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Conformational Analysis of 2-Halotetrahydrothiopyran *S*-Oxides. Diminution of the Anomeric Effect in S(O)–C–X Compared to S–C–X Segments.[1]

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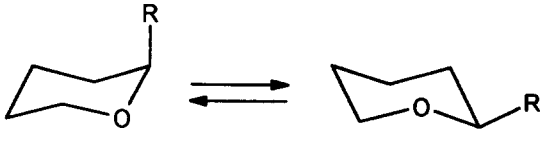
Abstract. Direct integration of appropriate ^{1}H and ^{13}C NMR signals in the low-temperature (below coalescence) spectra of the title heterocycles permitted the estimation of the equilibrium constant for their conformation equilibria. The small but definite predominance of the isomers with axial C–Br and C–Cl bonds in *cis*-2-halotetrahydrothiopyran *S*-oxide is contrary to expectation in terms of simple additivity rules, and supports the existence of a $n_{S(O)} \rightarrow \sigma^{*}_{C-X}$ stereoelectronic interaction, which seems to be, nevertheless, less important than the corresponding $n_S \rightarrow \sigma^{*}_{C-X}$ interaction in 2-halotetrahydrothiopyrans. The conformational preference of *trans*-2-halotetrahydrothiopyran *S*-oxides to adopt the diaxial conformation ($\Delta G°$ = ca. 0.3 kcal/mol) probably reflects the influence of repulsive electrostatic (dipole-dipole) interactions in the diequatorial conformer.

Introduction.

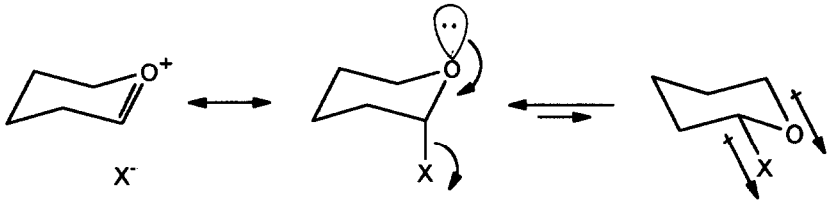
The conformational properties of monosubstituted tetrahydropyrans (e.g., eq 1) have been summarized by Eliel and coworkers.[2] The three most salient features of studies in this system are: (1) these heterocycles usually exist in the chair form, inverting at rates comparable with those determined in cyclohexane.[3] (2) Nonpolar substituents at C(2) show a large preference for the equatorial orientation, due of course to very close *syn* diaxial interaction with H(6ax) provoked by the short C–O bond distances.[4] (3) By contrast with nonpolar groups, electron-withdrawing substituents (such as halogen, RO, RS) at the 2-position prefer the axial orientation,[5] as a result of the anomeric effect.[6,7]



(1)

The origin of the anomeric effect in polar 2-substituted tetrahydropyrans has been accounted for in terms of (1) dipole-dipole repulsion in the equatorial conformer,[8-10] and (2) quantum mechanical

mixing of the lone pair orbital at oxygen and the antiperiplanar (ap) C–X antibond orbital ($n_O \rightarrow \sigma^*_{C-X}$ hyperconjugation) in the axial, stabilized conformer (eq 2).[11]

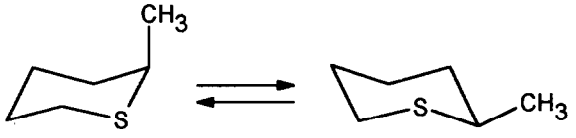


(2)

(repulsive)

The tetrahydrothiopyran (thiane, thiacyclohexane) ring also exists in a chair conformation with somewhat lower barrier for ring inversion ($\Delta G^{\neq}$ = 9.4 kcal/mol).[3,12]

The conformational free energy difference of methyl at the 2-position of tetrahydrothiopyran (ΔG° = - 1.42 kcal/mol;[13] eq 3) is lower than that in cyclohexane (ΔG° = - 1.74 kcal/mol[14]), and this is generally attributed to a reduction of *syn*-diaxial steric interactions owing to the long C–S bonds.[15]



(3)

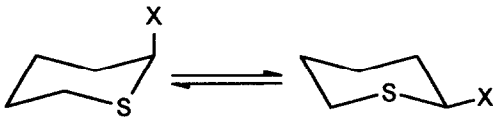
Electron-withdrawing substituents at C(2) in tetrahydrothiopyrans usually show a marked preference for the axial orientation (Table I) which supports the operation of a substantial anomeric effect.[16-18]

