

## Anchimerically Assisted Sulfoxide Reactions

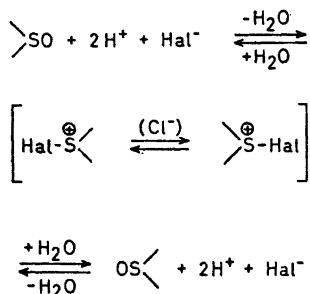
### III. Carboxyl Group Participation in the Epimerization of Optically Active 3-Benzylsulfinylbutyric Acid by Halide Ions in Acid Media

STIG ALLENMARK and  
CURT-ERIC HAGBERG

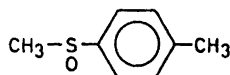
*Chemical Institute, University of Uppsala,  
S-751 21 Uppsala, Sweden*

Recently we reported a study on the racemization of some optically active sulfoxides by hydrochloric and hydrobromic acid.<sup>1</sup> This investigation led us to propose that anchimeric assistance by carboxyl group participation was the reason for the comparatively fast racemization of certain carboxylic substituted sulfoxides. We now present results from a study of the rates of racemization as a function of the halide ion concentration which further substantiate our proposal.

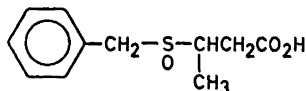
The currently accepted mechanism for the hydrogen halide-catalyzed racemization of sulfoxides is that fast halogen interchange takes place in a halosulfonium ion, followed by hydrolysis.<sup>2-4</sup>



Two different compounds were investigated with respect to this reaction, *viz.* (+)-methyl *p*-tolyl sulfoxide (I),  $[\alpha]_{\text{D}}^{25} = +145^\circ$  (acetone), and (+)-3-benzylsulfinylbutyric acid (II),  $[\alpha]_{\text{D}}^{25} = +76.6^\circ$  (ethanol); II being the compound with the lowest specific rotation of the two dextrorotatory diastereomers.<sup>1</sup>

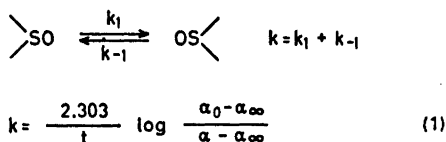


I



II

Both the racemization of I and the epimerization of II (racemization with respect to the sulfoxide group) were studied polarimetrically under identical conditions. The rate constants for the reactions, which are of the first-order, are given by eqn. 1 ( $\alpha$  denotes the optical rotation at time  $t$ ).



For the special case of racemization of I:  $k_1 = k_{-1}$  and  $\alpha_\infty = 0$ . The experimental data were found to fit eqn. 1 excellently. Reduction of the sulfoxide group<sup>3,4</sup> in solutions containing bromide ions did not occur to any observable extent.

The influence of the halide ion concentration upon  $k$  for the two cases was determined at approximately constant ionic strength. This was achieved by maintaining constant salt concentration with sodium perchlorate. Thus, the condition:  $C_{\text{NaHal}} + C_{\text{NaClO}_4} = 1.0 \text{ M}$  was fulfilled for all kinetic runs. A 50% (v/v) acetic acid-water mixture was used as solvent and the temperature was maintained at  $25.0^\circ$ .

A plot of the first-order rate constants for I and II, respectively, against the halide ion concentration reveals two quite different situations. These are shown by Figs. 1 and 2. In Fig. 1, which represents the racemization of I, there is an almost linear dependence yielding direct proportionality between  $k$  and the halide ion concentration. This means that in this case the halide ion is involved in the rate-determining step. Accordingly, the rate is

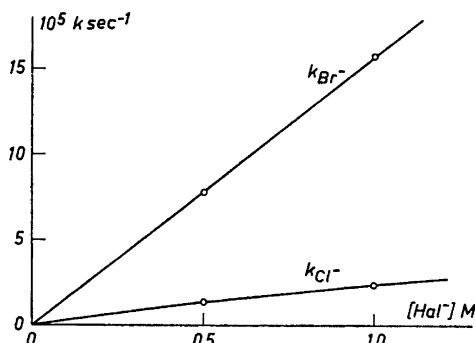


Fig. 1.  $k$  vs.  $[\text{Hal}^-]$  for the racemization of I.

