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Ring-chain tautomerism in spiro-1,3-oxathianes

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Abstract

The ring-chain tautomerism of spiro-1,3-oxathianes, in solution and in the solid phase is revealed. The kinetic parameters of the reaction are determined by NMR investigations using the *trans–cis* isomerization of substituted spiro-1,3-oxathianes. © 2000 Elsevier Science Ltd. All rights reserved.

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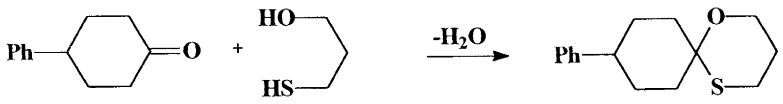
The stereochemistry of 1,3-oxathiane rings reveals peculiar features. The chirality of the unsubstituted ring[1] is due to a virtual tri-coordinated chiral centre[2] and surprisingly close values of many properties of 1,3-oxathianes to those of the average of the values measured for similar 1,3-dioxanes and 1,3-dithianes have been observed.[1]

A few examples of the isomerization of *cis* and *trans* 1,3-oxathiane derivatives have been reported (for 2,4,6-trimethyl-1,3-oxathiane[3,4] and 2-ethyloxycarbonyl-4,6-dialkyl-1,3-oxathianes[5]). These isomerization reactions were run in CCl_4, using BF_3–OEt_2 complex as catalyst, at 20–70°C and the equilibrium was reached in several days. The isomerization involved the opening of the heterocycle to give the open-chain form followed by closure of the ring and the formation of both diastereoisomers in a ratio determined by the different energies of the two structures.



1

Scheme 1.

The ring-chain tautomerism of spiro-1,3-oxathiane derivatives has now been investigated on 9-phenyl-1-thia-5-oxaspiro[5.5]undecane **1**. The compound was obtained (under equilibrium conditions) as a

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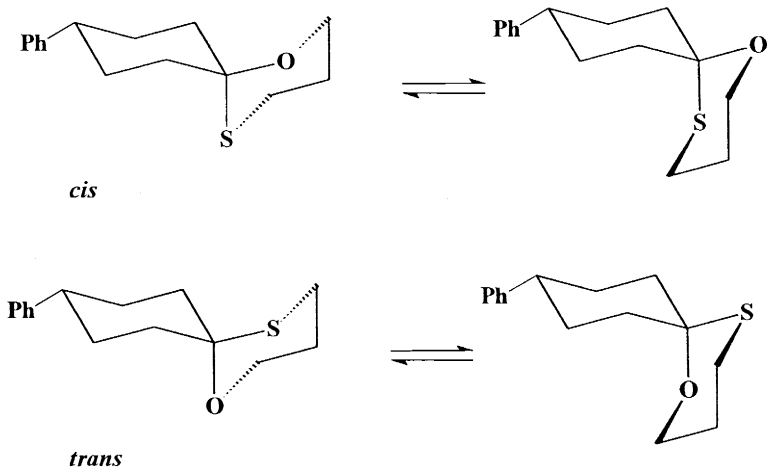
mixture of *trans* and *cis* isomers (solid; mp=90–92°C; *trans/cis*=1.38) by the reaction of 3-mercapto-1-propanol with 4-phenylcyclohexanone (Scheme 1).

The phenyl group is in equatorial position in both the *cis* and *trans* isomers of compound **1**, while the sulfur atom belonging to the heterocycle occupies the axial position (in the cyclohexane ring) in the *cis* isomer and the equatorial orientation in the *trans* one. Both diastereoisomers have a semiflexible structure, the cyclohexane ring is anancomeric (the Ph is the 'holding group'), whereas the heterocycle is flipping (Scheme 2).



Scheme 2.

The ^{1}H NMR spectrum of the mixture of isomers (Fig. 1) shows the protons at positions 2 and 4 of each isomer as two multiplets (overlapping doublet of doublet of doublets) the more deshielded one belonging to the protons at position 4 (*trans*: δ_4=3.89, δ_6=2.93; *cis*: δ_4=3.98, δ_6=2.83 ppm).

The equilibrium ratio between the *trans* and *cis* isomers (about 60:40) was determined from the intensities of the signals in the ^{1}H NMR spectrum of the product and it is in agreement with the ratio calculated considering the A-values reported for a methoxy (0.55–0.75 kcal/mol)[6] and a methylmercapto group (1 kcal/mol)[6] located in a cyclohexane ring. The *trans* isomer (solid; mp=129–130°C) was separated from the mixture of diastereoisomers by flash chromatography (hexane:ethyl acetate 12:1; R_f (*trans*)=0.4, R_f (*cis*)=0.3). The NMR spectrum recorded immediately after the separation exhibited only one set of signals confirming the success of the chromatographic separation. After storing for three weeks, ^{1}H NMR analysis of the same sample revealed the presence of both isomers in equilibrium. The isomerization reaction in the solid phase (due to the presence of traces of water and unreacted 3-mercapto-1-propanol) was confirmed by changes of the melting point of the sample. The isomerization involves, as the first step, the opening of the ring and the formation of an open-chain form, followed by ring closure leading to both the *cis* and *trans* isomers. These two structures are in equilibrium via the open-chain form.

