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PROPERTIES AND REACTIONS OF 1,3-OXATHIOLANES—III[1]

CONFORMATIONAL ENERGIES AND THE MOST PROBABLE CONFORMATIONS OF 2-ALKYL-5-METHYL- AND 2,2-DIALKYL-5-METHYL-1,3-OXATHIOLANES

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Abstract—Several 2-alkyl-5-methyl- and 2,2-dialkyl-5-methyl-1,3-oxathiolanes have been prepared and their conformational properties clarified through acid-catalysed equilibration of diastereoisomers and with the aid of ^{1}H NMR spectroscopy.

The collected data suggests a moderately flexible 5-membered ring which, however, shows several features of specific interactions and favoured conformations.

INTRODUCTION

CONFORMATIONAL analysis of 5-membered ring systems in spite of their wide distribution in nature has progressed slowly in comparison to the corresponding 6-membered ring systems.[2] This is largely due to the conformational mobility of 5-membered rings, the low barrier for the "pseudorotation" and the great number of conformations with nearly equal energies.

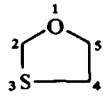
Two reports have been published dealing with conformational properties of some 2-substituted 1,3-oxathiolanes. Pasto *et al.*[3] assumed that a t-Bu substituent at position 2 biases the conformational mobility in 1,3-oxathiolanes and used chemical shift calculations to estimate conformational energies for pseudoaxial alkyl groups at that position. Wilson, Jr. *et al.*[4] investigated also the conformational status in 2-substituted 1,3-oxathiolanes with the aid of ^{1}H NMR techniques. They concluded that the most stable pseudorotamer is that with the C_5 as the "flap" atom whereas the former authors[3] regarded the conformation with the oxygen as the "flap" atom a favoured one. Both of the above reports left several questions without answers and showed clearly that more work is required.

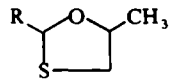
Several recent reports[5–9] have confirmed the validity of equilibration study in connection with NMR spectroscopy to clarification of conformational problems. It was very probable that a similar investigation, applied to suitably substituted 1,3-oxathiolanes, might lead to a better understanding of conformational effects in these compounds and in 5-membered rings in general.

The 5-methyl-substituted 1,3-oxathiolane system (Scheme 1) has several advantages for a conformational study. Because 1,3-oxathiolanes are cyclic acetals it is easy to synthesize several pairs of stereoisomeric 2-alkyl-5-methyl- and 2-alkyl-2,5-dimethyl-1,3-oxathiolanes. Secondly, these diastereoisomers are readily equilibrated by means of anhydrous acid[1a, 5b, 6, 9] through a reversible ring opening. It is well known that chemical equilibration is one of the most accurate tools of conformational analysis

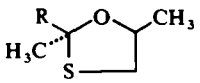
and moreover, the NMR spectra of 5-methyl-substituted 1,3-oxathiolanes are of the ABX type and thus easily analysable.

SCHEME 1

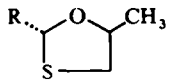




cis
I: R = H
II: R = CH_3
IV: R = Et
VI: R = i – Pr



trans
VIII: R = CH_3
IX: R = Et
X: R = i – Pr
XI: R = t – Bu



trans
III R = CH_3
V: R = Et
VII: R = i – Pr

RESULTS AND DISCUSSION

The 1,3-oxathiolanes studied were prepared by acid-catalysed condensation of 2-hydroxypropanethiol with appropriate aldehydes or ketones. Diastereoisomers of the 2-alkyl-5-methyl-1,3-oxathiolanes were separated by preparative gas chromatography and characterized by physical constants, NMR and chemical equilibration. Equilibrations were effected in ether solution using $BF_3 \cdot Et_2O$ as an acid catalyst. Equilibrated samples were analysed by GLPC to obtain equilibrium constants at various temperatures and from them enthalpy, entropy and free energy differences between the isomers were derived with the method of least squares.

Configurational assignment

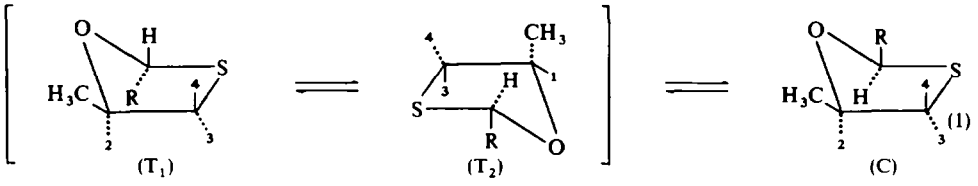
The configurational assignments for the 2,5-disubstituted 1,3-oxathiolanes were based on comparison with the known configurations of the correspondingly substituted 1,3-dioxolanes.[2a] Furthermore, inspection of molecular models[10] reveals that only the *cis* forms may have a vicinal coupling constant J_{45} around 10 Hz (Table 6). It is also seen that in all cases the compound of greater thermodynamic stability has the upfield H(2) chemical shift (with one exception: 2-isopropyl-5-methyl-1,3-oxathiolanes in CCl_4), the downfield R(2) chemical shift (with one additional exception: 2-isopropyl-5-methyl-1,3-oxathiolanes in C_6H_6), the downfield Me(5) chemical shift, the upfield H(5) chemical shift, and a smaller $^4J_{gem}$ in comparison with similar quantities for the thermodynamically less stable isomer. Consequently, the configurational assignment is easily made for the diastereoisomeric 2-alkyl-5-methyl-1,3-oxathiolanes (Tables 3–6).

