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Effect of solvent on the inversion of pyramidal sulfonium and selenonium compounds

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ABSTRACT: The effects of temperature and solvent on the *cis–trans* equilibrium and isomerization rates of different cyclic sulfonium and selenonium compounds were investigated by ^{1}H NMR spectroscopy. A non-dissociative process was considered to be the most probable mechanism for inversion of configuration. While the temperature had no apparent effect on the equilibrium, in which the *trans*-diastereoisomer dominated in all cases, changing the solvent from dimethylformamide to acetonitrile and to water led to increasing amounts of the *cis*-diastereoisomer. Additionally, the rate of stereomutation of the thiolanium compound was slowed by a factor of 2 and that of the selenolanium compound by a factor of 85. While the pyramidal (vertex) inversion is the most probable mechanism for the sulfonium compounds investigated, some evidence is presented that indicates that the selenonium compound could isomerize via an edge inversion mechanism. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: sulfonium compounds; selenonium compounds; *cis–trans* stereomutation; pyramidal inversion; edge inversion; isomerization kinetics; solvent effect

INTRODUCTION

Since the first synthesis of sulfonium and selenonium compounds by Cahours in 1865,[1] numerous investigations have focused on their preparation, stereochemistry and synthetic uses.[2] Some sulfonium compounds play an important role in biochemical processes, e.g. the natural coenzyme (*S*)-*S*-adenosyl-L-methionine.[3] Chiral tricoordinated sulfonium compounds can isomerize and lose their optical activity. In the case of (*S*)-*S*-adenosyl-L-methionine this process leads to a loss of biological activity.[4] Different mechanisms have been proposed for this isomerization.[5,6] A nucleophilic attack of the counterion (S_N2), followed by re-formation of the sulfonium compound, was suggested by Balfe *et al.* in 1930.[7] The second mechanism, a heterolytic scission (S_N1) into a neutral sulfide and a carbocation with successive recombination, may occur in the case of stabilized carbocations.[8] However, the most probable process is a non-dissociative one, pyramidal inversion (vertex inversion) via a trigonal-planar transition state. The rate of this process was found to depend largely on steric factors, bulky substituents having an accelerating effect.[9] The isomerization of cyclic sulfonium compounds is hindered.[10] On the other hand, solvents[11] and electronic influences of the substitutents[9] have only a minor effect on the rate of this stereomutation.

Edge inversion is another possible mechanism for the inversion at three-coordinate atoms. In this case the transition state has a T-shaped structure with an empty p-orbital. This mechanism was proved to be responsible for the inversion of some phosphorus,[12,] antimony and bismuth[13] compounds. However, so far no example of edge inversion has been found for group 16 elements and it seems to be unlikely for simple sulfonium compounds.[6]

The corresponding selenonium compounds have been reported to show increased configurational stability.[14] Recently, we reported the first measurement of the stereomutation rate of a selenonium compound. The inversion of configuration in water was about 50 times slower than that of the corresponding sulfonium compound. Unexpectedly, a 70-fold acceleration of the stereomutation rate of the selenonium compound was found in *N,N*-dimethylformamide (DMF).[15] The aim of this work was to study further the effect of the solvent on the inversion of configuration of selected sulfonium and selenonium compounds.

RESULTS AND DISCUSSION

The stereomutation of sulfonium and selenonium compounds has mostly been followed by measuring changes

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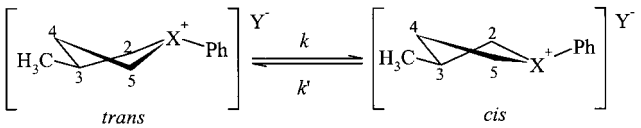
in the optical rotation. However, configurational changes of the cyclic chalcogenonium compounds **1–3** (Scheme 1) could easily be analyzed by NMR spectroscopy owing to the second stereogenic centre at C-3. Additionally, decomposition reactions of the substrates upon heating can be investigated. The synthesis of **1–3** by acidic condensation of aliphatic 1,4-diols with benzenethiol or -selenol gave mixtures of *cis*-and *trans*-diastereoisomers. For the sulfonium compounds **1** and **2**, the *trans*-configuration was assigned to the main product by comparison with literature data.[16] Because of the similarity of the NMR spectra, the same assignment was assumed for the selenonium compound **3**. For cyclic five-membered sulfonium compounds, a half-chair conformation was suggested in the literature.[16] The *trans*-diastereoisomer could be further enriched by fractional crystallization in all three cases.