The kinetic parameters of the isomerization (Scheme 3) in $CDCl_3$ were determined by NMR by recording the ^{1}H NMR spectra of the same sample over several periods of time (Fig. 1, Table 1) and by measuring the ratio between the isomers using the intensities of specific signals. The initial concentration of the single *trans* isomer was 9.74×10^{-2} M. The reaction was considered to be first order and the calculated values (using relations 1 and 2) of the constants are $k_1=8.71\times10^{-3}$ min^{-1} and $k_{-1}=1.20\times10^{-2}$ min^{-1}. The solvent ($CDCl_3$) was slightly acidic, the concentration of HCl being 3.34×10^{-4} M. Using neutralized and dried solvent, the equilibrium was reached in several days. The same result has been recorded in an experiment in which, to the neutralized solvent, a drop of water was added. In the

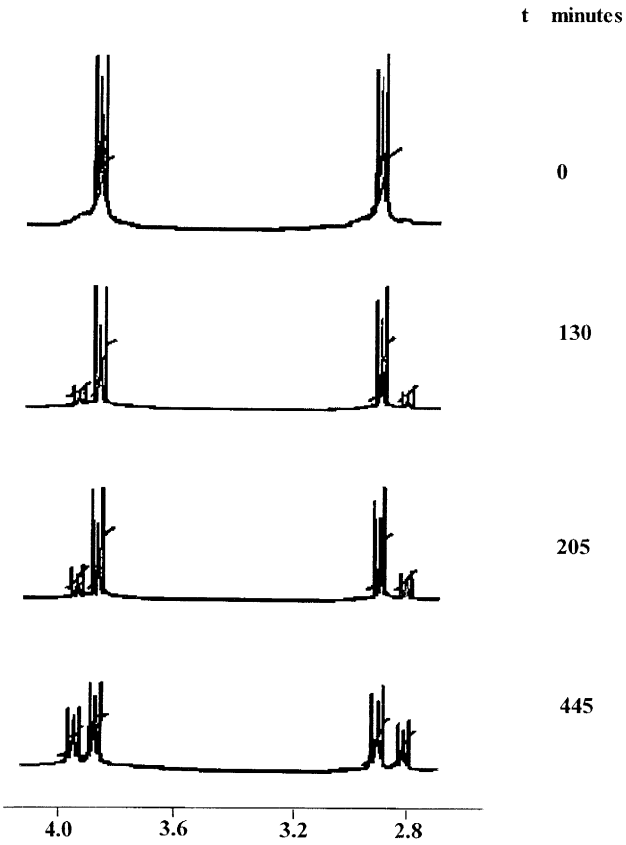
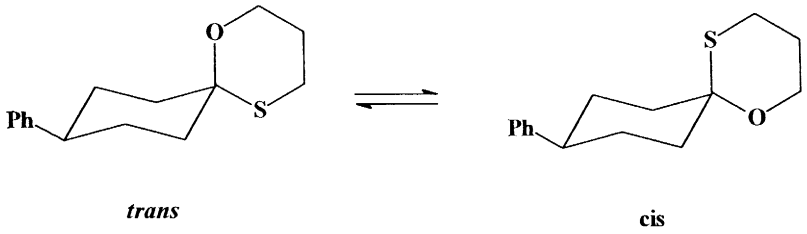


Fig. 1. ^{1}H NMR spectra at several mean times for compound **1**

experiment in which a drop of concentrated HCl is added to the solution of the pure *trans* isomer, the equilibrium is attained in a few minutes and the first recorded NMR spectrum showed the equilibrium composition already.

$$\ln\frac{x_e}{x_e - x} = (k_1 + k_{-1})\,.t \tag{1}$$

$$\frac{k_1}{k_{-1}} = K \tag{2}$$



trans **cis**

Scheme 3.

Where k_1 and k_{-1} are the direct and reversed reactions rate constants, K is the constant of equilibrium, x_e is the molarity of the *trans* isomer at equilibrium and x is the molarity of the same isomer at the 't' time.

Table 1
Data of kinetic measurements

Nr.	1	2	3	4	5	6	7	8	9
Time (minutes)	50	95	130	165	205	295	370	445	equil.
Ratio *trans/cis*	5.61	5.04	3.92	3.22	2.69	1.97	1.50	1.42	1.38

Conclusions: The *trans–cis* equilibration of spiro-1,3-oxathiane involves an equilibrium between the heterocycle and its open-chain form and proves ring-chain tautomerism for this type of compound. The rate of the equilibration reaction is strongly dependent on the acidity of the system. Ring-chain tautomerism can be reproduced in many substituted 1,3-oxathianes without being observed, the equilibration being between homomeric structures with a major contribution of ring form.

Experimental: ^{1}H NMR spectra were recorded at room temperature, using $CDCl_3$ as solvent, in 5 mm tubes using a Varian Gemini 300 Fourier transform NMR spectrometer equipped with a multinuclear probe operating at 300 MHz for protons and 75 MHz for carbon atoms. Compound **1** was prepared using a general method for the synthesis of 1,3-oxathiane derivatives.[7]

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