In the case of 2-alkyl-2,5-dimethyl-1,3-oxathiolanes the situation was more complicated. Thus the synthesis yielded in all cases predominantly the more stable diastereoisomer. The fact that kinetic control favoured the more stable isomers was checked by recording NMR spectra before and after equilibration experiments.

Moreover, we did not succeed in separation of diastereoisomers with the aid of preparative gas chromatography and the isomeric 2,5-dimethyl-2-isopropyl-1,3-oxathiolanes remained unresolved under all available analytical conditions. Consequently, the main basis for the configurational assignment was the obvious assumption that the t-Bu group is sufficiently bulky to favour the pseudoequatorial position. Accordingly, the thermodynamically more stable isomer of 2,5-dimethyl-2-t-butyl-1,3-oxathiolane has the *trans* configuration. Thus the main product in the synthesis of this compound which proved to be the thermodynamically more stable isomer was assigned the *trans* configuration. Comparison of chemical shifts and coupling constants in all three prepared 2,5-dimethyl-2-alkyl-l, 3-oxathiolanes led to the result that 2-ethyl and 2-isopropyl derivatives also existed mainly in the *trans* configuration after synthesis.

Chemical equilibration

For simplicity we take into account (Eq. 1) only the most probable pseudorotamers of *cis*- and *trans*-2-alkyl-5-methyl-1,3-oxathiolanes. The two other relatively stable



pseudorotamers of the *cis*-2,5-dialkyl-1,3-oxathiolanes (C′═C_5 as the flap atom and C″—C_4 as the flap atom) have the same arrangement of 4- and 5-H atoms. In other words $J_{24} + J_{23}$ remains practically constant (Tables 5 and 6). Similarly, the *trans* forms have two other T_1-type pseudorotamers (T_1' and T_1'') and two other T_2-type pseudorotamers (T_2' and T_2''). This means that the sum of the J_{45} coupling constants remains nearly constant and can be regarded as the sum of the respective coupling constants for T_1 and T_2.

Both *trans* conformations include either a pseudoaxial 5-methyl or 2-alkyl group. If these pseudoaxial interactions are of the same order of magnitude we can expect the excess entropy of the *trans* isomers to be around R ln2.

2,5-*Dimethyl*-,3-*oxathiolanes* (R = Me)

In this case the experimental entropy difference 1·33 cal/mol°K (Table 2) is very close to the proposed value R ln2. Hence the interaction energies for pseudoaxial Me groups at positions 2 and 5 do not deviate greatly from each others (Eq. 1). The conformational enthalpy change 1·11 kcal/mol is in surprisingly good agreement with the value $-\Delta G°(2\psi a - CH_3)$ = 1·13 kcal/mol estimated by Pasto *et al.*[3] with the aid of chemical shift calculations.

2-*Ethyl*-5-*methyl*-1,3-*oxathiolanes* (R = Et)

Again the excess entropy of the *trans* configuration suggests nearly equal contributions of T_1 and T_2 (Table 2). The slightly enhanced entropy change is readily

understood when taking into account the total pseudorotation circuits and the rotation of Et groups in all rotamers. The conformational enthalpy difference between the diastereoisomers 1.16 kcal/mol agrees closely with the conformational energy derived by Pasto *et al.*[3] for a pseudoaxial Et group at position 2 (Table 9).

2-Isopropyl-5-methyl-1,3-oxathiolanes (R = i − Pr)

If we compare the free energy differences between the diastereoisomeric 2,5-dialkyl-1,3-oxathiolanes with each other the predominance of *cis* configuration decreases with the increasing size of the 2-substituent. A similar trend is observable in the corresponding series of 2,4-dialkyl-1,3-dioxolanes[2a] although here it is very small. Even the enthalpy difference between the isomeric isopropyl derivatives is appreciably smaller than that for the other two pairs of diastereoisomers (Table 3). Without doubt we can assume that the conformational energy of a pseudoaxial isopropyl group at position 2 is somewhat greater than that for a ψa–Me group on position 5.[3] Consequently, the proportion of T_1 form decreases and that is why the excess entropy of the *trans* configuration decreases. In the *cis* form (C) isopropyl methyl groups exert steric interaction on the 5-Me group and its conformational enthalpy increases. As a consequence the enthalpy difference between the