While solvent polarity effects (increased axial preference in less polar solvents) support the importance of dipole-dipole interactions in the stabilization of the axial conformer of 2-polar substituted tetrahydrothiopyrans,[17] the available evidence is also in line with the operation of a $n_S \rightarrow \sigma^*_{C-X}$ stereoelectronic stabilizing interaction in the axial conformers.[16-18]

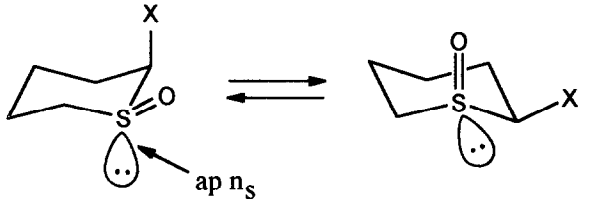
The aim of the present work was the examination of the conformational equilibria in several 2-polar substituted tetrahydrothiopyran *S*-oxides. It was reasoned that the reduced capacity of sulfur in sulfoxides to act as lone electron pair donor should be reflected in a substantial reduction of the $n_S \rightarrow \sigma^*_{C-X}$ hyperconjugative interactions which would otherwise stabilize the conformer with axial C–X in the conformational equilibria of the *cis* diastereomers (eq 4). Furthermore, no ap arrangement between n_S and C–X is possible in the *trans* diastereomers (eq 5). Thus, it might be anticipated that anomeric effects leading to a stabilization of axial C–X will be less important in S(O)–C–X segments than in S–C–X segments, at least as far as stereoelectronic arguments are concerned.[19,20]

The conformational equilibria depicted in eqs 4 and 5 should also take into account the slight but definite preference of the sulfinyl group to orient itself axially in thiane oxide (ΔG° = + 0.175 kcal/mol).[21]

Table I. Conformational Preference of Polar 2-Substituted Tetrahydrothiopyrans at Ambient Temperature in CCl_4.[16]



Substituent	$\Delta G°$ (kcal/mol)
Cl	1.75
OMe	1.53
O-*i*-Pr	1.35
O-*t*-Bu	0.74
SEt	0.42
S-*i*-Pr	0.25
S-*t*-Bu	-0.19



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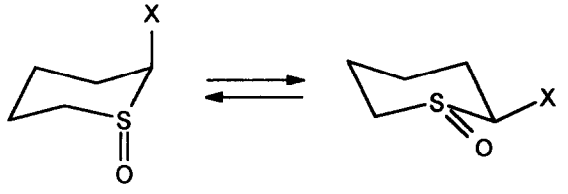


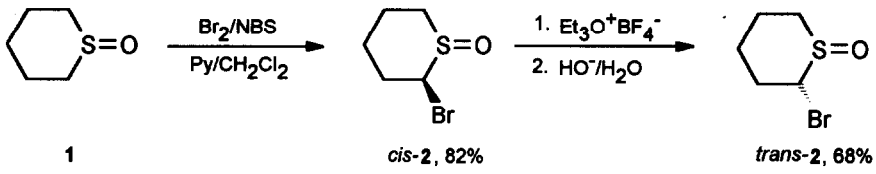
(5)

Results and Discussion.

A. Synthesis of the Compounds of Interest.

A1. *cis*- and *trans*-2-Bromotetrahydrothiopyran *S*-Oxide (*cis*- and *trans*-2).