also strongly dependent upon the nucleophilicity of the anion as observed by the ratio,  $k_{\text{Br}^-}/k_{\text{Cl}^-} \approx 6.5$ , derived from the slopes of the lines in Fig. 1. This is in complete agreement with the results of Modena *et al.*<sup>4</sup> which appeared quite recently and after the initiation of our investigation. Their paper also describes the hydrogen ion concentration dependence for the racemization of I, which indicated that the transition state contains two protons more than the reactant. Consequently, they formulate the rate-determining step in the following way:

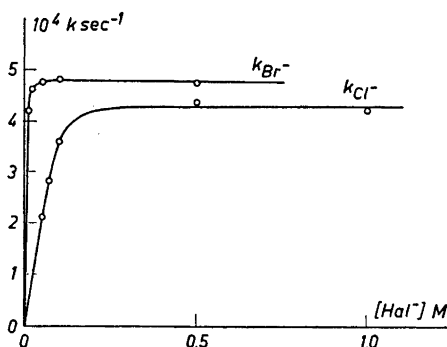
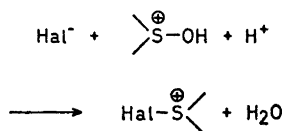
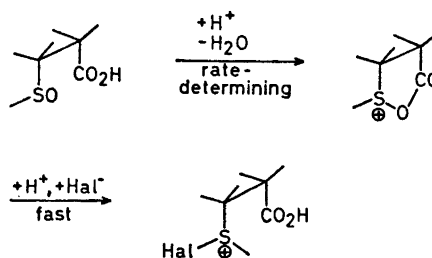


Fig. 2.  $k$  vs.  $[\text{Hal}^-]$  for the epimerization of II.

Acta Chem. Scand. 22 (1968) No. 5

Whether protonation precedes the halide ion attack or not is still a matter of debate.

Turning to Fig. 2, the following conclusions can be drawn. Only at very low halide ion concentrations is there an approximately linear relationship yielding direct proportionality between  $k$  and halide ion concentration. At concentrations greater than 0.25 M in chloride ion and greater than 0.04 M for bromide ion, the rate is quite independent of the halide ion concentration. Therefore, in the latter concentration ranges the halide ion cannot be involved in the rate-determining step. Furthermore, the observed ratio,  $k_{\text{Br}^-}/k_{\text{Cl}^-} \approx 1.1$ , shows that the rate is approximately independent of the nucleophilicity of the halide ion. The rate-determining step in this case is consequently to be found in the formation of a reactive intermediate. The reaction, up to the formation of the halosulfonium ion, therefore follows quite the same mechanistic pathway as reduction by hydriodic acid<sup>5,6</sup> *i.e.*:



Subsequent reaction between the halosulfonium ion and a halide ion will then result in racemization or reduction, depending upon the oxidizability of the halide ion.

The *ca.* 10% deviation of  $k_{\text{Br}^-}/k_{\text{Cl}^-}$  from unity should in our opinion be interpreted as a kinetic salt effect upon the over-all rate when substituting sodium chloride for sodium bromide.<sup>7</sup> Furthermore, a constant value of  $C_{\text{NaHal}} + C_{\text{NaClO}_4}$  does not mean of course that the  $H_0$ -function is maintained strictly constant.<sup>8</sup> These effects have, however, not been taken into account in this investigation.

Further kinetic studies of the racemization of sulfoxides will be published later.

*Acknowledgements.* We are grateful to Professor A. Fredga for his stimulating interest in this work and to the Swedish Natural Science Research Council for financial support.

