Conformational Analysis. Part VII. 2-Alkyl-4-methyl- and 2-Alkyl-2,4-dimethyl-1,3-dithiolans †

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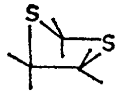
2-Alkyl-4-methyl- and 2-alkyl-2,4-dimethyl-1,3-dithiolans have been prepared and studied by means of the acid-catalysed equilibration of the diastereoisomers and ^{1}H n.m.r. spectroscopy. Free energy differences between diastereoisomers are small and within the range 0·13—0·54 kJ mol^{-1} for the dialkyl series and 0·71—1·00 kJ mol^{-1} for the trialkyl series. The data suggest that the dithiolan ring is quite a flexible system and a possible minimum energy conformation can be defined only if there is a bulky substituent at the 2-position.

FIVE-MEMBERED rings have been thought to exist in envelope (1) or half-chair (2) conformations[1-3] with several possible conformers in the pseudorotation circuit, but it is now clear[4,5] that this is an oversimplification. Conformational effects in five-membered ring systems are complicated by low barriers to pseudorotation and by the numerous nearly equi-energy conformers.



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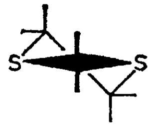

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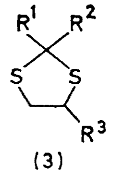

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Relatively little is known about sulphur-containing saturated five-membered heterocycles. Particularly lacking are data on 1,3-dithiolans. Earlier conformational data available for the 1,3-dithiolan system are based on vibrational spectra[6] and *X*-ray analysis.[7] Sternson *et al.*[8] analysed the AA′BB′ systems of the ring methylene protons of some 2-substituted 1,3-dithiolans and also used the carbon-13 satellites of the singlet resonance in the case of 1,3-dithiolan and 2,2-dimethyl-1,3-dithiolan. Their data supported the view that the 1,3-dithiolan ring is clearly more puckered than

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† Part VI, *Acta Chem. Scand.*, in the press.

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the ring of the corresponding oxygen analogue, 1,3-dioxolan.

To understand better the conformational effects of sulphur-containing five-membered heterocycles we have used chemical equilibration in conjunction with n.m.r. spectroscopy[4,5,9-13] to investigate 2-alkyl-4-methyl- and 2-alkyl-2,4-dimethyl-1,3-dithiolans.

EXPERIMENTAL

1,3-Dithiolans were prepared by boiling ethane-1,2-dithiol or propane-1,2-dithiol (both from Fluka, purum) with 10% excess of the appropriate aldehyde in a water entrainment unit until the formation of water ceased. Dichloromethane was used as solvent and toluene-*p*-sulphonic acid as catalyst. After neutralisation with diethylamine the solvent was distilled and the residue was fractionated at reduced pressure. Physical constants are collected in Table 1.

TABLE 1

Physical constants of alkyl-substituted 1,3-dithiolans (3)

R^1	R^2	R^3	B.p./°C (Torr)	n_D^{20}	d_4^{20}	Yield %
H	H	H	78—80 (27)	1·5902	1·2549	66
H	Me	H	80 (26)	1·5625	1·1735	83
Me	Me	H	70 (18)	1·5417	1·0913	90
H	H	Me	86—87 (26)	1·5684[a]	1·1630[a]	45
H	Me	Me[b]	83—84 (27)	1·5408	1·1026	87
H	Et	Me[b]	97—98 (27)	1·5302	1·0648	85
H	Pr^i	Me[b]	103—104(21)	1·5199	1·0343	88
H	Bu^t	Me[b]	109(20)	1·5152	1·0198	83
Me	Me	Me	80—81 (26)	1·5217	1·0412	80
Me	Et	Me[b]	100(27)	1·5211	1·0301	85
Me	Bu^t	Me[b]	118—120(26)	1·5159	1·0119	75

[a] At 25 °C. [b] For mixtures of diastereoisomers.

Equilibrations were carried out at 105 °C. Diethyl ether was used as solvent and boron trifluoride–ether as the acid catalyst. The samples contained solvent (450 μl) and substrate (50 μl). A catalytic amount (3—4 μl) of boron trifluoride–ether was added to each sample. In all cases equilibria were established after 4—6 weeks. The state of equilibrium was determined by n.m.r. techniques, measuring the ratio of areas of the 2- or 4-Me signals for the equilibrium mixtures of each pair of diastereoisomers.

Entropy and enthalpy differences could be determined only for *cis*- and *trans*-2,4-dimethyl-1,3-dithiolans, which gave separate peaks with g.l.c. using a 2 m × 1/8 in stainless steel column containing 5% Carbowax 20M on Chromosorb G (60—80 mesh). Equilibrations were carried out at 50, 85, 112, and 135 °C.

