_0-\beta]-\log[\beta_t-\beta]=kt/2.303$, where β_0 and β_t are the atom% of ^{18}O at times 0 and t, respectively, and β is that of natural CO_2.

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