Hydrogen Exchange Reactions of Sulfilimines and Sulfoximines1)

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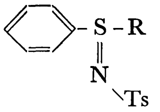
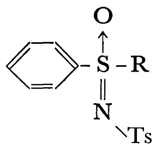
Alkyl phenyl sulfilimines, benzyl phenyl sulfilimine and the corresponding sulfoximines were found to exchange their α-hydrogens with deuteriums in heavy water when the medium was alkaline. No exchange was observed when the medium was acidic or neutral. The rates of exchange in a sulfilimine were greater than those of the corresponding sulfoximine. The kinetics of these H-D exchange reactions were investigated by use of pyridine as a catalyst, and the reaction mechanism was discussed.

The α-hydrogens of sulfoxides and sulfones are known to undergo H-D exchange, and the stereochemistry has been studied.2) However, H-D exchange in sulfilimines(I) and sulfoximines(II) has not been studied. In order to determine whether or not they also undergo H-D exchange and, if so, whether or not the exchange is stereospecific, an investigation was carried out.

Results and Discussion

When benzyl phenyl sulfilimine(Ia) or benzyl phenyl sulfoximine(IIa) was heated in a dioxane–D_2O mixture at 95 °C, no decrease in their NMR benzyl signals was observed. Addition of acetic acid or dilute HCl did not cause exchange either.





Ia: R = $PhCH_2$
Ib: R = CH_3
Ic: R = C_2H_5

IIa: R = $PhCH_2$
IIb: R = CH_3
IIc: R = C_2H_5

However, when a small amount (2∼5 mol%) of sodium hydroxide was added as a catalyst, the benzyl hydrogens of Ia undergo complete exchange on being heated at 95 °C for 10 min. The two benzyl hydrogens of Ia show an AB quartet in the NMR spectrum owing to chirality on the sulfur atom. However, the rates of exchange of these two hydrogens did not appear to differ, and no stereospecificity was observed. This finding differs from what was observed with benzyl sulfoxides.3)

The α-hydrogens of Ib, Ic, IIa and IIb also undergo exchange readily in D_2O in the presence of sodium hydroxide. The rates of H-D exchange in a 95% dioxane–5% D_2O mixture were determined by means of NMR with the tosyl methyl signal as a built-in standard, since the tosyl methyl hydrogens do not undergo exchange at all. In alkaline media, I is slowly hydrolyzed, but its rate is far smaller than that of H-D exchange and can be neglected.

The rates of H-D exchange of Ia∼Ic were determined with [NaOH] = 0.013 M at 10 °C. The exchange was of first order in I, and the pseudo first-order rate constants per one exchangeable hydrogen atom are as follows.

Ia: $k_{obs} = 6.35 \times 10^{-5}\ s^{-1}$
Ib: $k_{obs} = 2.10 \times 10^{-6}$
Ic: $k_{obs} = 1.39 \times 10^{-6}$

The ratio of reactivities per one α-hydrogen is Ia : Ib : Ic = 30 : 1 : 0.66. The presence of an adjacent phenyl group promotes the H-D exchange, whereas the presence of an adjacent methyl group retards the exchange.

These results show that the S=N bond of I is strongly polarized and α-carbanions are readily formed. However, in order to compare the effect of the S=N group with those of $\rangle C{=}O$, $\rangle SO_2$ and $\rangle S{=}O$ groups, accurate determination of the H-D exchange rate constants is necessary. For this, sodium hydroxide is unsuitable since the reaction proceeds too rapidly. When a very small amount of sodium hydroxide was used in the later stages of the reaction, part of the catalyst was neutralized with the *p*-toluenesulfonamide formed by hydrolysis of I. Pyridine was, therefore, chosen as catalyst, and the H-D exchange in pyridine–D_2O was studied.

Sulfilimines (Ia or Ib) or sulfoximines (IIa or IIb) (1∼2 mmol) were dissolved in pyridine (5 ml), and D_2O (0.5∼2.0 g, 24∼102 mmol) was added. The mixture was allowed to react in ampoules at a constant temperature. At suitable intervals, ampoules were cooled in ice, and their NMR absorptions were determined. The rates of exchange were calculated from the decrease of integrated intensity of α-methyl or α-methylene absorptions. Since D_2O is present in far excess of I or II, the backward reaction (D-H exchange) can be neglected. The apparent rate constants were calculated by using the following equation, as in the case of the NaOH-catalyzed reaction. The tosyl methyl group was used as a built-in standard. This method is similar to that of Hine *et al.*, who determined base-catalyzed H-D exchange rates of $CH_3OCH_2CO_2CH_3$ by using the methoxy methyl NMR signal as a built-in standard.4)

$$k_{obs} = \frac{2.303}{t} \log \frac{(M/R)_\infty - (M/R)_0}{(M/R)_\infty - (M/R)_t}$$