TABLE 2

Equilibria between isomeric 2,4-dialkyl and 2,2,4-trialkyl-1,3-dithiolans

1,3-Dithiolan		*K*	*T*/°K	$-\Delta G^0$/kJ mol⁻¹
2,4-Me_2	$(cis \rightleftharpoons trans)$	1·05 ± 0·02[a,b]	378	0·15 ± 0·06
		1·125 ± 0·02[c]	323	0·316
		1·132 ± 0·02[a]	358	0·369
		1·128 ± 0·02[c]	385	0·386
		1·125 ± 0·05[c]	408	0·400
2-Et-4-Me	$(trans \rightleftharpoons cis)$	1·09 ± 0·05[b]	378	0·26 ± 0·13
2-Pr^i-4-Me	$(trans \rightleftharpoons cis)$	1·15 ± 0·06[b]	378	0·45 ± 0·16
2-Bu^t-4-Me	$(trans \rightleftharpoons cis)$	1·19 ± 0·05[b]	378	0·54 ± 0·14
2,4-Me_2-2-Et	$(cis \rightleftharpoons trans)$	1·26 ± 0·03[b]	378	0·74 ± 0·08
2,4-Me_2-2-Bu^t	$(cis \rightleftharpoons trans)$	1·37 ± 0·03[b]	378	0·99 ± 0·07

[a] Standard deviation. [b] By n.m.r. analysis. [c] By g.l.c. analysis: $-\Delta H^0 = 0·01 \pm 0·06$ kJ mol⁻¹; $\Delta S^0 = 0·97 \pm 0·17$ J K⁻¹ mol⁻¹.

N.m.r. spectra were recorded on precalibrated paper with a Perkin-Elmer R 10 spectrometer (60 MHz). The solutions contained CCl_4 (450 μl) and substrate (50 μl).

The equilibration results are shown in Table 2, and the spectral data in Tables 3—5.

RESULTS AND DISCUSSION

We did not succeed in separating the diastereoisomers by preparative g.l.c. and with the exception of *cis*- and *trans*-2,4-dimethyl-1,3-dithiolans they remained unresolved under all available analytical conditions. The existence of *cis*- and *trans*-isomers was, however, observed from the n.m.r. spectra and the states of equilibria could also be analysed from the areas of suitable n.m.r. signals.

The 4- and 5-protons of the 1,3-dithiolans studied form an 'ABX' system from which the chemical shifts and coupling constants between these protons are simply resolved and the final parameters computed with the aid of an iterative ABC program.[14] The only difficulty was the overlapping of the AB and X parts of the diastereoisomers in the spectra of the isomer mixtures. In most cases the AB parts, however, separate sufficiently to allow the extraction of n.m.r. parameters for both components of the isomer mixtures with the exceptions of 2-Et-4-Me-, 2-Pr^i-4-Me-, and 2-Bu^t-2,4-Me_2-1,3-dithiolans. The computed values of the coupling constants were very close (within 0·2—0·4 Hz) to those calculated using the ABX method.

Configurational assignments were based on the n.m.r. parameters and relative stabilities of the diastereoisomers in comparison with those of the correspondingly substituted diastereoisomeric 1,3-oxathiolans and 1,3-dioxolans.[4,5,15]

The more stable isomer of 2,4-dialkyl-1,3-dithiolans was assigned the *cis*-configuration except for 2,4-dimethyl-1,3-dithiolans of which the *trans*-form is thermodynamically slightly more stable as with the isomeric

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TABLE 3

Chemical shifts of 2-, 4-, and 5-H [δ (p.p.m.) from Me_4Si; CCl_4 solution] and 2-H–2-R coupling constants for the various compounds [a] (Hz)

1,3-Dithiolan	$\delta_{H\text{-}4}$	$\delta_{H\text{-}5}$	$\delta_{H\text{-}5'}$	$\delta_{H\text{-}2}$	$J_{H\text{-}2}$
Parent	3·012	3·012	3·012	3·703	
2-Me	3·087	3·087	3·087	4·545	6·47
2,2-Me$_2$	3·327	3·327	3·327		
4-Me	3·860	3·292	2·948	4·018	
cis-2,4-Me$_2$	3·748	3·285	2·907	4·558	6·44
trans-2,4-Me$_2$	3·827	3·178	2·872	4·593	6·47
cis-2-Et-4-Me	3·732	3·132	2·830	4·377	6·75
trans-2-Et-4-Me				4·387	
cis-2-Pr^i-4-Me	3·683	3·097	2·782	4·217	6·65
trans-2-Pr^i-4-Me				4·240	
cis-2-Bu^t-4-Me	3·695	3·072	2·738	4·343	
trans-2-Bu^t-4-Me	3·700	3·167	2·812	4·352	
2,2,4-Me$_3$	3·903	3·308	2·998		
trans-2,4-Me$_2$-2-Et	3·868	3·247	2·912		
cis-2,4-Me$_2$-2-Et	3·800	3·227	2·953		
trans-2,4-Me$_2$-2-Bu^t	3·802	3·210	2·842		

[a] H-5 is *cis* and H-5′ *trans* relative to H-4.

