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ON THE STEREOCHEMISTRY OF SULPHONIUM SALTS FORMATION BY REACTION OF THIOETHERS WITH ALCOHOLS OR ETHERS IN ACID MEDIUM

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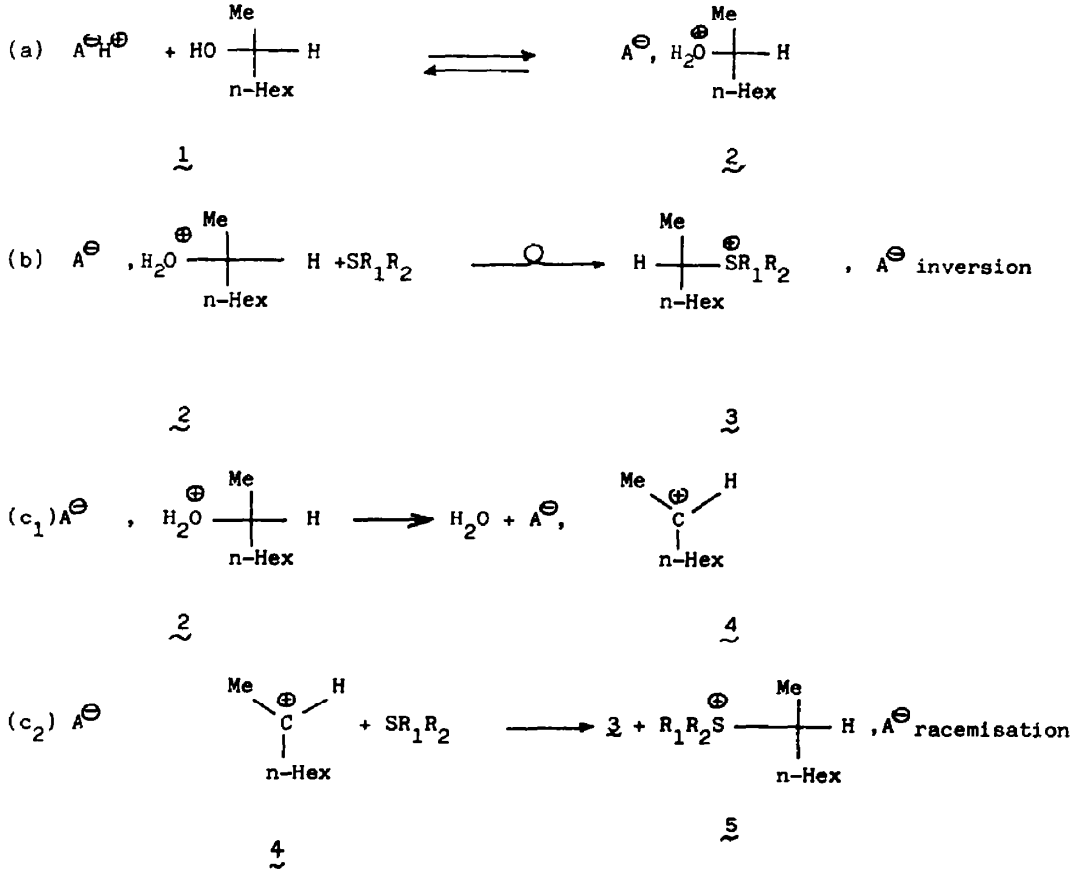
Abstract—The title reaction has been investigated with optically active 2-octanol and dimethyl sulphide, tetrahydrothiophene and tetrahydrothiapyran. Formation of the sulphonium salt took place substantially with inversion of configuration.

It has recently been shown[1] that various acids bring about the alkylation of aliphatic and aromatic sulphides by alcohols or ethers leading efficiently to the corresponding sulphonium salts. The present investigation was undertaken in order to gather more information about this reaction, a more precise knowledge of which could allow a more efficient utilisation.

It has been reported[8] that n-butylation of thioethers in the presence of perchloric acid takes place without skeletal isomerisation whereas the use of alkyl halides with silver salts is likely to give a mixture of isomers.[9]

A carbocation mechanism has been suggested[3a] for the acidic cleavage of anisole or phenetole by methionine leading to sulphonium salts (Scheme 1, a, c_1, c_2). However a S_N2 type displacement mechanism has been suggested 3b as a possible mechanism for the related hydrolysis of aliphatic and aromatic ethers by thiols in the presence of Lewis acids (Scheme 1, a, b). The stereochemical result of a substitution reaction is



Scheme 1.

an important factor that should always be considered in any discussion of mechanism.[2e,2f] It was therefore deemed necessary to gain information on the stereochemistry of the sulphonium salt formation using 2-octanol. Reaction conditions were found under which the racemic alcohol gave a 90% yield of racemic dimethyl 2-octyl sulphonium salt.

