

Anchimerically Assisted Sulfoxide Reactions

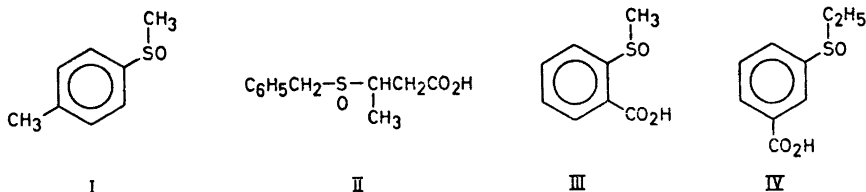
V. Assisted Racemization of Optically Active 2-Methylsulfinylbenzoic Acid

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The halide ion catalyzed racemization of (+)-2-methylsulfinylbenzoic acid in acid solution at 25° has been studied polarimetrically. The kinetic data show that the observed rate of racemization is a rather complex function of the halide ion concentration within a certain concentration range. A comparison with other optically active sulfoxides disclosed a considerable change of the halide ion concentration dependence with the nature of the reactant. These observations are discussed on the basis of the previously proposed reaction mechanism.

In previous papers we pointed out the striking difference in reaction rates¹ as well as halide ion concentration dependence² between (+)-methyl *p*-tolyl sulfoxide (I) and (+)-3-benzylsulfinylbutyric acid (II, $[\alpha]_D^{25} = +76.6^\circ$ (ethanol)) with respect to the racemization of the sulfoxide group. Thus, II was found to be intramolecularly catalyzed according to the previously proposed mechanism.² On the basis of our earlier results, however, we expected anchimeric assistance to be more effective in a more rigid system, and therefore an investigation of the racemization of 2-methylsulfinylbenzoic acid (III) was initiated. For a comparison, I and 3-ethylsulfinylbenzoic acid (IV) were also studied.



The use of Andersen's Grignard-synthesis³ makes I readily available. The four optical isomers of II were obtained by resolution of the corresponding sulfide and separation of the two optically active sulfoxide diastereomers

obtained by oxidation of each sulfide enantiomer.¹ Racemic III was prepared by methylation of thiosalicylic acid with dimethyl sulfate⁴ followed by oxidation with peracetic acid.⁵ Resolution was achieved with the use of brucine in ethanol.⁵ $[\alpha]_D^{25} = \pm 232^\circ$ (ethanol, $c=1.2$). Racemic and optically active IV were obtained by the method of Holloway, Kenyon and Phillips.⁶

The reaction between a sulfoxide and a hydrohalic acid is very much dependent upon the nature of the halide ion. Thus, with hydrochloric acid,⁷ complete racemization has been found, while hydrobromic acid^{8,9} has been reported to yield racemization with partial reduction, and hydriodic acid⁸⁻¹⁵ complete reduction. This runs quite parallel with the increasing oxidizability of the halide ion. If in the latter case, however, the concentration of iodide ions is sufficiently low, only partial reduction will occur¹⁶ and racemization will be a competitive reaction.

Racemization experiments were carried out polarimetrically at 25.0° in a reaction medium consisting of a 50 % (v/v) acetic acid-water mixture which was 2.00 or 0.25 M in perchloric acid and x M with respect to halide ion concentration. The lower acid concentration was used for the bromide ion catalyzed reactions. In order to try to compensate for salt effects upon the observed rates, the ionic strength was kept as constant as possible by means of added sodium perchlorate, giving a total salt concentration of 1.00 M and 3.00 M, respectively ($x + C_{\text{NaClO}_4} = 1.00$ M for $x = C_{\text{NaCl}}$ or C_{NaBr} , $x + C_{\text{NaClO}_4} = 3.00$ for $x = C_{\text{NaBr}}$).

Preliminary experiments with III and IV, performed under identical conditions, gave, as expected, a tremendous difference in rates of racemization with chloride as well as bromide ions, $k_{\text{III}}/k_{\text{IV}} > 10^3$ in both cases. The very favourable geometry in III for anchimeric assistance was further demonstrated by the fact that with a 1.00 M chloride ion concentration $k_{\text{III}}/k_{\text{II}}$ was found to be 26.

