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Conformational Analysis of Sulphur-containing Six-membered Heterocycles

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The review deals with one of the problems of dynamic stereochemistry—the conformational analysis of six-membered heterocycles containing bivalent sulphur. The general conformation characteristics of the above class of compounds are reviewed.
The bibliography includes 115 references.

CONTENTS

I. Introduction 107
II. General problems in the conformational analysis of sulphur-containing compounds 107
III. Conformations of six-membered sulphur-containing heterocycles 109
1. Derivatives of tetrahydrothiopyran
2. Derivatives of 1,2-dithiane
3. Derivatives of 1,3-oxathiane and 1,3-dithiane
4. Derivatives of 1,4-oxathiane and 1,4-dithiane
5. Heterocycles with several sulphur atoms
6. Sulphur-containing heterocycles with a multiple bond in the ring

I. INTRODUCTION

The extensive use of conformational concepts in the interpretation of various transformations of organic compounds is due to the relative simplicity and largely universal applicability of the main postulates of conformational analysis. On the one hand, it involves (at least in its commonest form) taking into account the steric interaction of non-bonded groups of atoms (usually repulsion), from which the most stable conformation is deduced, and, on the other, the steric hindrance in various conformations to the approach of the attacking agent. However, it is quite evident that the presence of a powerful additional non-steric interaction between two or more groups in the molecule could allow the relative stability to be determined precisely by this factor. Such additional interactions (usually regarded as "effects" specific to the given group) are associated mainly with the introduction of polar functional groups and heteroatoms. Hence the unusual conformational behaviour of heterocyclic compounds in relation to their alicyclic analogues becomes understandable.

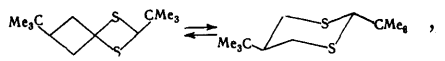
The replacement of a carbon atom in an alicyclic system by a heteroatom can lead to a change both of molecular geometry and of electronic structure. Although the influence of a change in geometry is to a rough approximation often insignificant, particularly in a purely qualitative treatment, nevertheless on passing to a quantitative treatment this inevitably leads to the conformational non-equivalence of the individual positions in the molecule and hence to a wide variety of conformational behaviour of these systems. Sometimes such geometrical changes are shown also on a qualitative level. The change in electronic structure leads to a change in the electric moments, polarity, and degree of solvation, etc. of heterocyclic systems compared with their alicyclic analogues, which is also bound to have an effect on their conformational properties.

The aim of the present review is to examine the conformational behaviour of six-membered systems containing a bivalent sulphur atom. Fairly extensive experimental data have now accumulated, demonstrating the fundamental difference between the conformational behaviour of sulphur-containing heterocycles and not only the corresponding alicyclic compounds but also the analogous oxygen-containing heterocycles. This is why we thought it useful to review the available literature data on the conformational behaviour of six-membered heterocycles containing a bivalent sulphur atom and to formulate its characteristic.

II. GENERAL PROBLEMS IN THE CONFORMATIONAL ANALYSIS OF SULPHUR-CONTAINING COMPOUNDS

The chair conformation of cyclohexane is the most stable and the difference between the energies of the boat and chair forms is estimated as 5–7 kcal mole^{-1} (Table 1) [1-3]. On passing to heterocyclic compounds, the fundamental problem is the change in the energy difference between the chair and flexible conformations (twist-boat). This difference may be related to a change in the barrier to rotation about the C-heteroatom bond compared with the C–C bond. The barrier to rotation about the C–S bond (2.1 kcal mole^{-1} in dimethyl sulphide [4]) is smaller than that to rotation about the C–C bond (3.4 kcal mole^{-1} in propane [5]). Thus, since the eclipsed conformations of sulphur-containing heterocycles are energetically less favourable than those of carbocyclic compounds, presumably compounds of the first kind will show a greater tendency towards existence in the boat conformations. We may note also that the flagstaff–flagstaff interaction, which destabilises the boat conformation, is likewise weakened by virtue of the greater length of the C–S bond. For example, in 1,3-dithiane this distance is 2.4 Å, while in 1,3-dioxane it is 1.46 Å. [6]

Numerous experimental data on the geometry of sulphur-containing heterocycles (derivatives of oxathiane [7,8] and dithianes [9-12]) show that they exist in the chair conformation, which is the main, most stable conformation. However, there are reliable experimental data showing a decrease of the energy difference between the chair and flexible forms. For example, the study of the epimerisation of 2,5-di-t-butyl-1,3-dithiane showed that the difference between the enthalpies of these conformations,



is 3.4 kcal mole^{-1} (Table 1). [13,14]

Table 1. Thermodynamic parameters of the conformational equilibria of the chair/twist type.

System	$\Delta G_{25°}$, kcal mole^{-1}	ΔH, kcal mole^{-1}	ΔS, cal mole^{-1} deg^{-1}	References
Cyclohexane	4.9	5.9	3.5	2
1,3-Dioxane	5.7	7.1	4.8	14,27,28
1,3-Dithiane	1.8	3.4	5.3	13,14

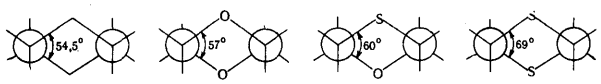
Cyclohexene exists in the stable half-chair conformation [15-17] and the "sofa" conformation is in many instances more stable only for polycyclic compounds [18]. There is also evidence that this conformation predominates for certain sulphur-containing heterocycles [19] (see Section III, 6).

