Properties and Reactions of 1,3-Oxathiolans. Part 6.[1-3] Chemical Equilibration and ^1H Nuclear Magnetic Resonance Conformational Study of 4,5-Dimethyl-, 2,4,5-Trimethyl-, and 2,2,4,5- and 2,4,4,5-Tetramethyl-1,3-Oxathiolans

By **Raimo Keskinen, Alpo Nikkilä,** and **Kalevi Pihlaja,*** Department of Chemistry, University of Turku, SF-20500 Turku 50, Finland

The 60 MHz ^1H n.m.r. spectra of nine differently substituted 4,5-dimethyl-1,3-oxathiolans have been recorded and analysed. The n.m.r. data are compared with those previously reported for the 4-methyl- and 5-methyl-1,3-oxathiolans. Epimeric derivatives were chemically equilibrated to determine the energy differences between the diastereoisomers in question. The thermodynamic quantities obtained were used to clarify different spatial interactions in these compounds.

IN previous reports we assigned configurations to numerous *r*-2,*c*- and -*t*-4-methyl-[2] and -5-methyl-1,3-oxathiolan derivatives[3] and the preferred conformations were inferred from the ^1H n.m.r. data and results of chemical equilibration. To test our conformational deductions on 1,3-oxathiolans and the energy contributions of pseudoaxial 4- and 5-methyl substituents, numerous 4,5-dimethyl-1,3-oxathiolans (Table 1) were synthesized, their ^1H 60 MHz n.m.r. spectra recorded, and the chemical equilibrations of epimeric diastereoisomers carried out.

EXPERIMENTAL

3-*Mercaptobutan*-2-*ol*.—Butane-2,3-diol was converted to chloroacetate (60%),[4] b.p. 338—343 K at 3.3 kPa, which was methanolysed to 3-chlorobutan-2-ol (80%), b.p. 323—324 K at 3.3 kPa, and then added dropwise to a concentrated KOH solution at 343 K to obtain 2,3-epoxybutane (70%), b.p. 328 K. 3-Mercaptobutan-2-ol (30—35%; 23.5%

---

[1] Part 5, K. Pihlaja, R. Keskinen, and A. Nikkilä, *Bull. Soc. chim. belges*, 1976, **85**, 435.

[2] Part 4, R. Keskinen, A. Nikkilä, K. Pihlaja, and F. G. Riddell, *J.C.S. Perkin II*, 1974, 466.

[3] Part 3, R. Keskinen, A. Nikkilä, and K. Pihlaja, *Tetrahedron*, 1972, **28**, 3943.

[4] R. J. Meltzer and J. A. King, *J. Amer. Chem. Soc.*, 1953, **75**, 1355.

racemate, 76.5% *meso*-form) b.p. 338—339 K at 2.5 kPa, n_D^{293} 1.479 2, d_{277}^{293} 1.008 9, was then obtained from the latter and thiourea.[5]

3-*Mercapto*-3-*methylbutan*-2-*ol*.—t-Amyl alcohol was first converted into 3-methylbut-2-ene (80%) b.p. 311 K, and then oxidized[6] to 3-methylbutane-2,3-diol (40%), b.p. 352—353 K at 1.6 kPa, which gave the chloroacetates (21%), b.p. 332—336 K at 2.0 kPa, which were then converted into a mixture of 3-chloro-3-methyl- and 3-chloro-2-methyl-butan-2-ol (52%), b.p. 315 K at 2.4 kPa. The chlorobutanols gave 2,3-epoxy-2-methylbutane (70%), b.p. 336—337 K, from which 3-mercapto-3-methylbutan-2-ol was obtained.[5] The product (yield 30%) boiled at 355 K and 2.3 kPa and consisted of 90% 3-mercapto-3-methyl- and 10% 3-mercapto-2-methyl-butan-2-ol.