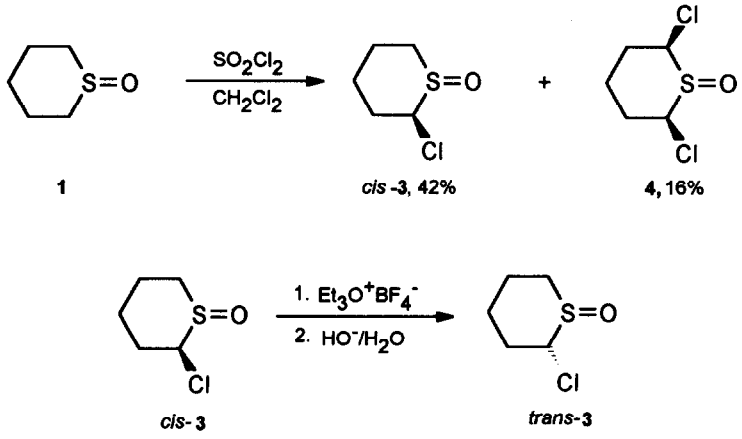
The α-halogenation of cyclic sulfoxides under basic conditions is usually a highly stereoselective reaction.[22] Indeed, as described by Iriuchijima and Tsuchihashi,[23] the bromination of thiane oxide **1** with Br_2, and *N*-bromosuccinimide/pyridine in methylene chloride afforded *cis*-2-bromotetrahydrothiopyran *S*-oxide (*cis*-**2**) in 82 % yield (Scheme I). The *trans* diastereomer (*trans*-**2**) was obtained via inversion of configuration at sulfur[24] by means of triethyloxonium tetrafluoroborate in methylene chloride at 0°C[25,26] (Scheme I).



Scheme I

A2. *cis*- and *trans*-2-Chlorotetrahydrothiopyran *S*-Oxide (*cis*- and *trans*-3).

According to the method of Iriuchijima, et al.[27] the reaction of thiane oxide **1** with sulfuryl chloride in pyridine and methylene chloride afforded *cis*-2-chlorotetrahydrothiopyran *S*-oxide (*cis*-**3**), as well as 2*c*,6*c*-dichlorotetrahydrothiopyran *r*-1-oxide (**4**, Scheme II) in a 72:28 ratio, and a combined yield of 58 %. *trans*-2-Chlorotetrahydrothiopyran *S*-oxide (*trans*-**3**) was prepared in 74 % chemical yield by inversion of the configuration at sulfur[24] with freshly prepared triethyloxonium tetrafluoroborate[25,26] (Scheme II).



Scheme II

B. Conformational Analysis.

Because of rapid ring inversion, the ambient temperature ^1H and ^{13}C NMR spectra of conformationally mobile heterocycles **1-4** present average signals for both the C–X axial and C–X equatorial conformers. Nevertheless, low-temperature (-75° to -100°C) NMR spectra do give rise to two sets of signals, which correspond to the axial and equatorial conformers. Table II lists the ^{13}C NMR chemical shifts for **1-4** at various temperatures.

Integration of the peak areas for each of the conformers in the spectra recorded well below the coalescence temperature afforded the equilibrium constants, K,[28] and the conformational free energy differences, $\Delta G^\circ = -RT\ln K$, which are summarized in Table III.

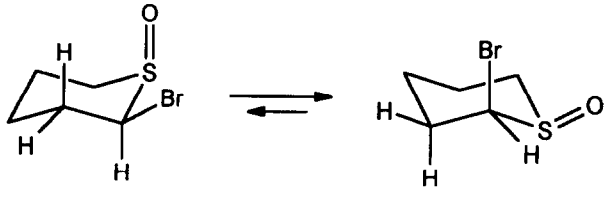
Table II. Room and Low Temperature C-13 Signal Assigments in Compounds **1-4** (ppm from TMS).

Compound	Solvent	C(2)	C(3)	C(4)	C(5)	C(6)
1	CD_2Cl_2[a]	49.30	19.34	25.06	19.34	49.30
1*ax*	CD_2Cl_2[b]	45.25	15.62	24.76	15.62	45.25
1*eq*	CD_2Cl_2[b]	52.22	23.37	24.34	23.37	52.22
cis-**2**	$CDCl_3$[a]	64.81	28.89	22.28	17.40	46.66
cis-**2**	CD_2Cl_2[a]	65.82	29.58	23.35	17.93	47.62
cis-**2**eq	CD_2Cl_2[b]	62.41	30.23	25.79	12.73	46.97
cis-**2**ax	CD_2Cl_2[b]	68.37	26.87	17.82	21.94	45.24
trans-**2**	CD_2Cl_2[a]	60.34	27.50	21.44	17.45	44.98
trans-**2**ax	CD_2Cl_2[b]	56.15	23.58	18.91	14.76	40.38
trans-**2**eq	CD_2Cl_2[b]	69.15	35.28	26.29	23.13	54.04[c]
cis-**3**	$CDCl_3$[a]	71.97	28.82	22.04	17.56	46.27
cis-**3**	CD_2Cl_2[a]	72.78	29.14	22.80	17.75	47.04
cis-**3**eq	CD_2Cl_2[b]	71.97	31.06	25.79	13.69	47.45
cis-**3**ax	CD_2Cl_2[b]	73.40	27.10	17.82	22.74	44.89
trans-**3**	$CDCl_3$[a]	67.29	26.13	19.67	16.40	43.38
trans-**3**	CD_2Cl_2[a]	68.72	27.43	20.74	17.60	44.70
trans-**3**ax	CD_2Cl_2[b]	64.21	23.43	18.02	14.61	40.30
trans-**3**eq	CD_2Cl_2[b]	78.38	34.71	25.49	22.99	52.84
4	CD_2Cl_2[a]	71.78	25.41	24.86	25.41	71.78
4	CD_2Cl_2[b]	71.40	24.94	24.45	24.94	71.40