Here special emphasis must be laid on the fundamental difference between sulphur-containing heterocycles and their oxygen analogues. Bearing in mind that the barrier to rotation about the C–O bond is greater than for the C–S bond [20] (2.7 kcal mole^{-1} in methyl ether [21]), the energy difference between the chair and boat conformations of oxygen-containing systems is presumably the same as for cyclohexane. There has been a fairly lively discussion of this problem in the literature; however, the evidence in support of the dominance of boat conformations is frequently based on incorrect theoretical postulates or an incorrect interpretation of experimental data. (See, for example, the discussion concerning 1,4-dioxane derivatives [22-24].) The theoretical estimates of the enthalpy differences between the two conformations of tetrahydropyran [25] (3.9 kcal mole^{-1}) and 1,3-dioxane [26] (2.2 kcal mole^{-1}) evidently cannot be regarded as satisfactory because they were derived taking into account the barrier in methanol, whereas it would be more logical to employ the barriers to rotation in ethers†. Reliable experimental data on the thermodynamics of epimerisation and the heats of formation of 1,3-dioxane derivatives yield 7.1 kcal mole^{-1} for the difference between the enthalpies of the chair and boat forms [14,27-29]. The thermodynamic parameters of the conformational equilibrium of the chair–twist type for the cyclic compounds under consideration are compiled in Table 1.

Thus the specific features of sulphur-containing heterocycles should be revealed in a tendency towards an increased fraction of boat conformations in conformational equilibrium; this should be particularly true of heterocycles with several heteroatoms.

Next, the replacement of a carbon atom by a sulphur atom in a six-membered alicyclic compound should lead to an appreciable distortion of the geometry of the ring, since the length of the C–S bond (1.81 Å) [30] is much greater than that of the C–C bond (1.52 Å) and the C–S–C angle (about 100°) [7-12] differs appreciably from the tetrahedral value. This should lead to an increase of the degree of puckering of the ring and a change in the magnitude of the 1,3-diaxial repulsion.

We shall consider the effect of these factors on the conformational characteristics. An increase in the degree of puckering should lead to an increase of the dihedral angles in the ring.



(I) (II) (III) (IV)

The dihedral angles for cyclohexane [31] (see Buys and Geise [32] for a compilation of data on cyclohexane), dioxane [31], oxathiane [33,34], and dithiane [34,35] are shown in diagrams (I)–(IV). The "average dihedral angle" has been introduced [34] as a parameter characterising the puckering or flattening of the ring. For the above compounds, the values of this parameter are 54.5°, 57.9° (Romers et al. [34]), 58.3° (Schultz et al. [33]), and 65° (Schultz et al. [33]) respectively, which also confirms the above view. Thus, whereas the cyclohexane ring is flattened, the introduction of a sulphur atom leads to an appreciable increase of the dihedral angles.

Table 2. The parameters R for certain six-membered compounds of type X⬡Y.

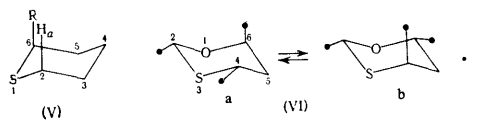
X	Y	I_{trans}, Hz	I_{cis}, Hz	R	Refs.	X	Y	I_{trans}, Hz	I_{cis}, Hz	R	Refs.
CD_2	CD_2	8.04	3.65	2.20	40	S	S	8.11	2.40	3.38	36
O	O	6.11	2.78	2.20	36	O	CD_2	7.41	3.87	1.9	37
O	S	7.35	2.65	2.77	36	S	CD_2	8.54	3.26	2.61	37

Analogous data were obtained in a study of the conformations in solution by ^{1}H NMR. The protons of adjacent methylene groups of 1,4-heterocyclic systems give rise to the AA'BB' signal in the spectrum, from which one can obtain experimental values of I_{cis} and I_{trans}. The first is equal to I_{ae} and the second to $\frac{1}{2}(I_{aa} + I_{ee})$. Their ratio $R = I_{trans}/I_{cis}$ is a parameter characterising the distortion of the chair conformation [36-39]. For a normal chair, $R \simeq 2.2$, while for a puckered chair the parameter should be greater [36-40]. Table 2 lists the values of I_{trans}, I_{cis}, and R for a series of six-membered rings. Evidently all the sulphur-containing compounds have significantly higher values of the parameter R, reaching 3.38, which is evidence of a very marked increase of the dihedral angle in the ring.

We shall examine the variation of the 1,3-*syn*-axial interaction in sulphur-containing rings. The $C_{(2)}$–$C_{(6)}$ distance in tetrahydrothiopyran (V) is greater than in

†The conclusion that the energy difference between the above conformations of 1,3-dioxane is reduced [6] is likewise unsatisfactory owing to the neglect of the eclipsed butane conformations.

cyclohexane, because the smaller C–S–C valence angle compared with C–C–C does not compensate the increased C–S bond length. For example, the $C_{(2)}$–$C_{(6)}$ distance in dithiane is 2.8 Å,[9-12,34] while in cyclohexane the distance is 2.5 Å.[31,32,41] Consequently this should lead to an increase of the distance between R and H_a in tetrahydrothiopyran and hence to decreased 1,3-*syn*-axial repulsion. Consequently the quantity ΔGR, characterising the difference between the free energies of the equatorial and axial conformers[42], will have a smaller absolute magnitude in a series of sulphur-containing heterocycles than in the cyclohexane series, as has been confirmed experimentally[43-47]. In this connection it is important to emphasise also that the reverse situation obtains with oxygen-containing compounds: since the $C_{(2)}$–$C_{(6)}$ distance in this case is 2.3 Å, the steric interaction between R and H_a is much more pronounced[14,29]. This can be clearly illustrated for the isomerisation of trimethyloxathianes (VI, a and b):



(V) a (VI) b

It has been found that for this equilibrium $-\Delta H = 1.15$ kcal mole^{-1}, $-\Delta S = 0.04$ e.u., and $-\Delta G_{25^\circ} = 1.16$ kcal mole^{-1}.[44] Thus the methyl group in the axial position is located "preferentially" next to the sulphur atom at $C_{(4)}$. Pihlaja and Pasanen[44-46] calculated by an additive procedure the contributions of the individual interactions in 1,3-heterocyclic six-membered systems, the relevant data being presented in Table 3.

