

Conformational Analysis of 2-Alkyl-1,4-dithianes and Related Compounds by NMR Spectroscopy and MMX

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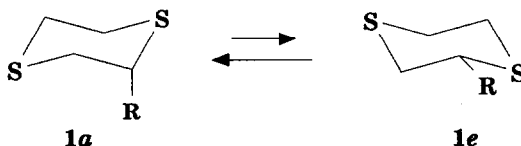
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Dedicated to Professor Ernest L. Eliel on the occasion of his 70th birthday.

Abstract: According to NMR (¹H, ¹³C) spectroscopy and molecular mechanics calculations 2-alkyl substituted 1,4-dithianes exist preferentially in the conformation with equatorially oriented substituents. The conformational free energy for the methyl group in 2-methyl-1,4-dithiane is estimated to be -1.20 ± 0.14 kcal/mol. For 1,4-dithianes with substituents of the CH₂X type (X=acetoxy, halogen) the predominance of axial conformers is observed originating from an intramolecular electrostatic attraction.

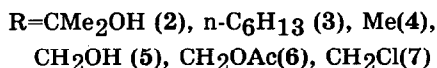
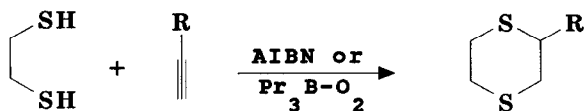
In contrast to a thoroughly performed conformational analysis of 1,3- and 1,4-dioxanes^{1,2}, 1,3- and 1,4-oxathianes^{3,4} and 1,3-dithianes⁵ the data on conformational behaviour of 1,4-dithianes are quite limited^{6,7}.

The conformational peculiarity of 2-substituted 1,4-dithianes **1** (R=Hal, OR', SR') previously studied consists in the strong predominance of axial conformer **1a** due to the absence of an essential syn-1,3-diaxial repulsion and the stabilization by anomeric orbital interactions⁶.

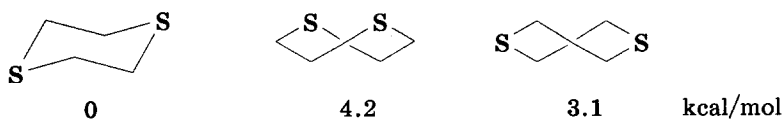


To the best of our knowledge, no examples of the opposite conformational properties of other 1,4-dithiane derivatives have so far been described. In particular, the conformational behaviour of the methyl derivative or other alkyl derivatives has not been studied.

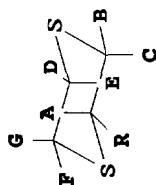
To complete the conformational picture of this class of cyclohexane heteroanalogs we accomplished the conformational analysis of various 1,4-dithianes with an alkyl or functionalized alkyl substituent at C-2 by ^1H and ^{13}C NMR (Tables 1-3) and molecular mechanics calculations (MMX; PCMODEL program) (Table 4). These compounds have become easily accessible now after our development of a very facile general method for 1,4-dithiane ring construction using the homolytic cycloaddition of 1,2-ethanedithiol to alkynes⁸.



According to the results of MMX calculations a steric energy of a chair conformation for 1,4-dithianes is much lower than the energy of twist forms. So the last ones can be neglected, and for this reason we consider the conformational equilibrium of only two chair forms - **1a** and **1e**.



The full analysis of ^1H NMR spectra (300 MHz) using the program PANIC allowed us to measure averaged vicinal spin-spin couplings (Table 1; Fig.1). The spectra were treated as a superposition of two weakly connected spin systems ABC and DEFG, because the long-range couplings through sulfur atoms are quite small. We estimated the conformer populations (n_i) using the formula $J_{\text{obs}} = J_a \cdot n_a + J_e \cdot n_e$ and two trans coupling constants for the SCH₂CH₂S fragment (J_{DF} and J_{EG}). The limiting parameters, J_a and J_e , were taken from the spectrum of compound 2 assuming its conformational equilibrium to be completely shifted to the equatorial form due to a large steric volume of R=CMe₂OH. The MMX data support this assumption. Firstly, the 1-hydroxy-1-methylethyl group is a rather good conformational 'anchor' indeed: a free energy difference between most stable rotamers of this group in the *e*- and *a*-positions is calculated to be 2.75 kcal/mol, i.e. the contribution of conformer **2a** is less than 1%. Introducing a correction connected with this conformational non-homogeneity we determined for **1e** J_{DF} 4.1 Hz and J_{EG} 12.0 Hz and for **1a** J_{DF} 12.0 Hz and J_{EG} 4.1 Hz, and used these values for subsequent calculations. Secondly, a torsion angle SCCS is practically constant for all compounds studied (69-71° according to MMX), therefore the limiting parameters J_e and J_a also have to be constant.