TABLE 1

Physical constants of 4,5-dimethyl-1,3-oxathiolans

Substitution	B.p. (K) [*p*/kPa]	n_D^{293}	d_{277}^{293}	Yield (%)
4,5-Me_2	348—351 [6.4] [a]	1.478 4 *trans*	1.044 4 [a]	32 [a]
		1.484 7 *cis*		
2,4,5-Me_3	333—343 [6.7] [a]	1.465 0 *r*-2,*t*-4,*c*-5[b]		60 [a]
		1.466 3 *r*-2,*c*-4,*t*-5[b]		
		1.471 1 *r*-2,*c*-4,*c*-5[b]	0.992 6	
		1.470 2 *r*-2,*t*-4,*i*-5[b]		
2,2,4,5-Me_4	343—345 [6.7] [b]	1.457 8 *trans*	0.953 1	69 [a]
		1.465 0 *cis*	0.965 5	
2,4,4,5-Me_4	353 [7.7] [a]	1.460 3 *cis*		37 [a]
		1.456 8 *trans*		

[a] For mixtures of diastereoisomers. [b] Values of 298 K.

TABLE 2

Equilibria between isomeric 2,4,5-trimethyl- and 2,4,4,5-tetramethyl-1,3-oxathiolans at different temperatures

	K			
1,3-Oxathiolan	278 K	298 K	318 K	338 K
2,4,5-Me_3 (*meso*) [b]	3.99 ±0.10 [a]	3.48 ±0.13	3.09 ±0.04	2.81 ±0.06
2,4,5-Me_3 (±) [c]		3.37 ±0.10	2.98 ±0.06	2.64 ±0.10
2,4,4,5-Me_4 [d]	4.46 ±0.07 [e]	3.97 ±0.23	3.55 ±0.22	

K determined using g.l.c. analysis.

[a] Standard deviation. [b] *K* = [*syn*]/[*anti*]. [c] *K* = [*r*-2, *t*-4, *c*-5]/[*r*-2, *c*-4, *t*-5]. [d] *K* = [*cis*-2,5]/[*trans*-2,5]. [e] Value at 280 K.

TABLE 3

Thermodynamic parameters for isomer equilibria

Equilibrium	$-\Delta H°$/J mol^{-1}	$-\Delta S°$/J mol^{-1} K^{-1}	$-\Delta G_{298}$/J mol^{-1}
r-2, *t*-4, *t*-5 ⇌ *r*-2, *c*-4, *c*-5	4 567 ± 75 [a]	4.94 ± 0.24	3 095
r-2, *c*-4, *t*-5 ⇌ *r*-2, *t*-4, *c*-5	5 160 ± 207	7.18 ± 0.65	3 020
r-2,4,4, *t*-5 ⇌ *r*-2,4,4, *c*-5	4 442 ± 29	3.43 ± 0.10	3 420
trans-2,4 ⇌ *cis*-2,4	−176 ± 18	−0.10 ± 0.06	−146
trans-2,5 ⇌ *cis*-2,5	4 657 ± 322	5.56 ± 1.00	2 996

[a] Standard deviation.

4,5-Dimethyl-, 2,4,5-trimethyl-, 2,2,4,5-tetramethyl-, and 2,4,4,5-tetramethyl-1,3-oxathiolans were prepared conventionally[3,4] from 3-mercaptobutan-2-ol or 3-mercapto-3-methylbutan-2-ol and a suitable aldehyde or ketone.[3] The physical constants of the compounds are collected in Table 1.

Equilibrium constants were determined at three or four temperatures as stated before[2,3] (Table 2) and the thermodynamic parameters (Table 3) derived from them by a linear regression programme written for HP 65 calculator.

^1H N.m.r. spectra were recorded on a Perkin-Elmer R 10 spectrometer. The solutions contained 450 μl of solvent CCl_4 and 50 μl of substrate.

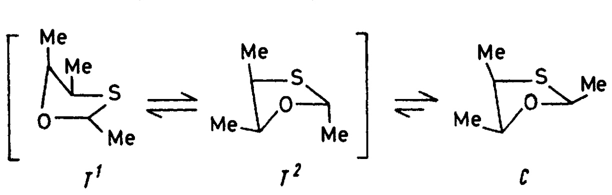
Spectral Analysis.—The spectra examined consisted of AM_3XR_3 type spin multiplets. The final parameters were computed using LAME programme on DEC-10 computer system in Turku.