Table 3. The contributions of the 1,3-interactions for heterocycles with heteroatoms in the 1,3-positions[44].

Heteroatom		Interaction energy, kcal mole^{-1}				
1	3	$H_{(2)}$-$Me_{(6)}$ or $H_{(6)}$-$Me_{(2)}$	$H_{(2)}$-$Me_{(4)}$ or $H_{(4)}$-$Me_{(2)}$	$H_{(4)}$-$Me_{(6)}$ or $H_{(6)}$-$Me_{(4)}$	$Me_{(5)}$-1	($Me_{(5)}$-3
O	O	2.035	2.035	0.885	0.46	0.46
S	S	0.885	0.885	0.805	0.52	0.52
O	S	2.20	1.05	0.73	0.74*	

*The sum $Me_{(5)} - 1 + Me_{(5)} - 3$.

Table 3 shows that the energies of the *syn*-axial interaction of the methyl group and the hydrogen atom in the 2- and 6-positions in dioxane and dithiane are 2.035 and 0.885 kcal mole^{-1}, i.e. differ by a factor of 2.3. We may mention for comparison that ΔG for methylcyclohexane is 1.7 kcal mole^{-1}.[42]

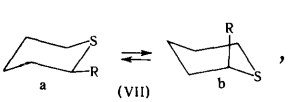
The introduction into the ring of a heteroatom with a lone pair of electrons gives rise to the problem of their interaction with the axial substituent. The problem of the existence of the "steric volume" of the electron pair of the heteroatom as an effective conformational parameter is controversial[13,48-55]. Table 3 shows that the repulsion of the axial methyl group in the 5-position from the oxygen atom (0.46 kcal mole^{-1}) is weaker than its repulsion from the sulphur atom (0.52 kcal mole^{-1}), which may be attributed to the increase of the van der Waals radius. However, both these values are fairly low, which is the reason for the possible existence of axial conformers.

The most striking example is provided by 2,5-*cis*-disubstituted derivatives of 1,3-dioxane and 1,3-dithiane[52-55] in which even the t-butyl group can assume the axial conformation[52]. However, in the presence of a polar substituent the situation becomes more complicated. Dipole–dipole repulsion or attraction between the substituent and the heteroatom[44] as well as interaction between the orbitals of the lone electron pairs of the ring heteroatom and the substituent become possible ("the hockey-stick effect")[29,56,57]; see Section III, 4). However, *a priori* estimates for dipole interactions in sulphur-containing compounds are difficult. On the other hand, the overlapping of the orbitals should become more marked on passing from oxygen to sulphur by virtue of the greater spread of the 3*p* orbital of sulphur compared with the 2*p* orbital of the oxygen atom. Possibly one should also consider the difference between the degrees of hybridisation of oxygen and sulphur atoms (the C–O–C and C–S–C valence angles should be compared) and consequently the difference between the steric directions of the orbital axes of the lone electron pairs[13]. We may also note that the most striking effect of the conformational characteristics of heterocyclic compounds is probably the anomeric effect[58-60]. Bearing in mind the polar nature of this effect, it should be expected also for sulphur-containing compounds[59]. Finally the sulphur atom can be formally quadrivalent and sexivalent and hence tricoordinate and tetracoordinate respectively. Such compounds have many interesting conformational characteristics (see, for example, Refs. 61–63); but their discussion is outside the scope of the present review.

III. CONFORMATIONS OF SIX-MEMBERED SULPHUR-CONTAINING HETEROCYCLES

1. Derivatives of Tetrahydrothiopyran

There are no data on the geometry of tetrahydrothiopyran (thiane), but ^{1}H NMR spectroscopic data[36-38] (Table 2) show that the compound exists in the puckered chair form. The experimental barrier to the inversion of tetrahydrothiopyran is 11.7 kcal mole^{-1} [37] (cf. 10.7 kcal mole^{-1} for tetrahydropyran[37]) and is therefore close to the value for cyclohexane derivatives[64]. Systematic conformational studies on functional derivatives of tetrahydrothiopyran have not been made either. In stereochemical studies on compounds of this series attention was concentrated on the problem of the anomeric effect. The equilibrium (VII) has been investigated[43,47,65] for a wide range of 2-substituted tetrahydrothiopyrans and the presence of a distinct anomeric effect was demonstrated [the predominance of conformer (VIIb) in the conformational equilibrium]:

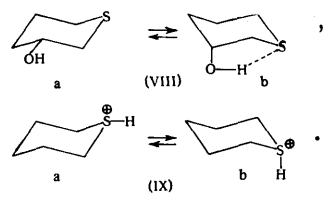


a (VII) b

where R = Cl,[47] OH,[66] OR,[43,47] SAlk,[43,47] SAr,[43] or $SP(S)(OR)_2$.[43]

The effect of the solvent on the position of conformational equilibrium is consistent with the polar nature of the anomeric effect: on passing from CCl_4 to CH_3CN, the contribution of conformer (VIIb) diminishes. The anomeric effect is shown to a greater extent with the

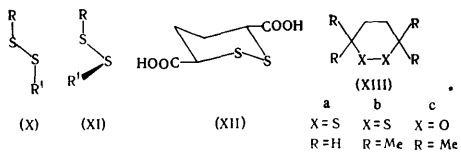
C–S–C–OR fragment than with C–O–C–SR.[59] This behaviour was explained by the weakening of the 1,3-*syn*-axial repulsion in tetrahydrothiopyran (see Section II). It must be emphasised that the anomeric effect has been found for the C–S–C–SR fragment and therefore the repulsion between the two sulphur atoms is fairly strong and must be taken into account as one of the factors in conformational equilibrium (0.7 kcal mole^{-1} in carbon tetrachloride[43]). As expected, the anomeric effect for 2-chlorotetrahydrothiopyran is fairly pronounced (1.75 kcal mole^{-1}).[47] We may also note that an appreciable "benzene effect" has been found for 2-alkoxytetrahydrothiopyrans[34,47]. An interesting conformational features has been noted for 3-hydroxytetrahydrothiopyrans[67]. Infrared spectroscopy revealed the presence of an intramolecular hydrogen bond in this compound, but the existence of the latter is possible only for the axial conformation (VIIIb). We may also note that the axial conformer (IXb) predominates in the conformational equilibrium of the protonated form (IX)[37]:



