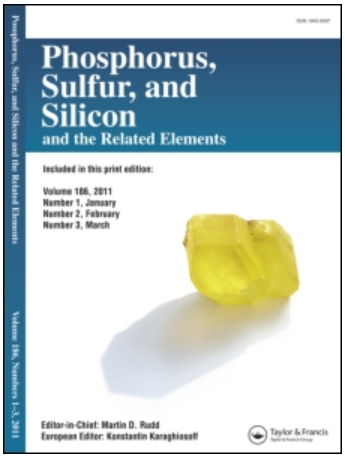

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N-BROMOSUCCINIMIDE-CATALYSED TRANSESTERIFICATION AND RACEMIZATION OF SULPHINATES

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N-BROMOSUCCINIMIDE-CATALYSED TRANSESTERIFICATION AND RACEMIZATION OF SULPHINATES[1]

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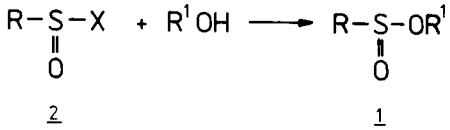
Both aliphatic and aromatic sulphinates undergo transesterification reaction in the presence of N-bromosuccinimide. Isopropanolysis of optically active alkyl arenesulphinates was found to give racemic isopropyl arenesulphinates. The rate of racemization of optically active isopropyl *p*-toluenesulphinate was found to be first order with respect to both N-bromosuccinimide and isopropyl alcohol, suggesting that the reaction is a bimolecular nucleophilic substitution at the sulphur atom. The para electrodonating substituents in the aromatic ring accelerate slightly the rate of racemization. At the same time the rate of racemization was found to be retarded by the increase of steric requirements of the substituent at the sulphinyl sulphur atom suggesting that the initial formation of bromoxonium salt is the rate-determining step. Completely nonstereospecific isopropanolysis of optically active alkyl *p*-toluenesulphinates suggests that a sulphurane is formed as an intermediate in the exchange step of the reaction.

INTRODUCTION

Organic sulphinates 1 have been known to be very useful precursors for the synthesis of a variety of sulphinyl derivatives.[2] They can be simply and in high yields prepared by the condensation of either sulphinyl chlorides[3] **2a** or sulphinic acids[4] **2b** with various alcohols (Equation 1).



(1)

2

a X = Cl
b X = OH

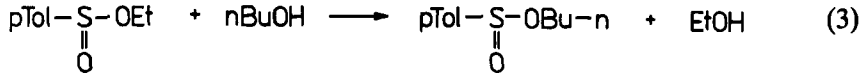
1

Although transesterification of sulphinates (Equation 2) has only limited applicability as a synthetic procedure, it plays an important role in the stereochemical studies of sulphinic acid derivatives as a simple model of nucelophilic substitution reaction at the sulphinyl sulphur atom.[5]

(2)

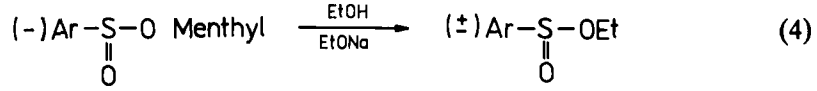
The thermal transesterification of levorotatory ethyl *p*-toluenesulphinate **1b** with *n*-butanol reported by Phillips[6] as early as 1925 and considered since that time as a first nucleophilic substitution reaction at chiral sulphur atom involving a

Walden type inversion was recently repeated and found[7] to give completely racemic sulphinate **1e** (Equation 3).



(3)

Also diastereoisomerically pure (−) menthyl (−) arenesulphinates **1k** and **1l** were converted into the corresponding racemic ethyl arenesulphinates **1b** and **1i** in ethanol solution in the presence of sodium ethoxide.[8] (Equation 4).