1: X = S, Y = ClO_4
2: X = S, Y = PF_6
3: X = Se, Y = PF_6

Scheme 1

Upon heating, the *trans*-diastereoisomer isomerized to the *cis*-diastereoisomer until thermal equilibrium was reached. We followed this process by the relative change in signal intensities of the methyl group in the ^{1}H NMR spectra of **1–3**. We assumed a non-dissociative mechanism to be most probable one for inversion of configuration at the chalcogenonium centre since, on the one hand, an S_N1 mechanism would lead to unstable carbocations and, on the other, the present counterions are poor nucleophiles for an S_N2 mechanism. On the basis of first-order kinetics we determined the rate constants k by linear regression with

$$kt = \frac{K}{K+1}\ln\frac{(K+1)x_{t=0}-1}{(K+1)x_t-1} \quad (1)$$

where t = time, $x_{t=0}$ and x_t = partial quantities of the *trans*-isomer at time $t = 0$ and t, respectively, and K = equilibrium constant, and the activation parameters by applying the Eyring equation.

Table 1 summarizes the kinetic and thermodynamic parameters for the *trans* → *cis* stereomutation at the chalcogenonium centre for **1–3**. The different counterions of **1** and **2** should have only a very small influence on the process due to dissociation in solution. The values of the equilibrium constants K show little temperature dependence but, in contrast, vary with the chalcogen atom and the solvent. For the selenolanium compound **3** a higher amount of the *cis*-diastereoisomer is found in the thermal equilibrium in comparison with the thiolanium compounds **1** and **2**. This indicates a lengthening of bonds due to the larger selenium atom, which enlarges the geometry of the ring and decreases intra-ring interactions in the *cis*-diastereoisomer. Changing the solvent from DMF to acetonitrile and finally to water leads to increasing amounts of the *cis*-diastereoisomer in the thermal equilibria. The same behaviour had formerly been found for thianium compounds in the solvents acetonitrile and water.[17]

Comparing the rate constants k of the *trans* → *cis* stereomutation, it is obvious that the selenolanium ion **3** isomerizes more slowly than the thiolanium ions **1** and **2**. When a pyramidal inversion mechanism is assumed, the results are in accordance with *ab initio* MO calculations, where higher activation energies for the trimethylselenonium ion compared with the trimethylsulfonium ion had been found.[18] Changing the solvent from water via acetonitrile to DMF has an accelerating effect on the stereomutation velocity. However, for the sulfonium compounds **1** and **2**, k increases by a factor of

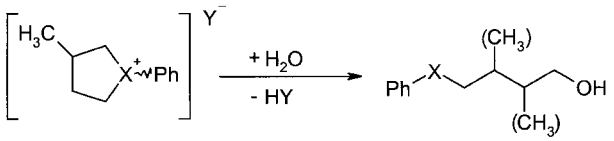
Table 1. Kinetic and thermodynamic parameters for the *trans* → *cis* stereomutation of the chalcogenonium salts *1–3*

