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RACEMIZATION OF SULFINIC ESTERS WITH TRICHLOROACETIC ANHYDRIDE

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Abstract—Both alkane- and arene-sulfinates undergo racemization and oxygen exchange reaction with trichloroacetic anhydride. The rate of racemization of (−)menthyl (−)*p*-toluenesulfinate was found to be twice that of oxygen exchange, suggesting the reaction involves a Walden inversion. When reaction was carried out in benzene, the rate of racemization was found to be first order with respect to both sulfinic ester and trichloroacetic anhydride. The substituent effect is large ($\rho = -1.53$) suggesting that the initial acylation is the rate-determining step. The rate of racemization was found to be retarded by the addition of perhaloacetic acid while very small catalytic effect of mercuric chloride was observed.

Recently there has been much concern on racemization of sulfoxides. Sulfoxides have been found to be racemized photochemically,[1] by thermal induced homolytic cleavage,[2] by reversible allylic rearrangement through allyl sulfenate esters[3] and by pyramidal inversion[4] at higher temperature. It has also been shown that racemization of sulfoxides takes place quite rapidly by reversible nucleophilic substitution at room temperature in hydrochloric acid,[5] sulfuric acid[6] and dinitrogen tetroxide(N_2O_4),[7] and at somewhat higher temperatures in acetic anhydride solution,[8] phosphoric acid solution[9] and in weak carboxylic acid.[10]

In contrast to sulfoxides the racemization of the optically active sulfinic esters has been investigated very little despite the importance in the organic sulfur stereochemistry[11] as the main source of the optically active sulfoxides.

The sulfinic esters which give stable carbonium ions upon heterolysis have been known to be racemized and rearranged to sulfones through ion-pair intermediates in polar solvents[12] (Fig. 1).

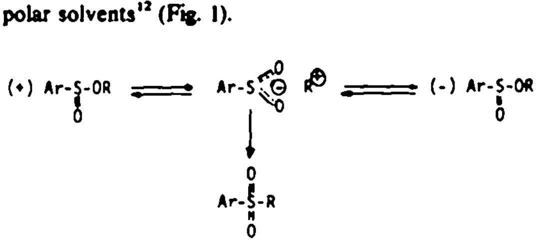


Fig. 1.

Earlier, Herbrandson and Dickerson[13] found that diastereomeric (−)menthyl(−)arenesulfinates in nitrobenzene epimerize in presence of hydrogen chloride and chloride anion. A mechanism involving reversible formation of a sulfinyl chloride was proposed (Fig. 2) and the epimerization was accounted for by rapid chloride anion exchange at sulfur in the sulfinyl chloride intermediate.

Meanwhile we found that optically active sulfinic seters are readily racemized with trichloroacetic anhydride without cleaving S-OR linkage. This paper will deal with a detailed account of our kinetic study on the racemization reaction of enantiomeric alkyl alkanesulfinates(1) and diastereomeric (−)menthyl (−)arenesulfinates(2) with trichloroacetic anhydride.

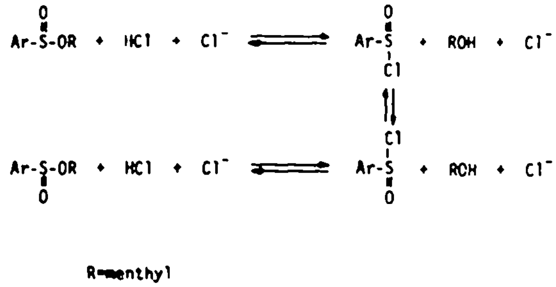
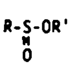
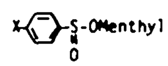


Fig. 2.