1. Allenmark, S. and Hagberg, C.-E. *Acta Chem. Scand.* **22** (1968) 1461.
2. Mislow, K., Simmons, T., Melillo, J. T. and Ternay, A. L. *J. Am. Chem. Soc.* **86** (1964) 1452.
3. Mislow, K. *Record Chem. Progr.* **28** (1967) 229.
4. Landini, D., Montanari, F., Modena, G. and Scorrano, G. *Chem. Commun.* **1968** 86.
5. Allenmark, S. *Arkiv Kemi* **26** (1967) 37.
6. Allenmark, S. and Johnsson, H. *Acta Chem. Scand.* **21** (1967) 1672.
7. Long, F. A. and McIntyre, D. *J. Am. Chem. Soc.* **76** (1954) 3243.
8. Paul, M. A. and Long, F. A. *Chem. Rev.* **57** (1957) 17.

Received May 16, 1968.

### An Alternate Route for the Formation of Malonate in *Penicillium islandicum*

STEN GATENBECK and  
ANN KERSTI MAHLÉN

*Division of Biochemistry, Chemical Centre,  
Box 740, S-220 07 Lund 7, Sweden*

The main pathway for the formation of malonyl coenzyme A in most organisms, is the biotin dependent addition of CO<sub>2</sub> to acetyl coenzyme A.<sup>1</sup> Related to this reaction is the transcarboxylation between acetyl coenzyme A and methylmalonyl coenzyme A which has been demonstrated with an enzyme preparation from wheat germ.<sup>2</sup>

Free malonate is a common metabolite in higher plants. The occurrence of malonate can be looked upon as the result of the action of thiolesterase on malonyl coenzyme A. The presence of malonyl coenzyme A thiolesterase has been shown in several investigations.

Recently de Vellis *et al.*<sup>3</sup> have studied the malonic acid synthesis in the bush bean (*Phaseolus vulgaris*). With crude preparation from the roots using a variety of

labelled substrates they came to the conclusion that the malonate was formed from oxalacetate by  $\alpha$ -decarboxylation. Shannon *et al.*<sup>4</sup> have partially purified the enzyme from bush bean roots and they have been able to show that the enzyme is of the peroxidase type requiring the presence of manganous ions and hydrogen peroxide.

Many microorganisms especially among fungi produce in addition to fatty acids large amounts of other substances of acetate-polymalonate origin. The origin of the malonate itself in these substances has not been investigated, possibly due to the general opinion that it is formed by carboxylation of acetyl coenzyme A. In the formation of the acetate-polymalonate products as well as in fatty acid synthesis the reacting malonyl coenzyme A units have undergone decarboxylations and consequently the final products do not represent the intact malonate structure.

Free malonate is a rare product among microorganisms. *Penicillium islandicum*, however, produces when grown on Czapek-Dox medium an acid polysaccharide, islandic acid,<sup>5</sup> composed of glucose and malonic acid in the approximate molecular ratio 1:1. In addition to islandic acid *P. islandicum* produces considerable amounts of anthraquinone derivatives derived from acetate-polymalonate.<sup>6</sup>

In the following we have studied the possible conversion of oxalacetate to malonate. As oxalacetate is a labile compound and penetrates through the cell wall very poorly, uniformly C-14 labelled aspartate and 2,3-C-14 labelled fumarate have been used as tracer substrates. Theoretically, four possible metabolic routes can be set up from oxalacetate to malonyl coenzyme A, the latter compound being the likely reacting metabolite in the esterification of the hydroxyl groups of the polysaccharide. The four possible pathways are: 1) Oxidative decarboxylation, analogous to the thiamine pyrophosphate-lipoic acid system in the oxidative decarboxylation of pyruvate and  $\alpha$ -ketoglutarate, *i.e.* an immediate formation of malonyl coenzyme A. 2) Peroxidase type of oxidative decarboxylation of oxalacetate to malonate followed by the action of thiokinase. 3) Reduction of oxalacetate to malate prior to cleavage to glyoxalate and acetyl coenzyme A, the latter being carboxylated to malonyl coenzyme A. 4)  $\beta$ -Decarboxylation of oxalacetate to pyruvate which is subsequently oxidatively decarboxylated to acetyl coenzyme A