Compound (solvent)	θ (°C)	K[a]	k ($10^{-s}s^{-1}$)	ΔG_{353}^{m} (kJ mol^{-1})
2 ([d_7]DMF)	60.0	0.453 ± 0.029	1.30 ± 0.11	
	80.0	0.460 ± 0.072	8.58 ± 1.17	114.5
	100.0	0.536 ± 0.216	82.3 ± 3.0	
3 ([d_7]DMF)	80.0	0.773 ± 0.116	7.02 ± 0.27	115.1
	80.0	0.616 ± 0.123[b]	5.90 ± 2.50[b]	115.6[b]
	100.0	0.763 ± 0.040	76.2 ± 0.6	
	120.0	0.763 ± 0.123	370 ± 46	
2 (D_3CCN)	80.0	0.581 ± 0.040	5.45 ± 0.31	115.8
3 (D_3CCN)	80.0	0.812 ± 0.073	0.611 ± 0.034	122.2
1 (D_2O)	80.2	0.618 ± 0.047[b]	3.91 ± 0.26[b]	116.9[b]
3 (D_2O)	80.3	—[b,c]	0.082 ± 0.33[b,d]	128.2[b]

[a] K = [*cis*]/[*trans*].
[b] Lit.[15]
[c] Not determinable owning to decomposition reactions.
[d] Based on the assumption of $K = 0.643$.

approximately 2, which confirms literature results,[11] whereas in the case of **3** k increases by a factor of about 85. This is equivalent to a decrease in the free enthalpy of activation, which is shown in Fig. 1.

The large solvent effect on the velocity of the stereomutation of the selenonium compound **3** is in striking contrast to the pyramidal inversion mechanism, which should not depend on the solvent.[6] On the other hand, an edge inversion mechanism should be accelerated by nucluophilic solvents, because the vacant p-orbitals appearing at the T-shaped transition state can be stabilized by coordination of external nucleophiles.[13] Because of this, stereomutation should proceed faster in strong nucleophilic solvents such as *N*,*N*-dimethylformamide, which has a donor number of 31.0 kcal mol^{-1} (1 kcal = 4.184 KJ), than in acetonitrile (14.1 kcal mol^{-1}).[19] Furthermore, the barriers for edge inversion decrease within a group with increasing atomic weight.[13] Thus, the edge inversion of selenonium compounds is more likely than that of sulfonium compounds. Apart from isomerization, side reactions, i.e. decomposition reactions, are taking place. This is indicated by the appearance of two doublets between $\delta = 0.9$ and 1.0 in the ^{1}H NMR spectra of **1**–**3** and a shift of the signals of the aromatic H-atoms of about $\Delta\delta = 0.5$. New signals in the ^{13}C NMR spectra around $\delta = 62$ point to the formation of alcohols (see Scheme 2). The decomposition is more pronounced in DMF than in acetonitrile, being dependent on the water content of the solvent. In conclusion, we assume S_N2 reactions of the chalcogenonium compounds with water to be the cause of decomposition. The selenonium compound **3** reacts faster than the sulfonium compounds **1** and **2**, probably because selenoethers are better leaving groups.



1: X = S, Y = ClO_4
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Scheme 2

These side reactions are irrelevant for the experiments performed in CD_3CN because at the end of the kinetic run less than 2% of **2** and **3** had decomposed. On the other hand, the decomposition reactions are much faster in DMF. Nevertheless, model calculations performed analogously to the literature[15] show that their influence on the stereomutation rate was negligible.

CONCLUSION

Water acts as an inhibitor of the *trans* → *cis* stereomutation of **1**–**3** while at the same time favouring the *cis*-configuration, whereas DMF accelerates this stereomutation favouring the *trans*-configuration. The changes observed are much stronger for the selenium than for the sulfur compounds. A possible explanation could be the assumption of an edge inversion rather than a pyramidal inversion mechanism in the case of selenium. This process should be considerably accelerated by nucleophilic solvents such as DMF. Further research is needed to elucidate the interactions between tricoordinated selenonium compounds and solvent molecules.