[a]Room Temperature; [b]Low Temperature (-90°C); [c] Observed by solvent signals.

B1. ***cis*-2-Bromotetrahydrothiopyran *S*-Oxide (*cis*-2).**

The ambient-temperature low-field ^1H NMR spectrum of *cis*-**2** in CD_2Cl_2 shows a single peak at $\delta = 5.07$ ppm. At -90°C, however, two sets of signals are recorded: a double of doublets (dd) at $\delta = 4.87$, with $J_{anti} = 12.5$ Hz and $J_{gauche} = 2.6$ Hz, which was assigned to H(2ax) in conformer *cis*-**2**eq, and a near singlet at 5.51 ppm, ascribable to H(2eq) in conformer *cis*-**2**ax (eq 6).



cis-**2***eq* *cis*-**2***ax* (6)

Table III. Low-temperature Conformational Equilibria of 2-Substituted Thianes 1-Oxide and 2-Substituted Thianes.

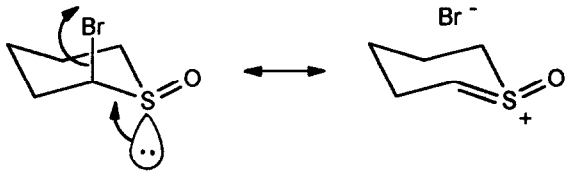
Substituent	Solvent	Temperature (°K)	K	ΔG° (kcal/mol)	Method
cis-Br	CD_2Cl_2	183	1.22	- 0.07[a]	^{1}H-RMN
cis-Br	CD_2Cl_2	167	1.21	- 0.06 ± 0.02	^{1}H-RMN, ^{13}C-RMN
trans-Br	CD_2Cl_2	183	0.43	+ 0.30 ± 0.03	^{1}H-RMN, ^{13}C-RMN
trans-Br	CD_2Cl_2	167	0.47	+ 0.25 ± 0.03	^{1}H-RMN
cis-Cl	CD_2Cl_2	183	1.13	- 0.04 ± 0.02	^{13}C-RMN
cis-Cl	CD_2Cl_2	167	1.05	- 0.02 ± 0.01	^{13}C-RMN
trans-Cl	CD_2Cl_2	183	0.47	+ 0.27 ± 0.04	^{1}H-RMN, ^{13}C-RMN
trans-Cl	CD_2Cl_2	167	0.55	+ 0.20 ± 0.04	^{1}H-RMN, ^{13}C-RMN

[a]Only one measurement.

The *cis*-2ax/*cis*-2eq conformer ratio was measured as 55:45, which allows the estimation of the conformational free energy difference in eq 8: $\Delta G^\circ_{183K} = -RT\ln K = -0.07$ kcal/mol. Essentially identical values of ΔG° were obtained by integration of the ^{13}C NMR signals for all carbons in the spectrum recorded at -106°C: $\Delta G^\circ_{167K} = -0.06 \pm 0.02$ kcal/mol.

The small but definite thermodynamic predominance of the isomer with equatorial sulfinyl group and axial C–Br bond is *not* in line with expectation based on simple additivity of the conformational preferences of isolated systems. Indeed, for thiane oxide (**1**) the axial conformer is favored by *ca.* 0.2 kcal/mol,[21] and equatorial bromocyclohexane is prefered by *ca.* 0.5 kcal/mol.[29] Thus, there must be an interaction between the neighboring sulfinyl and carbon-halogen moieties, which stabilizes *cis*-2ax by approximately 0.8 kcal/mol.[30]

Concerning the origin of this conformational effect, it is noted that the O=S–C–Br segment presents a *gauche* arrangement in both *cis*-2ax and *cis*-2eq (eq 6); therefore, the steric and electrostatic interactions should be fairly similar in these conformers.[31] Nevertheless, *cis*-2ax does present an antiperiplanar arrangement between the sulfur lone pair, $n_{S(O)}$, and the carbon-bromine bond. The hypothesis that a $n_{S(O)} \rightarrow \sigma^*_{C-Br}$ hyperconjugative interaction is responsible for the observed stabilization of *cis*-2ax (eq 7) seems reasonable.