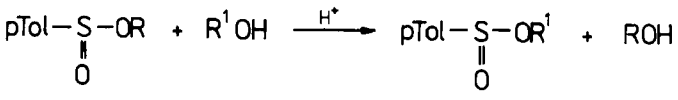


(4)

1k Ar = Ph
1L Ar = p-Tol

1b or 1i

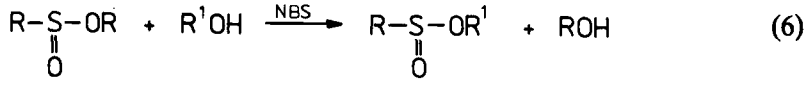
However, predominant inversion of configuration was recently observed[7] in an acid-catalysed alcoholysis of optically active *p*-toluenesulphinates **1f** and **1g** (Equation 5). Moreover, univocal evidence supporting the Walden inversion in



1f R = Allyl
1g R = Propargyl

this type of reactions of sulphinates was provided by kinetic measurements in which the rate of the acid-catalysed racemization of chiral [^{14}C] methyl *p*-toluenesulphinate **1a** in methanol was compared with that of isotopic methoxy-methoxy exchange under exactly the same conditions.[7]

In an extention of our studies in this direction we found now that *N*-bromosuccinimide (NBS) catalyses transesterification of both alkane- and arene-sulphinates (Equation 6).



(6)

This paper deals with synthetic and stereochemical aspects of this reaction as well as with kinetic investigation on racemization of chiral isopropyl alkane and arenesulphinates **1** in isopropyl alcohol in the presence of NBS.

RESULTS

When racemic alkyl arenesulphinates **1a**, **1f**, **1g** and **1h** were treated with NBS in an excess of an appropriate alcohol at room temperature the corresponding transesterification products were isolated in 51 to 83% yields (see Table I)

TABLE I

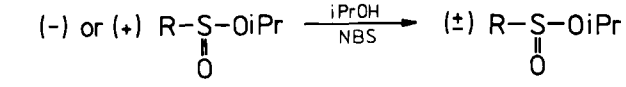
N-Bromosuccinimide (NBS) catalyzed transesterification of sulphinates R—S(O)OR[1] **1**[a]

Starting sulphinate **1**				Alcohol R^2OH	NBS	Time	Product **1**			
No	R	R^1	g	(ml)	(g)	(h)	No	R	R^2	Yield [%]
a	*p*-Tol	Me	0.4	*i*Pr(18)	0.1	10	d	*p*-Tol	*i*Pr	82
a	*p*-Tol	Me	1.7	*n*Pr(45)	0.7	10	c	*p*-Tol	*n*Pr	80
a	*p*-Tol	Me	1.8	*n*Bu(45)	0.7	15	e	*p*-Tol	*n*Bu	79
f	*p*-Tol	Al[b]	1.2	*i*Pr(14)	0.16	20	d	*p*-Tol	*i*Pr	51
g	*p*-Tol	Pro[c]	1.1	*i*Pr(12)	0.1	20	d	*p*-Tol	*i*Pr	52
h	Ph	Me	3.4	Et(90)	0.3	30	i	Ph	Et	83
i	Ph	Et	1.0	*i*Pr(35)	0.3	15	j	Ph	*i*Pr	72

[a] All reactions were carried out at room temperature.
[b] Al = $—CH_2—CH=CH_2$.
[c] Pro = $CH_2—C\equiv CH$.

Next, we have investigated the stereochemistry of the reaction using optically active *p*-toluene-sulphinates **1a**, **1f** and **1g** and isopropyl alcohol. The reactions were carried out at room temperature using ca 0.2–1.0 molar equivalents of NBS in respect to sulphinate. When the reaction was completed, the usual work-up always racemic isopropyl *p*-toluenesulphinate **1d** (see Table II)

Most probably the racemization observed is due to the competitive symmetrical alkoxy-alkoxy exchange in isopropyl *p*-toluenesulphinate **1d**. However, another possible way to account for a full racemization may be considered. One may assume that the NBS-catalysed transesterification of sulphinates **1** proceeds by an addition-elimination mechanism involving a sulphurane intermediate which undergoes racemization before decomposition into the final products. In order to gain better insight into the mechanism of the NBS-catalysed transesterification of sulphinates we carried out a detailed kinetic study on the reacemization of the optically active isopropyl arene(alkane)sulphinates **1d**, **1j**, **1m**, **1n**, **1o** and **1p** in isopropyl alcohol in the presence of NBS. (Equation 7).