^{1}H NMR data have shown that the geometries of the rings of tetrahydrothiopyran and its *S*-methylsulphonium salt are almost identical and *R* is in the range 2.3–2.6.[68]

2. Derivatives of 1,2-Dithiane

For aliphatic disulphides, the transoid conformation (X) is not the most stable, as might have been expected on the basis of elementary stereochemical considerations. The disulphide molecule has the zig-zag shape (XI),[69–72] as shown by quantum-mechanical calculations of the potential curves for barriers to rotation about the S–S bond, and is consistent with the concept of the so called "*gauche*-effect"[73,74]. It is important to emphasise in this connection that such geometry of the disulphide bridge makes it possible to incorporate it without much strain in the chair conformation of the six-membered ring.



There are few experimental data for 1,2-dithianes. X-Ray diffraction analysis of *trans*-1,2-dithiane-3,6-dicarboxylic acid (XII) showed that the compound exists in the chair conformation with the carboxy-groups in the equatorial positions[75,76].

A study of the temperature variation of the ^{1}H NMR spectra of 1,2-dithiane (XIIIa) showed that the free energy of the inversion of the chair form is 11.6 kcal mole^{-1}.[77] Similarly $\Delta G^{\neq}_{-20^\circ C}$ for the tetramethyl derivative (XIIIb) is 13.8 kcal mole^{-1} ($\Delta S^{\neq}$ = 6.7 e.u.)[77]. This value is smaller than for the corresponding oxygen-containing analogue (XIIIc), where $\Delta G^{\neq}_{12^\circ}$ = 14.6 kcal mole^{-1} ($\Delta S^{\neq}$ = 14.4 e.u.).

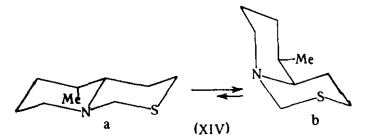
It is particularly interesting that the curves giving the energy as a function of the coordinate for the conformational transition of the last two compounds differ appreciably from one another[77]. The authors attribute this to different transition states in the inversion of these compounds. Compound (XIIIc) undergoes inversion via an asymmetric boat form (minimum) with two maxima corresponding to conformations with planar five-atom fragments. The maximum for the sulphur-containing compound (XIIIb) corresponds to the symmetrical boat conformation. This conformation is impossible for compound (XIIIc) owing to the powerful repulsion of the methyl group in the "flagstaff" position; such repulsion for the sulphur-containing compound (XIIIb) is much weaker owing to the increase of the C–S distance.

3. Derivatives of 1,3-Oxathiane and 1,3-Dithiane

Six-membered systems with heteroatoms in the 1,3-positions have recently been studied extremely vigorously. The results of these investigations have been described in several reviews[6,13,14,29,44]. Therefore we shall confine ourselves to an examination of the general relations formulated in Section II. The preferential conformation of 1,3-dithiane is the chair form with an inversion barrier of 10.4 kcal mole^{-1}.[78]

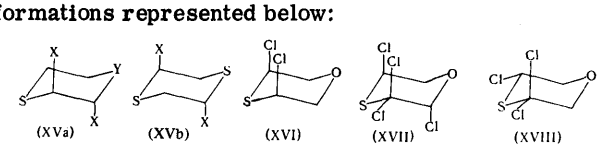
The powerful influence of hydrogen bonds on the relative stabilities of the conformations may also be noted. Thus the axial isomer of 5-hydroxy-1,3-dithiane is more stable than the equatorial isomer [ΔG = 0.5 kcal mole^{-1} (Luttringhaus et al.[79]) and 0.8 kcal mole^{-1} (Abraham and Thomas[80])].

Derivatives of 1-aza-3-thiabicyclo[4,4,0]decane exist in the chair conformation, like *trans*-decalin[81]. However, in the presence of the axial methyl group in the 7-position of compound (XIV) the conformation with the *trans*-junction becomes less stable and conformer (XIVb) with the *cis*-junction of the rings predominates in the conformational equilibrium[81]:

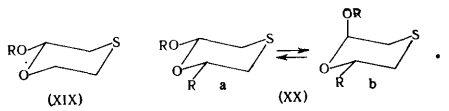


4. Derivatives of 1,4-Oxathiane and 1,4-Dithiane

Numerous studies on the geometries of oxathiane[7,8,34,82,83] and dithiane[9–12,34,35,84,85] showed that these compounds exist in the chair conformation. The inversion barrier for 1,4-dithiane itself is unknown; however it amounts to 10.05 kcal mole^{-1} for the perfluoro-derivative[86]. A distinct anomeric effect has been found for the *trans*-2,3- and *trans*-2,5-dihalogeno-derivatives (XV, a and b), since the halogen atoms occupy the axial positions[7,9,10]. Judging from the infrared spectra and the dipole moments, the same conformation exists also in solution. It has been found[82] that *trans*-3,5-dichloro-oxathiane (XVI) and also polychloro-oxathianes (XVII) and (XVIII) have the conformations represented below:



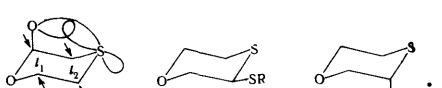
However, we may note that these assignments are based on the spin–spin interaction constants which sometimes had an "intermediate" value of the order of 6 Hz. Possibly this indicates the occurrence of conformational equilibria. Although the anomeric effect has been found for the majority of the compounds, for example (XV) and (XVI), certain questions remain obscure. For example, it is not clear why the diaxial repulsion between two chlorine atoms leads to the predominance of conformation (XVIII) but is not found in compound (XVII). The anomeric effect has been found also for a series of polyfluoro-derivatives of oxathianes and dithianes [87,88].