(7)

B2. *cis*-2-Chlorotetrahidrothiopyran *S*-Oxide (*cis*-3).

The conformational behavior of this chloro derivative was quite similar to that reported for its bromo analogue *cis*-2 in the previous Section. For example, average signals for H(2), δ = 4.85 ppm,

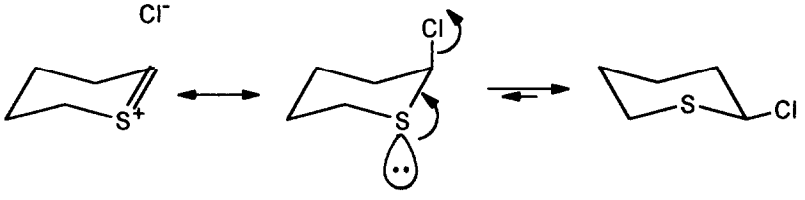
and for H(3), δ = 2.70 ppm, are observed in the ambient temperature ^{1}H NMR spectrum of *cis*-**3** (eq 8).

cis-3eq *cis*-3ax (8)

Nevertheless, H(2) presents two signals at temperatures lower than -50°C: δ = 5.30 and δ' = 6.65 ppm. Similarly, H(3) splits at T < -50°C into two signals at δ = 3.0, and δ' = 2.6 ppm. Integration of the corresponding signals indicated that the *cis*-3ax ⇌ *cis*-3eq equilibrium constant is very close to 1; that is, $\Delta G^\circ_{167K} \cong$ 0.0 kcal/mol. ^{13}C NMR data (Table II) confirmed these data: the 67.8 MHz spectra in CD_2Cl_2 at -90°C and -106°C showed two sets of carbon signals in 1.13 and 1.05 *cis*-3ax/*cis*-3eq rations; i.e., ΔG°_{183K} = - 0.05 kcal/mol, and ΔG°_{167K} = - 0.02 kcal/mol.[32]

Simple additivity of the conformational energies of chlorocyclohexane (ΔG° = - 0.5 kcal/mol)[29] and thiane oxide (ΔG° = + 0.2 kcal/mol)[21] affords a calculated ΔG° (eq 8) = + 0.7 kcal/mol, which by comparison with the observed $\Delta G^\circ \cong$ 0 suggests the manifestation of a conformational effect stabilizing *cis*-3ax to the extent of *ca.* 0.7 kcal/mol.[30] Here again, $n_{S(O)} \rightarrow \sigma^*_{C-Clax}$ hyperconjugation (cf. eq 7) might account for the origin of the stabilization.

It is revealing to compare the magnitude of the apparent $n_{S(O)} \rightarrow \sigma^*_{C-Cl}$ stereoelectronic effect operating in *cis*-**3**, worth *ca.* 0.7 kcal/mol,[33] and the corresponding magnitude of the apparent $n_S \rightarrow \sigma^*_{C-Cl}$ anomeric effect operating in 2-chlorothiane (eq 9 and Table I).[16] The experimentally determined predominance of the axial conformer ΔG° = + 1.75 kcal/mol)[16] suggests, by comparison with the equatorial predominance of chlorocyclohexane (ΔG° = - 0.5 kcal/mol)[29] a stabilizing stereoelectronic interaction worth *ca.* 2.25 kcal/mol in the axial conformer.[30] Thus, as originally anticipated (see Introduction) the sulfinyl lone pair seems to be a weaker donor to the antibonding C(2)–Cl orbital *vis-a-vis* the sulfide lone pair; that is, the occupied orbital $n_{S(O)}$ is of lower energy than n_S, and its two orbital-two electron interaction with σ^*_{C-Cl} is less effective due to diminished overlap.[33]

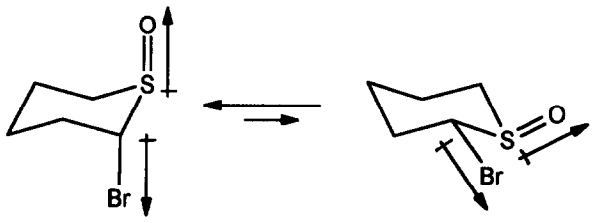


(9)

B3. *trans*-2-Bromotetrahydrothiopyran *S*-Oxide (*trans*-2).

