

## CONFORMATIONAL BEHAVIOUR OF TRANS-2,3-BIS(R-THIO)-1,4-DIOXANES

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**Summary:** The conformation of eight *trans*-2,3-Bis(R-thio)-1,4-dioxanes has been studied in chloroform solution using  $^1\text{H}$  NMR techniques. Among the alkylthio substituted compounds, the population of diaxial conformer increases from methylthio (71%) to *tert*-butylthio (85%). The arylthio substituted compounds exist largely as diaxial conformers (ca. 90%). The alleviation of anomeric effects in *trans*-2,3-bis(R-oxy)-1,4-dioxanes bearing bulky alkoxy groups is discussed at the light of these results.

Although the origin of the anomeric effect and related stereoelectronic phenomena<sup>1</sup> appears to be clear on a molecular basis<sup>2</sup>, many experimental results in this field are still awaiting a completely satisfactory explanation.

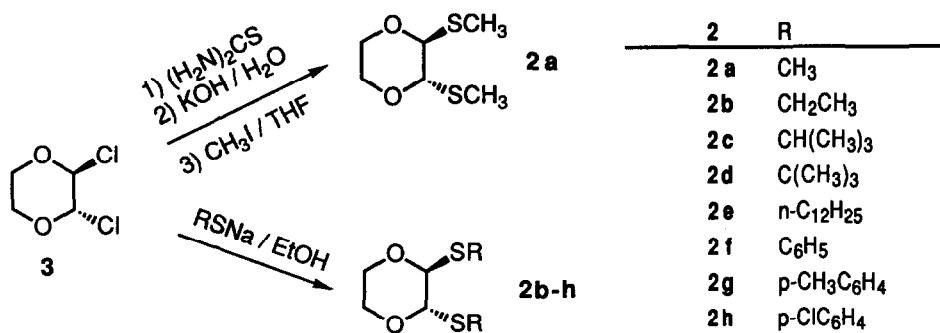
In recent times, we<sup>3</sup> and others<sup>4</sup> have reported some examples of alleviated anomeric effects among the *trans*-2,3-bis(R-oxy)-1,4-dioxanes (1). Such behaviour has only been found when very bulky R-oxy groups (*tert*-butoxy, trimethylsiloxy, 2,6-dimethylphenoxy) are present as substituents on the 1,4-dioxane ring, and has been attributed to two different origins. Whereas we have proposed a unified explanation based on the modulation of stereoelectronic effects by the steric effects of the R-oxy substituents for all the reported cases<sup>3</sup>, Aped et al. have attributed the alleviation of anomeric effects in *tert*-butoxy and trimethylsiloxy substituted 1,4-dioxanes to electronic (inductive and hyperconjugative) effects of the *tert*-butyl and trimethylsilyl groups<sup>5</sup>. The question, however, remains still open.



We thought that a conformational study on *trans*-2,3-bis(R-thio)-1,4-dioxanes (2) containing R groups of variable size and electron donating nature could bring light on this subject. In fact, a similar approach was followed by De Hoog and Havinga<sup>6</sup> to discriminate between steric<sup>7</sup> and electronic effects<sup>8</sup> as the main factor controlling the changes in the position of the conformational equilibrium in the 2-alkoxytetrahydropyran<sup>7,8</sup> and 2-alkylthiotetrahydropyran<sup>6,7</sup> series. In the present case, *gauche* interactions<sup>9</sup> between the 2,3-substituents of the 1,4-dioxane ring need also be taken into account.

We report in the present communication the synthesis and conformational analysis of *trans*-2,3-bis(R-thio)-1,4-dioxanes **2a-h**.

The bis(methylthio) derivative **2a** was prepared from *trans*-2,3-dichloro-1,4-dioxane (**3**) via the bis-thiuronium salt<sup>10</sup>. The remaining derivatives **2b-h** were obtained by reaction of **3** with the corresponding thiolates in absolute ethanol<sup>11</sup>.



