

## Anchimerically Assisted Sulfoxide Reactions

### II. Preparation of Some Optically Active Carboxylic Substituted Sulfoxides and Their Rates of Racemization in Acid Solution

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The rate of racemization of the sulfoxide group has been studied in acid media containing halide ions. A marked rate-difference was observed between sulfoxides having a carboxylic group in the  $\beta$ -position, and (+)-methyl *p*-tolyl sulfoxide; the latter compound being much more slowly racemized. The rate of the reaction is highly dependent upon the concentration and nucleophilicity of the halide ion.

Although the resolution of compounds with tricoordinate asymmetric sulfur into enantiomers was performed many years ago,<sup>1-3</sup> rather few investigations on their racemization have been carried out. In 1964, however, Mislow *et al.*<sup>4</sup> reported a study of hydrogen chloride catalyzed racemization of optically active alkyl *p*-tolyl sulfoxides in water-dioxane mixtures. Quite recently the thermal<sup>5</sup> and photochemical<sup>6</sup> racemizations of sulfoxides and also the racemization of a sulfonium perchlorate<sup>7</sup> have been investigated.

Because the reduction of sulfoxides in aqueous hydriodic acid can be assisted by a carboxylic group if the latter is situated in a favourable position,<sup>8</sup> we found it of interest to study such compounds in their optically active forms with respect to racemization at the sulfoxide group. The optically active compounds we have prepared are given in Table 1. The enantiomers corresponding to III and IV have not yet been obtained optically pure.

Racemic 3-benzylthiobutyric acid (m.p. 35.5–38.0°) was obtained by addition of benzyl mercaptan to crotonic acid according to Owen and Sultanbawa.<sup>9</sup> Resolution was obtained *via* the brucine salt which yielded the (+)-form with  $[\alpha]_D^{25} = +17.4^\circ$ ,  $[\alpha]_{365}^{25} = +50.0^\circ$  (ethanol,  $c = 0.68$  g/100 ml) and *via* the cinchonidine salt from which the (–)-form was liberated. The optical purity of the latter was slightly lower,  $[\alpha]_D^{25} = -15.5^\circ$ ,  $[\alpha]_{365}^{25} = -45.5^\circ$  (ethanol,  $c = 0.43$  g/100 ml). Oxidation of the (+)-form with hydrogen peroxide in acetone gave a mixture of the two diastereomeric sulfoxides (I and III) which were separated by repeated recrystallization. Similarly, oxida-

Table 1. Specific rotations of the various sulfoxide-acids in ethanol.

No.	Compound	$[\alpha]_D^{25}$ , conc. (g/100 ml)
I	$C_6H_5CH_2-S-\underset{\text{O}}{\text{CH}}(CH_3)CH_2CO_2H$	+76.6° $c = 0.61$
II	$C_6H_5CH_2-S-\underset{\text{O}}{\text{CH}}(CH_3)CH_2CO_2H$	-76.3° $c = 0.59$
III	$C_6H_5CH_2-S-\underset{\text{O}}{\text{CH}}(CH_3)CH_2CO_2H$	-117.2° $c = 0.53$
IV	$C_6H_5CH_2-S-\underset{\text{O}}{\text{C}}(CH_3)=C(CO_2H)_2$	-219.0°* $c = 0.55$

\* The optical purity of this compound is not maximal.

tion of the (—)-form yielded a diastereomeric mixture from which II was isolated. Thus, I and III have opposite configurations only at sulfur, whereas II and III have opposite configurations only at carbon.

Compound IV was obtained by resolution of the racemic sulfoxide-acid<sup>10</sup> with brucine. IR-spectra (KBr) of the optically active product and of the racemic material showed that no decarboxylation or other undesirable reaction had occurred during this procedure.

A full report on the preparation of the optically active compounds described here will be given later.<sup>11</sup>

The reactions we have investigated polarimetrically at 25°C have been: 1) epimerization of I, 2) racemization of IV, and 3) racemization of (+)-methyl *p*-tolyl sulfoxide<sup>12,13</sup> (V),  $[\alpha]_D^{25} = +145^\circ$  (acetone), for comparison under identical conditions. Compound V has been the subject for previous racemization studies in other media.<sup>4,14</sup> A 50 % (v/v) mixture of acetic acid and water has been used as solvent in all cases, whereas the concentrations of strong inorganic acids have been varied. In a series of experiments, a perchloric acid concentration of 2.0 M was kept constant throughout and the effect of various lower concentrations of hydrochloric acid and of hydrobromic acid upon the rate was studied. All reactions showed good first-order kinetics.