TABLE 1. EQUILIBRIA BETWEEN ISOMERIC 2,5-DIALKYL- AND 2,2,5-TRIALKYL-1,3-OXATHIOLANES AT DIFFERENT TEMPERATURES

1,3-Oxathiolanes	5°C K[a]	25°C K[a]	45°C K[a]	65°C K[a]	75 C K[a]
2,5-diMe[c]	3·80 ± 0·10[b]	3·36 ± 0·16	2·97 ± 0·09	2·75 ± 0·05	2·50 ± 0·08
2-Et-5-Me[c]	3·29 ± 0·15	2·85 ± 0·18	2·53 ± 0·10	2·26 ± 0·07	
2-i-Pr-5-Me[c]	2·55 ± 0·10	2·37 ± 0·09	2·16 ± 0·08	2·03 ± 0·06	
2-Et-2,5-diMe[d]	1·58 ± 0·04	1·525 ± 0·04	1·49 ± 0·03	1·445 ± 0·11	
2-t-Bu-2,5-diMe[d]		4·99 ± 0·17			

[a] GLPC area ratios. The values shown are the means of 2–3 parallel samples which were analysed 6–12 times.

[b] Standard deviation.

[c] K = [*cis*]/[*trans*].

[d] K = [*trans*]/[*cis*].

Response ratios assumed to be unity. In reality we measured the response ratio for 2-isopropyl-5-methyl-1,3-oxathiolanes (RR = [*trans*]/[*cis*] = 1·079 ± 0·010) and for 2-isopropyl-2,4-dimethyl-1,3-oxathiolanes (RR = [*cis*]/[*trans*] = 1·013 ± 0·004) and for 2-t-butyl-2,4-dimethyl-1,3-oxathiolanes (RR = [*cis*]/[*trans*] = 1·007 ± 0·002).

diastereoisomers is smaller than one can expect merely on the basis of 1,3-*trans* annular interactions. However, the equilibration results (Tables 1 and 2) suggest that the value 2·01 kcal/mol[3] for the conformational energy of a pseudoaxial isopropyl group at position 2 is too high. It is not likely that so small a difference exists in this case between the conformational energies for 1,3-oxathiolane (2·01 kcal/mol) and for cyclohexane (2·15 kcal/mol[6b]). If we compare the values for Me and Et groups in both series of compounds (Table 9) we see that the values in alkylcyclohexanes are greater by a factor of 1·52. Consequently, the conformational energy of a pseudoaxial

TABLE 2. THERMODYNAMIC QUANTITIES FOR THE STUDIED ISOMER EQUILIBRIA

Equilibrium	$-\Delta H°$, cal/mol	$\Delta S°$, cal/mol°K	$-\Delta G°$, cal/mol[a]
trans-2,5-diMe ⇌ *cis*-2,5-diMe	1113 ± 77	1·33 ± 0·24	716
trans-2-Et-5-Me ⇌ *cis*-2-Et-5-Me	1165 ± 17	1·82 ± 0·06	622
trans-2-i-Pr-5-Me ⇌ *cis*-2-i-Pr-5-Me	*722 ± 32	0·73 ± 0·10	†504
2-Et-*cis*-2,5-diMe ⇌ 2-Et-*trans*-2,5-diMe	266 ± 19	0·05 ± 0·06	251
2-t-Bu-*cis*-2,5-diMe ⇌ 2-t-Bu-*trans*-2,5-diMe	—	—	953

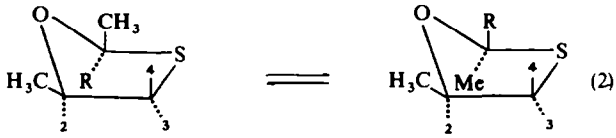
[a] At 25°.

* 773 cal/mol after correction with the response factor (Table 1).

† 555 cal/mol after correction with the response factor (Table 1).

isopropyl group at position 2 in the 1,3-oxathiolane ring should be around 1·4 kcal/mol. The latter value is even in close agreement with the other result of Pasto *et al.*[3] that $\Delta G°$ (Me) − $\Delta G°$ (i − Pr) equals to 0·28 kcal/mol (1·4 − 1·1 = 0·3 kcal/mol).

2,5-Dimethyl-2-alkyl-1,3-oxathiolanes



(2)

For simplicity we consider the configurational equilibria with the aid of only one suitable pseudorotamer (C_t and C_c) for each configuration (Eq. 2). Both the vicinal coupling constants J_{45} and chemical shifts for the more stable *trans* configuration are in accordance with the C_t conformation. The almost negligible entropy difference between *cis*- (C_c: R = Et) and *trans*-2,5-dimethyl-2-ethyl-1,3-oxathiolanes (C_t: R = Et) lends support to the fact that both isomers have only one favoured conformation or similar sets of pseudorotamers. The Me inside rotamer of the Et group is unfavoured in both isomers because of steric contradiction between the Me group and H_2 in C_c and between the Me group and H_4 in C_t. The experimental enthalpy difference 0·27 kcal/mol does not differ greatly from the result of *Pasto et al.*[3] ($\Delta G°$(Me) − $\Delta G°$(Et) = 0·19 kcal/mol).