(1)



(2)

a: R=Me, R′=Pr^n
b: R=Me, R′=Pr^i
c: R=Me, R′=Bu^t
d: R=Me, R′=neopentyl
e. R=Bu^n, R′=Pr^n

a: X=H,
b: X=Me,
c: X=Cl

RESULTS AND DISCUSSION

When optically active neopentyl methanesulfinate(1d) or (−)menthyl (−)*p*-toluenesulfinate(2b) was treated with trichloroacetic anhydride in benzene solution at room temperature, the sulfinic ester, recovered nearly quantitatively by quenching with a large amount of water, was found to have lost its activity. NMR and IR spectra of the recovered esters were found to be identical to those of the starting ones. When optically active neopentyl methanesulfinate(1d) was treated with trichloroacetic anhydride in benzene, the rate of racemization(k_{rac}) was found to follow a linear correlation with the concentration of trichloroacetic anhydride and hence the rate was found to depend on both the sulfinic ester and trichloroacetic anhydride (first order each) as shown in Table 1.

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Table 1. Determination of kinetic order of racemization reaction in benzene at 25.5 ± 0.1°C[a]

No.	Concn. of $(Cl_3CCO)_2O$ mole/l	relative concn.	$k \times 10^4$ $(sec^{-1})^{b)}$	relative rate
1	0.286	1	6.30	1
2	0.292	1.03	6.55	1.04
3	0.441	1.54	9.20	1.46
4	0.595	2.08	12.8	2.03

a) Ester = 7.02×10^{-2} mole/l

b) $k_2 = 21.7 \pm 0.6 \times 10^{-4}\ M^{-1}\cdot sec^{-1}$

Second order rate constants for the racemization of a series of alkyl alkanesulfinates(1) with trichloroacetic anhydride, which were calculated by dividing the first order rate constants of racemization by trichloroacetic anhydride concentration, are listed in Table 2.

Similar rate constants for the racemization of a series of diastereomeric (−)menthyl (−)arenesulfinates(2) with another pertinent data are collected in Table 3.

Inspection of the kinetic data in the Tables 2 and 3 reveals that the rates of racemization of the alkanesulfinates(1) are higher than those of arenesulfinates(2) and vary by the nature of both R and R' groups in 1. The kinetic data in Table 3 also indicate that the rate of racemization of (−)menthyl (−)p-toluenesulfinate(2b) was about twice that of oxygen exchange. This means that the reaction involves a Walden inversion. The energy and entropy (at 25.5°C) of activation for the racemization were found to be 14.5 kcal/mole and −26.8 e.u., respectively. For racemization of neopentyl methanesulfinate(1d) the entropy of activation was found to be −28.5 e.u. These small values of the entropies of activation are also in keeping with the S_N2 type mechanism.

Table 2. Kinetic data on racemization of alkyl alkanesulfinates(1), R–S(O)OR' with trichloroacetic anhydride in benzene solution[a]

No.	R	R'	Temp.±0.1°C	$k_2 \times 10^4$ $(M^{-1}\cdot sec^{-1})$
1	Me	Pr^n (1a)	25.5	40.2 ± 0.9
2	Me	Pr^i (1b)	25.5	72.7 ± 1.5
3	Me	Bu^t (1c)	25.5	17.2 ± 0.3
4	Me	Np (1d)$^{b)}$	25.5	21.7 ± 0.6$^{c)}$
5	Me	Np (1d)	31.2	33.0 ± 0.9$^{c)}$
6	Me	Np (1d)	40.3	62.9 ± 1.2$^{c)}$
7	Bu^n	Pr^n (1e)	25.5	14.4 ± 0.5

a) Ester = 7×10^{-2} mole/l, $(Cl_3CCO)_2O$ = $2\text{-}3 \times 10^{-1}$ mole/l.

b) Np = neopentyl.

c) Ea = 13.2 kcal/mole, $\Delta S^{\neq} = -28.5$ e.u. (at 25.5°C).