RESULTS AND DISCUSSION

The diastereoisomers were separated by preparative g.l.c.[3] except *r*-2,4,4,*c*-5-tetramethyl-1,3-oxathiolan (Table 1) which was not purified for n.m.r. analysis. The isomers were characterized by physical constants, n.m.r., and chemical equilibration. Equilibrations were carried out as stated before[2,3] in ether solution using BF_3,Et_2O as acid catalyst. Equilibrated samples were analysed by g.l.c.[2,3] to obtain equilibrium constants at various temperatures (Table 2), from which enthalpy, entropy, and free energy differences between the isomers were derived (Table 3).

Configurational Assignments.—The configurational assignments for the 4,5-substituted 1,3-oxathiolans were based on the n.m.r. parameters. On the basis of the magnitude of the vicinal, $J_{4,5}$, coupling constants the mutual orientation of 4- and 5-methyl groups was easily established (*cf*. ref. 2). Those isomers for which $J_{4,5}$ is 4.36—4.85 Hz (Table 5) have *cis*-4,5-Me_2 configurations and those for which $J_{4,5}$ is 6.40—9.31 Hz have *trans*-4,5-Me_2 configurations (Table 5). On the basis of chemical shifts of H(2), H(4), H(5), Me(2), and Me(5) (Table 4) it was evident[2,3] that in the case of 2,4,5-trimethyl-1,3-oxathiolans the isomer with the shortest retention time was *r*-2,*t*-4,*c*-5-trimethyl-1,3-oxathiolan and the isomer with the longest retention time was *r*-2,*t*-4,*t*-5-trimethyl-1,3-oxathiolan. This situation is in agreement with earlier evidence taking into account that the analytical conditions employed in equilibrium measurements were practically identical with those employed for the 2,4-[2] and 2,5-dimethyl[3] derivatives. In the case of 2,4,4,5-tetramethyl-1,3-oxathiolans only one isomer was obtained pure enough for n.m.r. analysis which proved (Table 4) that its configuration was *r*-2,*t*-5.[3]

Chemical Equilibration.—The equilibrium between *r*-2,*t*-4,*t*-5- and *r*-2,*c*-4,*c*-5-trimethyl-1,3-oxathiolans is most clearly illustrated by equation (1). Like *cis*-2-alkyl-5-methyl-[3] and *cis*-2-alkyl-4-methyl-1,3-oxathiolans[2] *r*-2,*c*-4,*c*-5-trimethyl-1,3-oxathiolan exists predominantly in conformation *C* where both 2- and 5-methyl groups attain essentially equatorial positions whereas the *trans*-isomer is a mixture of two conformations or conformer families T^1 and T^2. In all conformations C(5) is



(1)

---

[5] F. G. Bordwell and H. M. Andersen, *J. Amer. Chem. Soc.*, 1953, **75**, 4959.

[6] G. Wagner, *Ber.*, 1888, **21**, 1230.

TABLE 4

Chemical shifts[a] for the various compounds in CCl_4

1,3-Oxathiolan	δ[H(2)]	δ[H(5)]	δ[H(4)]	δ[Me(2)]	δ[Me(4)]	δ[Me(5)]
cis-4,5-Me_2	4.92 4.68	3.91	3.36		1.14	1.24
trans-4,5-Me_2	4.86	3.46	3.00		1.30	1.30
r-2, *t*-4, *c*-5-Me_3	5.21	3.47	3.11	1.49	1.28	1.30
r-2, *c*-4, *t*-5-Me_3	5.27	3.84	3.09	1.50	1.30	1.24
r-2, *c*-4, *c*-5-Me_3	4.92	3.94	3.32	1.52	1.16	1.25
r-2, *t*-4, *t*-5-Me_3	5.34	4.27	3.44	1.45	1.18	1.18
2,2,*cis*-4,5-Me_4		4.26	3.29	1.61 1.53	1.17	1.22
2,2,*trans*-4,5-Me_4		3.74	3.13	1.56	1.25	1.26
r-2,4,4, *t*-5-Me_4	5.20	3.65		1.49	1.34 1.26	1.15

[a] Tetramethylsilane as standard.