Table 1. ^1H - ^1H Spin-spin Coupling Constants^{a)} in 1,4-Dithianes 2-7

Compound	R	J_{AB}	J_{AC}	J_{AF}	J_{AG}	J_{BF}	J_{BD}	J_{EG}	J_{FG}	J_{DE}	J_{FC}	J_{FE}	J_{FG}
2	C(OH)Me ₂	1.94	10.77	4.16	2.42	2.43	1.09	11.97	-13.64	1.06	-13.64	-13.69	-13.82
3	n-C ₆ H ₁₃	2.51	9.63	4.82	2.53	2.62	0.84	10.83	-13.80	0.85	-13.80	-13.71	-13.99
4	CH ₃	2.45	9.95	5.14	2.39	2.37	0.92	11.15	-13.69	0.80	-13.69	-13.84	-13.78
5	CH ₂ OH	2.58	8.48	6.89	2.36	2.49	0.71	9.45	-13.77	0.72	-13.77	-13.75	-13.75
6	CH ₂ OCOCH ₃	2.6	7.2	b)	b)	b)	b)	b)	b)	b)	b)	b)	b)
7	CH ₂ Cl	2.54	6.64	8.89	2.53	2.33	0.60	7.49	-13.94	0.60	-13.94	-13.94	-13.98

a) The average accuracy of J_{HH} measurement is 0.09 Hz

b) Full analysis was not performed due to the very complex character of the spectrum.

Table 2. Chemical Shifts (δ , ppm) in ^1H NMR Spectra of 1,4-Dithianes 2-7

Compound	R	Protons							
		A	B	C	D	E	F	G	R
2	C(OH)Me ₂	3.01	3.06	2.82	2.29	2.81	2.94	3.03	1.15 and 1.27 (CH ₃) 3.1 (OH)
3	n-C ₆ H ₁₃	2.87	2.84	2.69	2.75	2.80	2.88	2.93	0.88 (CH ₃), 1.2-1.6 (CH ₂)
4	CH ₃	3.01	2.79	2.65	2.05	2.97	2.73	2.78	1.19 (CH ₃)
5	CH ₂ OH	2.96	3.05	2.79	2.94	2.84	2.80	2.79	3.63, 3.68 (CH ₂) 3.99 (OH)
6	CH ₂ OCOCH ₃	3.14	3.04	2.81	a)	a)	a)	a)	2.02 (CH ₃), 4.27 (CH ₂)
7	CH ₂ Cl	3.11	3.19	2.96	2.80	2.89	2.79	3.10	3.82, 4.11 (CH ₂ Cl)

a) Full analysis was not performed due to the complex character of the spectrum.

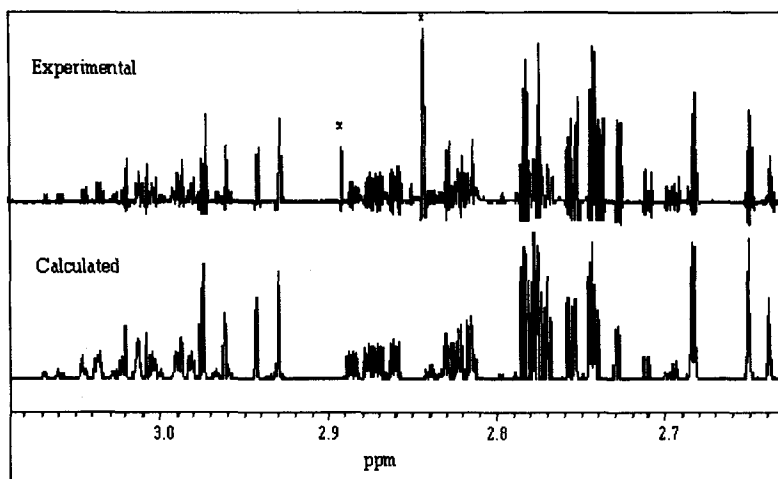


Fig.1 Part of the PMR spectrum of 2-methyl-1,4-dithiane 4 showing the ring protons.

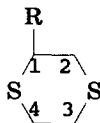
It is interesting to note a relatively large value of ${}^5J_{\text{HH}}$ between H_B and H_F (Table 1). The coupling decreases along with diminishing of the equatorial conformer population. The same is observed for W-coupling ${}^4J_{\text{HH}}$ between H_B and H_D .

The data in Table 4 reveal a prevalence of the equatorial conformers for the alkyl substituents; the A-value for methyl is about 1.2 kcal/mol, and this result seems to be quite reasonable. At the same time an increase of axial conformer population, n_a , is observed in the order $\text{CH}_3 < \text{CH}_2\text{OH} < \text{CH}_2\text{OAc} < \text{CH}_2\text{Cl}$. Moreover, the most bulky substituents of this series - CH_2OAc and CH_2Cl - prefer the axial position. This result is completely unexpected in the light of the properties of methyl and hexyl derivatives, and the MMX calculations (see Table 4).