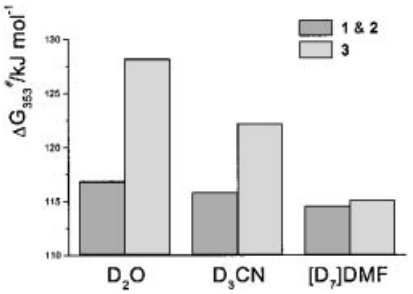

Figure 1. Free enthalpies of activation at 80 °C for the *trans* → *cis* isomerization of the thiolanium compounds **1** and **2** and the selenolanium compound **3** as a function of the solvent

EXPERIMENTAL

General. Melting-points were recorded on a Büchi 510 apparatus and are uncorrected. IR spectra were measured as KBr disks under normal conditions on a Perkin-Elmer FTIR 1750 Fourier transform infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained at ambient pressure and temperature on a Bruker AC 200 spectrophotometer at 200.14 and 50.323 MHz, respectively, using the non-volatile sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standard. Tentative assignments are marked with an asterisk.

Synthesis. Benzenethiol and hexafluorophosphoric acid were obtained commercially (Merck, Fluka) and used without further purification. 2-Methylbutane-1,4-diol was prepared by reduction of methylsuccinic acid with lithium aluminium hydride following van Bekkum *et al.*,[20] and benzeneselenol according to Foster.[21]

*cis/trans-3-Methyl-1-phenylthiolanium-hexafluorophosphate (**2**).* Following a patented procedure,[22] aqueous hexafluorophosphoric acid (75%, 32 g, 0.164 mol) was added to a mixture of 2-methylbutane-1,4-diol (4.0 g, 0.038 mol) and benzenethiol (3.8 g, 0.034 mol) in a polyethylene bottle. This mixture was stirred for 16 h at 50 °C and 3 d at 20 °C. Water was added carefully (20 ml) and the mixture was extracted with dichloromethane

(5 × 20 ml). The combined extracts were washed with aqueous sodium hydrogencarbonate (2 × 10 ml) and water (10 ml) and dried with magnesium sulfate. Removal of the solvent by distillation gave a solid which was washed with a mixture of dichloromethane (5 ml) and pentane (10 ml). The product was recrystallized from ethanol to give colourless needles of **2** (2.1 g, 0.0065 mol, 19%); m.p. 75–78 °C [*trans*: *cis* = 75.6:24.4 (^{1}H NMR)].

trans-**2**: ^{1}H NMR ([d_7]DMF): δ = 1.25 (3 H, d, ^3J = 6.2 Hz, CH_3), 1.99 [1 H, dtd, ^2J = 13.3, ^3J(3-H) = ^3J(5-H_b) = 10.3, ^3J(5-H_a) = 8.0 Hz, 4-H_a], 2.46–2.81 (1 H, m, 4-H_b) 2.82–3.11 (1 H, m, 3-H), 3.47 (1 H, dd, ^2J = 13.5, ^3J = 10.3 Hz, 2-H_a), 3.72 [1 H, ddd, ^2J = 13.1, ^3J(4-H_a) = 10.3, ^3J(4-H_b) = 7.1 Hz, 5-H_b], 3.82 [1 H, ddd,^2J = 13.5, ^3J = 6.5, ^4J(4-H_b) = 1.2 Hz, 2-H_b], 4.15 [1 H, ddd, ^2J = 13.1, ^3J(4-H_a) = 8.0, ^3J(4-H_b) = 3.5 Hz), 5-H_a], 7.56–7.96 (5 H, m, Ar-H) ppm. ^{13}C NMR ([d_7]DMF): δ = 18.9 (CH_3), 38.6 (C-4), 40.2 (C-3), 50.9 (C-5), 55.3 (C-2), 129.5 (C-1′), 132.2 (C-2′/6′)*, 133.4 (C-3′/5′)*, 137.0 (C-4′) ppm.