R: Integrated intensity of the tosyl methyl signal.
M: Integrated intensity of the α-methyl or α-methylene signal.
$(M/R)_\infty$: Value calculated for $t = \infty$.
$(M/R)_0$: Value calculated for $t = 0$; it is 1 for Ib or IIb, and 2/3 for Ia or IIa.

For the calculation of rate constants, the first-order rate equation described above was used with assumption that the H-D exchange is not stereospecific and rates of exchange of three α-methyl or two α-methylene hydrogens are equal. This might be reasonable since the rates of exchange of two benzyl hydrogens of Ia were equal.

TABLE 1. RELATIONSHIP BETWEEN k_{obs} AND D_2O CONCENTRATION

Substrate	$[D_2O]$ (mol/l)	Temperature (°C)	k_{obs}[a] (s^{-1})
Ia	4.31	60.0	1.57×10^{-5}
	8.60	60.0	3.26×10^{-5}
	4.48	70.0	3.91×10^{-5}
	8.60	70.0	8.15×10^{-5}
Ib	4.69	70.0	1.94×10^{-5}
	8.14	70.0	2.78×10^{-5}

a) k_{obs} was calculated for one α-hydrogen atom.

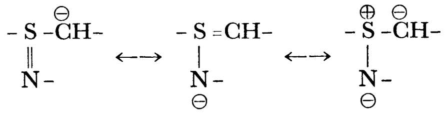
Since pyridine was the catalyst and the solvent, the catalyst concentration was constant. When the relationship between k_{obs} and $[D_2O]$ was examined at 60 °C and 70 °C, k_{obs} was approximately proportional to $[D_2O]$ as shown in Table 1. Thus, the rate constant k was calculated by dividing k_{obs} with $[D_2O]$.

$$\begin{aligned} v &= k_{\text{obs}}[\text{Ia}] \\ &= k[D_2O][\text{Ia}] \\ &= k'[\text{Py}][D_2O][\text{Ia}] \end{aligned}$$

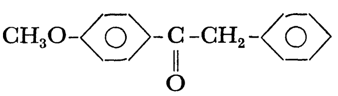
The values of k_{obs}, k $(=k_{\text{obs}}/[D_2O])$ and the activation parameters are shown in Table 2. No exchange was observed with Ic and IIc under these conditions.

The data in Table 2 show that the H-D exchange in benzyl sulfilimine and benzyl sulfoximine is faster than that in the corresponding methyl analog. This is probably due to the stabilization of the carbanion by resonance with the adjacent phenyl group.

The H-D exchange in sulfoximines (IIa and IIb) is much slower than that in sulfilimines(Ia and Ib). If the effect of the $\rangle\text{S=N}'$ or $\underset{\underset{\text{O}}{\downarrow}}{\rangle\text{S}}\text{=N}'$ group is only inductive effect alone, the $\underset{\underset{\text{O}}{\downarrow}}{\rangle\text{S}}\text{=N}'$ group containing an additional oxygen atom should facilitate the abstraction of α-hydrogens to a greater extent. However, the experimental findings are to the contrary; the H-D exchange in I is 10 times that in II and its activation energy is about 1 kcal/mol smaller than that of II. These results are surprising, and the only possible explanation seems to be the more extensive stabilization of the carbanion by the resonance with the $\rangle\text{S=N}'$ group than with the $\underset{\underset{\text{O}}{\|}}{\rangle\text{S}}\text{=N}'$ group, but at present no other data supporting such difference are available.

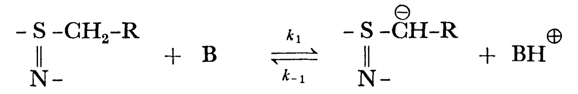


In order to compare the ability of $\rangle\text{S=N}'$ and $\underset{\underset{\text{O}}{\downarrow}}{\rangle\text{S}}\text{=N}'$ for stabilizing carbanions with that of $\rangle\text{C=O}$, the H-D exchange of benzyl *p*-methoxyphenyl ketone(III) was measured in pyridine–D_2O by using its methoxy hydrogens as a built-in standard. The reaction was of first-order in III, and at 70 °C k_{obs} was 2.68×10^{-4} s^{-1} and k $(=k_{\text{obs}}/[D_2O])$ was 5.85×10^{-5} $M^{-1}s^{-1}$ (both k_{obs} and k were calculated for one methylene hydrogen). These values are about 7 times that of Ia and 60 times that of IIa. Thus the ability of $\rangle\text{S=N}'$ or $\underset{\underset{\text{O}}{\downarrow}}{\rangle\text{S}}\text{=N}'$ for stabilizing carbanions is much less than that of $\rangle\text{C=O}$.