(XIX) (XX)

Unusual results were obtained in a study of the alkoxy-derivatives of oxathiane. Detailed studies of various 2-alkoxyoxathianes by ^{1}H NMR showed that the equatorial conformer (XIX) predominates in the conformational equilibrium [56], in sharp contrast to 2-alkoxy-derivatives of tetrahydropyran, tetrahydrothiopyran, and 1,4-dioxane [59]. For example, at least 50% of the equatorial form is present in conformation equilibrium for 2-methoxy- and 2-butoxy-1,4-oxathianes, These data were confirmed by a study of the epimerisation of 2-alkoxy-6-methyl-, 2-alkoxy-6-hydroxymethyl-, and 6-acetoxymethyl-2-alkoxy-1,4-oxathianes (XX) [89–92]. Epimerisation leads to an equilibrium in which the diequatorial isomer (XXa) (67%) predominates, in sharp contrast to the behaviour of tetrahydropyrans[59].

A possible explanation of this phenomenon was based on the "hockey-stick" effect [56,57]. The overlapping of the orbitals of the substituent and the sulphur atom leads to repulsion, because the two orbitals are populated by four electrons. Such repulsion probably depends on the nature of the heteroatoms (S > 0) and fine geometrical details [for example, the relative distances l_1 and l_2 in compound (XXI)]:

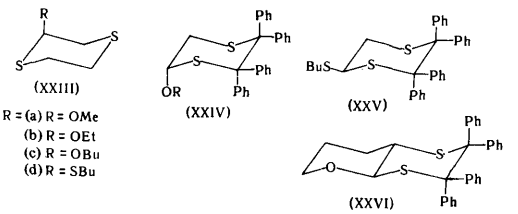


(XXI) (XXIIa) (XXIIb)

The position of conformational equilibrium for 3-propylthio- and 3-butylthio-1,3-oxathianes [93,94] depends on the solvent. In acetonitrile these compounds exist almost entirely in the equatorial conformation (XXIIa). An increased content of the axial conformer (XXIIb) (25–40%) is observed in carbon tetrachloride.

The data on the conformational behaviour of dithiane derivatives are non-systematic. The anomeric effect has been discovered for a series of 2-alkoxy- and 2-alkylthio-1,4-dithianes by ^{1}H NMR, [94] i.e. the axial conformation (XXIII) predominates. However, as noted by the authors themselves, these data are based on arbitrarily selected standard values of Iaa, Iae, and Iee and in the absence of a large set of data for model compounds this conclusion must be treated with caution. A distinct predominance of the axial conformer was found for the tetraphenyl derivative (XXIV). [95] However, the corresponding butylthio-derivative (XXV) exists in the equatorial conformation [95]. Possibly as a result of the large bulk of the sulphur atom, the 1,3-repulsion between the butylthio-substituent and the axial phenyl group predominates in this case over the anomeric effect. The axial conformation (XXIV) is possible owing to the weakening of the 1,3-repulsion (see Section II).

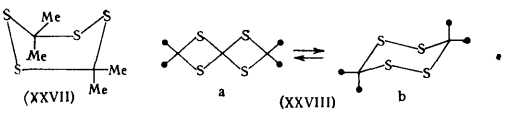
The reaction of thiobenzophenone with dihydropyran leads to the bicyclic compound (XXVI) having the *trans*-configuration [95,96]. In this connection it is interesting to investigate its epimerisation and to compare its stability with that of the *cis*-isomer.



(XXIII) R = (a) R = OMe (b) R = OEt (c) R = OBu (d) R = SBu (XXIV) (XXV) (XXVI)

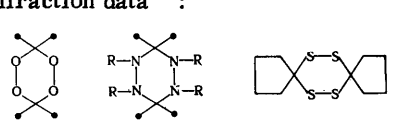
5. Heterocycles with Several Sulphur Atoms

As early as 1937, it was shown by X-ray diffraction that 1,3,5-trithiane exists in the chair conformation [97,98]. The inversion barrier is 11.0 kcal mole^{-1}. [99] However, X-ray diffraction analysis of 3,3,6,6-tetramethyl-1,2,4,5-tetrathiane (XXVII) showed that in the crystal lattice this compound has the true boat conformation (XXVII), the sulphur atoms being displaced from the plane [100]:



(XXVII) a (XXVIII) b

The study of the conformations of this compound in solution by ^{1}H NMR demonstrated the presence in the equilibrium mixture of two conformers: the more stable twist-form (XXVIIIa) and the less stable chair conformation (XXVIIIb). [101] At −15°C the (XXVIIIa)/(XXVIIIb) ratio in carbon disulphide is 2.6 and $\Delta G^{\neq}_{50}{}^{\circ} = 16$ kcal mole^{-1}. It must be emphasised that the oxygen analogue (XXIX) [102] and the nitrogen analogue (XXX) [103] of compound (XXVII) exist in the chair conformations. We may also note that the inversion barrier for the thia-derivative (XXVIII) is higher than for compounds (XXIX) ($\Delta G^{\neq}_{30}{}^{\circ} = 15.4$ kcal mole^{-1}) and (XXX) ($\Delta G^{\neq} = 11.7$ kcal mole^{-1}). An equilibrium between the chair and twist conformations, with the former predominating (80%) was observed also for the bistetramethylene derivative (XXXI). [101] The stability of the chair conformation of (XXXI) was also demonstrated by X-ray diffraction data [101]:



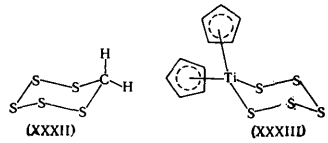
(XXIX) (XXX) (XXXI)

It is interesting that, when crystals of tetrathiane (XXVIII) are cooled to −80°C and dissolved at this temperature in carbon disulphide, a solution of the pure twist form is formed. Bearing in mind the above X-ray diffraction data, this finding implies that the boat/twist transition (XXVII) → (XXVIIIa) has an extremely low potential barrier [101].