We had no success in determining the relative stabilities of the isomeric 2,5-dimethyl-2-isopropyl-1,3-oxathiolanes because of their poor resolution under all available GLPC conditions. As we encountered difficulties in the equilibration of 2,5-dimethyl-2-t-butyl-1,3-oxathiolanes. That is why only the free energy difference was measured in the latter case. The result shows that a t-Bu group at position 2 favours the pseudo-equatorial position by about 2·0 kcal/mol (Tables 2 and 9). Pasto *et al.*[3] concluded this predominance to exceed 2·9 kcal/mol but a free energy difference around 2 kcal/mol is, however, still enough to justify their main conclusions.

The preceding discussion illustrates mainly the differences in the conformational energies with the aid of pseudoaxial interactions. The real situation may more or

less deviate from this consideration but the good agreement between our results and the conformational energies reported by Pasto *et al.*[3] confirms the view that the 1,3-oxathiolane ring is a moderately "biased" system.

NMR spectra

The ^{1}H NMR spectra of 2-substituted and 2,2-disubstituted 1,3-oxathiolanes have been previously investigated.[3,4] Typical H(4)—H(5) vicinal coupling constants in these reports span the following ranges (Eq. 3): J_{14} 4·4–5·8 Hz; J_{13} 2·2–3·2 Hz; J_{24} 9·6–10·6 Hz and J_{23} 3·8–5·5 Hz.

(3)

Inspection of Table 3 indicates several common features in the chemical shifts of H(5) (H_1 or H_2), H(4) (H_3) and H(4') (H_4). The 2-alkyl-5-methyl-1,3-oxathiolanes with the *cis* configuration ($\delta(H_2)$ ab. 237 Hz in CCl_4) and those with the *trans* configuration ($\delta(H_{1-2})$ 260–266 Hz in CCl_4) (*cf* Eq. 1) are easily identified. The similarity of the chemical shifts of H(4) and H(5) protons in all 2,2,5-trialkyl-substituted 1,3-oxathiolanes confirms their similar configurations (*cf* Eq. 2). Table 4 lists the chemical shifts for the alkyl groups in the compounds studied and again a good correlation is observed between the configurational assignments and the chemical shift values. All spectra were recorded both in CCl_4 and C_6H_6 solutions and the values for ASIS are also shown in Tables 3 and 4.

Table 5 contains the values of the different methyl-hydrogen coupling constants. For 2,5-dimethyl-1,3-oxathiolanes (II and III) $^2J_{Me}$ has been measured separately from the signal of the methyl group and from that of the acetal hydrogen H(2). $^2J_{Me}$ values for the isomer pairs IV, V and VI, VII show clearly that the rotation of the ethyl or isopropyl group is more hindered in the *trans* configurations V and VII. In other words the *anti* arrangement of H(2) and the ethyl —CH_2— or isopropyl —CH— protons becomes more favoured leading to an increase in the value of $^2J_{Me}$. This is in good agreement with the pseudoaxial character of ethyl and isopropyl groups in V and VIII, respectively.

The most informative NMR results are, however, the values of the vicinal coupling constants in Tables 6 and 7. As stated *cis*-2-alkyl-5-methyl-1,3-oxathiolanes (II, IV and VI) consist principally of pseudorotamers in which H(4)–H(5) vicinal coupling constants correspond to J_{24} and J_{23} (Eq. 1 and 3). A similar situation prevails in all 2,5-dimethyl-2-alkyl derivatives (VIII–XI). In contrast, 5-methyl- (I) and *trans*-2-alkyl-5-methyl-1,3-oxathiolanes (III, V and VII) are mixtures of two separate (series of) pseudorotamers of which the one has the J_{24}, J_{23} arrangement and the other the J_{14}, J_{13} arrangement (Eq. 3). Unfortunately, we do not know the exact values of J_{14} and J_{13}.

Nevertheless, it is possible to test our conformational conclusions. Let us assume that $J_{24} + J_{23}$ of the *cis*-2-alkyl-5-methyl-1,3-oxathiolanes is equal to the same sum in the T_1 forms of the *trans* configurations (Eq. 1). Further we must assume that the sum of all four vicinal coupling constants J_{45} (T_1) + J_{45}(T_2) remains constant in

TABLE 3. CHEMICAL SHIFTS OF H(4) AND H(5) PROTONS IN CCl_4 AND C_6H_6. H(5) EQUALS TO H_1 OR H_2, H(4) TO H(3) AND H(4') TO H_4 (*cf* EQ. 3). ALL VALUES IN HZ FROM TMS