Thus, while the alkyl derivatives 3, 4 show the 'normal' predominance for the equatorial conformer, the compounds 5 - 7, containing functionalized methyl groups, demonstrate an obvious effect of the axial conformer stabilization. We might estimate the value of the effect as a difference between the $\Delta G_{\text{e-a}}$ values for R- and Me- substituted models: $\Delta\Delta G = \Delta G_{\text{R}} - \Delta G_{\text{Me}}$. It is about 1.4 kcal/mol for 7.

The comparison of molecular mechanics calculations with experimental data (Table 4) shows that there is a moderate agreement for compounds 3 - 5. For 6 and 7 the calculations lead to the wrong prediction of almost the same relative stability of the equatorial conformer as for 2-methyl-1,4-dithiane 4. In our opinion, this discrepancy arises from a poor parametrization of Coulombic potentials in molecular mechanics.

Indeed, there is little doubt that this effect is a manifestation of the electrostatic attraction of the sulfur atom in the ring with positively charged carbon and hydrogen atoms in $\text{R}=\text{CH}_2\text{X}$. These partial charges are in a gauche position when R is axial (scheme 8).

Table 3. Chemical Shifts (δ , ppm) in ^{13}C NMR Spectra of 1,4-Dithianes 2-7

Compound	R	Carbons				C-R
		C-1	C-2	C-3	C-4	
2	C(OH)Me ₂	55.5	30.9	29.4	32.1	25.4 and 29.3 (CH ₃) 72.6 (C-OH)
3	n-C ₆ H ₁₃	42.8	29.6	35.8	30.6	14.5, 23.4, 27.3, 30.0, 32.6, 36.5
4	CH ₃	37.5	37.0	30.8	28.9	22.0
5	CH ₂ OH	43.5	32.8	29.6	29.1	64.8
6	CH ₂ OCOCH ₃	39.2	31.8	29.5 (or 28.4)	28.4 (or 29.5)	28.8 (CH ₃), 65.6 (CH ₂), 170.8 (C=O)
7	CH ₂ Cl	40.6	31.8	29.4	27.8	46.7

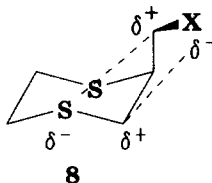
Table 4. Conformer Populations and Free Energy Differences (kcal/mol)

Compound	R	^1H NMR		MMX	
		$n_a, \%$	ΔG_{e-a}	$\Delta E_{e-a}^a)$	$\Delta G_{e-a}^b)$
2	C(OH)Me ₂	0	-	-2.75	-2.75
3	n-C ₆ H ₁₃	12.0 \pm 4.2	-1.20 \pm 0.14	-0.78	-0.77
4	CH ₃	12.0 \pm 2.5	-1.20 \pm 0.14	-1.00	-1.00
5	CH ₂ OH	33.8 \pm 2.8	-0.40 \pm 0.07	-0.96	-
6	CH ₂ OCOCH ₃	54 ^{c)}	0.1	-0.74	-0.97
7	CH ₂ Cl	58.9 \pm 3.1	0.22 \pm 0.08	-0.90	-0.97

a) The energy difference between the most stable rotamers of group R in *e*- and *a*-positions

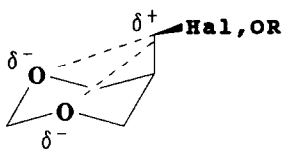
b) Calculated for 25°C using relative enthalpies of all 3 possible rotamers in each (*e* or *a*) conformation

c) Estimated using J_{AC} value for the compounds 5-7.



The MMX data support this idea but only qualitatively. The second analogous Coulombic interaction, $X(\delta^-) \cdots (\delta^+)CH_2(S)$, can occur in the equatorial conformer as well.

It is instructive to note that exactly the same electrostatic attraction has been previously postulated to explain the preferred axial position of 5-halomethyl and $ROCH_2$ groups in 1,3-dioxanes, scheme 9 (see detailed discussion in refs.⁹).



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The interactions of this type in X-C-C-C-Y fragments are rather widespread and they force these fragments to adopt a gauche, gauche-conformation (*gg*) 10. The most simple appropriate models are 1,3-dihalogenopropanes, which prefer the *gg*-conformation in vapour, liquid and solid phases¹⁰.

Considering the data of this work and refs.^{6,7} we can conclude that the most typical conformational behaviour for substituted 1,4-dithianes is the predominance of the axial conformer due to different internal reasons. Only alkyl substituents can safely be expected to be equatorial. Thus the 'normal' behaviour for cyclohexane series does not seem to hold for the 1,4-dithiane series.

EXPERIMENTAL SECTION

NMR spectra were recorded on a AM 300 Bruker instrument. The chemical shifts were measured relative to the solvent - acetone- d_6 signals: 2.05 ppm (1H) and 30.0 ppm (^{13}C). The assignments of ^{13}C signals were performed using two-dimensional ^{13}C - 1H correlation spectra¹¹. The iterative program PANIC was used for the calculations of high resolution NMR spectra.

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