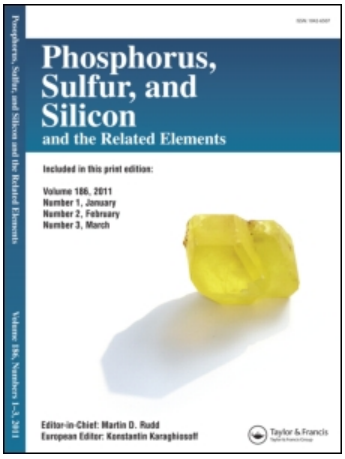

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MECHANISTIC ASPECTS OF CYCLIC SULPHONIUM SALT FORMATION AND HYDROLYSIS OF 1,*n*-HALO(ALKYLTHIO)ALKANES

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Cyclization rate constants for various 1,*n*-halo(alkylthio)alkanes X—$(CH_2)_n$—S—R with $n = 4$ and $n = 5$ were determined in CH_3CN, CH_2Cl_2, C_6H_{14}, $CDCl_3$ and H_2O/CH_3CN (9:1) at $T = 25°C$. The rate of formation of the five- and six-membered cyclic sulphonium salts depends on the halogen atom (I > Br > Cl), the number of methylene groups between sulphur and halogen ($n = 4 > n = 5$), on the alkyl group R and on the solvent. In aqueous CH_3CN hydrolysis becomes competetive. The hydrolysis rate constants of several 1,*n*-halo(alkylthio)alkanes with $n > 3$ were determined in water at $T = 25$ and 60°C and compared to those of some alkyl halides and the mustard derivative 1-chloro-2-methylthioethane. Hydrolysis of the chloro compounds is slower than of the bromo and iodo analogoues and depends on the number of methylene groups (*n*) between halogen and sulphur.

INTRODUCTION

Only little is known about the rates of cyclization of 1,*n*-halo(alkylthio)alkanes to the corresponding sulphonium salts.[1] Bennett *et al.* investigated the rates of cyclization of 1-chloro-5-methylthiopentane, 1-chloro-5-ethylthiopentane and 1-chloro-6-ethylthiohexane to the six- and seven-membered cyclic sulphonium compounds in acetone-water (1:1) at $T = 70–90°C$.[2,3] The cyclization of the corresponding bromo and iodo analogues and the 1-chloro-4-alkylthiobutanes could not be investigated until now, because these compounds were not available. Recently a simple synthesis under mild conditions for 1,*n*-halo(alkyl-thio)alkanes has been reported in the literature.[4] In order to gain more knowledge about the influence of other halides than chloride, the alkyl groups R and the solvent on the rates of cyclization, we investigated this reaction for a broad range of 1,*n*-halo(alkylthio)alkanes **1–3** in different solvents. Measurements of cyclization rates of these compounds in aqueous systems are difficult, because 1,*n*-halo-(alkylthio)alkanes undergo hydrolysis in water easily. In contrast to the well investigated hydrolysis of 1-chloro-2-methylthioethane (mustard derivative),[5–8] little is known about reactions of compounds **1–3** in aqueous systems. Böhme *et al.* determined the rate of hydrolysis of 1-chloro-3-ethylthiopropane in dioxane/water mixtures at $T = 100°C$.[9]

In this paper we report the results on these kinetic investigations of various compounds **1–3** in water and other solvents.

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$$X—(CH_2)_n—S—R$$

1 X = Cl

2 X = Br

3 X = I

$n = 3 - 6$; R = alkyl

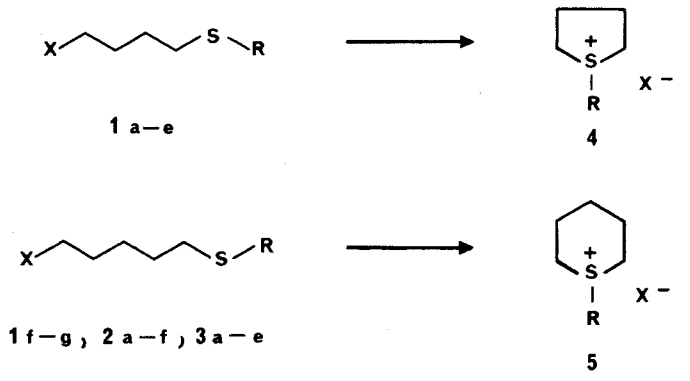
Compounds **1–3** were synthesized according to the literature.[4] Newly prepared compounds are referred to in the experiment part.