Thus a minimal difference between the energies of the twist and chair conformations (0.49–0.6 kcale mole^{-1}) is characteristic of tetrathiane (XXVIII). This finding can be explained both by the factors discussed in section (II) and

by additional factors among which mention may be made of the *syn*-axial interaction of the electron pairs ("the rabbit ear effect"[104]) and the influence of the *gem*-dialkyl groups (the Thorpe–Ingold hypothesis concerning the deviation of the valence angles[105,106]).

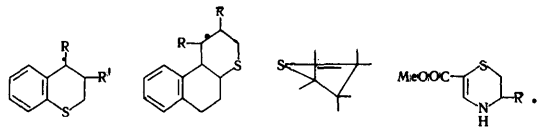
Pentathiane exists in an exceptionally stable chair conformation (XXXII).[107] The ^1H NMR spectrum at room temperature shows the signal of the AB-system of the equatorial and axial protons. The authors point out the possibility of inversion at elevated temperatures but do not quote experimental details. The separate signals of the two cyclopentadienyl rings are also shown for the analogous cyclic pentathia-compound (XXXIII) at +30°C. However, coalescence is observed at 90°C and at 120°C the spectrum consists of a sharp singlet, which indicates rapid (on the NMR time scale) inversion of the six-membered ring of compound (XXXIII)[108].



(XXXII) (XXXIII)

6. Sulphur-containing Heterocycles with a Multiple Bond in the Ring

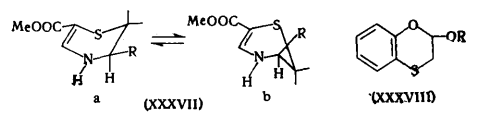
As stated above (section II), the half-chair conformation is the most stable for cyclohexene[15–17]. The "sofa" conformation is encountered in isolated cases[18]. The data concerning the most stable conformations of unsaturated sulphur-containing systems are unfortunately limited. The "sofa" conformation (XXXVI) has been adopted for a series of thiachromans (XXXIV) and dihydronaphthothiapyrans (XXXV):[19]



(XXXIV) (XXXV) (XXXVI) (XXXVII)

However, this conclusion was based only on the spin–spin interaction constants using the Karplus equation and cannot be regarded as very reliable. The "sofa" conformation was also postulated for derivatives of 2,3-dihydro-6-methoxycarbonyl-1,4-thiazine (XXXVII)[109–111], but the evidence supporting this is doubtful too.

A number of studies have been made on the conformations of functional derivatives. A distinct anomeric effect was found for 2-alkoxybenzoxathianes (XXXVIII):[112]



a (XXXVII) b (XXXVIII)

The content of the axial conformer is in excess of 80% and is almost independent of the nature of the alkoxy-group. Interesting data were obtained for compounds of type (XXXVII)[109–111]. The methyl derivative (XXXVII) (R = CH_3) contains equal amounts of the equatorial and axial forms, (XXXVIIa) and (XXXVIIc), in conformational equilibrium. The axial conformers (XXXVIIb) of compounds (XXXVII, R = OH, OAc, CH_2Cl, and CH_2I) predominate in the conformational equilibrium. The equilibrium position for the methoxycarbonyl derivative (XXXVII, R = $COOCH_3$) depends on the solvent: the conformer (XXXVIIa) predominates in non-polar solvents, while in polar solvents the equilibrium is displaced towards the axial form (XXXVIIb). Evidently a detailed interpretation of these results is fairly difficult.

The numerous "exceptions" found in conformational studies on heterocyclic compounds clearly show that the introduction of heteroatoms with lone electron pairs, which cause an appreciable change in the geometrical relations in the molecule, leads to the appearance of a new set of properties, the understanding of which requires a development of the principles of conformational analysis. Although experimental studies have clearly demonstrated the inadequacy of the theoretical concepts in the field of conformational analysis, nevertheless it is already possible to discover in broad outline the principal characteristics of the conformational behaviour of heterocycles. As shown by the present review, sulphur-containing compounds exhibit interesting and even unique conformational features, the further study of which will undoubtedly promote a general progress in this branch of stereochemistry.

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Further reports were published[113–115] during the period when the review was considered by the editors.

REFERENCES

1. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis" (Translated into Russian), Izd. Mir, Moscow, 1969, p. 54.
2. N. L. Allinger and L. A. Freiberg, J. Amer. Chem. Soc., 82, 2393 (1960).
3. N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, J. Amer. Chem. Soc., 90, 1199 (1968).
4. L. Pierce and M. Hayashi, J. Chem. Phys., 35, 479 (1961).
5. K. S. Pitzer, J. Chem. Phys., 12, 310 (1944).
6. A. V. Bogatskii, A. I. Gren', Yu. Yu. Samitov, L. M. Krinitskaya, L. N. Vostrova, V. N. Somchinskaya, V. P. Mamontov, and T. I. Davidenko, Khim. Geterotsikl. Soed., 582 (1971).
7. N. de Wolf, C. Romers, and C. Altona, Acta Cryst., 22, 715 (1967).
8. R. S. McEven and G. A. Sim, J. Chem. Soc. (A), 271 (1967).
9. H. T. Kalff and C. Romers, Acta Cryst., 18, 164 (1965).
10. H. T. Kalff and C. Romers, Rec. Trav. chim., 85, 198 (1966).
11. H. T. Kalff and C. Romers, Acta Cryst., 20, 490 (1966).
12. J. Watkin and T. A. Hamor, J. Chem. Soc. (B), 1692 (1971).
13. E. L. Eliel and R. O. Hutchins, J. Amer. Chem. Soc., 91, 2703 (1969).
14. E. L. Eliel, Accounts Chem. Res., 3, 1 (1970).
15. V. N. Naumov, V. G. Dashevskii, and N. M. Zaripov, Dokl. Akad. Nauk SSSR, 185, 604 (1969).
16. J. F. Chiang and S. H. Bauer, J. Amer. Chem. Soc., 91, 1898 (1969).
17. N. L. Allinger and J. T. Sprague, J. Amer. Chem. Soc., 94, 5734 (1972).
18. R. R. Sobti, J. Bordnev, and S. G. Levine, J. Amer. Chem. Soc., 93, 5588 (1971).