TABLE 4

Chemical shifts of 2- and 4-Me and 2-R [δ (p.p.m.) from Me_4Si] and the 4-Me–4-H, 2-Me–2-H, and 2-R–2-H coupling constants (Hz)

1,3-Dithiolan	δ4-Me	*J*4-Me	δ2-Me	*J*2-Me	δ2-R	*J*2-R
2-Me			1·580	6·42		
2,2-Me$_2$			1·565			
4-Me	1·465	6·73				
cis-2,4-Me$_2$	1·430	6·54	1·602	6·60		
trans-2,4-Me$_2$	1·383	6·53	1·567	6·66		
cis-2-Et-4-Me	1·405	6·56			1·783 [a] 1·033 [b]	7·07 [a] 6·69 [b]
trans-2-Et-4-Me	1·385	6·59			1·805 [a] 1·017 [b]	
cis-2-Pr^i-4-Me	1·403	6·42			1·917 [c] 1·042 [d]	6·61 [c] 6·34 [d]
trans-2-Pr^i-4-Me	1·377	6·53				
cis-2-Bu^t-4-Me	1·398	6·46			1·033	
trans-2-Bu^t-4-Me	1·372	6·48			1·033	
2,2,4-Me$_3$	1·403	6·50	1·768 1·747			
trans-2,4-Me$_2$-2-Et	1·403	6·42	1·685		1·922 [a] 1·070 [b]	7·50 [a]
cis-2,4-Me$_2$-Et	1·387	6·52	1·705		1·882 [a] 1·052 [b]	7·28 [a]
trans-2,4-Me$_2$-2-Bu^t	1·385	6·45	1·793		1·150	
cis-2,4-Me$_2$-2-Bu^t			1·818		1·133	

[a] C*H*$_2$CH$_3$. [b] CH$_2$C*H*$_3$. [c] C*H*(CH$_3$)$_2$. [d] CH(C*H*$_3$)$_2$.

TABLE 5

4-H–5-H Coupling constants (Hz)

1,3-Dithiolan	J_{gem}	J_{trans}	J_{cis}
4-Me	−11·41	6·42	5·03
cis-2,4-Me$_2$	−11·26	7·25	4·91
trans-2,4-Me$_2$	−11·34	6·82	4·77
cis-2-Et-4-Me	−11·31	7·32	4·94
cis-2-Pr^i-4-Me	−11·16	7·72	5·05
cis-2-Bu^t-4-Me	−11·31	8·34	4·82
trans-2-Bu^t-4-Me	−11·21	7·12	4·64
2,2,4-Me$_3$	−11·48	7·61	4·87
trans-2,4-Me$_2$-Et	−11·53	7·79	4·89
cis-2,4-Me$_2$-Et	−11·34	7·72	4·72
trans-2,4-Me$_2$-2-Bu^t	−11·36	8·10	4·60

2,4-dimethyl-1,3-oxathiolans.[15] The 2-alkyl-2,4-dimethyl-1,3-dithiolans have the more stable isomers with the 2- and 4-Me groups *trans*.

The 2-H signals of *cis*-2,4-dialkyl-1,3-dithiolans always appear at higher field than those of the *trans*-isomers Table 3). Furthermore, *cis*-2,4-dialkyl-1,3-dithiolans and the analogous *cis*-2,4-dimethyl isomers in the trialkyl series have downfield 2- and 4-Me chemical shifts in comparison with those of the *trans*-isomers (Table 4).

Chemical Equilibrations.—Chemical equilibrations led to the equilibrium constants and standard free energy differences shown in Table 2.

In the case of diastereoisomeric 2,4-dimethyl-1,3-dithiolans the *trans*-isomer is thermodynamically slightly more stable [0·15 (n.m.r.) or 0·38 (g.l.c.) kJ mol^{-1}] in agreement with the situation for the diastereoisomeric 2,4-dimethyl-1,3-oxathiolans [15] where the free energy difference is also 0·15 kJ mol^{-1} in favour of the *trans*-form. Increasing the size of the 2-substituent slightly but palpably raises the proportion of the *cis*-isomer in the 2,4-dialkyl series in contrast to 1,3-dioxolans.[5] This indicates that the 1,3-transannular non-bonded interactions in alkyl-substituted 1,3-dithiolans are small, although the increasing size of the 2-substituent tends to decrease the 'pseudoaxial' character of this substituent and hence the *trans*-form becomes thermodynamically less favoured. The similarity of the results from the equilibration experiments lend further support to the postulate that all the *cis*-isomers have almost the same ring conformations as do also all the *trans*-isomers, although the preferred conformations in the *cis*- and *trans*-series may differ from each other.