RESULTS AND DISCUSSION

The cyclization rate constants for compounds **1a–g**, **2a–f**, **3a–e** (cf. Table I) were determined by monitoring the decrease in their concentration in different solvents (acetonitrile, dichloromethane, hexane and deuterated chloroform, respectively), by means of GC and NMR, as well as via the formation of the corresponding cyclic sulphonium salts **4** and **5** (Scheme 1) in water-acetonitrile (9:1) by ion chromatography. All measurements were carried out at $T = 25°C$. The calculated first order rate constants are summarized in Table I. Cyclization rate constants of the 1-iodo- and 1-bromo-4-alkylthiobutanes could not be determined as these compounds cannot be isolated due to too rapid cyclization to the corresponding five-membered sulphonium compounds.

Cyclization rate constants in water-acetonitrile could only be determined for the chloro compounds. The bromo and iodo analogues undergo fast hydrolysis under these conditions. Cyclization of the 1-halo-6-alkylthiohexanes was not investigated due to the very slow rate of formation of the seven-membered cyclic sulphonium compounds at $T = 25°C$.

As seen from Table I the cyclization behaviour depends on the halogen atoms, the number of methylene groups between halogen and sulphur, the alkyl groups R at the sulphur atom and on the solvent. Regarding the halogen atom, cyclization rate constants decrease in the order I > Br > Cl. For the same halogen



SCHEME 1

TABLE I

Calculated rate constants for cyclization of **1a–g**, **2a–f**, **3a–e** in different solvents (5×10^{-2} M; $T = 25$°C)

Compound	X	n	R	k (s^{-1})				
				CH_3CN	CH_2Cl_2	C_6H_{14}	$CDCl_3$	H_2O/CH_3CN (9:1)
1a	Cl	4	CH_3	2.8×10^{-5}	2.1×10^{-5}	2×10^{-7}	2.0×10^{-5}	4.9×10^{-5}
1b	Cl	4	C_2H_5	1.7×10^{-5}	1.6×10^{-5}		1.7×10^{-5}	2.8×10^{-5}
1c	Cl	4	C_3H_7	7.4×10^{-6}	6.4×10^{-6}		6.4×10^{-6}	1.0×10^{-5}
1d	Cl	4	i-C_3H_7	4.6×10^{-6}	4.0×10^{-6}		4.2×10^{-6}	9.2×10^{-6}
1e	Cl	4	t-C_4H_9	2.4×10^{-6}	2.2×10^{-6}		2.1×10^{-6}	2.9×10^{-6}
1f	Cl	5	CH_3	3.4×10^{-7}	2.5×10^{-7}		2.6×10^{-7}	
1g	Cl	5	C_2H_5	2.0×10^{-7}	1.9×10^{-7}		1.7×10^{-7}	
2a	Br	5	CH_3	5.1×10^{-5}	5.7×10^{-5}	4.0×10^{-7}	5.6×10^{-5}	
2b	Br	5	C_2H_5	3.2×10^{-5}	3.2×10^{-5}		3.1×10^{-5}	
2c	Br	5	C_3H_7	1.9×10^{-5}	2.1×10^{-5}		2.1×10^{-5}	
2d	Br	5	i-C_3H_7	9.7×10^{-6}	9.5×10^{-6}		9.4×10^{-6}	
2e	Br	5	C_4H_9	1.7×10^{-5}	1.4×10^{-5}		1.5×10^{-5}	
2f	Br	5	t-C_4H_9	6.2×10^{-6}	5.2×10^{-6}		5.0×10^{-6}	
3a	I	5	C_2H_5	1.0×10^{-4}	6.4×10^{-5}	9.0×10^{-7}	6.3×10^{-5}	
3b	I	5	C_3H_7	7.0×10^{-5}	5.5×10^{-5}	6.9×10^{-7}	5.6×10^{-5}	
3c	I	5	i-C_3H_7	6.1×10^{-5}	5.1×10^{-5}	6.0×10^{-7}	5.1×10^{-5}	
3d	I	5	C_4H_9	6.4×10^{-5}	4.8×10^{-5}		4.6×10^{-5}	
3e	I	5	t-C_4H_9	5.5×10^{-5}	3.2×10^{-5}		3.2×10^{-5}	

atom the five-membered ring is found to be formed ≈80 times faster than the six-membered ring. A similar ratio of cyclization rates has been reported for the ring closure of 1-chloro-5-ethylthiopentane (**1g**) and 1-chloro-6-ethylthiohexane (**1o**) at 100°C [3]. Bulky alkyl groups on the sulphur atom, e.g. *t*-butyl instead of methyl, lower the cyclization rate constants by a factor of ≈100 (**1e** vs. **1a** or **2f** vs **2a**). As compared to other solvents (acetonitrile, dichloromethane, chloroform, water-acetonitrile) the rates of cyclization in hexane are much smaller. The open chain compounds **1–3** can be best stored in hexane solutions at −10°C as also the pure compounds cyclize rapidly.