19. W. D. Cottvill, F. J. Cotta, C. F. France, R. Livingstone, J. R. Atkinson, and J. Cottam, J. Chem. Soc., Perkin II, 787 (1972).
20. H. Kessler, A. Rieber, and W. Rundel, Chem. Comm., 475 (1968).
21. U. Blakis, P. H. Kasai, and R. J. Meyer, J. Chem. Phys., 38, 2753 (1963).
22. E. Gaspi, A. Wittstruck, and D. A. Piatak, J. Org. Chem., 27, 3183 (1962).
23. C. Altona and C. Romers, Acta Cryst., 16, 1225 (1963).
24. C. L. Chen and R. F. Le Fevre, J. Chem. Soc., 558 (1965).
25. See Ref. 1, p. 295.
26. L. K. Yuldasheva and R. P. Arshinova, Teor. Eksper. Khim., 3, 641 (1967).
27. K. Pihlaja, Acta Chem. Scand., 22, 716 (1968).
28. K. Pihlaja and J. Hekkila, Acta Chem. Scand., 21, 2390, 2430 (1968).
29. E. Eliel, Angew. Chem., 84, 779 (1972).
30. H. R. Buys and N. Le Wolf, Tetrahedron Letters, 551 (1970).
31. M. Davis and O. Hassel, Acta Chem. Scand., 17, 1181 (1963).
32. H. R. Buys and H. J. Geise, Tetrahedron Letters, 2991 (1970).
33. G. Schultz, J. Hargittai, and L. Hermann, J. Mol. Structure, 14, 353 (1972).
34. C. Romers, C. Altona, H. R. Buys, and E. Havinga, in "Topics in Stereochemistry", Interscience, New York, 1969, Vol. 4.
35. O. Hassel and H. Viervoll, Acta Chem. Scand., 1, 149 (1949).
36. J. B. Lambert, J. Amer. Chem. Soc., 89, 1836 (1967).
37. J. B. Lambert, R. J. Keske, and D. K. Weary, J. Amer. Chem. Soc., 89, 5921 (1967).
38. J. B. Lambert, Accounts Chem. Res., 4, 87 (1971).
39. H. R. Buys, Rec. Trav. chim., 88, 1003 (1969).
40. E. W. Garbisch, and M. G. Griffith, J. Amer. Chem. Soc., 90, 6543 (1968).
41. R. A. Wohe, Chimia (Switz.), 18, 219 (1964).
42. J. Hirsch, "Selected Problems in Stereochemistry" (Translated into Russian), Izd. Mir, Moscow, 1970, p. 199.
43. N. S. Zefirov, V. S. Blagoveshchenskii, I. V. Kazimirchik, and O. P. Yakovleva, Zhur. Org. Khim., 7, 594 (1971).
44. P. Pasanen and K. Pihlaja, Tetrahedron, 28, 2617 (1972).
45. K. Pihlaja and P. Pasanen, Acta Chem. Scand., 24, 2257 (1971).
46. K. Pihlaja and P. Pasanen, Acta Chem. Scand., 22, 2401 (1968).
47. A. J. de Hoog, "Conformations of 2-Alkoxytetrahydropyrans and Related Compounds", Thesis of dissertation, Labor vincit, Leiden, 1971.
48. N. L. Allinger and J. C. Tai, J. Amer. Chem. Soc., 87, 1227 (1965).
49. M. D. Brown, M. J. Cook, and A. R. Katritzky, J. Chem. Soc. (B), 2358 (1971).
50. R. W. Balclock and A. R. Katritzky, Tetrahedron Letters, 1159 (1968).
51. J. B. Lambert, R. G. Keske, R. E. Cathcart, and A. P. Jovanovich, J. Amer. Chem. Soc., 89, 3761 (1967).
52. E. Eliel and C. Knoeber, J. Amer. Chem. Soc., 88, 5347 (1966).
53. A. V. Bogatskii, Yu. Yu. Samitov, and N. L. Garkovik, Zhur. Org. Khim., 2, 1335 (1966).
54. A. V. Bogatskii, Yu. Yu. Samitov, and Z. L. Bogatskaya, Zhur. Org. Khim., 5, 2230 (1969).
55. L. Anogiolini, R. P. Duke, R. A. Jones, and A. R. Katritzky, Chem. Comm., 1308 (1971).
56. N. S. Zefirov, V. S. Blagoveshchenskii, I. V. Kazimirchik, and N. S. Surova, Tetrahedron, 27, 3111 (1971).
57. N. S. Zefirov, Zhur. Org. Khim., 6, 1761 (1970).
58. S. J. Angyal, Angew. Chem., 81, 172 (1969).
59. N. S. Zefirov and N. N. Shekhtman, Uspekhi Khim., 40, 593 (1971) [Russ. Chem. Rev., No. 4 (1971)].
60. J. C. Martin, Ann. Chim. [14], 6, 205 (1971).
61. J. B. Lambert, C. E. Muxan, and D. S. Bailey, J. Amer. Chem. Soc., 94, 209 (1972).
62. C. H. Green and D. G. Hellier, J. Chem. Soc., Perkin II, 458 (1972).
63. B. A. Arbuzov, Bull. Soc. chim. France, 27, 1311 (1960).
64. J. E. Anderson, Quart. Rev., 426 (1965).
65. N. S. Zefirov, V. S. Blagoveshchenskii, and I. V. Kazimirchik, Zhur. Org. Khim., 5, 1150 (1969).
66. J. M. Cox and L. W. Owen, J. Chem. Soc. (C), 1130 (1967).
67. R. Borsdorf, H. Remane, and M. Mühlstädt, Z. Chem., 10, 459 (1970).
68. J. B. Lambert, P. H. Jonson, R. J. Keske, and C. E. Mixan, J. Amer. Chem. Soc., 94, 8172 (1972).
69. D. W. Scott, H. L. Finke, M. E. Gross, G. B. Guthrie, and H. M. Huffman, J. Amer. Chem. Soc., 72, 2424 (1950).
70. G. Winnewisser, M. Winnewisser, and W. Gordy, J. Chem. Phys., 49, 3465 (1968).
71. C. W. N. Cumper, J. F. Read, and A. I. Vogel, J. Chem. Soc., 5323 (1965).
72. G. C. Pappalardo and G. Sonsisvalle, Tetrahedron, 28, 4147 (1972).
73. S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csirmadia, J. Chem. Soc. (B), 136 (1971).
74. S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csirmadia, Chem. Comm., 96 (1970).
75. O. Foss and L. Schotte, Acta Chem. Scand., 11, 1424 (1957).
76. O. Foss, K. Johnsen, and T. Reistad, Acta Chem. Scand., 18, 2345 (1964).
77. G. Claeson, G. Androes, and M. Calvin, J. Amer. Chem. Soc., 83, 4357 (1961).
78. H. Friebolin, S. Kabuss, W. Maier, and A. Luttringhaus, Org. Magn. Res., 1, 67 (1969).
79. A. Luttringhaus, S. Kabus, H. Prinzbach, and F. Langenbucher, Annalen, 653, 195 (1962).
80. R. J. Abraham and W. A. Thomas, J. Chem. Soc., 335 (1965).
81. T. A. Crabb and R. F. Newton, Tetrahedron, 26, 3941 (1970).
82. H. T. Kalff and E. Havinga, Rec. Trav. chim., 85, 637 (1966).
83. N. de Wolf and P. W. Henniger, Rec. Trav. chim., 86, 1227 (1967).
84. R. E. Marsh, Acta Cryst., 8, 91 (1955).
85. R. E. Marsh and J. D. McCullough, J. Amer. Chem. Soc., 73, 1106 (1951).
86. J. J. Anderson, D. R. Davis, and J. D. Roberts, J. Org. Chem., 35, 1195 (1970).
87. J. Burdon and I. W. Parsons, Tetrahedron, 27, 4553 (1971).
88. J. Burdon and W. I. Parsons, J. Chem. Soc. (C), 355 (1971).
89. A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, Chem. Comm., 1086 (1968).