The equilibrium constant, *K*, for the *trans*-diaxial ⇌ *trans*-diequatorial conformational equilibrium in this heterocycle (eq 10) was determined from integration of appropriate signals in the low-temperature (well below coalescence) ^{1}H and ^{13}C NMR spectra in solvent CD_2Cl_2. The results indicate a predominance of the diaxial isomer: *K* at 183 K = 0.43, and thus ΔG°_{183K} = + 0.30 kcal/mol; *K*

at 167 K = 0.47, and thus $\Delta G^{\circ}_{167K} = + 0.25$ kcal/mol. The small difference in ΔG° values is well within the experimental error limit,[32] so $\Delta G^{\circ}_{average} = + 0.28 \pm 0.03$ kcal/mol.



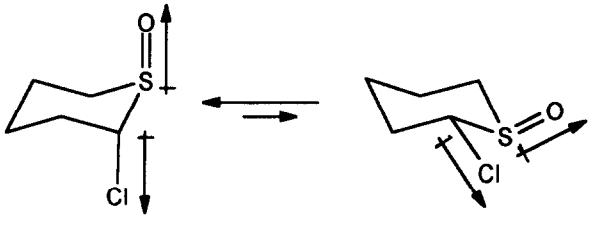
(10)

trans-2ax *trans*-2eq

Simple additivity of the conformational preferences for the axial sulfinyl group in thiane oxide, and for equatorial bromocyclohexane (see Section B1) gives a calculated $\Delta G^{\circ} = - 0.3$ kcal/mol in the absence of interactions between the bromine and the sulfinyl group. The difference with the experimentally observed $\Delta G^{\circ} = + 0.3$ kcal/mol shows the influence of a conformational effect which stabilizes *trans*-2ax (eq 10), and which probably originates from the favorable antiperiplanar orientation of the bond dipoles in this arrangement. By contrast, diequatorial *trans*-2eq suffers from a repulsive electrostatic interaction between dipoles (eq 10). This argument is supported by the qualitative observations of Iriuchijima, et al.[27] who found that *trans*-2eq actually predominates in polar solvents such as methanol, water and dimethylsulfoxide, whereas *trans*-2ax dominates the equilibrium in nonpolar media (CCl_4, $CDCl_3$, benzene).

B4. *trans*-2-Chlorotetrahydrothiopyran *S*-Oxide (*trans*-3).

Integration of the signals for H(2), and for all carbons in the ^1H and ^{13}C NMR spectra below coalescence temperature (at 270 MHz and 67.8 MHz, respectively, and in solvent CD_2Cl_2) afforded $\Delta G^{\circ}_{183K} = + 0.27 \pm 0.04$ kcal/mol and $\Delta G^{\circ}_{167K} = + 0.20 \pm 0.04$ kcal/mol (eq 11).



(11)

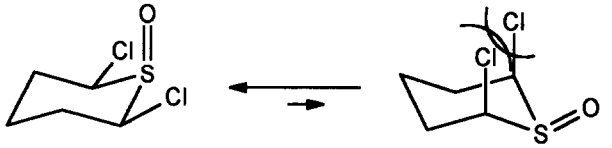
trans-3ax *trans*-3eq

These results are quite similar to those recorded for the bromo analogue *trans*-2 (previous Section), and indicate also here that dipole-dipole interactions provoke a stabilization of the diaxial isomer worth *ca.* 0.6-0.7 kcal/mol.[34] As discussed in Section B2, the anomeric effect responsible for the large predominance of axial 2-chlorothiane (eq 9) is much more important: *ca.* 2.25 kcal/mol. Of course, the $n_{S(O)}$ lone pair orbital in *trans*-2 and *trans*-3 is unable to orient ap to the acceptor C–X

bond in these heterocycles. Obviously, other potentially stabilizing two orbital-two electron interactions such as $n_{C-Cl} \rightarrow \sigma^*_{S-O}$ or $n_{S-O} \rightarrow \sigma^*_{C-Cl}$ do not offer a good donor/acceptor orbital combination.[6,7]

B5. *r*-1-Oxide-2*c*,6*c*-dichlorotetrahydrothiopyran (4).