The cyclic sulphonium salts **4** and **5** were characterized by elemental analyses and ^{1}H-NMR. Chemical shifts (^{1}H-NMR) for some selected examples are given in the experimental part.

The hydrolysis rate constants for the reaction fo compounds **1h–r**, **2f–p** and **3f–j** (cf. Table II) in water were determined by monitoring the conductivity (digital conductometer) as well as the halide ion concentration (ion chromatography) at $T = 25$ and 60°C, both methods being complementary and giving identical results. The solute concentration was kept below 5×10^{-4} M. Under these conditions the HX generated in the hydrolysis processes does not affect the rates of hydrolysis. The first order hydrolysis rate constants for **1h–r**, **2f–p** and **3f–j** are summarized in Table II. Hydrolysis rate constants for the 1-halo-4-alkylthiobutanes and 1-halo-5-alkylthiopentanes could not be determined due to the already described rapid cyclization of these substrates to the five- and six-membered sulphonium compounds **4** and **5**, respectively.

TABLE II

First order rate constants for hydrolysis of **1h–r**, **2f–p** and **3f–j** and selected haloalkanes (5×10^{-4} M) in water

Compound	X	n	r	k (s^{-1}) 25°C	k (s^{-1}) 60°C
1h	Cl	3	CH_3	7.9×10^{-8}	9.0×10^{-6}
1i	Cl	3	C_2H_5	5.3×10^{-8}	8.4×10^{-6}
1j	Cl	3	C_3H_7	2.4×10^{-8}	3.5×10^{-6}
1k	Cl	3	i-C_3H_7	2.2×10^{-8}	3.3×10^{-6}
1l	Cl	3	t-C_4H_9	1.8×10^{-8}	2.7×10^{-6}
1m	Cl	3	c-C_6H_{11}	3.6×10^{-9}	5.5×10^{-7}
1n	Cl	6	CH_3	1.6×10^{-8}	2.3×10^{-6}
1o	Cl	6	C_2H_5	1.0×10^{-8}	2.3×10^{-6}
1p	Cl	6	C_3H_7		9.2×10^{-7}
1q	Cl	6	i-C_3H_7		8.9×10^{-7}
1r	Cl	6	t-C_4H_9		7.4×10^{-7}
2g	Br	3	CH_3	4.3×10^{-6}	$2.3 - 10^{-4}$
2h	Br	3	C_2H_5	2.8×10^{-6}	2.1×10^{-4}
2i	Br	3	C_3H_7	3.8×10^{-6}	2.2×10^{-4}
2j	Br	3	i-C_3H_7	5.4×10^{-6}	2.1×10^{-4}
2k	Br	3	t-C_4H_9	2.4×10^{-6}	7.3×10^{-5}
2l	Br	3	c-C_6H_{11}	7.6×10^{-7}	7.2×10^{-5}
2m	Br	6	C_2H_5	2.4×10^{-7}	1.8×10^{-6}
2n	Br	7	C_2H_5	2.8×10^{-8}	1.6×10^{-6}
2o	Br	8	C_2H_5	1.3×10^{-8}	7.1×10^{-7}
2p	Br	10	C_2H_5	7.3×10^{-9}	1.2×10^{-7}
3f	I	3	CH_3	5.0×10^{-6}	3.1×10^{-4}
3g	I	3	C_2H_5	1.3×10^{-6}	6.4×10^{-5}
3h	I	3	i-C_3H_7	3.3×10^{-6}	1.4×10^{-4}
3i	I	3	t-C_4H_9	3.9×10^{-6}	5.0×10^{-5}
3j	I	3	c-C_6H_{11}	5.2×10^{-7}	2.1×10^{-5}
C_3H_7Cl				2.2×10^{-8}	
C_3H_7Br				2.6×10^{-7}	
$C_6H_{13}Cl$				1.8×10^{-8}	