A reference sample of known optical purity was then secured starting from (−)-(*R*)-2-octanol (o.p. 94.8%)[4a] through the tosylate[4b] and (+)-(*S*)-methyl 2-octyl sulphide. The optical purity at this stage was found to be higher than any value found in the literature;[4d] we therefore assumed the optical purity of the sulphide to be that of the starting alcohol, i.e. 94.8%. This methyl 2-octylsulphide was then treated with trimethyloxonium tetrafluoroborate in methylene chloride[5] or anisole in methanesulphonic acid followed by tetrafluoroboric acid for anion exchange when dimethyl 2-octyl sulphonium tetrafluoroborate was formed in 63% and 85% yield respectively with the same rotation; the perchlorate may be similarly prepared substituting perchloric acid for tetrafluoroboric acid.

Assuming that these salts have the same optical purity as the starting sulphide, this places the specific rotation of optically pure (+)-(*S*) salts at $[\alpha]_D^{20} = +5.03°$ and $[\alpha]_D^{20} = +4.66°$ (c = 10, EtOH) for the tetrafluoroborate and the perchlorate respectively. The substitution reaction of (−)-(*R*)-2-octanol (o.p. 94.8%) by dimethyl sulphide was then carried out under various conditions. Preliminary experiments had shown that, with comparable amounts of dimethylsulphide and 2-octanol at room temperature, considerable isomerisation took place. This of course points to a carbocation process (Scheme 1,c).

The S_N2 route (Scheme 1,b) would be favoured over the S_N1 one by increased concentration of nucleophile. In fact with a large (10 or 20 times) molar excess of sulphide, and use of methanesulphonic acid, the reaction was regiospecific and considerable (>80%) inversion of configuration was observed; the chemical and optical yields are shown in Table 1.

Table 1. Alkylation of sulphides R_2S with (−)-(*R*)-2-octanol (10 mmoles, o.p. 94.8%) and methanesulphonic acid at 20°C

Run	R or R-R	(mmoles)	acid mmoles	CH_2Cl_2 cm^3	time (days)	Anion(a) in 3+5	Chemic Yield	$[\alpha]_D^{20}$, ° (c=10,EtOH)	%(b) inversion
1	CH_3	100	100	--	7	ClO_4	75	3.61	81.7
2	CH_3	100[c]	100	--	1.91	ClO_4	47	3.70	83.5
3	CH_3	200	40	--	1.75	ClO_4	12	3.65	82.6
4	CH_3	200	100	--	1.71	ClO_4	33	3.85	87
5	CH_3	200	100	30	2.65	ClO_4	24	3.88	87.8
6	CH_3	"	"	"	5	ClO_4	47	3.62	81.9
7	$(CH_2)_4$	100[e]	100		7	BF_4	94	-8.16[d]	68.8
8	$(CH_2)_4$	200	100	30	2.65	BF_4	30	-6.14[d]	51.8
9	$(CH_2)_4$	"	"	"	5	BF_4	53	-6.86[d]	57.9
10	$(CH_2)_5$	100[e]	100	--	7	ClO_4	75	-8.45[d,f]	57
11	$(CH_2)_5$	200	100	30	2.65	ClO_4	37	-9.85[d]	66.4
12	$(CH_2)_5$	"	"	"	5	ClO_4	55	-10.22[d]	68.9

a) Isolation was carried out after anion exchange ; see experimental.

b) Estimated % inversion = $10^4 \frac{[\alpha] \text{ of product}}{(\text{estimated maximum } [\alpha] \text{ of salt})(\% \text{ o.p. of alcohol})}$

c) Addition of molecular sieves to the mixture.

d) $[\alpha]_D^{20}$, (c=5,$CHCl_3$) e) heterogeneous mixture f) mixture of octyl-2(88) octyl-3 (9.5) and octyl-4(2.5) sulphonium.

We checked the regioselectivity of the attack of sulphide on 2-octanol by reaction of the sulphonium salt formed with potassium benzoate[6].

$$PhCO_2K + 2\text{-octylSR}_2^{\oplus}X^{\ominus} \rightarrow PhCO_2\text{-2-octyl} + PhCO_2R + 2\text{-octylSR} + RSR + KX.$$

In each example indicated in Table 1, the only octyl benzoate formed is 2-octyl benzoate as shown by gas–liquid chromatography.