In the ^{18}O exchange reaction of diaryl sulfoxides in both dinitrogen tetroxide and highly concentrated sulfuric acid, k_{ex}/k_{rac} is unity, while the entropies of activation are substantially large and positive.[6,7] The racemization reaction of diaryl sulfoxides in warm acetic anhydride and less concentrated sulfuric acid is considered to be of S_N2 type process and gives a k_{ex}/k_{rac} value of roughly 1/2. The entropies of activation of these reactions are also quite small,[4,8] $\Delta S^{\neq} = -28.6$ e.u. (at 120°) for acetic anhydride and −18.9 e.u. (at 30°) for diluted sulfuric acid respectively. Kinetic data in Table 3 reveal that the polar effect of p-substituent is markedly larger than that in the racemization of diaryl sulfoxides in warm acetic anhydride. The rates are nicely correlated with the Hammett equation and a negative ρ value (for σ), −1.53, was obtained. These results indicate that in contrast to racemization reaction of sulfoxides in acetic anhydride solution,[8] the first step of the reaction, i.e. acylation, is the rate-determining one, though the k_{ex}/k_{rac} value of roughly 1/2 indicates that the energy barrier for the oxygen exchange process (S_N2) must be quite similar to that of the initial acylation. Thus, the over-all process of the reaction can be illustrated as shown in Fig. 3.

The data in Tables 4 and 5 reveal that the rate of racemization of n-propyl methanesulfinate(1a) is retarded after addition of trichloroacetic acid or trifluoroacetic acid. This observation is also in keeping with the suggested mechanism because a decrease of the rate of racemization is considered to be due to deactivation of sulfinyl oxygen either by hydrogen bonding or protonation, which suppresses the initial acylation. In connection to this observation it is worthy to note that the racemization of neopentyl methanesulfinate(1d) with trichloroacetic anhydride is 25 times slower than with trifluoroacetic anhydride (Table 6). The large enhancement of the rate of racemization with trifluoroacetic anhydride is undoubtedly associated with its more elec-

Table 3. Kinetic data on racemization of (−)menthyl (−)arenesulfinates(2) with trichloroacetic anhydride[a]

No.	X in $p\text{-}XC_6H_4S(O)OMenthyl$		Solvent	Temp ± 0.1°C	$k_2 \times 10^4$ $(M^{-1}\cdot sec^{-1})$
1	H	(2a)	C_6H_6	25.5	2.98 ± 0.05
2	Me	(2b)	C_6H_6	25.5	5.25 ± 0.13$^{b,c)}$
3	Me		C_6H_6	35.7	12.1 ± 0.5$^{c)}$
4	Me		C_6H_6	45.1	24.0 ± 1.0$^{c)}$
5	Me		THF	25.5	2.27 ± 0.14
6	Me		THF$^{d)}$	25.5	4.51 ± 0.18
7	Cl	(2c)	C_6H_6	25.5	1.32 ± 0.06

a) Ester = 7×10^{-2} mole/l; $(Cl_3CCO)_2O$ = $2\text{-}5 \times 10^{-1}$ mole/l.

b) k_2(exchange) = $2.72 \pm 0.12 \times 10^{-4}\ M^{-1}\cdot sec^{-1}$; k_{ex}/k_{rac} = 0.52.

c) Ea = 14.5 kcal/mole; $\Delta S^{\neq} = -26.8$ e.u. (at 25.5°C).

d) 493.7 mg of $HgCl_2$ was added to 10 ml reaction mixture.

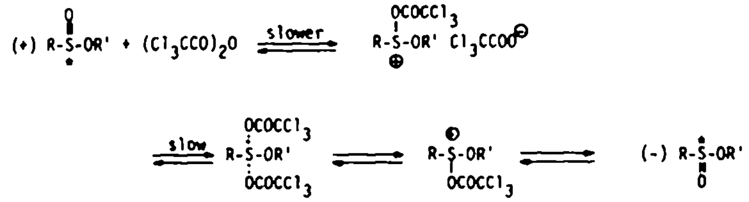


Fig. 3.