TABLE 5

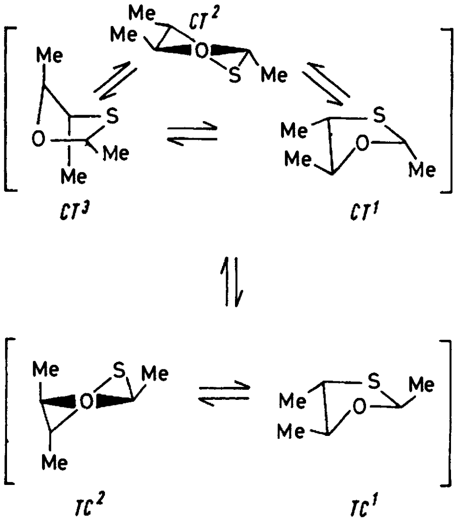
Values of H(4),H(5), H(4),Me(4), H(5),Me(5) and H(2),H(2′) or Me(2) coupling constants (Hz) for the various 1,3-oxathiolans

Substitition	$J_{cis}^{4,5}$	$J_{trans}^{4,5}$	$J_{4,Me}$	$J_{5,Me}$	$J_{2,Me\ or\ 2,2'}$
cis-4,5-Me_2	4.75		6.89	6.42	4.93
trans-4,5-Me_2		7.84	6.57	6.09	
r-2, *t*-4, *c*-5-Me_3		8.42	6.62	5.97	5.88
r-2, *c*-4, *t*-5-Me_3		6.40	6.48	6.32	6.10
r-2, *c*-4, *c*-5-Me_3	4.85		6.90	6.34	5.85
r-2, *t*-4, *t*-5-Me_3	4.74		6.95	6.55	6.00
2,2, *cis*-4,5-Me_4	4.36		7.03	6.37	
2,2, *trans*-4,5-Me_4		9.31	6.60	6.06	
r-2,4,4, *t*-5-Me_4				6.40	5.82

the flap atom but it is, however, obvious that these conformations may be more or less distorted towards the corresponding half-chair or envelope form where oxygen lies at the tip. This distortion would minimize the pseudoaxial interaction due to the 4-methyl substituent without an appreciable effect on the other nonbonded interactions. *trans*-Conformations include either a pseudoaxial 5-methyl (T^1) or 2-methyl (T^2) group. The experimental entropy difference 4.94 ± 0.24 J mol^{-1} K^{-1} is within the experimental error for 2,5-dimethyl-1,3-oxathiolans, 5.56 ± 1.00 J mol^{-1} K^{-1} (Table 3).[3] Taking into account that the experimental entropy difference for 2,4-dimethyl-1,3-oxathiolans[2] is *ca.* 0 (Table 3), and the fact[2] that the conformational energies of pseudoaxial methyl groups in positions 2 and 5 do not deviate greatly from each other the value $-\Delta H°_{2,5\text{-}Me_2} + (-\Delta H°_{2,4\text{-}Me_2}) = 4.66 - 0.18 = 4.44 \pm 0.23$ kJ mol^{-1} should be roughly equal to the conformational enthalpy difference between *C* and *T*, in excellent agreement with the experimental value, 4.57 ± 0.08 kJ mol^{-1} (Table 3).

The configurational equilibrium between *r*-2,*c*-4,*t*-5- and *r*-2,*t*-4,*c*-5-trimethyl-1,3-oxathiolans may be considered in the light of equation (2). The excess entropy of the *r*-2,*c*-4,*t*-5-configuration, 7.18 ± 0.64 J mol^{-1} K^{-1} (Table 3), is an indication of its conformational flexibility in comparison with that of the *r*-2,*t*-4,*c*-5-form. Obviously the *r*-2,*t*-4,*c*-5-form exists predominantly in the triequatorial C(5) envelope (TC^1) but includes somewhat the corresponding half-chair conformation (TC^2) where 4,5-methyl groups are pseudoaxially orientated. The *r*-2,*c*-4,*t*-5-form has at least two conceivable C(5) envelopes, namely CT^1 and CT^3, and may also exist somewhat in both O(1) envelopes and in the triequatorial half-chair form CT^2. The justification of this conformational situation will be discussed in more detail in context with the n.m.r. results.