Similar experiments were next carried out with tetrahydrothiophene (THT). In order to secure an authentic sample of the corresponding 2-octylsulphonium salt (+)-(*S*)-2-octanethiol was prepared[4c] ($[\alpha]_D^{20} = +29.2°$ (c = 5, $CHCl_3$); +32.6° (c = 1.48, EtOH)). Treatment of the thiolate anion (BuLi/Et_2O/HMPT) by methyl iodide afforded (+)-(*S*)-methyl 2-octyl sulphide $[\alpha]_D^{20} = +9.6°$ (c = 5, $CHCl_3$). Comparison with the product obtained above leads to an estimated optical purity of 92% for the thiol.

With 1,4-butanediol and methanesulphonic acid, the (−)-(*S*)-2-octyl tetrahydrothiophenium tetrafluoroborate $[\alpha]_D^{20} = -8.75°$ (c = 10, EtOH), $[\alpha]_D^{20} = -11.5°$ (c = 5, $CHCl_3$) was obtained. Assuming this salt has the same optical purity as the starting thiol this gives a specific rotation of $[\alpha]_D^{20} = -9.52°$ (c = 10, EtOH), $[\alpha]_D^{20} = -12.50°$ (c = 5, $CHCl_3$) for the optically pure salt. Displacement of the hydroxyl group by tetrahydrothiophen in (−)-(*R*)-2-octanol gave the results shown in Table 1. It will be seen that under the same reaction conditions there is more racemisation than with dimethylsulphide.

Similar experiments were then carried out with tetrahydrothiapyran. The authentic (−)-(*S*)-2-octyltetrahydrothiapyranium perchlorate $[\alpha]_D^{20} = -14.4°$ (c = 5, $CHCl_3$) was prepared from (+)-(S)-2-octanethiol of 92% optical purity via the (+)-(*S*)-5-hydroxypentyl-2-octylsulphide $[\alpha]_D^{20} = +11.65°$ (c = 5, $CHCl_3$). The optically pure sample of this salt was thus estimated to have $[\alpha]_D^{20} = -15.65°$ (c = 5, $CHCl_3$). The displacement reaction of (−)-(R)-2-octanol by tetrahydrothiapyran gave the results shown in Table 1, similar to those observed with tetrahydrothiophene.

CONCLUSION

The regioselectivity and considerable inversion observed with a high concentration of dimethyl sulphide is consistent with, but of course does not prove, S_N2 alkylation by the oxonium salt **2** of the type often drawn in textbooks.[2] Most nucleophiles would be too basic and deprotonate rather than substitute **2**. Halide ions however displace water in a way similar to the alkylation of nucleophiles by trimethyl oxonium ions. Sulphur is a reasonably good nucleophile and a very poor Brönsted base so that it undergoes alkylation rather than deprotonate[7] the salt. Thanks to this set of properties the alkylating power of the readily formed oxonium salts **2** can be stored in the form of sulphonium salts which themselves are powerful alkylating agents.[6]

EXPERIMENTAL

Alkylation of sulphides by 2-octanol

Dimethyl 2-octyl sulphonium salts (racemic) **3–5** ($R_1 = R_2 = CH_3$); *Perchlorate.* To a stirred solution of methanesulphonic acid (6.5 cm³ 0.1 mole) and dimethyl sulphide (7.5 cm³; 0.103 mole) (±)2-octanol (1.60 cm³; 10 mmoles) was added dropwise under nitrogen. The homogeneous mixture was stirred for 7 days at room temperature. Ether was then added until two layers appeared. The lower layer was washed several times with dry ether, water is added followed by 70% aqueous perchloric acid (2 cm³, 23 mmoles) and the aqueous solution was extracted with methylene chloride (4 portions of 20 cm³). The organic extract was washed with distilled water to neutrality and dried over magnesium sulphate. After removal of the solvent in vacuo the oily residue was dried over phosphorus pentoxide under high vacuum to give an oil (2.05 g; 75%).

Tetrafluoroborate. Following the above procedure, addition of 34% aqueous tetrafluoroboric acid (5 cm³, 24 mmoles) gave the tetrafluoroborate salt as an oil with approximately the same yield. $C_{10}H_{23}SBF_4$. The physical data of racemic perchlorate and tetrafluoroborate were identical with those of optically active dimethyl (+)-(S)-2-octylsulphonium tetrafluoroborate (see below).