This suggests that the alkyl group of 2-alkyl-2,4-dimethyl-1,3-dithiolans prefers to some degree the 'pseudoequatorial' orientation and accordingly the *trans*-2,4-Me$_2$ isomers are thermodynamically more stable. The standard free energy differences and the effect of the substituent size are of the same order of magnitude as in the 2,4-dialkyl series.

N.m.r. Spectra.—The values of the geminal coupling constants for 1,3-dithiolans (Table 5) are considerably more negative than those for 1,3-dioxolans and 1,3-oxathiolans. In 1,3-dioxolans the geminal couplings range from −7·1 to −7·3 Hz,[5] in 1,3-oxathiolans from −9·0 to −9·2 Hz on the oxygen side [15] and from −9·7 to −10·2 Hz on the sulphur side,[4] while in 1,3-dithiolans the range is between −11·2 and −11·5 Hz. The great decrease in the J_{gem} values is due to the electronegativity difference between oxygen and sulphur and the increasing puckering of the ring when going from 1,3-dioxolans to 1,3-dithiolans *via* 1,3-oxathiolans.[4,5,8] The conformational data based on the vibrational spectra of some 1,3-dithiolans [6] and *X*-ray analysis of bis-1,3-dithiolan-2-yl [7] suggest that the 1,3-dithiolan ring preferentially assumes a C_2 half-chair (2) conformation. The very negative J_{gem} values for 5-H$_2$ show that these protons should be staggered with the lone pair orbitals of the sulphur atoms.[16] This situation is best met in the C_s envelope (1) conformations or in the C_2 half-chair (2) conformations the latter of which is an intermediate between two envelope forms (1).

In any case, however, the energy differences between the different possible limiting conformations are rela-

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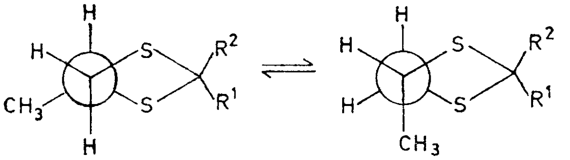
tively small. Thus, in the light of the previous considerations[6,7] and the present results, the *cis*- and *trans*-configurations of 2-alkyl-4-methyl- and 2-alkyl-2,4-dimethyl-1,3-dithiolans are most profitably regarded as the half-chair conformations (1a) and (1b) (Scheme).



cis series; R^1 = Me, Et, Pr^i, Bu^t; R^2 = H
R^1 = Me; R^2 = Me, Et, Pr^i, Bu^t
trans series; R^1 = H; R^2 = Me, Et, Pr^i, Bu^t
R^1 = Et, Pr^i, Bu^t, R^2 = Me

SCHEME

The vicinal coupling constants of *cis*-isomers in the 2,4-dialkyl series are larger than corresponding couplings in the *trans*-isomers. The magnitude of J_{trans} (Table 5) increases with increasing size of the 2-alkyl substituent. Probably conformation (1a) is somewhat favoured with respect to (1b) which possibly includes more severe 1,3-transannular interactions. This suggestion is also in agreement with the increase of the J_{trans} values in both epimer sets.

2-Alkyl-2,4-dimethyl-1,3-dithiolans also slightly favour conformation (1a), the proportion of which increases with increasing size of the 2-alkyl group. This effect is further demonstrated by the increase of the J_{trans} and decrease of the J_{cis} values.

The conclusion that both epimeric sets of diastereoisomers (Scheme) have nearly equal populations of different conformers is in accordance with the observation that, in general, the coupling constants, chemical shifts, and energy of both diastereoisomers closely resemble each other.

Conclusion.—Both the results of equilibration studies and the investigation of n.m.r. spectra lead to the conclusion that 1,3-dithiolan ring is a relatively flexible system like 1,3-dioxolan. However, carbon–sulphur bonds are considerably longer than carbon–oxygen bonds. Hence 1,3-transannular non-bonded interactions in 1,3-dithiolans are very small and even less than in 1,3-dioxolans. A ring containing an S–C–S bond angle of 110° seems to have such great steric requirements of its own that these exceed the steric requirements of the substituents. When the substituents become larger, *e.g.* Bu^t groups, their steric requirements may confine the ring to certain definite minimum energy conformations which are, owing to the increased puckering, moderately easy to visualise with the aid of conformational models.* These energy minima have the half-chair structures (Scheme) where the S–C(2)–S plane passes between C(4) and C(5) or, of course, may exist as a dynamic equilibrium between these limiting structures.

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* Dreiding models were used.