(III)

The base-catalyzed H-D exchange of sulfilimines is considered to proceed *via* the following steps (similar steps can be formulated for the H-D exchange of sulfoximines).

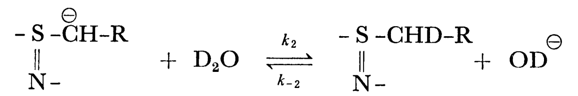


$$\underset{\underset{\text{N-}}{\|}}{\text{-S}}\text{-CH}_2\text{-R} + \text{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\underset{\text{N-}}{\|}}{\text{-S}}\text{-}\overset{\ominus}{\text{C}}\text{H-R} + \text{BH}^{\oplus} \quad (1)$$

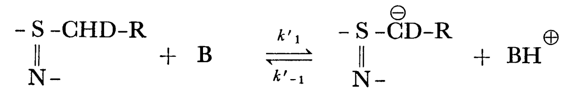
TABLE 2. H-D EXCHANGE RATES AND ACTIVATION PARAMETER[a]

Substrate	Temperature (°C)	$[D_2O]$ (mol/l)	$10^6\times k_{\text{obs}}$ (s^{-1})	$10^6\times k$ ($s^{-1}M^{-1}$)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (e. u.)
Ia	49.5	4.48	5.00	1.12		
	54.0	4.48	7.75	1.73		
	60.0	4.31	15.7	3.63		
	65.0	4.48	22.9	5.10		
	70.0	4.48	39.1	8.70	21.4	−19.6
Ib	60.0	4.69	3.70	0.79		
	65.0	4.69	10.7	2.28		
	70.0	4.69	19.4	4.13		
	75.0	4.44	26.4	5.93		
	80.0	4.44	68.0	14.8	31.4	+8.6
IIa	60.0	4.75	1.67	0.352		
	75.0	4.32	7.85	1.82		
	80.0	4.32	11.6	2.68		
	85.0	4.32	16.2	3.73	22.2	−21.5
IIb	60.0	5.08	0.0453	0.00893		

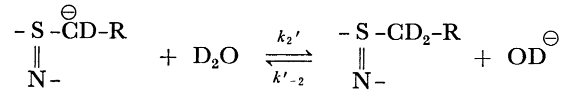
a) Both k_{obs} and k were calculated for one α-hydrogen atom, error ranges being ±20%.



$$-\underset{\underset{\displaystyle N-}{\|}}{S}-\overset{\ominus}{C}H-R + D_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} -\underset{\underset{\displaystyle N-}{\|}}{S}-CHD-R + OD^{\ominus} \quad (2)$$



$$-\underset{\underset{\displaystyle N-}{\|}}{S}-CHD-R + B \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} -\underset{\underset{\displaystyle N-}{\|}}{S}-\overset{\ominus}{C}D-R + BH^{\oplus} \quad (3)$$



$$-\underset{\underset{\displaystyle N-}{\|}}{S}-\overset{\ominus}{C}D-R + D_2O \underset{k'_{-2}}{\overset{k_2'}{\rightleftharpoons}} -\underset{\underset{\displaystyle N-}{\|}}{S}-CD_2-R + OD^{\ominus} \quad (4)$$

For the sake of simplicity, only steps (1) and (2) are considered, since (3) and (4) are repetitions of (1) and (2), and $k_1'=k_1$, $k'_{-1}=k_{-1}$, $k_2'=k_2$ and $k'_{-2}=k_{-2}$. Since I and II are very weak acids, the concentration of carbanions must be very small. On the basis of the usual steady-state assumption, the following equation is derived.

$$v = \frac{k_1k_2}{k_{-1}[BH^+]+k_2[D_2O]}[I][B][D_2O]$$

If $k_{-1}[BH^+]\gg k_2[D_2O]$,

$$v = \frac{k_1}{k_{-1}[BH^+]}k_2[I][B][D_2O]$$

and

$$k_{obs} = \frac{k_1}{k_{-1}[BH^+]}k_2[B][D_2O]$$

If $k_{-1}[BH^+]\ll k_2[D_2O]$,

$$v=k_1[I][B] \quad \text{and} \quad k_{obs}=k_1[B]$$

In this case, a large kinetic isotope effect is expected, and changes in $[D_2O]$ should not alter the rate.