(7)

1 d R = p-Tol
j R = Ph
m R = p-MeO-C_6H_4
n R = p Cl-C_6H_4
o R = Me
p R = iPr

When optically active isopropyl *p*-toluenesulphinate **1d** was treated with NBS in isopropyl alcohol at room temperature the sulphinate ester recovered by quenching with a large amount of water was found to be completely racemic. ^{1}H-NMR and IR spectra of the recovered ester were found to be identical with those of the starting ones. When optically active **1d** was treated with NBS in isopropyl alcohol, the rate of racemization was found to follow a linear correlation with the concentration of NBS and hence the rate was found to

TABLE II

N-Bromosuccinimide catalyzed transesterification of (−)-(S) O-Alkyl *p*-toluenesulphinates *p*Tol-S(O)OR[1] **1** with Isopropyl Alcohol.[a]

No	Starting sulphinate **1** R	$[\alpha]_{589}$	e.e.(%)	iPrOH g	NBS (g)	Time (mg)	(h)	*p*-Tol-S(O)OiPr (**1d**) $[\alpha]_{589}$	e.e.(%)
a	Me	−156.7	(72)	0.35	7	38.8	52	0.0	0
b	Al[b]	−102.7	(70)	0.3	7	38.8	36	0.0	0
g	Pro[c]	−18.1	(16.3)	0.3	15	300	6	0.0	0

[a] All reactions were carried out at room temperature.
[b] Al = CH_2—CH═CH_2.
[c] PrO═CH_2—C≡CH.

depend on both the sulphinic ester and NBS (first order each) as shown in Table III.

The racemization of optically active **1d** by NBS in the presence of isopropyl alcohol was studied at various initial concentration of alcohol in dioxane solution keeping the sulphinic ester and NBS concentrations and temperature constant (at 2×10^{-1} M, 4.36×10^{-2} M and 45°C respectively). The rate of racemization was found to follow a linear correlation with the concentration of isopropyl alcohol, hence the rate was found to depend on the first order of the concentration of isopropyl alcohol (see Table IV).

First order rate constants for the racemization of a series of alkyl arene(alkane) sulphinates **1** with NBS in isopropyl alcohol are listed in Table V. This table contains also the values of the second order rate constants for the racemization calculated by dividing the first order rate constants by NBS concentration.

The kinetic data in Table V indicate that the racemization of isopropyl isopropanesulphinate **1p** was ca 10 times slower than the racemization of the corresponding methanesulphinate **1o**. The comparison of the rate of racemization of arenesulphinates indicates that this rate decreases when the electron-withdrawing groups are present and increases when the electron donating groups are present in the para position of the aromatic ring.

The influence of temperature on the rate of racemization of isopropyl isopropanesulphinate **1p** and *p*-toluenesulphinate **1d** was investigated at three different temperatures and these data have been used for the calculation of activation parameters. The energy and entropy of activation (at 25°C) for the

TABLE III

Determination of kinetic order of racemization reaction[a]

No	Concn of NBS mole/l · 10^3	relative concn	$K \times 10^4$ (sek^{-1})	Relative rate
1	5.45	1.00	6.08	1.0
2	8.72	1.60	10.02	1.64
3	16.35	3.00	18.12	2.98
4	21.80	4.00	24.20	3.98

[a] Ester **1d** = 2.1×10^{-1} mole/l in *i*-PrOH; Tem = 70.2°C.

TABLE IV.

Determination of kinetic order of racemization reaction[a,b,c]

No	Concn of *i*-PrOH mol/l	relative concn	$K \times 10^4$ (sek^{-1})	relative rate
1	1.33	1.00	1.48	1.00
2	2.00	1.50	2.20	1.48
3	2.66	2.00	2.91	1.97

[a] In dioxane solution at 45°C.
[b] Ester (**1d**) = 2.0×10^{-1} mole/l.
[c] N-Bromosuccinimide = 4.36×10^{-3} mole/l.