	1,3-Oxathiolane	$\delta_{H(5)}$ CCl_4	$\delta_{H(5)}$ C_6H_6	Δ	$\delta_{H(4)}$ CCl_4	$\delta_{H(4)}$ C_6H_6	Δ	$\delta_{H(4')}$ CCl_4	$\delta_{H(4')}$ C_6H_6	Δ
I	5-Me-	237·8	217·9	19·8	150·0	134·2	15·8	180·0	159·4	20·6
II	*cis*-2,5-diMe	236·6	219·4	17·2	156·9	146·8	10·1	179·7	161·0	18·7
III	*trans*-2,5-diMe-	266·0	248·5	17·5	151·4	140·3	11·1	184·7	163·8	20·9
IV	*cis*-2-Et-5-Me-	237·7	221·5	16·2	151·6	142·1	9·5	177·6	159·3	18·3
V	*trans*-2-Et-5-Me-	261·4	245·7	15·7	155·2	140·3	14·9	180·0	161·4	18·6
VI	*cis*-2-i-Pr-5-Me-	237·8	223·1	14·7	147·6	139·8	7·8	175·8	158·1	17·7
VII	*trans*-2-i-Pr-5-Me-	259·9	249·4	10·5	154·5	140·8	13·7	177·4	161·3	16·1
VIII	2,2,5-triMe-	254·1	242·9	11·2	167·7	151·0	16·7	187·3	162·9	24·4
IX	*trans*-2,5-diMe-2-Et	255·0	243·8	11·2	153·4	146·1	7·3	177·0	160·5	16·5
X	*trans*-2,5-diMe-2-i-Pr-	255·3	243·2	12·1	149·6	139·7	9·9	175·9	157·1	18·8
XI	*trans*-2,5-diMe-2-t-Bu-	255·2	246·6	8·6	145·9	139·9	6·0	173·9	158·5	15·4

TABLE 4. CHEMICAL SHIFTS OF H(2), ME(2), ME(5) AND R(2) PROTONS IN CCl_4 AND C_6H_6. ALL VALUES IN HZ FROM TMS

Compound No.	$\delta_{H(2)}$			$\delta_{Me(2)}$			$\delta_{Me(5)}$			$\delta_{R(2)}$		
	CCl_4	C_6H_6	Δ	CCl_4	C_6H_6	Δ	CCl_4	C_6H_6	Δ	CCl_4	C_6H_6	Δ
I	283·2	273·0	10·2	—	—	—	81·9	63·2	18·7	—	—	—
	293·4	284·8	8·6									
II	306·5	304·6	1·9	91·1	88·5	2·6	82·7	66·2	16·5	—	—	—
III	316·9	315·8	1·1	88·6	84·2	4·4	76·8	60·7	16·1	—	—	—
IV	300·4	301·3	−0·9	—	—	—	82·4	65·9	16·5	104·6[α]	107·0[α]	−2·4
										59·1[β]	56·1[β]	3·0
V	304·9	308·3	−3·4	—	—	—	76·9	61·4	15·5	101·1[α]	100·1[α]	1·0
										56·3[β]	52·6[β]	3·7
VI	295·0	296·1	−1·1	—	—	—	82·0	65·2	16·8	56·2	59·1	−2·9
										58·3	60·6	−2·3
VII	291·1	298·0	−6·9	—	—	—	76·3	61·3	15·0	54·1	60·3	−6·2
										57·8	63·9	−6·1
VIII	—	—	—	93·3	91·2	2·1	80·6	66·1	14·5	—	—	—
				95·8	97·8	−2·0						
IX	—	—	—	90·9	91·3	−0·4	79·7	65·2	14·5	106·6[α]	110·2[α]	−3·6
										58·5[β]	63·2[β]	−4·7
X	—	—	—	89·3	90·9	−1·6	80·1	63·4	16·7	52·9	57·7	−4·8
										59·9	62·2	−2·3
XI	—	—	—	92·7	94·7	−2·0	80·7	63·6	17·1	60·2	66·3	−6·1

[α] = CH_2 in ethyl group.
[β] = CH_3 in ethyl group.

TABLE 5. THE VALUES OF H(5)-Me(5) AND H(2)-R(2) COUPLING CONSTANTS (Hz) FOR THE VARIOUS COMPOUNDS IN CCl_4 AND C_6H_6

Compound No.	J_{5-Me}		J_{2-Me}		J_{2-H}		J_{Me-R}	
	CCl_4	C_6H_6	CCl_4	C_6H_6	CCl_4	C_6H_6	CCl_4	C_6H_6
I	6·04	6·23	—	—	5·29	5·21	—	—
II	5·82	6·15	5·63	5·70	5·58	5·91	—	—
III	6·28	5·98	6·04	5·80	5·66	5·75	—	—
IV	6·14	6·07	—	—	5·48	5·83	6·89	6·95
V	6·32	6·17	—	-	5·94	6·26	6·75	7·14
VI	6·14	5·90	—	—	6·00	6·25	6·67	6·61
VII	6·17	5·71	—	—	6·86	7·07	6·73	6·48
VIII	5·98	6·18	—	—	—	—	—	—
IX	6·12	6·17	—	—	—	—	7·07	7·25
X	6·03	6·29	-	—	—	—	6·95	6·45
XI	5·64	5·20	—	—	—	—	—	—

TABLE 6. THE VALUES OF H(4)-H(5) COUPLING CONSTANTS IN THE VARIOUS COMPOUNDS. ALL SPECTRA WERE ANALYZED ACCORDING TO THE ABX METHOD WHERE H(5) IS EQUAL TO X, H(4) TO B AND H(4') TO A