The proton NMR spectra (270 MHz, CD_2Cl_2) of **4** present a double of doublets (J_{anti} = 9.2 Hz, and J_{gauche} = 2.6 Hz) for H(2) both at ambient temperature and at low temperature (167 K). This observation is in line with a conformational equilibrium in which the isomer with equatorial chlorines predominates to a large extent (eq 12) in order to avoid the 1,3-*syn* diaxial repulsive interaction between chlorines.



4-dieq 4-diax (12)

Experimental Section.

General Information. Proton NMR spectra were recorded on Jeol PMX-60SI (60 MHz), Varian EM-390 (90 MHz) or Jeol GSX-270 (270 MHz) spectrometers. ^{13}C NMR spectra were recorded on a Jeol FX-90Q (22.49 MHz) or Jeol GSX-270 (67.8 MHz) instruments operated in pulsed Fourier transform mode and locked on solvent deuterium. Chemical shifts are given in parts per million downfield from TMS. The temperature indicator of the Jeol GSX-270 spectrometer was calibrated by recording variable-temperature ^{13}C NMR spectra of an acetone/CCl_4 mixture and using the observed CH_3COCH_3 *vs.* CCl_4 $\Delta\delta$ values for assessment of temperature.[35] Deuterated solvents ($CDCl_3$, CD_2Cl_2 or THF-d_8) were purchased from Aldrich.

Flasks, stirring bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12h at 120°C and allowed to cool in a desiccator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.[36]

The purification of reaction products was carried out by fractional distillation, recrystallization from suitable solvents, and by means of flash chromatography.[37]

Melting points were determined with a Mel-Temp apparatus in an open capillary tube, and are uncorrected.

Tetrahydrothiopyran S-Oxide **(1)** was prepared by oxidation of the corresponding sulfide[38] according to the method of Leonard and Johnson.[39] ^1H NMR (270 MHz, CD_2Cl_2) δ 1.45-1.70 (m, 4H, $H_{3,5trans}$ and H_4), 2.0-2.25 (m, 2H, $H_{2,6trans}$), 2.60-3.0 (m, 4H, $H_{2,6cis}$ and $H_{3,5cis}$). ^{13}C NMR (67.8 MHz, CD_2Cl_2) δ 19.4 ($C_{3,5}$), 25.1 (C_4), 49.3 ($C_{2,6}$).

cis-2-Bromotetrahydrothiopyran S-Oxide (cis-2). According to the procedure of Iriuchijima and Tsuchihashi,[23] tetrahydropyran *S*-oxide (1, 0.89 g, 7.55 mmol) was brominated with

N-bromosuccinimide. The crude product was purified by flash chromatography (EtOAc-hexane, 80:20). Recrystallization from CH_2Cl_2-Et_2O (2:1) afforded 1.21 g (82% yield) of *cis*-**2** as a white solid, mp 62-62.5°C (lit.[26] mp 61-62°C). ^1H NMR (CD_2Cl_2, 270 MHz) δ 1.48-1.73 (m, 2 H, $H_{4,5}$), 1.76-1.90 (m, 1 H, H_4), 2.02-2.21 (m, 2 H, $H_{3,5}$), 2.42-2.56 (m, 1 H, H_3), 2.71-2.81 (m, 1 H, H_6), 2.96-3.05 (m, 1 H, H_6), 5.04 (dd, J^1= 8.6 Hz, J^2 = 1.3 Hz, H_2). ^{13}C NMR (22.49 MHz, $CDCl_3$) and ^{13}C NMR (22.49 MHz, CD_2Cl_2) in Table II.