Table 4. Influence of trichloroacetic acid on the racemization reaction of *n*-propyl methanesulfinate(1a) with trichloroacetic anhydride in benzene solution at 25.5 ± 0.1°[a]

No.	Cl_3CCOOH (mg)[b]	$k \times 10^4$ (sec^{-1})	rel. rate
1	0	5.77	1.00
2.	38.4	5.22	0.90
3	68.7	3.94	0.68
4	92.0	2.88	0.50
5	140.5	2.09	0.36
6	251.2	1.33	0.23

[a] Ester = 1.7×10^{-1} mole/l; $(Cl_3CCO)_2O$ = 1.428×10^{-1} mole/l.
[b] Acid was added to 10 ml reaction mixture.

Table 5. Influence of trifluoroacetic acid on the racemization of *n*-propyl methanesulfinate(1a) with trichloroacetic anhydride in benzene solution at 25.5 ± 0.1°[a]

No.	CF_3COOH (mg)[b]	$k \times 10^4$ (sec^{-1})	rel. rate
1	0	4.80	1.00
2	18.7	3.73	0.78
3	65.3	2.84	0.59

[a] Ester = 1.99×10^{-1} mole/l; $(Cl_3CCO)_2O$ = 1.94×10^{-1} mole/l.
[b] Acid was added to 10 ml reaction mixture.

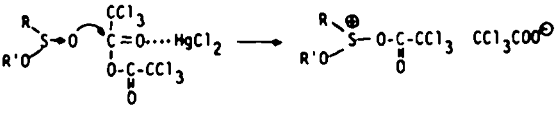
Table 6. Effect of anhydride $(RCO)_2O$ on the racemization of neopentyl methanesulfinate(1d) in benzene solution at 25.5 ± 0.1°[a]

R	Anhydride concn. (mole/l)	k (sec^{-1})	k_2 ($M^{-1} \cdot sec^{-1}$)
CCl_3	2.917×10^{-1}	$(6.32 \pm 0.16) \times 10^{-4}$	$(21.7 \pm 0.6) \times 10^{-4}$
CF_3	2.058×10^{-2}	$(1.12 \pm 0.08) \times 10^{-3}$	$(545 \pm 4) \times 10^{-4}$

a) Ester = 7×10^{-2} mole/l.

trophilic character than that of trichloroacetic anhydride. Thus, the first rate-determining step of reaction, acylation, should be markedly facilitated with trifluoroacetic anhydride and hence the over-all rate of reaction is eventually increased.

The racemization of sulfoxides is known to be catalyzed markedly by a small amount of Lewis acids such as mercuric chloride.[8] However, the addition of 0.5 g $HgCl_2$ accelerates the rate of racemization of (−)-menthyl (−)*p*-toluenesulfinate(2b) only two-fold. This small catalytic effect of mercuric chloride is also considered to be due to the acceleration of the first acylation step, since in this step the leaving of trichloroacetate group will be facilitated by co-ordination with mercuric chloride as shown below.



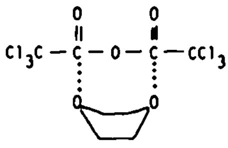
The solvent effect on the rate of racemization of neopentyl methanesulfinate(1d) was examined and the results are collected in Table 7.

Apparently the reaction is slower in a nucleophilic solvent, dioxane, but faster in a less nucleophilic and polar solvent such as acetonitrile. The data in Table 3 also indicate that the rate of racemization of (−)menthyl (−)*p*-toluenesulfinate(2b) is about 2 times lower in THF than in benzene. Slower racemization in dioxane and THF is due mainly to a special interaction between solvent and trichloroacetic anhydride. Since both dioxane and THF are nucleophilic solvents, they would interact with anhydride to form a loose complex and this interaction may suppress the acylation of sulfinyl oxygen of low basicity, thus reducing the rate of racemization.