	1,3-Oxathiolane	$J_{AB} = J_{gem}$		J_{AX}		J_{BX}	
		CCl_4	C_6H_6	CCl_4	C_6H_6	CCl_4	C_6H_6
I	5-Me-	9·86	9·79	8·64	8·70	5·16	5·20
II	*cis*-2,5-diMe-	9·69	9·59	9·78	9·71	5·04	4·95
III	*trans*-2,5-diMe-	10·05	10·15	6·69	6·67	5·09	5·17
IV	*cis*-2-Et-5-Me-	9·78	9·81	9·98	9·85	4·79	4·62
V	*trans*-2-Et-5-Me-	10·17	10·03	6·63	6·60	5·23	5·17
VI	*cis*-2-i-Pr-5-Me-	9·80	9·84	10·00	10·31	4·77	4·52
VII	*trans*-2-i-Pr-5-Me-	10·27	10·17	6·32	6·28	5·25	5·26
VIII	2,2,5-triMe-	9·91	10·06	9·99	9·76	4·58	4·43
IX	*trans*-2,5-diMe-2-Et-	10·08	10·26	10·14	10·52	4·29	4·14
X	*trans*-2,5-diMe-2-i-Pr-	10·17	10·25	10·23	10·43	4·31	4·07
XI	*trans*-2,5-diMe-2-t-Bu-	10·21	9·97	10·64	10·65	3·87	4·16
		$J_{44'} = J_{34}$		J_{24} or J_{14}		J_{23} or J_{13}	

TABLE 7. THE SUMS OF THE VICINAL COUPLING CONSTANTS OF THE 1,3-OXATHIOLANES AND THE SUMS OF ALL FOUR VICINAL COUPLING CONSTANTS OF THE CORRESPONDING 1,3-OXATHIOLANES WITHOUT A Me GROUP AT POSITION 5

1,3-Oxathiolane	$J_{45} + J_{4'5}$, Hz		ΣJ^a, Hz
	CCl_4	C_6H_6	CCl_4
I	13·80	13·90	23·40[b]
II	14·82	14·66	23·80[b]
III	11·78	11·84	23·80[b]
IV	14·77	14·47	23·86[c]
V	11·86	11·77	23·86[c]
VI	14·77	14·83	24·09[b]
VII	11·57	11·54	24·09[b]
VIII	14·57	14·19	
IX	14·43	14·66	
X	14·54	14·50	
XI	14·51	14·81	

[a] ΣJ in C_6H_6 assumed to be 0·10 Hz smaller.
[b] Values of Pasto *et al.*[3]

the various T_1, T_2 pseudorotamer pairs and that this sum does not deviate greatly from ΣJ for the corresponding 2-alkyl derivative. Taking these limitations into account we get

$$J_{45}(T_2) = J_{14} + J_{13} = \sum J - J_{45}(C) \quad (4)$$

where J_{45} (C) = J_{24} + J_{23} for the *cis* isomer in question and further

$$\sum J_{trans} = x_B J_{45}(T_2) + (1 - x_B) J_{45}(T_1) \quad (5)$$

where x_B would like to represent the proportion of the pseudoaxial 5-methyl group and J_{45} (T_1) equals to the observed value of ΣJ_{cis}. Table 7 lists the values of ΣJ, ΣJ_{cis} and ΣJ_{trans} for the different compounds. After applying Eq. (5) the relative populations of the two possible pseudorotamer (familie)s were obtained with the results shown in Table 8. The calculated free energy differences are in surprisingly

TABLE 8. THE RELATIVE POPULATION OF THE TWO POSSIBLE CONFORMER FAMILIES OF 5-METHYL-1,3-OXATHIOLANE AND *trans*-2-ALKYL-5-METHYL-1,3-OXATHIOLANES IN CARBON TETRACHLORIDE AND BENZENE AND THE CORRESPONDING FREE ENERGY DIFFERENCES AT 33·2°

Compound	5-Me				
	% Pseudo-eq	% Pseudo-ax	Solvent	K	$-\Delta G°$, kcal/mol
5-Me (I)	87·4	12·6	CCl_4	6·93	1·15
5-Me	87·4	12·6	C_6H_6	6·93	1·15
trans-2,5-diMe (III)	48·0	52·0	CCl_4	1·09	0·05
trans-2,5-diMe	49·8	50·2	C_6H_6	1·01	0·00
trans-2-Et-5-Me (V)	48·8	51·2	CCl_4	1·05	0·03
trans-2-Et-5-Me	47·9	52·1	C_6H_6	1·09	0·05
trans-2-isoPr-5-Me (VI)	41·3	58·7	CCl_4	1·42	0·21
trans-2-isoPr-5-Me	42·0	58·0	C_6H_6	1·38	0·20

good agreement with the enthalpy differences derived from the equilibration experiments. The conformational energy of a pseudoaxial Me group at position 5 seems to be about 1·15 kcal/mol and the difference $\Delta G°$ (5a—Me) − $\Delta G°$ (2a—Me) very close to zero (Table 8). Similarly, $\Delta G°$(5a—Me) − $\Delta G°$(2a—Et) equals to 0·04 kcal/mol and thus the conformational energy of a pseudoaxial Et group at position 2 is ab. 1·19 kcal/mol in close agreement with the Pasto's value 1·16 kcal/mol. We are also able to get a value for the conformational interaction of a pseudoaxial isopropyl group at position 2 since $\Delta G°$ (5a-Me) − $\Delta G°$ (2a-*i*-Pr) equals to 0·21 kcal/mol and hence $-\Delta G°$ (2a-*i*-Pr) is ab. 1.36 kcal/mol in good agreement with our preceding estimate 1·4 kcal/mol. A summary from the conformational energies of 1,3-oxathiolanes is presented in Table 9 together with some comparative data for alkylcyclohexanes and alkyl-substituted 1,3-oxathianes.