90. K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, Chem. Comm., 433 (1965).
91. K. W. Buck, P. A. Hamor, and D. J. Watkin, Chem. Comm., 759 (1966).
92. K. W. Buck, P. A. Fahin, A. B. Foster, A. R. Perry, M. H. Qadir, and J. M. Webber, Carbohydr. Res., 2, 14 (1966).
93. V. S. Blagoveshchenskii, I. V. Kazimirchik, A. A. Alekseeva, and N. S. Zefirov, Zhur. Org. Khim., 8, 1325 (1972).
94. I. V. Kazimirchik, Candidate's Thesis, Moscow State University, 1972.
95. A. Ohno, Y. Ohniski, and G. Tsuchihashi, J. Amer. Chem. Soc., 91, 5038 (1969).
96. G. Tsuchihashi, M. Yamauchi, and M. Fukuyama, Tetrahedron Letters, 1971 (1967).
97. N. F. Moerman and E. H. Wibenga, Z. Krist., 97, 323 (1937).
98. V. Busetti, M. Mammi, and G. Carazzolo, Z. Krist., 119, 310 (1963).
99. J. E. Anderson, J. Chem. Soc. (B), 2030 (1971).
100. A. Fredga, Acta Chem. Scand., 12, 891 (1958).
101. C. H. Bushweller, J. Amer. Chem. Soc., 91, 6019 (1969).
102. R. W. Murray, P. R. Stovy, and M. L. Kaplan, J. Amer. Chem. Soc., 88, 526 (1966).
103. J. E. Anderson and J. D. Roberts, J. Amer. Chem. Soc., 90, 4186 (1968).
104. R. O. Hitchins, L. D. Kopp, and E. L. Eliel, J. Amer. Chem. Soc., 90, 7174 (1968).
105. P. V. R. Schleyer, J. Amer. Chem. Soc., 83, 1368 (1961).
106. T. C. Bruice and W. C. Bradbury, J. Amer. Chem. Soc., 90, 3808 (1968).
107. F. Feher, B. Degen, and B. Sohnen, Angew. chem., 80, 320 (1968).
108. H. Kopf, B. Block, and M. Schmidt, Chem. Ber., 101, 272 (1968).
109. A. R. Dunn and R. J. Stoodley, Tetrahedron Letters, 2978 (1969).
110. A. R. Dunn, I. McMillan, and R. J. Stoodley, Tetrahedron, 24, 2985 (1968).
111. A. R. Dunn and R. J. Stoodley, Tetrahedron, 28, 3315 (1972).
112. M. A. Fedorovskaya, Candidate's Thesis, Moscow State University, Moscow, 1972.
113. R. M. Clay, J. M. Kellie, and F. G. Riddell, J. Amer. Chem. Soc., 95, 4632 (1973).
114. M. J. Cook and A. P. Tonge, Tetrahedron Letters, 849 (1973).
115. J. B. Lambert, C. E. Mixan, and D. H. Johnson, J. Amer. Chem. Soc., 95, 4635 (1973).

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