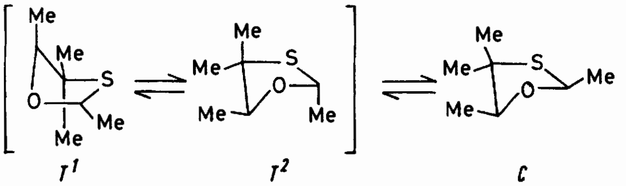
In the case of 2,4,4,5-tetramethyl-1,3-oxathiolans only the *trans*-2,5-isomer was separated for n.m.r. investigation. Chemical equilibration, however, gave results



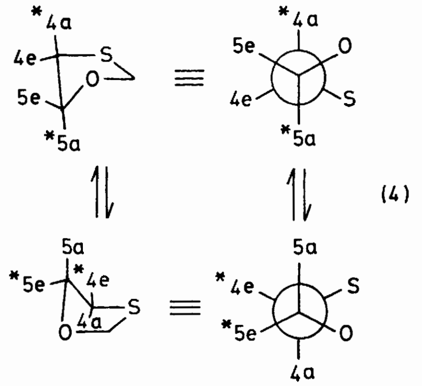
(2)

which are in accord with earlier findings.[2,3] The diminished entropy difference 3.43 J mol^{-1} K^{-1} (Table 3) reflects the fact that T^2 form includes an extra e,e-Me,Me-*gauche* interaction which makes it less stable by comparison with T^1 than was the case in equation (1). This leads inevitably to a decrease in the entropy of mixing of the *trans*-isomer in equation (3).

N.m.r. Spectra.—Typical $J_{4,5}$ values for 1,3-oxathiolans [2,3,7,8] extend over the ranges [equation (4)] $J_{4a,5e}$ 4.4—5.8, $J_{4e,5e}$ 2.2—3.2, $J_{4a,5a}$ 9.6—11.0, and $J_{4e,5a}$ 3.8—5.5 Hz. The 4,5-dimethyl-1,3-oxathiolans with the *trans*-4,5 configuration were easy to identify on the basis of the magnitude of the vicinal coupling constants (Table 5). Moreover, the chemical shifts of different protons (Table 4) show that most of the relationships met in the chemical shifts of 5-methyl- [3] and 4-methyl-1,3-oxathiolans [2] are also valid in the case of 4,5-dimethyl-1,3-oxathiolans. Thus the configurational assignments were easily done. In some cases the 4- and 5-methyl signals partly coalesced but the assignment of the signals was, however, possible on the basis of the coupling constants between methyl protons and the relevant ring proton. On the sulphur side, at position 4, this coupling is distinctively larger, 6.48—7.03 Hz (6.2—6.9 Hz for the 4-methyl series [2]), than on the oxygen side, at position 5, 5.97—6.55 Hz (5.82—6.32 Hz for the 5-methyl series [3]) (Table 5).



(3)



(4)

The coupling constants between 4- and 5-protons in the 1,3-oxathiolans were easy to evaluate. However, the extra splittings due to the 4- and 5-methyl groups did not accurately obey first-order rules and therefore the final parameters were computed with the aid of the LAME programme.

The values of the vicinal coupling constants (Table 5) point out that *trans*-4,5-dimethyl-1,3-oxathiolans are mixtures of at least two pseudorotamers (or rotamer families) of which one has the $J_{4a,5a}$ [*e.g.* CT^1, CT^2, and TC^1 in equation (2)] arrangement and the other the $J_{4e,5e}$ [CT^3 and TC^2 in equation (2)] arrangement.

Inspection of molecular models shows that in the case of 2,2,*trans*-4,5-tetramethyl-1,3-oxathiolan practically no $J_{4e,5e}$-type conformations exist due to strong non-bonded interactions and that is why we can use it as an anancomeric model for the $J_{4a,5a}$ arrangement (J_{trans} 9.31 Hz) in 4,5-dimethyl-1,3-oxathiolans. Unfortunately we do not know the exact value of $J_{4e,5e}$ in a similar environment but in *cis*-2,4-dimethyl-1,3-oxathiolan $J_{4e,5e}$ is 2.49 Hz [2] and hence we assume that it is reasonable to estimate $J_{4e,5e}$ at 2 Hz. Employing equation (5) it is possible to evaluate the free energy differences between the conformer families with $J_{4a,5a}$ and $J_{4e,5e}$ arrangements for *trans*-4,5-dimethyl-, *r*-2,*c*-4,*t*-5-trimethyl- and *r*-2,*t*-4,*c*-5-trimethyl-1,3-oxathiolans.

$$trans\text{-}4,5\text{:}\ J_{obs} = xJ_{4a,5a} + (1 - x)J_{4e,5e} \qquad (5)$$

Equation (5) gives the results shown in Table 6 for the equilibria between the conformer families in question.