TABLE V

Kinetic data on racemization of O-isopropyl sulphinates R—S(O)OiPr with N-bromosuccinimides in isopropanole solution

Run	R	Temp 0.1°C	$K_1 \times 10^5$ (sek^{-1})	$K_2 \times 10^5$ (1 $mole^{-1}$ sek^{-1})
1	Me	25.0	1.55	71.1
2	*i*Pr	25.0	0.158	7.2[c]
3	*i*Pr	50.0	2.60	119.3[c]
4	*i*Pr	70.0	18.70	857.8[c]
5	Ph	25.0	2.00	91.7
6	*p*-Tol	25.0	2.44	112.0[d]
7	*p*-Tol	45.0	21.74	995.4[d]
8	*p*-Tol	70.2	242.0	11100.0[d]
9	*p*-MeO—C_6H_4	25.0	3.53	161.9
10	*p*-Cl—C_6H_4	25.0	1.85	84.9

[a] Ester = 2×10^{-1} mole/l.
[b] N-Bromosuccinimide = 2.18×10^{-2} mole/l.
[c] E_a = 20.2 kcal mol^{-1} (84.4 kJ mol^{-1}); $S = -13.7$ e.u. (57.3 J mol^{-1} K^{-1} (at 25°C).
[d] E_a = 21.5 kcal mol^{-1} (89.9 kJ mol^{-1}); $S = -14.7$ e.u. (61.4 J mol^{-1} K^{-1} (at 25°C).

TABLE VI

Kinetic data on the racemization reaction of O-isopropyl *p*-toluenesulphinate (**1d**) with N-bromosuccinimide and isopropyl alcohol in different solvents[a,b,c]

Run	Solvent	$K_1 \times 10^5$ (sek^{-1})	Relative rate
1	*i*PrOH	21.7	1.9
2	CH_3CN	121.1[d]	12.0
3	dioxane	29.1[d]	2.0
4	benzene	10.2[d]	1.0

[a] Temp = 45.0°C.
[b] N-Bromosuccinimide 4.36×10^{-3} mole/l.
[c] Ester **1d** = 2×10^{-1} mole/l.
[d] *i*PrOH = 2.62 mole/l.

racemization of sulphinate **1p** were found to be $Ea = 84.4\ kJ\ mol^{-1}$ and $S^{\neq} = -57.3\ J\ mol^{-1}\ K^{-1}$, respectively. For the racemization of *p*-toluenesulphinate **1d** these values were found to be $Ea = 89.9\ kJ\ mol^{-1}$ and $S^{\neq} = -61.4\ J\ mol^{-1}\ K^{-1}$, respectively.

The solvent effect on the rate of racemization of isopropyl *p*-toluenesulphinate **1d** was examined and the results are collected in Table VI.

Apparently, the reaction is slowest in nonpolar benzene as solvent faster in a nucleophilic solvent-, dioxane, and much faster in a less nucleophilic and strongly polar solvent such as acetonitrile.

DISCUSSION

The racemization of isopropyl *p*-toluenesulphinate **1d** is first order with respect to NBS and to isopropyl alcohol. This indicates that the NBS catalysed racemization and transesterification of sulphinates in alcohol solution occurs through the formation of an intermediate compound from the ester and NBS followed by its decomposition in the reaction with an alcohol molecule to give the reaction product (enantiomer or product of transesterification).

There are two possible ways of activation of sulphinate esters by NBS in an alcohol solution. Thus, reaction of the sulphinic ester with alkyl hypobromite **2** (formed in situ from an alcohol and NBS) to give *S*-bromosulphoxonium salt **3** may take place. It is also possible that oxonium salt **4** is formed in the first step of the reaction. Thus, the over-all process of the reaction can be illustrated as shown in Figure 1.

Regardless of which way (a or b) is correct, one piece of information is obtained with certainty: racemization (and transesterification) of sulphinic esters catalysed by NBS is a typical bimolecular process. The entropy of activation (at 25°C) for the racemization of isopropyl *p*-toluenesulphinate **1d** was found to be $-57.3\ J\ mol^{-1}\ K^{-1}$. For racemization of isopropanesulphinate **1p** the entropy of activation (at 25°C) was found to be $-61.4\ J\ mol^{-1}\ K^{-1}$. These values of the entropy of activation are in the range usually associated with a bimolecular mechanism.[9]