cis-**2**: ^{1}H NMR ([d_7]DMF): δ = 1.36 (3 H, d, ^3J = 6.4 Hz, CH_3), 2.16–2.41 (1 H, m, 4-H_a), 2.60–3.12 (2 H, m, 4H_b/3-H), 3.33 (1 H, dd,^2J = 12.5, ^3J = 11.3 Hz, 2-H_a), 3.74–4.17 (2 H, m, 5-H_b/2-H_b), 4.28 [1 H, ddd, ^2J = 12.1, ^3J(4-H_a) = 7.7, ^3J(4-H_b) = 1.0 Hz, 5-H_a], 7.52–7.90 (5 H, m, Ar-H) ppm. ^{13}C NMR ([d_7]DMF): δ = 19.1 (CH_3), 38.5 (C-4), 41.2 (C-3), 50.4 (C-5), 56.6 (C-2), 129.7 (C-1′), 132.5 (C-2′/6′)*, 133.6 (C-3′/5′)*, 136.9 (C-4″) ppm.

cis-/trans-**2**: IR (KBr): ν = 2969 (w, CH), 1475 (w, Ar), 1444 (m, Ar), 840 (st, PF_6^-), 752 (m, Ar), 684 (m, Ar), 559 (st, PF_6^-), cm^{-1}.

Fractional crystallization from ethanol led to a further enrichment of *trans*-**2**; m.p. 82–84 °C [*trans*: *cis* = 86.6:13.4 (^{1}H NMR)].

*cis/trans-3-Methyl-1-phenylselenolanium-hexafluorophosphate (**3**).* The synthesis was performed as decribed[15] using 2-methylbutane-1,4-diol, benzeneselenol and aqueous hexafluorophosphoric acid; yield 34%, m.p. 74–76 °C [*trans*: *cis* = 75.1:24.9 (^{1}H NMR)]. Fractional crystallization from ethanol led to a further enrichment of *trans*-**3**; m.p. 89–91 °C [*trans*: *cis* = 86.1:13.9 (^{1}H NMR)].

Kinetic measurements. Solutions of the chalcogenonium salts were prepared and the non-volatile $Me_3Si(CH_2)_3SO_3Na$ was added as internal standard. The samples were filled in NMR tubes, which were sealed and put into thermostated polyethylene glycol baths. After suitable time intervals, the samples were cooled and the NMR spectrum was recorded in the pulse Fourier transform mode (below: SW = sweep width in ppm, TD = number of points of FID, AQ = acquisition time in s, SI = number of points of spectrum and NS = number of scans). The kinetic runs comprised 5–12 measurements and were finished with reaching the thermal equilibrium. Integration of the signals of the methyl groups attached to the ring C-3 atom led to the relative amounts of the *cis*- and *trans*-isomer. The rate constants were obtained from linear regression using Eqn. (1). The correlation coefficients were in most cases better than 0.995. The free enthalpy of activation was calculated by the Eyring absolute kinetic equation.

2 (30.4 mg) and standard (3.2 mg) in [d_7]DMF (3.0 ml); θ 60.0 ± 0.6, 80.0 ± 0.8, and 100.0 ± 0.9 °C; SW 8.99, TD 16384, AQ 4.555, SI 16384, NS 40; integration of doublets δ_H (*trans*-**2**) 1.23 and δ_H (*cis*-**2**) 1.30.

3 (33.2 mg) and standard (3.2 mg) in [d_7]DMF (3.0 ml); θ 80.0 ± 0.8, 100.0 ± 0.9, and 120.0 ± 1.0 °C; SW 8.99, TD 16384, AQ 4.555, SI 16384, NS 40; integration of doublets δ_H (*trans*-**3**) 1.25 and δ_H (*cis*-**3**) 1.29.

2 (5.4 mg) and standard (0.7 mg) in D_3CCN (0.5 ml); θ 80.0 ± 0.8 °C; SW 8.19, TD 16384, AQ 4.997, SI 16384, NS 40; integration of doublets δ_H (*trans*-**2**) 1.24 and δ_H (*cis*-**2**) 1.32.

3 (5.4 mg) and standard (0.8 mg) in D_3CCN (0.5 ml); θ 80.0 ± 0.8 °C; SW 8.19, TD 16384, AQ 4.997, SI 16384, NS 40; integration of doublets δ_H (*trans*-**3**) 1.22 and δ_H (*cis*-**3**) 1.26.

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