In fact, two types of H-D exchange in labile hydrogens have been reported. In the case of the exchange of α-hydrogens of toluene in cyclohexylamine in the presence of lithium cyclohexylimide, the isotopc effect (k_H/k_D) was greater than 10, indicating that the first step (the abstraction of proton) is rate-determining.[5] In the case of the exchange of α-hydrogens of toluene in DMSO in the presence of potassium *t*-butoxide, k_H/k_D was 0.6, indicating that the second step is rate-determining.[6]

When the D-H exchange of α,α-dideuteriobenzyl phenyl sulfilimine (Ia-d_2) was measured in pyridine–H_2O at 70 °C, the following values were obtained.

$$k_{obs} = 2.07\times10^{-5}\,s^{-1}$$

$$k_D^{70°} = k_{obs}/[H_2O] = 4.84\times10^{-6}\,s^{-1}M^{-1}$$

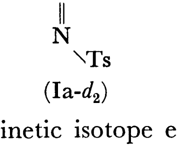
$$(k_H/k_D)_{70°C} = 1.80$$

For α,α,α-trideuteriomethyl phenyl sulfilimine (Ib-d_3), the following values were obtained.

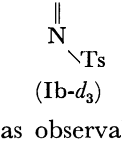
$$k_{obs} = 8.40\times10^{-6}\,s^{-1}$$

$$k_D = k_{obs}/[H_2O] = 1.89\times10^{-6}\,M^{-1}s^{-1}$$

$$(k_H/k_D) = 2.19$$



(Ia-d_2)



(Ib-d_3)

Thus, kinetic isotope effect was observable, and the abstraction of the α-hydrogens must be involved in the rate-determining steps. However, the k_H/k_D values were not so great, and k_{obs} was proportional to the concentration of water. Thus, $k_{-1}[BH^+]$ might be slightly greater than $k_2[D_2O]$.

Experimental

Materials. *N*-*p*-Toluenesulfonylsulfilimines (Ia, Ib and Ic) were prepared from the reaction between the corresponding sulfides and chloramine-T in methanol.[7]

N-*p*-Toluenesulfonylsulfoximines (IIa, IIb and IIc) were prepared by the oxidation of the corresponding sulfilimines with perbenzoic acid in chloroform,[8] and recrystallized from methanol.

α,α,α-Trideuteriomethyl phenyl *N*-*p*-toluenesulfonylsulfilimine(Ib-d_3). An anhydrous dioxane solution (60 g) of Ib (2.88 g) was mixed with an NaOH (20 mg) solution in D_2O (99.75%, 4.0 g). After the mixture was heated at 80 °C for several hours, it was concentrated under reduced pressure and cooled. Colorless crystals obtained were washed with D_2O and recrystallized from methanol.

α,α-Dideuteriobenzyl phenyl *N*-*p*-toluenesulfonylsulfilimine(Ia-d_2). A mixture of Ia (4.0 g), dioxane (40 g), D_2O (4.0 g) and NaOH (16 mg) was heated at 70 °C for 1 hr. After the solvents were removed under reduced pressure, the residue was washed with D_2O and recrystallized from methanol.

Kinetics. Exchange in Ia in the presence of NaOH. A mixture of Ia (1.200 g), D_2O (99.75 atom%, 5.0 ml, containing 2.23×10^{-2} mol/l NaOH) and spectroscopic-grade dioxane (100 ml) was allowed to stand at 10 °C. At suitable intervals, 10-ml samples were withdrawn, acidified with acetic acid and evaporated under reduced pressure. The residue was washed with D_2O, dried in vacuum and its NMR spectrum was determined in $CDCl_3$. The rate of exchange was calculated from the decrease in the methylene signal in comparison with the tosyl methyl signal.

Exchange in Ib in pyridine. A mixture of Ib (1.708 g) and pyridine (15.56 ml, containing 5.175 mol/l D_2O) was divided into ampoules (0.5 ml each), which were placed in a constant-temperature bath. Ampoules were withdrawn at suitable interval and cooled with ice. The rate of exchange was calculated from the decrease in the *S*-methyl signal in comparison with the tosyl methyl signal.

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