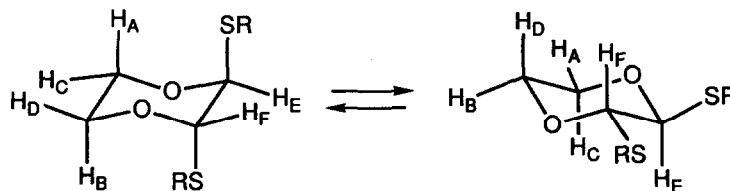
The <sup>1</sup>H NMR spectra of 2a-h were recorded in CDCl<sub>3</sub> solution, and the complex signal corresponding to the O-CH<sub>2</sub>-CH<sub>2</sub>-O moiety was analyzed as an AA'BB' system by means of the PANIC program. On the other hand, the coupling constants between the homotopic hemithioacetal protons were measured by means of the <sup>13</sup>C satellites. The spectroscopic data are summarized in Table I.

Table I. Chemical Shifts and Coupling Constants in *trans*-2,3-bis(R-thio)-1,4-dioxanes

2	$\delta_E = \delta_F^a$	$\delta_A = \delta_B^b$	$\delta_C = \delta_D^b$	$J_{AB}^b$	$J_{CD}^b$	$J_{AD} = J_{BC}^b$	$J_{AC} = J_{BD}^b$	$J_{EF}^c$
2a <sup>d</sup>	4.83	4.28	3.59	8.35	3.83	3.22	-11.95	3.10
2b <sup>e</sup>	4.96	4.32	3.57	8.97	3.44	3.04	-11.67	2.91
2c <sup>f</sup>	4.96	4.28	3.52	9.10	3.18	3.01	-11.56	2.75
2d <sup>e</sup>	5.15	4.39	3.52	9.92	2.50	3.42	-11.87	1.70
2e <sup>d</sup>	4.93	4.32	3.56	8.96	3.40	3.11	-11.85	2.55
2f <sup>d</sup>	5.43	4.56	3.66	10.37	1.67	3.50	-11.96	1.60
2g <sup>f</sup>	5.32	4.53	3.63	10.10	1.97	3.50	-11.89	1.52
2h <sup>d</sup>	5.35	4.53	3.66	10.36	2.07	3.55	-12.06	1.50

<sup>a</sup>Directly measured. <sup>b</sup>From AA'BB' analysis. <sup>c</sup>From <sup>13</sup>C satellites. <sup>d</sup>At 200 MHz. <sup>e</sup>At 250 MHz. <sup>f</sup>At 400 MHz.

According to previous results, the following conformational equilibrium can be postulated for 2a-h.



The absence of geometrical distortions in the chair conformations was secured by calculation of the  $\Psi$  dihedral angle of the ring according to Lambert<sup>12</sup> (Table II). Population analyses were subsequently performed starting from the

calculated coupling constants of the AA'BB' systems, taking as standard values the observed  $J_{aa}$  and  $J_{ee}$  values for deuterated dioxanes ( $J_{aa} = 11.7$  Hz;  $J_{ee} = 1$  Hz)<sup>13</sup> in the equations:

$$J_{AB} = xJ_{aa} + (1-x)J_{ee} \quad \text{and} \quad J_{CD} = yJ_{aa} + (1-y)J_{ee}$$

where  $x$  and  $y$  are respectively the molar fraction of diaxial and diequatorial conformers. The results are summarized in Table II.

Table II. Conformational Equilibria and Free Energy Differences for 2a-h

2	R	$\Psi$ ( $^\circ$ )	%diaxial from $J_{AB}$	%diaxial from $J_{CD}$	%diaxial mean	$\Delta G^\circ_{ea}$ (kJ/mol)
2a	CH <sub>3</sub>	55.9	68	74	71	22
2b	CH <sub>3</sub> CH <sub>2</sub>	57.1	75	77	76	29
2c	(CH <sub>3</sub> ) <sub>2</sub> CH	57.1	76	80	78	3.2
2d	(CH <sub>3</sub> ) <sub>3</sub> C	55.3	84	86	85	4.3
2e	n-C <sub>12</sub> H <sub>25</sub>	56.6	74	78	76	29
2f	C <sub>6</sub> H <sub>5</sub>	54.5	88	94	91	5.8
2g	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	54.5	85	91	88	5.0
2h	p-ClC <sub>6</sub> H <sub>4</sub>	54.7	88	90	89	5.2