TABLE 6

Relative population of the two possible conformer families of *trans*-4,5-dimethyl-1,3-oxathiolans in CCl_4 and the corresponding free energy differences at 306 K

1,3-Oxathiolan	J_{obs}	$J_{4a,5a}$ 9.31 Hz portion (%)	$J_{4e,5e}$ 2.0 Hz portion (%)	K	$-\Delta G°$/kJ mol^{-1}
trans-4,5-Me_2	7.84	80	20	4.0	3.5 ± 1.0
r-2, *t*-4, *c*-5-Me_3	8.42	88	12	7.3	5.1 ± 1.0
r-2, *c*-4, *t*-5-Me_3	6.40	60	40	1.5	1.0 ± 0.5

The free energy difference, 3.5 kJ mol^{-1}, between the diequatorial and the diaxial C(5)-envelope of *trans*-4,5-dimethyl-1,3-oxathiolan is in good agreement with the different interactions involved in these conformations. The free energy difference, 1.0 kJ mol^{-1}, between the conformation families in the case of the *r*-2,*c*-4,*t*-5 derivative [equation (2)] confirms the view that some of the half-chair form (CT^2) must be included since otherwise the proportion of the $J_{4a,5a}$ arrangement should be $<50\%$. The free energy difference, 5.1 kJ mol^{-1}, between the C(5)-envelope (TC^1) and the half-chair form (TC^2) in the case of the *r*-2,*t*-4,*c*-5 form allows us to estimate (assuming $\Delta S°$ *ca.* 0) that the half-chair form as such is *ca.* 6 kJ mol^{-1} less stable than the C(5)-envelope: [1,2] $\Delta H°$(envelope — half-chair) = $\Delta H°$(2a-Me) + $\Delta H°$(4e,5e-Me,Me) — $\Delta H°$(5a-Me) — $\Delta H°$(4a-Me) + 5.1 = 4 + 3 — 5 —1 + 5.1 ~6.

Conclusions.—Together with the data presented earlier the results of equilibration studies and n.m.r. analysis are best explained with the aid of envelope structures where C(5) is the flap atom though in some cases the corresponding half-chair form where C(4) is above and sulphur below the plane defined by the remaining three atoms as well as the O(1)-envelope may appear to be favoured. This proposition is in agreement with the opinions of Pasto *et al.*[7] and Wilson *et al.*[8] as well as the

---

[7] D. J. Pasto, F. M. Klein, and T. W. Doyle, *J. Amer. Chem. Soc.*, 1967, **89**, 4368.

[8] G. E. Wilson, jun., M. G. Huang, and F. A. Bovey, *J. Amer. Chem. Soc.*, 1970, **92**, 5907.

recent conformational energy calculations and conclusions of Wilson[9] dealing with 2-methyl-1,3-oxathiolan. According to Wilson the most stable conformation of 2-methyl-1,3-oxathiolan has both the sulphur and the methyl β to the flap atom and the methyl *anti* to it with respect to the ring plane.

Our results do not confirm that the 1,3-oxathiolan ring itself has a clearcut preference for a certain conformation. The steric requirements of the ring are, however, as important as those of the substituents (the same ring conformation predominates in both 2,4-, 2,5-, and 2,4,5-series). The energy barrier between the envelope forms with C(5) or O(1) as the flap atom is not high enough to bias the ring in either of these conformations.[9] Thus the steric requirements of the substituents may greatly effect the position of the energy minimum.

A methyl substituent in the 4-position has no great steric demands of its own though they may be reflected in the most probable conformation through further substitution. Pseudoaxial alkyl substituents at positions 2 and 5 show remarkable conformational interactions the magnitude of which varies from 4.3 (2a-Me)[2] to 8.6 (2a-Bu^t)[1] kJ mol^{-1}.

We thank the Science Research Council of the Finnish Academy (A. N.) and the Emil Aaltonen Foundation (R. K.) for financial support and Mr. M. Hotokka for technical assistance in the computer work.

[6/882 *Received*, 10*th May*, 1976]

---

[9] G. E. Wilson, jun., *J. Amer. Chem. Soc.*, 1974, **96**, 2426.