Table 7. Kinetic data on the racemization reaction of neopentyl methanesulfinate(1d) with trichloroacetic anhydride in different solvents at 25.5 ± 0.1°[a]

No.	Solvent	$k_2 \times 10^4$ ($M^{-1} \cdot sec^{-1}$)
1	Benzene	21.7 ± 0.6
2	Dioxane	5.45 ± 0.18
3	Acetonitrile	64.9 ± 1.3

a) Ester = 7×10^{-2} mole/l;
$(Cl_3CCO)_2O$ = 2-3 $\times 10^{-1}$ mole/l.



The racemization is undoubtedly of ionic character and hence expected to be accelerated in a more polar solvent acetonitrile because the initial acylation of the sulfinyl oxygen would be facilitated in this solvent.

Since the mechanism of racemization of the sulfinic esters with trichloroacetic anhydride is different from that of the sulfoxides in warm acetic anhydride,[8] it is interesting to measure the rate of racemization of same sulfoxides in presence of trichloroacetic anhydride. The results are collected in Table 8.

Comparison of this data with the data from Tables 2 and 3 reveals that the racemization of sulfoxides is about 10^3 times faster than that of the sulfinic esters. This

Table 8. Kinetic data on the racemization reaction of sulfoxide, $p-\mathrm{Tol}-\mathrm{S(O)}-\mathrm{R}$, with trichloroacetic anhydride in benzene solution at 25.5 ± 0.1°[a]

No.	R	k_2 ($M^{-1}\cdot sec^{-1}$)
1	Me	too fast to be measured
2	Bu^t	58.7 ± 2.0
3	Ph	11.6 ± 0.7

a) Sulfoxide = 3×10^{-2} mole/l;
$(Cl_3CCO)_2O$ = 3.5×10^{-3} mole/l.

strong enhancement of the rate of racemization of sulfoxides is undoubtedly caused by the much higher nucleophilicity of the sulfinyl oxygen in sulfoxides than that of the sulfinic esters.

EXPERIMENTAL

Materials

Optically active alkyl alkanesulfinates(1) were synthesized as reported,[14] by reaction of the corresponding sulfinyl chloride with alcohol in presence of an optically active tertiary amines, and purified by distillation. *n*-Propyl methanesulfinate(1a): b.p. 32°/2 mmHg, $[\alpha]_D$ +27.28°(c = 1.03, EtOH) [lit.[14] $[\alpha]_D$ −26.92°(EtOH)]. *i*-Propyl methanesulfinate(1b): b.p. 33°/5 mmHg, $[\alpha]_D$ −28.95°(c = 1.24 EtOH) [lit[14] $[\alpha]_D$ −16.28°(EtOH)]. *t*-Butyl methanesulfinate(1c): b.p. 34–35°/5 mmHg, $[\alpha]_D$ −21.7°(c = 1.93 EtOH) [lit.[14] $[\alpha]_D$ −15.80°(EtOH)]. Neopentyl methanesulfinate(1d): b.p. 44–45°/3 mmHg, $[\alpha]_D$ +25.70°(c = 1.72 EtOH) [lit.[14] $[\alpha]_D$ −22.12°(EtOH)]. *n*-Propyl *n*-butanesulfinate(1e): b.p. 62–63°/1.5 mmHg, $[\alpha]_D$ + 23.1°(c = 0.93 EtOH) [lit.[14] $[\alpha]_D$ +22.7°(EtOH)].

Optically active (−)*menthyl* (−)*arenesulfinates*(2) were obtained by the reaction of the corresponding sulfinyl chloride with (−) menthol in presence of pyridine and purified by recrystallization. (−)Menthyl (−)benzenesulfinate(2a): m.p. 48–50°C, $[\alpha]_D$ −203.3°(c = 2.16 acetone), [lit.[15] m.p. 49–51°, $[\alpha]_D$ −205.5°(acetone)]. (−)Menthyl (−)*p*-toluenesulfinate(2b): m.p. 102–104°, $[\alpha]_D$ − 203.4°(c = 2.34 acetone), [lit.[15] m.p. 108–109.1°C, $[\alpha]_D$ − 210°(acetone)]. (−)Menthyl (−)*p*-chlorobenzenesulfinate(2c): m.p. 87–88°C, $[\alpha]_D$ − 181.1° (c = 0.66 acetone).