Considering reaction 1) first, *i.e.* the interconversion  $I \xrightleftharpoons[k_{-1}]{k_1} III$ , the observed rate constant,  $k$ , is the sum of the rate constants for the forward and the reverse reactions, respectively:  $k = k_1 + k_{-1}$ , where  $k_1$  differs from  $k_{-1}$ . It can be easily deduced that a plot of  $\log(\alpha - \alpha_\infty)$  as a function of time,  $t$ , gives a straight line with a slope  $= -k/2.303$ . Here  $\alpha$  and  $\alpha_\infty$  denote the optical rotation at time  $t$  and at equilibrium, respectively. Then,  $k_1$  and  $k_{-1}$  can be calculated from the equilibrium composition and the value found for  $k$ . Eqn. (1) can be shown to hold:

$$k_1 = k \cdot \frac{\alpha_0 - \alpha_\infty}{\alpha_0 - \alpha_0'} \quad \text{where } \alpha_0' = \frac{[\alpha_{III}]_D^{25}}{[\alpha_I]_D^{25}} \cdot \alpha_0 \quad (1)$$

Here  $\alpha_0$  and  $\alpha_0'$  denote the optical rotations of optically pure I and III, respectively, at  $t=0$ . In this way the  $k_1$ -values given in Table 2 have been obtained.

An advantage with the study of these epimerization rates is that the optical rotation at  $t=\infty$  is not zero, which makes the calculation of a specific rotation at equilibrium possible. This specific rotation will have a constant value for different kinetic runs provided that the reaction medium is not greatly altered and as long as no side-reactions occur. We have used this specific rotation at equilibrium to show that the only reaction of I in the presence of

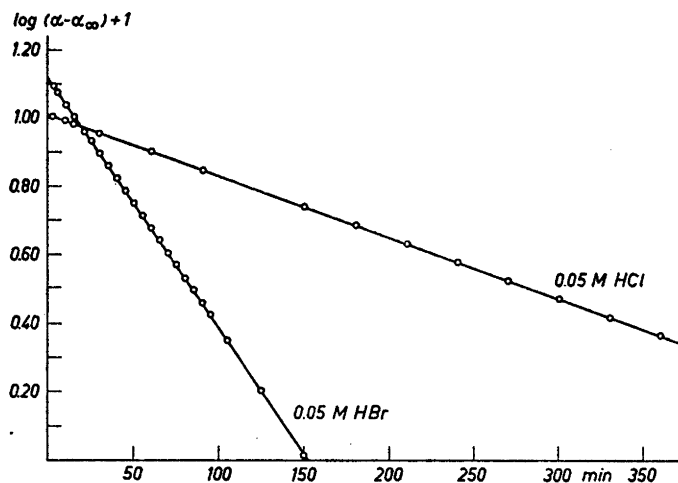


Fig. 1. Illustration of the dependence of the epimerization rate upon the nucleophilicity of the halide ion.

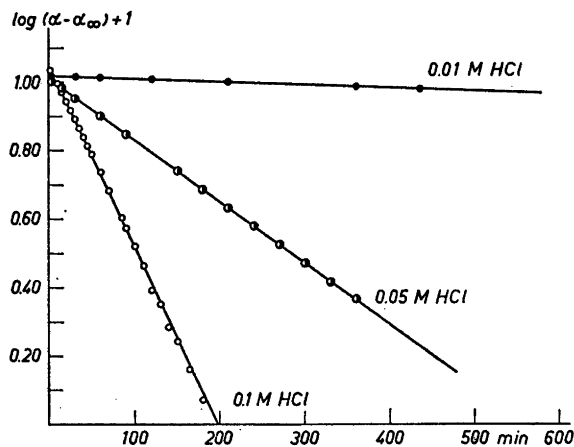


Fig. 2. Illustration of the dependence of the epimerization rate upon the concentration of hydrochloric acid.

hydrobromic acid is epimerization, as is the case when hydrochloric acid is used. A marked rate-difference was observed, however; under otherwise identical conditions the exchange of 0.05 M hydrochloric acid against 0.05 M hydrobromic acid caused a 4-fold increase in  $k_1$ , which is to be expected because of the greater nucleophilicity of the bromide ion in comparison with the chloride ion. The situation is shown in Fig. 1.