Earlier we reported the rate of epimerization of II to be independent of the halide ion concentration at $[\text{Br}^-] > 0.04$ M and at $[\text{Cl}^-] > 0.25$ M.² Because we felt that the halide ion concentration dependence should be different for the reaction of III, we studied k_{III} as a function of $[\text{Hal}^-]$. The results are

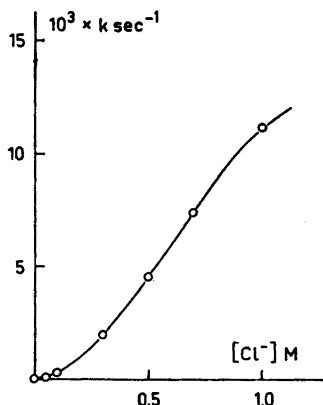


Fig. 1. k_{III} vs. $[\text{Cl}^-]$, $C_{\text{NaCl}} + C_{\text{NaClO}_4} = 1.00$ M

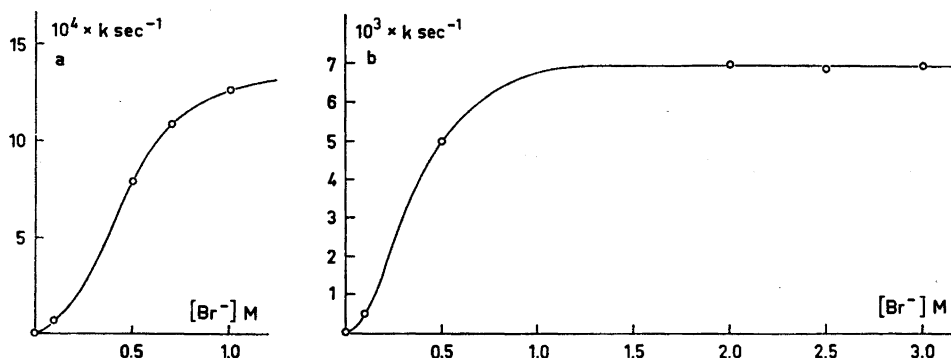


Fig. 2. k_{III} vs. $[Br^-]$. a) $C_{NaBr} + C_{NaClO_4} = 1.00$ M. b) $C_{NaBr} + C_{NaClO_4} = 3.00$ M.

shown in Table 1. In Table 2 values of k_{II} are given for comparison. From these data it is evident that much higher halide ion concentrations are required to make k_{III} independent. This situation is illustrated by Figs. 1 and 2.

The sigmoid curves obtained suggest the rather complex nature of the halide ion concentration dependence within a certain concentration range. The latter occurs approximately below $x = 1$ M for bromide ions. Fig. 2 also gives some further information. Firstly, the positive salt effect from the added sodium perchlorate upon the over-all rate is evident. Secondly, this salt effect seems to have only a minor influence upon the value of the bromide ion concentration at which k_{III} reaches a constant value.

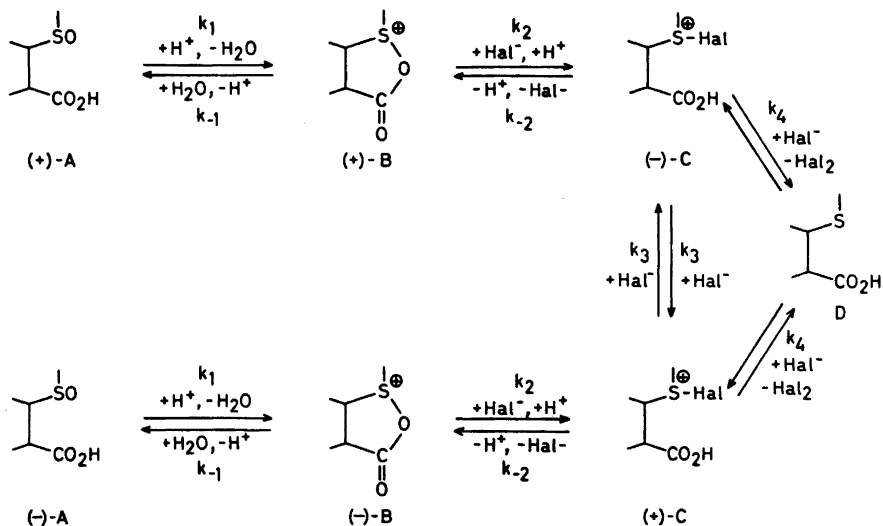
In the absence of halide ions no loss of optical activity at all was observed under these conditions. Perhaps such a reaction could have been detected at higher perchloric acid concentrations¹⁷ but it would still have been too slow to interfere with the halide ion catalyzed racemization.

A full understanding of this halide ion concentration dependence, however, requires a detailed analysis of the postulated reaction mechanism^{2,18} for carboxyl-assisted racemization and reduction of sulfoxides. The various steps in this reaction are shown in Scheme 1.