The halosulphoxonium salts formed as intermediates in the reaction of sulphoxides with compounds containing electropositive halogen are well documented.[10] However, the formation of such an intermediate in the reaction between sulphinic esters **1** and alkyl hypobromite **2** can be excluded on the basis of the observation that aryl alkyl sulphoxides (in which the sulphinyl sulphur atom has stronger nucleophilic character in comparison with sulphinic esters) do not react with NBS in alcohol solutions.[11]

If the mechanism presented by the way b in Figure 1 is correct, the attack of alkoxy oxygen of **1** on electropositive bromide of **2** is crucial, and will be favored by the increase of negative charge on that oxygen atom. Any structural feature tending to diminish the accumulation of a negative charge on this oxygen in **1** should retard the rate of racemization (and transesterification). Thus, an electron-releasing group (e.g., a methoxy group in para position of the phenyl ring) should enhance the rate of reaction, while an electron-attracting group

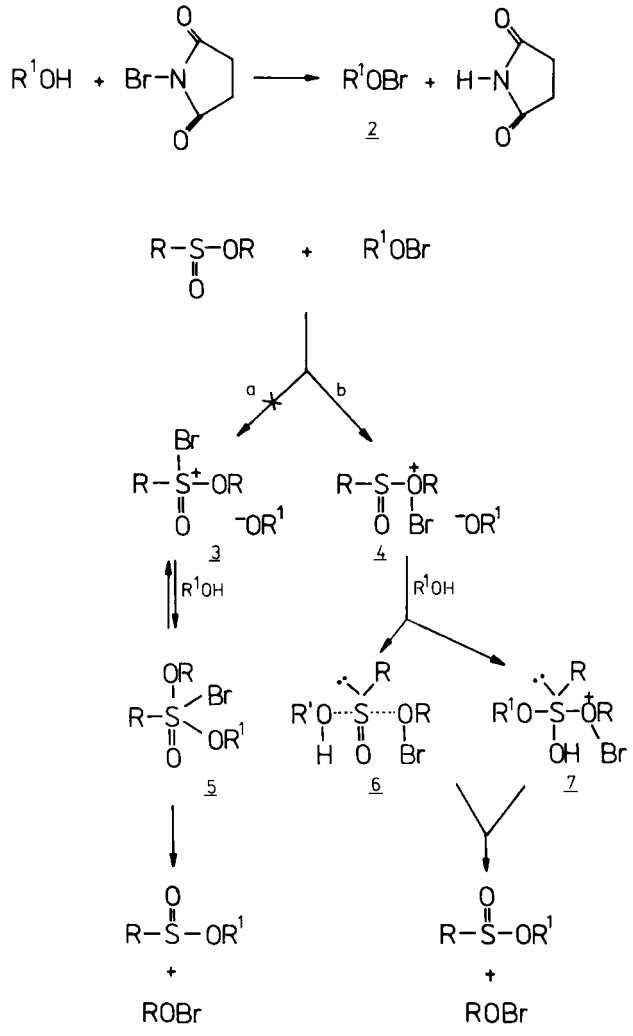


FIGURE 1

(e.g., chlorine) should exhibit the opposite effect. This was found to be the case. A plot of $\log k/k_H$ versus σ for *p*-substituted isopropyl phenylsulphinates gave rough linear correlation with considerable scatter. A much better correlation was obtained using σ^+ values, the point for the methoxy substituent now falling on the line. The ρ-value obtained (-0.31) is a composite value reflecting the effect of substituents on both the formation of bromoxonium salt **4** and its subsequent reaction with an alcohol molecule. The sign of the ρ value clearly indicates that substituents have a much greater effect on the first step, since electron withdrawing substituents would be expected to accelerate the rate of the step involving nucelophilic attack on the sulphinyl sulphur atom. This observation coupled with the fact that the rate of reaction is not too much sensitive to the steric requirements of the group attached to the sulphinyl sulphur atom (as seen

in Table 5 the rate constants of racemization of methanesulphinate **1o** and isopropanesulphinate **1p** differ only by factor of **1o**) clearly indicate that the formation of bromoxonium salt **4** is the rate limiting step.