Authentic dimethyl (+)-(S)-2-octyl sulphonium salts (+)-(S) **3** ($R_1 = R_2 = CH_3$). *Methyl 2-octyl sulphide* (−)-(*R*)-2-octanol, $[\alpha]_D^{20} = -9.45°$ (c = 5, EtOH), (o.p. 94.8%) gives[4b] quantitatively the corresponding tosylate $[\alpha]_D^{20} = -4.55°$ (c = 5, acetone) ([α] lit = −4° (c = 5, acetone)[4d] which was treated with lithium methyl thiolate in hexamethylphosphoramide[10] to give methyl (+)-(*S*)-2-octyl sulphide (70%) $[\alpha]_D^{20} = +9.95°$ (c = 11.8, $CHCl_3$) ([α] lit = +8.78° in the same conditions, (*cf* Ref. 4d)), $[\alpha]_D^{20} = +11.7°$ (c = 10, EtOH) estimated o.p. 94.8%. This sulphide was then methylated by two different routes.

Methylation by trimethyloxonium tetrafluoroborate.[5] Methyl (+)-(*S*)-2-octylsulphide (1.04 g; 6.5 mmoles) was added to a suspension of $Me_3O^+BF_4^-$ 980 mg; 6.6 mmoles) in methylene chloride (10 cm³). After stirring the mixture for three hours at room temperature, more solvent is added; the solution is thoroughly washed with distilled water and dried ($MgSO_4$). After removal of the solvent under vacuum, a colourless oil (1.08 g, 63%) is obtained $[\alpha]_D^{20} = +4.77°$ (c = 10, EtOH). 250 MHz ^{1}H NMR (d^6 acetone, TMS) δ = 3.72 (1 H, m); 2.98 (3 H, s); 2.93 (3 H, s); 1.53 (3 H, d, 7 H_z); 0.89 (3 H, t). 22.63 MHz ^{13}C NMR (d^6 acetone) δ = 49.2 (CH–S); 30.27–29.91–27.38–24.80–21.17 (CH_2); 20.78 and 18.91 (CH_3S); 12.43 and 12.11 (CH_3) IR (film) = 3010 (S); 2920 (VS); 2850 (S); 1455 (S); 1420 (S); 1080 (VS).

Methylation by anisole–methanesulphonic acid[3a]. To a stirred solution of methanesulphonic acid (3.2 cm³; 49.5 mmoles) was added successively methyl(+)-(S)-2-octyl sulphide (1.2 g; 7.5 mmoles) and anisole (1.38 cm³; 12.7 mmoles). After stirring for 3 days at room tenperature, the solution was washed with anhydrous ether and diluted with distilled water. 70% aqueous perchloric acid (1.5 cm³; 17.2 mmoles) or 34% aqueous tetrafluoroboric acid (3 cm³; 14.4 mmoles) was then added, and the aqueous solution is extracted with methylene chloride (3 × 20 cm³); the organic extract after washing and drying was concentrated under reduced pressure and the residue dried over P_2O_5 to give the perchlorate (1.75 g; 85%) $[\alpha]_D^{20} = +4.42°$ (c = 10, EtOH) or the tetrafluoroborate with the same yield $[\alpha]_D^{20} = +4.77°$ (c = 10, EtOH). NMR data as above. The dimethyl (+)-(*S*)-2-octylsulphonium Reineckate was prepared according to Ref. 11 m.p. = 130.5°C (from aq. acetone); $C_{14}H_{29}S_5N_6Cr$.

Authentic 1[(−)-(S)-2-octyl]thiolanium tetrafluoroborate **3** ($R_1R_2 = -(CH_2)_4$)

To a stirred solution of methanesulphonic acid (6.5 cm³: 0.1 mole) was successively added under nitrogen (+)-(S)-2-octanethiol $[\alpha]_D^{20} = +29.2°$ (c = 5, $CHCl_3$) (estimated o.p. 92%, $[\alpha]_{lit} = 32.8°$[12]) and 1,4-butanediol (0.95 cm³; 10 mmoles). The mixture was stirred at 50° for 10 h. The cooled solution was washed with anhydrous ether, diluted with distilled water, and treated with 34% aqueous tetrafluoroboric acid (excess). The aqueous solution is extracted with methylene chloride. After washing, the organic

layer is dried and the solvent evaporated under reduced pressure giving a colourless oil (2.145 g; 74%) $[\alpha]_D^{20} = -8.75°$ (c = 10, EtOH), $[\alpha]_D^{20} = -11.5°$ (c = 5, $CHCl_3$). 80 MHz ^{1}H NMR ($CDCl_3$, TMS) δ = 3.6 (5 H, b.m.); 2.4 (4 H, b.m.); 1.52 (3 H, d, 7 Hz) 0.90 (3 H, t). 22.63 MHz ^{13}C NMR ($CDCl_3$, TMS) δ = 50.59 (CH–S); 41.07–39.97 (CH_2S); 32.3–31.10–28.45–25.41–22.11 (CH_2); 15.24 and 13.75 (CH_3). Reineckate[11] m.p. = 143.5° (from aq. acetone); $C_{16}H_{31}S_5N_6Cr$.