In Scheme 1 the (+)- and (-)-signs are used to distinguish between different configurations at sulfur, irrespective of the sign of optical rotation. Thus, the steps involving the rate constants k_2 , k_{-2} , and k_3 all occur with inversion of configurations. Further, let the k_i 's ($i=1-4$) denote pseudo first-order rate constants, *i.e.*: $k_1 = k_1'[H^+]$, $k_{-1} = k_{-1}'[H_2O]$, $k_2 = k_2'[Hal^-]$, $k_3 = k_3'[Hal^-]$, $k_4 = k_4'[Hal^-]$.

Neglecting the formation of D, *i.e.* reduction, which was not observed in our experiments,* we can treat the racemization according to this scheme

* We are aware of the fact that even if D cannot be detected, it might be an intermediate in a route yielding racemization of the halosulfonium ion. Whether this occurs or not, however, has no bearing on our final kinetic expression and because of lack of evidence we prefer to represent the racemization step as a direct halide ion interchange at sulfur.



Scheme 1.

by considering the following equations.

For simplicity, let (+)A stand for [(+)-A], \dot{A} for $d[(+)-A]/dt$ and so on.

We obtain:

$$(\dot{+})\dot{A} = -k_1(+)\dot{A} + k_{-1}(+)\dot{B} + 0(+)\dot{C} + 0(-)\dot{A} + 0(-)\dot{B} + 0(-)\dot{C}$$

$$(\dot{+})\dot{B} = k_1(+)\dot{A} - (k_{-1} + k_2)(+)\dot{B} + 0(+)\dot{C} + 0(-)\dot{A} + 0(-)\dot{B} + k_{-2}(-)\dot{C}$$

$$(\dot{+})\dot{C} = 0(+)\dot{A} + 0(+)\dot{B} - (k_3 + k_{-2})(+)\dot{C} + 0(-)\dot{A} + k_2(-)\dot{B} + k_3(-)\dot{C}$$

The use of matrix algebra¹⁹⁻²¹ and assuming steady-state conditions for the intermediates B and C will facilitate the solution of these differential equations to yield an expression for the polarimetrically observed rate constant. Thus, the polarimetric behaviour will be determined by the eigenvalues of the matrix K_α .

$$K_\alpha = \begin{bmatrix} -k_1; & k_{-1}; & 0 \\ k_1; & -(k_{-1} + k_2); & -k_{-2} \\ 0; & -k_2; & -(2k_3 + k_{-2}) \end{bmatrix}$$

However, the steady-state approximation will contract K_α to \bar{K}_α .

$$\bar{K}_\alpha = -k_1 - [k_{-1}; 0] \begin{bmatrix} -(k_1 + k_2); & -k_{-2} \\ -k_2; & -(2k_3 + k_{-2}) \end{bmatrix}^{-1} \begin{bmatrix} k_1 \\ 0 \end{bmatrix} =$$

$$- \frac{k_1}{1 + (k_{-1}/k_2) [1 + (k_{-2}/2k_3)]}$$

Thus, the polarimetrically observed rate constant, k , can be expressed as:

$$k = \frac{k_1}{1 + (k_{-1}/k_2'[\text{Hal}^-]) [1 + (k_{-2}/2k_3'[\text{Hal}^-])]} \quad (1)$$

and rewritten as:

$$k = \frac{a[\text{Hal}^-]}{[\text{Hal}^-] + b} \cdot \frac{[\text{Hal}^-]}{[\text{Hal}^-] + c} \quad (2)$$

It is evident that when $k_{-1}/k_2'[\text{Hal}^-] \rightarrow 0$ i.e. $k_2'[\text{Hal}^-] \gg k_{-1}$, eqn. 1 reduces to $k = k_1$, which corresponds to the constant upper limit in Figs. 1 and 2. It can also be shown by derivation of eqn. 2 with respect to $[\text{Hal}^-]$, that k has a real minimum at $[\text{Hal}^-] = 0$ and reaches asymptotically a maximum value when $[\text{Hal}^-] \rightarrow \infty$. This agrees very well with the sigmoid curves obtained experimentally.

From a similar treatment of the epimerization of II (i.e. (+)-A \rightleftharpoons (-)-A', where A and A' are diastereomers), it can be found that the expression corresponding to eqn. 2 will be:

$$k = \frac{a'[\text{Hal}^-]}{[\text{Hal}^-] + b'} \cdot \frac{[\text{Hal}^-]}{[\text{Hal}^-] + c'} + \frac{a''[\text{Hal}^-]}{[\text{Hal}^-] + b''} \cdot \frac{[\text{Hal}^-]}{[\text{Hal}^-] + c''} \quad (3)$$

Consequently, eqn. 2 is the special case of eqn. 3 were A equals A' (racemization). As we have shown earlier¹ for II, the rates of the forward ((+)-A \rightarrow (-)-A') and reverse ((-)-A' \rightarrow (+)-A) reactions differ only to a small extent and eqn. 2 can be used to a good approximation in this case.