^{18}*O-Labeled optically active* (−)*menthyl* (−)*p-toluenesulfinate*(2b) was prepared by the same procedure using ^{18}O-labeled *p*-toluenesulfinyl chloride which was prepared from ^{18}O-labeled sulfinic acid, m.p. 101–103°, $[\alpha]_D$ −201.5° (c = 1.34 acetone), 0.463 excess atom% of ^{18}O.

Optically active sulfoxides were prepared from (-)menthyl (-)*p*-toluenesulfinate [m.p. 102–104° with $[\alpha]_D$ − 203.4° (acetone)] and appropriate Grignard reagents according to the method developed by Andersen.[16] *p*-Tolyl methyl sulfoxide: m.p. 72–73°, $[\alpha]_D$ + 144.9° (c = 1.01 acetone), [lit.[17] m.p. 73–74°, $[\alpha]_D$ + 145.5° (acetone)]. *p*-Tolyl *t*-butyl sulfoxide: m.p. 88–90°, $[\alpha]_D$ + 168.8° (c = 0.28 acetone), [lit.[17] m.p. 89.5–90°, $[\alpha]_D$ + 161° (acetone)]. *p*-Tolyl phenyl sulfoxide: m.p. 92–93°, $[\alpha]_D$ + 27.1° (c = 5.19 EtOH), [lit.[17] m.p. 92–93°C, $[\alpha]_D$ + 27.0° (EtOH)].

Solvents obtained commercially were purified according to the usual procedure.

Trichloroacetic anhydride obtained commercially was purified by distillation. b.p. 86–87°/2 mmHg.

Kinetic procedure. The rates of racemization and oxygen exchange were measured by the following method using UNION OR-50D Polarimeter and HITACHI-6m type mass spectrometer.

Kinetic procedure I (*Racemization and oxygen exchange*). The reactions were carried out in sealed tubes in which sulfinic ester and trichloroacetic anhydride of a set mole were dissolved in benzene. A sealed tube containing about 10 ml of the mixture was drawn out at time intervals from the bath and quenched with water. After addition of 50 ml of ether, the organic layer was washed with 5% Na_2CO_3 aq and water. After dried over $MgSO_4$ solvent was distilled off. Then the sulfinic ester resulted was thoroughly dried and subjected to both ^{18}O analysis and specific rotation measurements. The ^{18}O-atom% was calculated from the mass peak hights 44 and 46 of CO_2* and the rate constant for oxygen exchange was calculated from equation log $\beta_0 - \beta/\beta_t - \beta = kt/2.303$, where β_0 and β_t are atom% of ^{18}O at time 0 and time t, respectively, and β is the atom% of ^{18}O of natural CO_2. The first order rate constants for the racemization were calculated from equation log $\alpha_0 - \alpha_r/\alpha_t - \alpha_r = kt/2.303$, where α_0 and α_t are the specific rotations, $[\alpha]$, at time 0 and t, respectively, and α_r is specific rotation $[\alpha]_D$ of racemic mixture. Second order rate constants were calculated by division of first order rate constants by trichloroacetic anhydride concentration.

Kinetic procedure II for racemization. In the polarimetric cell was placed a soln containing an optically active sulfinic ester and trichloroacetic anhydride of a set mole, the rate was measured directly by checking the rotation, α, with a polarimeter which was set at a desired temp. First order rate constants for racemization of enentiomeric ester 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. In racemization of diastereomeric esters following equation was used. Log $\alpha_0 - \alpha/\alpha_t - \alpha = kt/2.303$ where α_0 and α_t are the rotatory powers at time 0 and t, respectively, and α is the final rotatory power. The second order rate constants were calculated by division of first order rate constants by the trichloroacetic anhydride concentration. The rate constants obtained by this method are in good agreement with those obtained by isolating the product under kinetic procedure I.

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