Due to the lack of reference  $J$  values for the system (RS)(R'O)CH-CH(OR')(SR), a complementary population analysis based on  $J_{EF}$  could not be performed. However, a very significant correlation ( $r = 0.97$ ) could be established between  $J_{EF}$  and the population of diequatorial (or diaxial) conformer for 2a-h, and this allowed the derivation of reference  $J$  values ( $J_{ee} = 0.56$  Hz;  $J_{aa} = 9.56$  Hz) for the bis-hemithioacetal system, which can be useful for future studies.

Focusing our attention on the results of the conformational study, it is instructive to see that among the aromatic derivatives 2f-h, the population of diaxial conformer is only slightly modified by the electronic nature of the *para*-substituent, but the variation is not systematic. Thus, both the electron donor methyl group ( $\sigma_{para} = -0.17$ )<sup>14</sup> and the electron acceptor chlorine atom ( $\sigma_{para} = +0.23$ )<sup>14</sup> provoke a slight diminution in the population of diaxial conformer. Similar results were obtained in the *trans*-2,3-diaryloxy-1,4-dioxane<sup>3b</sup> and 2-aryloxytetrahydropyran<sup>15</sup> series.

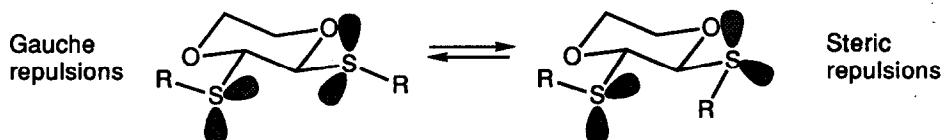
Quite interestingly, the population of diaxial conformer increases along the series 2a to 2d, when both the steric bulk and the electron donating nature of the R groups also increase. This unprecedented result is of great significance in connection with the origin (steric or electronic) of the alleviation of anomeric effects in *trans*-2,3-bis(R-oxy)-1,4-dioxanes (1). Thus, if one admits, in accord with common chemical knowledge, that the electronic effects of alkyl groups, either inductive or hyperconjugative, are the same in front of oxygen or sulfur, it is strongly suggested that simple electronic effects of the R groups cannot simultaneously account for the conformational behaviour of derivatives 1 and 2.

In order to explain the behaviours of 1, where the population of diaxial conformer decreases when the steric bulk of the substituent alkoxy group increases, and 2, where an opposite evolution is observed, it is important to consider the main interactions involving the 2,3-substituents in the chair conformers of these species.

In the diaxial conformers, the main interactions are repulsive, of 1,3-diaxial type, and should increase with the steric bulk of the R groups. Within the R-oxy series (1), however, this increase should be more pronounced due to the fact that C-O bonds are shorter than C-S. (It should be noted that the long C-S bonds project the R groups away from the axial ring protons when the stereoelectronic requirements for the *exo*-anomeric effect are fulfilled)

In the diequatorial conformers, *gauche* interactions<sup>9</sup> should be the important ones. In derivatives 1, both the strong *exo*-anomeric effect and the *attractive gauche effect*<sup>9</sup> favour the rotamer in which both R-oxy groups are antiperiplanar

to the C<sub>2</sub>-C<sub>3</sub> bond. The relative stability of this rotamer should be essentially independent on the steric bulk of the R group. In derivatives **2**, in turn, both the weaker exo-anomeric effect based on sulfur and the *repulsive gauche effect*<sup>β</sup> between the sulfur lone pairs could contribute to increase the population of rotamers which are not free of steric interactions. It is thus expected that increasing the bulk of the R group in **2** will lead to a destabilization of the diequatorial conformer relative to the diaxial one.



In summary, once the different nature (attractive or repulsive) of the gauche interactions between the O/O and S/S pairs is taken into account, the conformational behaviour of **1** and **2** can be explained through the modulation by the steric effects of the R groups of the fundamental anomeric and exo-anomeric effects present in these substances.

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