As seen from Table II hydrolysis of the chloro compounds is slower than of the bromo and iodo analogues, these two latter reacting with similar rates. For the same halogen atom the rate constants decrease with increasing chain length (number of methylene groups) between sulphur and halogen. Both these effects correlate with the results obtained in the hydrolysis of primary haloalkanes.[10,11] By comparing the rate constants of e.g. 1-bromo-3-methylthiopropane (**2f**) ($k = 4.3 \times 10^{-6}\ s^{-1}$) and 1-bromopropane ($k = 2.6 \times 10^{-7}\ s^{-1}$) it can be seen that the hydrolysis of the borominated thioether **2f** is around 15 times faster. Comparison of the hydrolysis rate constants for the 1,n-halo(alkylthio)alkanes **1–3** with that for 1-chloro-2-methylthioethane (**6**) ($k = 1.48 \times 10^{-2}\ s^{-1}$ [5]) shows that hydrolysis of the mustard derivative **6** occurs much faster which probably is due to the pronounced anchimeric assistance by sulphur in **6**.

The results obtained show that 1,n-halo(alkylthio)alkanes undergo both cyclization and hydrolysis in aqueous systems. Depending on the number of methylene groups (n) between halogen and sulphur mainly cyclization ($n = 4, 5$) or hydrolysis ($n = 2, 3, \geq 6$) occurs.

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EXPERIMENTAL

General. NMR measurements were carried out on a Varian EM 360 (90 MHz) and a Bruker WM 270 (270 MHz) in $CDCl_3$ as solvent. Chemical shifts are given in ppm relative to TMS ($\delta = 0$) as internal standard. The mass spectra were measured at 70 eV on a Finnigan MAT mass spectrometer. GC-analyses were carried out on a 50 m SE 30 capillary column (Macherey–Nagel) using a temperature program (starting temperature: Cl-compounds: 80°C, Br-compounds: 100°C, I-compounds: 120°C; rate: 10°C/min) on a Varian gas chromatograph. The carrier gas was He, using a FID detector. Dodecane, tetradecane, pentadecane, 1,2-dicyanoethane and 1,4-dicyanobutane (Aldrich) were used as internal standards.

Conductivity measurements were performed on a Knick (Typ 600) digital conductometer.

The halide ion-concentration was measured on a AS 4 column (Dionex) on a Dionex 2010 ion chromatography, using a 2 mM aqueous solution of $Na_2CO_3/NaHCO_3$ (1:1).

Sulphonium salts were detected by ion chromatography according to [**12**] on a Opti-dbb ion pair column (Melz) on a Dionex 2010 ion chromatograph.

Starting materials. Compounds **1–3** were synthesized according to [**4, 13**]. The analytical data of the newly synthesized compounds **1f**, **1k–n**, **1p–r**, **2a** and **2j–l** are given in the following:

1-chloro-5-methylthiopentane (**1f**): MS (M^+): 152; ^{1}H-NMR: 1.8–2.1 (m; 6H), 2.1 (s; 3H; —S—*CH*$_3$), 2.6 (t; 2H; —S—*CH*$_2$—), 3.6 (t; 2H; Cl—*CH*$_2$—)
1-chloro-3-isopropylthiopropane (**1k**): MS (M^+): 152; ^{1}H-NMR: 1.3 (d; 6H; —CH(*CH*$_3$)$_2$), 2.1 (m; 2H; —S—CH$_2$—*CH*$_2$—), 2.6 (t; 2H; —S—*CH*$_2$), 2.8 (m; 1H; —S—*CH*—(CH$_3$)$_2$), 3.6 (t; 2H; Cl—*CH*$_2$—)
1-chloro-3-tert.butylthiopropane (**1l**): MS (M^+): 166; ^{1}H-NMR: 1.3 (s; 9H; —S—C—(*CH*$_3$)$_3$, 2.1 (m; 2H; —S—CH$_2$—*CH*$_2$), 2.6 (t; 2H; —S—*CH*$_2$—), 3.6 (t; 2H; Cl—*CH*$_2$—)
1-chloro-3-cyclohexylthiopropane (**1m**): MS (M^+): 192; ^{1}H-NMR: 1.2–1.6 (m; 10H), 2.1 (m; 2H; —S—CH$_2$—*CH*$_2$—), 2.4–2.8 (m; 3H), 3.6 (t; 2H; Cl—*CH*$_2$—)
1-chloro-6-methylthiohexane (**1n**): MS (M^+): 166; ^{1}H-NMR: 1.2–1.9 (m; 8H), 2.1 (s; 3H; —S—*CH*$_3$), 2.6 (t; 2H; —S—*CH*$_2$), 3.6 (t; 2H; Cl—*CH*$_2$—)
1-chloro-6-propylthiohexane (**1p**): MS (M^+): 194; ^{1}H-NMR: 1.1 (t; 3H; —CH$_2$—*CH*$_3$), 1.3–2.1 (m; 10 H), 2.6 (t; 4H; —*CH*$_2$—S—*CH*$_2$—), 3.6 (t; 2H; Cl—*CH*$_2$—)
1-chloro-6-isopropylthiohexane (**1g**): MS (M^+): 194; ^{1}H-NMR: 1.3 (d; 6H; (*CH*$_3$)$_2$—CH—), 1.5–2.1 (m; 8H), 2.6 (t; 2H; —*CH*$_2$—S—), 2.8 (m; 1H; —S—*CH*—(CH$_3$)$_2$), 3.6 (t; 2H; Cl—*CH*$_2$—)
1-chloro-6-tert.butylthiohexane (**1r**): MS (M^+): 208; ^{1}H-NMR: 1.3 (s; 9H; —S—C(*CH*$_3$)$_3$), 1.5–2.1 (m; 8H), 2.6 (t; 2H; —*CH*$_2$—S—), 3.6 (t; 2H; Cl—*CH*$_2$—)
1-bromo-5-methylthiopentane (**2a**): MS (M^+): 198, 196; ^{1}H-NMR: 1.4–2.1 (m; 6H), 2.1 (s; 3H; —S—*CH*$_3$), 2.6 (t; 2H; —S—*CH*$_2$—), 3.5 (t; 2H; Br—*CH*$_2$—)
1-bromo-3-isopropylthiopropane (**2j**): MS (M^+): 198, 196; ^{1}H-NMR: 1.3 (d; 6H; (*CH*$_3$)$_2$CH—), 2.1 (m; 2H; —CH$_2$—*CH*$_2$—CH$_2$—S), 2.6 (t; 2H; —*CH*$_2$—S—), 2.8 (m; 1H; —S—*CH*(CH$_3$)$_2$), 3.5 (t; 2H; Br—*CH*$_2$—)
1-bromo-3-tert.butylthiopropane (**2k**): MS (M^+): 212, 210; ^{1}H-NMR: 1.3 (s; 9H; —C(*CH*$_3$)$_3$), 2.1 (m; 2H; —CH$_2$—*CH*$_2$—CH$_2$—S—), 2.6 (t; 2H; —*CH*$_2$—S—); 3.5 (t; 2H; Br—*CH*$_2$—)
1-bromo-3-cyclohexylthiopropane (**2l**): MS (M^+): 238, 236; ^{1}H-NMR: 1.2–2.1 (m; 12H), 2.7 (t; 3H), 3.5 (t; 2H; Br—*CH*$_2$—)

^{1}H-NMR data (270 MHz; δ) of selected cyclic sulphonium salts **4** and **5** ($X^- = I^-$) in $CDCl_3$:
S-methyl-thiolanium salt (**4a**): 3.69 (m; 2H), 3.40 (s; 3H —S—*CH*$_3$), 2.50 (m; 2H).
S-ethyl-thiolanium salt (**4b**): 3.94 (q; 2H, —S—*CH*$_2$—CH$_3$), 3.67 (m; 2H), 2.50 (m; 2H), 1.52 (t; 3H).
S-isopropyl-thiolanium salt (**4d**): 4.22 (m; 1H; —S—*CH*—(CH$_3$)$_2$), 3.85 (m; 1H), 3.70 (m; 1H), 2.51 (m; 2H), 1.55 (d; 6H).
S-tert.butyl-thiolanium salt (**4e**): 3.93 (m; 1H), 3.50 (m; 1H), 2.57 (m; 1H), 1.64 (s; 9H).
S-methyl-thianium salt (**5a**): 3.95 (m; 1H), 3.84 (m; 1H), 3.38 (s; 3H; —S—*CH*$_3$), 2.23 (m; 1H), 1.96 (m; 1H), 1.88 (m;2H).
S-ethyl-thianium salt (**5b**): 3.95 (m; 1H), 3.94 (q; 2H; —S—*CH*$_2$—CH$_3$), 3.82 (m; 1H), 2.30 (m; 1H), 1.93 (m; 2H), 1.51 (t; 3H).

S-isopropyl-thianium salt (**5d**): 4.75 (m; 1H; —S—*CH*—$(CH_3)_2$), 4, 18 (m; 1H), 3, 62 (m; 1H), 2.39 (m; 1H), 2.00 (m; 1H), 1.80 (m; 2H).
S-tert.butyl-thianium salt (**5e**): 3.70 (m; 1H), 3.50 (m; 1H), 2.52 (m; 1H), 2.00 (m; 1H), 1.80 (m; 2H), 1.71 (s; 9H).

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