CONCLUSION

The results of both our equilibration studies and investigation of NMR spectra lead to the conclusion that 1,3-oxathiolane ring is much less flexible than 1,3-dioxolane ring.[2a] The conformational situation in the studied 1,3-oxathiolanes differs substantially but not fundamentally from that found in 1,3-oxathianes[2d] and cyclohexanes.[2a]

6-Membered rings exist generally in a well-defined conformation—the chair form. The substituents on the chair are either equatorially or axially orientated and consequently, equatorially and axially substituted 1,3-oxathianes and cyclohexanes have different energetics and spectral properties. In 1,3-oxathiolane itself, there is no

TABLE 9. THE ENERGY CONTRIBUTIONS OF DIFFERENT PSEUDOAXIAL INTERACTIONS IN 1,3-OXATHIOLANES AND THE VALUES OF THE CORRESPONDING CONFORMATIONAL ENERGIES IN ALKYLCYCLOHEXANES AND ALKYL-SUBSTITUTED 1,3-OXATHIANES[2d, 6b]

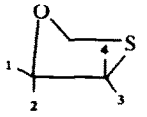
Alkyl Group	Conformational energy, kcal/mol 1,3-oxathiolanes	1,3-Oxathianes[2d]	Cyclohexanes[6b]
5a- or 6a-Me	1·15 (J_{45})	2·93 (CE)	1·70
2a-Me	1·11 (CE)	3·25 (CE)	1·70
	1·17 (J_{45})		
	1·13 (CS; Ref 3)		
2a-Et	1·16 (CE)	3·25 (CE)	1·75
	1·19 (J_{45})		
	1·16 (CS; Ref 3)		
2a-i-Pr	1·36 (J_{45})	3·55 (CE)	2·15
	1·4 (CE; est.)		
2a-t-Bu	2·0 (CE)		ab. 5
Δ(2a-Et,2a-Me)	0·02 (J_{45})		
	0·05 (CE)		
	0·27 (CE; *gem* subst.)		
	0·19 (Ref 3; *gem* subst.)		
Δ(2a-i-Pr,2a-Me)	0·22 (J_{45})		
	0·28 (Ref 3; *gem* subst.)		

CE is by chemical equilibration; J_{45} with the aid of vicinal coupling constants and CS by means of chemical shifts.

clear-cut preference for a certain ring conformation but substitution of the ring may greatly affect to the depths of separate minimum energy wells. However, our results confirm the opinion of Pasto *et al.*[3] that alkyl-substituted 1,3-oxathiolanes have only one preferred pseudorotameric state. Also Wilson *et al.*[4] came to a similar conclusion although they selected a slightly different pseudorotamer as the most probable one.

If we compare the observed enthalpy differences between the *cis*- and *trans*-2,5-dialkyl-1,3-oxathiolanes (0·7–1·2 kcal/mol) with those between *cis*- and *trans*-1,3-

TABLE 10. THE DIHEDRAL ANGLES BETWEEN H(4) AND H(5) PROTONS ACCORDING TO VARIOUS AUTHORS



Angle between protons	Pasto *et al*[3]	Wilson, Jr., *et al*[4]	This work
13	91°	90·7°	90 ± 5°
14	25°	30·3°	30 ± 5°
23	33°	38·3°	40 ± 5°
24	148°	159·3°	155 ± 5°

dimethyl-cyclopentanes (0·5 kcal/mol[2a]) it is seen that the former values are greater by a factor of 1·5–2·4. In this respect a close resemblance prevails in the system 1,3-oxathiolane-cyclopentane and 1,3-oxathiane-cyclohexane because the conformational energies of axial alkyl groups in 1,3-oxathianes[2d] are greater than those in cyclohexanes[6b] by a factor of 1·7–1·8 (dealing only with 2 and 6 positions). This is further support for the consideration that alkyl-substituted 1,3-oxathiolanes generally have a minimum energy conformation which is suitable to demonstrate the real situation. In our mind this model would be an envelope with the O atom at the tip.