trans-2-Bromotetrahydrothiopyran S-Oxide (trans-2). Following the procedure of Iriuchijima and Tsuchihashi,[23] a solution of triethyloxonium tetrafluoroborate (0.43g, 2.2 mmol) in 25 mL of dry methylene chloride was treated dropwise with 0.25 g (1.3 mmol) of *cis*-**2** in 10 mL of dry methylene chloride. The resulting oil was purified by gradient flash chromatography (hexane-EtOAc, 70:30 → 30:70) to give 170 mg (68% yield) of *trans*-**2** as a white solid, mp 61-61.5°C (lit.[26] mp 59.5-60°C). ^1H NMR (CD_2Cl_2, 270 MHz) δ 1.50-1.73 (m, 2 H, $H_{4,5}$), 1.73-1.90 (m, 1 H, H_4), 1.94-2.06 (m, 1 H, H_3), 2.15-2.30 (m, 1 H, H_5), 2.66-2.80 (m, 2 H, $H_{3,6}$), 3.19-3.30 (m, 1 H, H_6), 4.71-4.74 (m, 1 H, H_2). ^{13}C NMR (CD_2Cl_2, 67.8 MHz) in Table II.

cis-2-Chlorotetrahydrothiopyran S-Oxide (cis-3). Following the method of Iriuchijima and coworkers,[27] 2.0 g (16.9 mmol) of thiane *S*-oxide (**1**) was chlorinated with 1.83 g (13.6 mmol) of SO_2Cl_2. The crude product was purified by flash chromatography (EtOAc-hexane, 4:1) to afford 730 mg (42% yield) of *cis*-**3**, mp 70-70.5°C (lit.[27] mp 65.5-66.5°C), as well as 430 mg (16% yield) of *cis*-2,6-dichlorotetrahydrothiopyran *S*-oxide (**4**), mp 135.5-136°C (lit.[27] 134-135°C).

cis-**3**: ^1H NMR (270 MHz, $CDCl_3$) δ 1.50-1.73 (m, 2 H, $H_{4,5}$), 1.80-1.94 (m, 1 H, H_4), 2.03-2.20 (m, 1 H, $H_{3,5}$), 2.38-2.52 (m, 1 H, H_3), 2.76-2.86 (m, 1 H, H_6), 3.05-3.15 (m, 1 H, H_6), 4.96 (dd, J^1 = 8.6 Hz, J^2 = 2.0 Hz, 1 H, H_2). ^{13}C NMR (67.8 MHz, $CDCl_3$) in Table II.

r-1-Oxide-2c, 6c-dichlorotetrahydrothiopyran (**4**). ^1H NMR (270 MHz, CD_2Cl_2) δ 1.48-1.66 (m, 1 H, H_4), 1.90-2.10 (m, 3 H, $H_{3,4,5}$), 2.26-2.41 (m, 2 H, $H_{3,5}$), 4.66 (dd, J^1 = 9.2 Hz, J^2 = 2.6 Hz, 2 H, $H_{2,6}$). ^{13}C NMR (67.8 MHz, CD_2Cl_2) in Table II.

trans-2-Chlorotetrahydrothiopyran S-Oxide (trans-3). Following the procedure of Iriuchijima and coworkers,[27] a solution of 0.95g (5.0 mmol) of triethyloxonium tetrafluoroborate in 25 mL of CH_2Cl_2 was treated with 0.5g (2.0 mmol) of *cis*-**3** in 10 mL of CH_2Cl_2. The crude product was purified by flash chromatography (EtOAc-hexane, 4:1) to give 405 mg (74% yield) of *trans*-**3** as a white solid, mp 42-44°C (lit.[27] 43-44°C). ^1H NMR (270 MHz, $CDCl_3$) δ 1.53-1.73 (m, 2 H, $H_{4,5}$), 1.79-2.02 (m, 2 H, $H_{3,4}$), 2.17-2.34 (m. 1 H, H_5), 2.65-2.83 (m, 2 H, $H_{3,6}$), 3.07-3.17 (m, 1 H, H_6), 4.68-4.70 (m, 1 H, H_2). ^{13}C NMR (67.8 MHz, $CDCl_3$) in Table II.

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31. Interestingly, molecular mechanics calculations (MM2 program in Hyperchem package, Release 2 for Windows Autodesk, Inc., Sausalito, CA, 1992) suggest that *cis*-**2**ax should be 0.9 kcal/mol higher in energy than *cis*-**2**eq, in the absence of quantum mechanical effects. According to these calculations, dipole-dipole electrostatic interactions are essentially equal in *cis*-**2**ax and *cis*-**2**eq, although substantial ring puckering causes the O-S-C-Br torsional angle to be smaller in *cis*-**2**ax (39.8°) than in *cis*-**2**eq (70.3°), which is reflected in increased van der Waals steric repulsion in the former: 2.65 *vs* 2.12 kcal/mol.
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