Authentic 1-[(−)-(S)-2-*octyl*] *thianium perchlorate* **3** ($R_1R_2 = -(CH_2)_{-5}$)

5-*Hydroxypentyl*-(+)-(S)-2-*octyl sulphide*. To a solution of (+)-(S)-2-octanethiol ($[\alpha]_D^{20} = +29.2°$ (c = 5, $CHCl_3$); $[\alpha]_D^{20} = +32.6°$ (c = 1.48, EtOH); $[\alpha]_{D\,lit}^{23} = +32.8°$ (c = 1.48, EtOH)[12]; o.p. 92%) (7 g, 48 mmoles) and triphenylmethane (100 mg, indicator) in dried ether (20 cm^3) and hexamethylphosphoramide (5 cm^3) under argon was added at 0° with stirring a solution of n-butyl-lithium in hexane until a red colouration appeared. A solution of 5-bromopentylacetate[13] (7.7 cm^3; 48 mmoles) dissolved in a mixture Et_2O–HMPA (30 cm^3, 1:1) was added. After stirring at room temperature for 15h, the solution was poured in ice water and extracted with ether. The organic layer was washed, dried and concentrated in vacuo. Ethyl alcohol (100 cm^3) and 2 N sodium hydroxide (45 cm^3) were added to the crude product. After 1 h 30 min at 50°, the solvent was removed in vacuo and the residue extracted with ether. The ether solution was washed, dried ($MgSO_4$) and concentrated. Distillation (125°/10^{-3} mm) afforded the product (6.16 g; 90%; pure by gas liquid chromatography). $[\alpha]_D^{20} = +11.65°$ (c = 5, $CHCl_3$). IR (film): 3340, 1455, 1375 and 1065 cm^{-1}. 90 MHz ^{1}H NMR ($CDCl_3$, TMS): δ = 3.62 (2 H, t); 2.73 (1 H, m); 2.52 (2 H, t); 1.8–1 (19 H, m) 0.87 (3 H, t.)

1-[(−)-(S)-*octyl*] *thianium perchlorate*

To a stirred solution of methanesulphonic acid (13 cm^3, 200 mmoles) was added the above hydroxyalkyl sulphide (2.32 g; 10 mmoles); after stirring 14 hr at 50°, the reaction mixture was cooled and washed with ether. Water was then added followed by 70% aqueous perchloric acid (1 cm^3; 11.5 mmoles). After extraction with methylene chloride and washing to neutrality, removal of solvent under vacuum afforded crystalline solid (2.45 g; 7.8 mmoles; 78%) which could not be recrystallised, m.p. = 55–7°. $[\alpha]_D^{20} = -14.4°$ (c = 5, $CHCl_3$). 250 MHz ^{1}H NMR ($CDCl_3$, TMS): δ = 3.82 (1 H, m); 3.52 (2 H, m); 3.37 (2 H, dxt, 12 Hz and 2 Hz); 2.34 (2 H, m); 1.54 (3 H, d, 7 Hz). 22.63 MHz ^{13}C NMR ($CDCl_3$) δ = 51.1 (CH–S); 35.44 and 34.66 (CH_2S); 31.3–28.71–25.6–22.62–22.43–22.17 (CH_2); 14.66 and 14.02 (CH_3). $C_{13}H_{27}SClO_4$.

Regiochemical purity of sulphonium salts: reaction with potassium benzoate[6]

To a stirred solution of the sulphonium salt (7.5 mmoles) in dry benzene (20 cm^3) was added anhydrous potassium benzoate (2.10 g; 15 mmoles). After stirring at 90° for three days the solvent was removed under reduced pressure; water is added to the residue and the aqueous solution was extracted with pentane. The benzoates were analysed by gas liquid chromatography (5% OV_1 and 5%FFAP). In the three cases (except for run 10, Table 1) the only octyl benzoate present was 2-octyl benzoate (comparison with an authentic sample). In the case of 2-octylthiolanium and 2-octylthianium salts, additional evidence for regiochemical purity of the sulphonium salt was given by the absence of isomeric esters resulting from the attack of potassium benzoate on the ring carbon vicinal to the sulphur. The proportions of attack at the secondary carbon (to give octyl-2 benzoate) were respectively 13, 5, and 60% for dimethyl 2-octyl sulphonium, 2-octylthiolanium, and 2-octyl thianium salts.

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