The second step, the reaction of the salt **4** with an alcohol molecule, is a typical nucleophilic substitution reaction at the sulphinyl sulphur atom. One of the most important questions to answer regarding such a nucleophilic exchange is the exact timing of the two covalency changes that occur during such a reaction. Kice and Walters[12] studied the rate of the acetate catalysed exchange of [$^2H_3$] methanol with methyl *p*-toluenesulphinate **1a** and found that the reaction involves specific methoxide ion catalysis and general base rather than nucleophilic catalysis. We found recently that alcoholysis of optically active sulphinates proceeds in the presence of strong organic acids with predominant inversion of configuration.[7] However, in both cases no firm conclusion about whether the exchange step does or does not involve a sulphurane intermediate could be made. The alkoxy-alkoxy exchange in sulphinates **1** catalysed by NBS may also occur via a transition state **6** or through a sulphurane intermediate **7**. From the kinetic data presented above no firm distinction between this two possibilities could be made. However, it should be noted that the isopropanolysis of optically active (−)-(S) allyl **1f** and (−)-(S)-propargyl **1g** *p*-toluenesulphinates is completely nonstereospecific. This is in a sharp contrast to the acid catalysed transesterification of this sulphinates[7] and may suggest that the sulphurane intermediate **7** is formed in the exchange step of NBS catalysed transesterification or racemization of sulphinates.

EXPERIMENTAL

Racemic sulphinic esters **1** were prepared as reported[3] by reaction of the corresponding sulphinyl chlorides with the appropriate alcohol in the presence of a tertiary amine and purified by distillation. Optically active O-alkyl arene(alkane)-sulphinates **1** were synthesized as reported either by the reaction of the corresponding sulphinyl chloride with alcohol in the presence of an optically active tertiary amine[13] or by reaction of optically active N,N-diethyl-*p*-toluenesulphinamide with alcohol in the presence of trifluoroacetic acid[14] and purified by distillation. O-isopropyl methanesulphinate **1o**, $[\alpha]_{589} = -26.8°$ (EtOH). O-Isopropyl isopropanesulphinate **1p**, $[\alpha]_{589} = +27.35°$ (EtOH). O-Methyl *p*-toluenesulphinate **1a**, $[\alpha]_{589} = -156.7°$ (EtOH). O-Isopropyl *p*-toluenesulphinate **1d**, $[\alpha]_{589} = +40.7°$ (EtOH). O-Allyl *p*-toluenesulphinate **1f**, $[\alpha]_{589} = -102.7°$ (EtOH). O-Propargyl *p*-toluenesulphinate **1g**, $[\alpha]_{589} = -18.1°$ (EtOH). O-Isopropyl phenylsulphinate **1j**, $[\alpha]_{589} = -42.6$ (EtOH). Isopropyl *p*-methoxyphenylsulphinate **1m**, $[\alpha]_{589} = -34.7°$ (EtOH).

Solvents and alcohols obtained commercially were purified according to the usual procedure.

N-Bromosuccinimide was BDH grade and was further purified by recrystallization from benzene.

N-Bromosuccinimide Transesterification of Sulphinates: General Procedure

To a solution of optically active or racemic sulphinate **1** in an appropriate alcohol N-bromosuccinimide was added at room temperature (amounts of the reagents

are given in Tables 1 and 2). After an appropriate time the reaction mixture was worked up by quenching with large excess of water. The water—alcohol solution was extracted with ether (4×30 ml). The combined ether solutions were dried over magnesium sulphate and evaporated to give products of transesterification, which were purified by distillation or chromatography on silica gel using a mixture of etherpentane (1 : 1) as eluent. Physical and spectroscopic properties of sulphinates 1 obtained by this procedure were in good agreement with the literature data.[3,4]

Kinetic procedure for racemization. In the polarimetric cell a solution containing an optically active sulphinic ester and NBS of a set mole was placed, the rate was measured directly by checking the rotation, α, with a polarimeter (Perkin–Elmer 141 photopolarimeter) which was set at a desired temperature. First order rate constants for racemization of sulphinates 1 were calculated from the equation $\log \alpha_0/\alpha_t = kt/2.303$ where α_0 and α_t are the rotation powers at time 0 and t, respectively. Second order rate constants were calculated by division of first order rate constants by the N-bromosuccinimide concentration. The duplicate experiments were always reproducible to ±5%.

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