We think that the reason for the difference in the shapes of the curves representing k as a function of $[\text{Hal}^-]$ for II and III, respectively, can be found in the ratio k_{-1}'/k_2' which is likely to be very sensitive to the nature of the substrate.

EXPERIMENTAL

Kinetic experiments. All kinetic work was performed with the use of a Perkin-Elmer Model 141 or 141 M photoelectric spectrometer. The optical rotations were determined as a function of time at the sodium D-line. All experiments gave clean first-order reactions. When Model 141 was used, between 10 and 30 readings at different points of time were made in each kinetic run and the rate constant evaluated by the graphic method. The reactions studied with model 141 M were followed continuously by the use of an external recorder giving the optical rotation as a function of time. In some cases the same reaction was studied by both methods with very good agreement between the two rate constants obtained.

A 50% (v/v) mixture of acetic acid and water was used as solvent throughout. A 0.05 M initial concentration of sulfoxide was chosen in each experiment. The concentrations of perchloric acid and sodium salts used in the various kinetic runs are given in Tables 1-3.

The solution in which the reaction was to take place was pre-heated to 25.0° and the reaction was started ($t=0$) by rapid dissolution of the sulfoxide. The resulting solution was then transferred as rapidly as possible to a polarimeter cell of length 10 mm and a volume of 1 ml, thermostatted at 25.0°.

All chemicals used were of analytical grade quality.

Preparation of the optically active sulfoxides. Compounds I and IV were prepared according to the methods given in Refs. 3 and 6, respectively. II has been briefly described earlier by the authors.¹ A full report will be given elsewhere.²² III was prepared by the methods given in Refs. 4 and 5, respectively. $[\alpha]_{\text{D}}^{25} = \pm 232^\circ$ (ethanol, $c=1.2$); Ref. 5: $[\alpha]_{\text{D}}^{20} = \pm 227.5^\circ$ (ethanol, $c=1.0$).

Table 1. The polarimetrically observed rate constant for the racemization of III, k_{III} , at different halide ion concentrations.

C_{HClO_4} M	C_{NaCl} M	C_{NaBr} M	C_{NaClO_4} M	$10^4 k_{III}$ sec ⁻¹
2.00	1.00	0.00	0.00	111.5
2.00	0.70	0.00	0.30	74.0
2.00	0.50	0.00	0.50	45.2
2.00	0.30	0.00	0.70	19.5
2.00	0.10	0.00	0.90	2.47
2.00	0.05	0.00	0.95	0.678
2.00	0.00	0.00	1.00	0
0.25	0.00	1.00	0.00	12.8
0.25	0.00	0.70	0.30	10.9
0.25	0.00	0.50	0.50	7.92
0.25	0.00	0.10	0.90	0.662
0.25	0.00	0.00	1.00	0
0.25	0.00	3.00	0.00	69.0
0.25	0.00	2.50	0.50	68.2
0.25	0.00	2.00	1.00	69.3
0.25	0.00	0.50	2.50	49.5
0.25	0.00	0.10	2.90	4.98

Table 2. The polarimetrically observed rate constant for the epimerization of II, k_{II} , at different halide ion concentrations.

C_{HClO_4} M	C_{NaCl} M	C_{NaBr} M	C_{NaClO_4} M	$10^4 k_{II}$ sec ⁻¹
2.00	1.00	0.00	0.00	4.22
2.00	0.50	0.00	0.50	4.37
2.00	0.10	0.00	0.90	3.60
2.00	0.07	0.00	0.93	2.83
2.00	0.05	0.00	0.95	2.12
2.00	0.00	1.00	0.00	4.97
2.00	0.00	0.50	0.50	4.75
2.00	0.00	0.10	0.90	4.82
2.00	0.00	0.05	0.95	4.77
2.00	0.00	0.02	0.98	4.62
2.00	0.00	0.01	0.99	4.20

Table 3. The polarimetrically observed rate constants for the racemization of I and IV, k_I and k_{IV} , respectively, at different halide ion concentrations.

Compound	C_{HClO_4} M	C_{NaCl} M	C_{NaBr} M	C_{NaClO_4} M	$10^5 k$ sec ⁻¹
I	2.00	1.00	0.00	0.00	2.40
I	2.00	0.50	0.00	0.50	1.31
I	2.00	0.00	1.00	0.00	15.8
I	2.00	0.00	0.50	0.50	7.80
IV	2.00	1.00	0.00	0.00	0.47
IV	2.00	0.50	0.00	0.50	0.23
IV	2.00	0.00	0.00	1.00	0

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