The concentration of a nucleophilic anion has a marked influence upon the rate. This is illustrated in Fig. 2 which shows the observed rates at different chloride ion concentrations. The effect of the slight variation in the hydrogen ion concentration here (2.0–2.1 M) is expected to be rather small.

For reaction 2), *i.e.* racemization of IV, the calculation of the corresponding  $k_1$ -value is simpler because eqn. 1 reduces to  $k_1=0.5 k$  owing to the fact that  $\alpha_{\infty}=0$  and  $\alpha_0=-\alpha_0'$ , which means that here  $k_1$  equals  $k_{-1}$ , a well-known fact because enantiomers react at equal rates in non-dissymmetric media. The same holds for reaction 3).

Table 2. First-order rate constants for the epimerization and racemization, respectively, of the various sulfoxides in 50 % (v/v) acetic acid at 25°.

Compound No.	$C_{HClO_4}$ M	$C_{HCl}$ M	$C_{HBr}$ M	$C_{\text{sulfoxide}}$ M	$10^6 \cdot k$ sec <sup>-1</sup>	$10^6 \cdot k_1$ sec <sup>-1</sup>	$[\alpha_{\infty}]_D^{25}$
I	0	1.00	0	0.035	42.2	25.4	−37.1°
I	2.00	0.010	0	0.043	3.95	2.22	−33.1°
I	2.00	0.050	0	0.041	68.3	39.1	−33.2°
I	2.00	0.10	0	0.045	207	116	−32.6°
I	2.00	0	0.050	0.052	270	154	−33.6°
IV	2.00	0.010	0	0.006	7.75	3.88	
V	2.00	0.010	0	0.048	0.122	0.061	
V	2.00	0.050	0	0.039	0.525	0.26	
V	2.00	0.10	0	0.066	1.46	0.73	
V	2.00	0	0.050	0.047	1.96	0.98	

From the  $k_1$ -values in Table 2 it is obvious that reaction 3) is much slower than reactions 1) or 2) under identical conditions. This rate-difference alone does not necessarily imply that the latter reactions are assisted by carboxylic group participation because structural differences around the sulfoxide group could as well account for the observed facts. We have, however, still reasons to believe that anchimeric assistance is an important factor in the reactions of the sulfoxide-acids. One argument is the order of increasing reaction rates for the different types of compounds investigated:  $V \ll I < IV$ , which parallels the order of rates of reduction in acidic iodide solution.<sup>8</sup>

We intend to continue our investigations on the epimerization and racemization of optically active sulfoxide-acids in various media.

*Experimental.* The detailed description of the syntheses of the optically active compounds will appear in a later publication.<sup>11</sup>

The kinetic work was performed with a Perkin-Elmer model 141 photoelectric polarimeter. Cells with a length of 10 cm and a volume of 1 ml, thermostated at 25.0° were used.

An accurately weighed amount of the sulfoxide (for I ~20 mg, giving an initial concentration of ~0.04 M) was dissolved in 2 ml of the solution (pre-heated to 25°) in which the reaction was to take place. The dissolution, being rapid, was taken as  $t=0$ . Then 1 ml of the solution was transferred to the polarimeter cell as fast as possible. The change in optical rotation at the sodium D-line was measured as a function of time and the constancy of the value obtained at equilibrium ( $\alpha_{\infty}$ ) for the epimerization reaction was carefully checked in each case.

All acids used for the preparation of the solutions were of *p.a.* quality.

*Note added in proof:* Quite recently a report on the reduction and racemization of sulfoxides by halide ions in aqueous perchloric acid appeared (Landini, D., Montanari, F., Modena, G. and Scorrano, G., *Chem. Commun.* 1968, 86). These authors found the order of reaction to be near 1 with respect to iodide ion (reduction) as well as bromide and chloride ion (racemization). They also point out the influence of the nucleophilicity of the halide ion upon the rate. Their results are consistent with ours in the particular concentration range we have used here. In a later work (Allenmark, S. and Hagberg, C.-E. *Acta Chem. Scand. In press*) we have studied the rate of our reaction over a wider halide ion concentration range, which very strikingly shows the difference in reaction mechanism between the carboxyl-assisted reaction investigated by us and the unassisted reaction investigated by the Italian research group.

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