Additional support for the above conclusion is obtained from the NMR results. A highly flexible 5-membered ring system does not give clearly different and easily analysable spectra for the diastereoisomeric 1,3-dialkyl-substituted derivatives. Moreover, coupling constant calculations would not give good agreement with the energy parameters determined by chemical equilibration. However, our results and those of Pasto *et al.*[3] and Wilson *et al.*[4] show that especially in the case of alkyl-substituted 1,3-oxathiolanes "biased" with a 5-Me group relatively simple and clearly distinct ^{1}H NMR spectra are obtained and compilations carried out on the basis of chemical shifts[3] or H(4)–H(5) vicinal coupling constants give excellent agreement with the equilibration results (Table 9). To demonstrate the dihedral angles which correspond to the various coupling constants Table 10 compares our guess with the angles proposed by other workers.[3,4]

Of course, our present results do not form a final and complete set of observations to explain the total conformational status of 1,3-oxathiolanes but it seems to be desirable to extend this study to some 4-methyl-substituted and 4,5-dimethyl-substituted

TABLE 11. PHYSICAL CONSTANTS OF THE PREPARED ALKYL-SUBSTITUTED 1,3-OXATHIOLANES

1,3-Oxathiolane	B.p. °C/torr	n_D^{25}	d_4^{25}	Yield, %
5-Me	62–64/64	1·4877	1·0810	13
2,5-diMe	40–42/35[a]	*cis* 1·4734	1·0189	40[a]
		trans 1·4748		
2-Et-5-Me	79–80/58[a]	*cis* 1·4701	0·9900	31[a]
		trans 1·4722		
2-i-Pr-5-Me	88–89/55[a]	*cis* 1·4654	0·9699	58[a]
		trans 1·4678		
2,2,5-triMe	42–44/29	1·4648	0·9788	25
2-Et-2,5-diMe	84–85/74[a]	1·4648[a]	0·9825[a]	58[a]
2-i-Pr-2,5-diMe	95–97/63[a]	1·4670[a]	0·9635[a]	59[a]
2-t-Bu-2,5-diMe	106–108/61[a]	1·4700[a]	0·9566[a]	31[a]

[a] For mixtures of diastereoisomers.

derivatives. It is very interesting to know if for instance pseudoaxial interactions due to 5-axial or 2-axial alkyl groups are much greater than those due to a pseudoaxial Me group at position 4. This is probable since a *syn*-axial interaction due to an axial Me group at position 4 is 1.15 kcal/mol less than that due to an axial Me group at position 6 in alkyl-substituted 1,3-oxathianes.[2d]

EXPERIMENTAL

Propylene oxide was prepared by dropwise addition of a 25:75 mixture of 2-chloropropanol and 1-chloro-2-propanol in a concentrated KOH soln at 70° whence the formed oxide distilled over.

2-Hydroxypropanethiol was prepared from the crude propylene oxide and thiourea by the method of Bordwell and Andersen.[11] The product boiled at 56–57°/14 torrs, its n_D^{20} was 1·4911 and d_4^{20} 1·071. The yield varied and was at most 44%.

1,3-Oxathiolanes were prepared by boiling equimolar mixtures of the aldehyde component and the 2-hydroxypropanethiol in a water entrainment unit until the formation of water ceased. Dichloromethane was used as solvent and *p*-toluenesulfonic acid as catalyst. After neutralization with diethylamine the solvent was distilled off and the residue fractionated at reduced pressure. All of the products were further purified by running through Perkin–Elmer F-21 preparative gas chromatograph equipped with a $\frac{3}{8}$ in × 4·5 m stainless steel column containing 5% Carbowax 20 M on Chromosorb G (60/80 mesh), or 10% FFAP on Chromosorb A (60/80 mesh). When possible also the *cis* and *trans* forms were separated (Table 11).

Equilibrations were carried out at several temps except 2-isopropyl-2,5-dimethyl- and 2-t-butyl-2,5-dimethyl-1,3-oxathiolanes to estimate the values of different thermodynamic quantities with the aid of least squares method. Diethyl ether was used as solvent and $BF_3 \cdot Et_2O$ as acidic catalyst. The samples consisted 10% v/v of the substrate and the catalyst in a 1:10 molar ratio to the 1,3-oxathiolane in question.

Before analysis each sample was quenched by addition of methanolic NaOMe. In all cases the equilibria were established after 2–6 weeks. Equilibria were considered reached when the same and reproducible ratios were obtained from both the initially *cis*-rich and *trans*-rich samples or from two separate samples which were analysed with at least a two weeks time interval.

If both stereoisomers in question were available the equilibration was started using samples including initially either the one or the other isomeric form. Two to four samples were equilibrated in each case. The equilibria were analysed using Perkin–Elmer F 11 gas chromatograph equipped with a 2 m × $\frac{1}{8}$ in column containing 5% Carbowax 20 M on Chromosorb G (60/80 mesh). To separate the isomeric 2-t-butyl-2,5-dimethyl-1,3-oxathiolanes a 10 m × $\frac{1}{8}$ in column containing 5% Carbowax 20 M and 0·5% KOH on Chromosorb G was used.

NMR spectra were recorded on Perkin–Elmer R 10 NMR spectrometer working on 60 MHz. The solutions contained 450 μl the solvent—carbon tetrachloride or benzene—and 50 μl of the substrate. These results are shown in Tables 3–6 and the equilibration results in Tables 1 and 2.

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