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Contrasting conformational behavior of 5-methylsulfonyl-1,3-dioxane and -1,3-dithiane in the minimization of steric and electrostatic repulsive interactions

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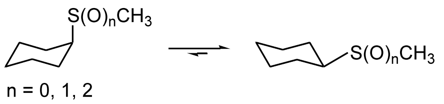
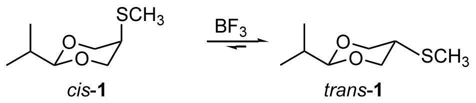
Abstract—The preparation of novel 1,3-dithiane derivatives, *cis*- and *trans*-2-*tert*-butyl-5-methylsulfonyl-1,3-dithiane, was achieved by acid-catalyzed condensation of 2-methylsulfonyl-1,3-propanedithiol with pivalaldehyde. The former dithiol was obtained from allylmethylsulfide via the Knochel–Normant bromination–rearrangement protocol. Configurational and conformational assignment of *cis*- and *trans*-**5** was based on ^{1}H NMR analysis, and revealed that the *trans* isomer adopts a normal chair conformation. By contrast, *cis*-**5** adopts a twist-boat conformation in order to minimize the steric and electrostatic repulsive interactions that an axial methylsulfonyl group engenders. Chemical equilibration *cis*-**5** ⇌ *tran*s-**5** shows the latter to be more stable by 1.50 kcal/mol. © 2002 Elsevier Science Ltd. All rights reserved.

The conformational behavior of monosubstituted cyclohexanes effectively models larger and more complex molecules. In particular, the free energy difference for the axial ⇌ equatorial equilibrium in such monosubstituted cyclohexanes ($\Delta G°$ values≡A values) is a convenient parameter that is a measure of steric size.[1] In this context, Eliel and Kandasamy described the conformational free energy differences for the methyl sulfide, methyl sulfoxide, and methyl sulfone groups in the cyclohexane ring.[2] The reported values, −1.00, −1.20, and −2.50 kcal/mol, respectively, clearly reflect the steric requirements of the sulfur functions (Eq. (1)).



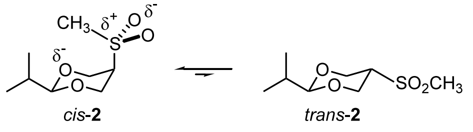
(1)

Whereas evaluation of steric effects is best achieved in the cyclohexane framework, electrostatic and stereoelectronic interactions are conveniently examined in six-membered heterocyclic derivatives.[3] For example, Eliel et al.[4] discovered that the CH_3S group attached at C(5) in a 1,3-dioxane has a stronger preference for the equatorial conformation ($\Delta G° = -1.82$ kcal/mol in solvent cyclohexane, Eq. (2)) than that measured for (methylthio)cyclohexane, this being the result of a repulsive interaction of the unshared electrons of sulfur with the unshared electrons of the ring oxygens (the so-called 'repulsive *gauche* effect'[5]).



(2)

In strong contrast, a similarly placed methylsulfonyl (CH_3SO_2) group prefers the axial conformation.[4] This unusual behavior was rationalized in terms of an attractive, electrostatic interaction between the (negative) endocyclic oxygens and the (positive) sulfonyl sulfur (Eq. (3)). That the methyl group at sulfur points into the ring was established from the NMR evaluation of ^{1}H NMR coupling constants.[4] This particular orientation of the methylsulfonyl group minimizes electrostatic repulsion between ring oxygens and sulfonyl oxygens (Eq. (3)).



(3)

Keywords: conformation; dithianes; dioxanes; sulfones; steric and strain effects; electrostatic effects.

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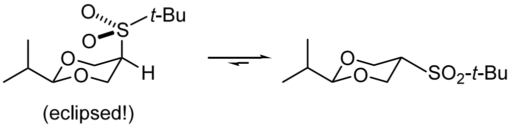
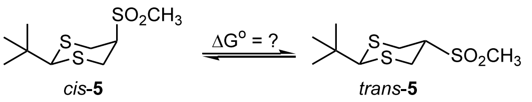
In this context, the positions of equilibrium between diastereomeric *cis*- and *trans*-**5**-(*tert*-butylthio)- and -5-(*tert*-butylsulfonyl)-2-isopropyl-1,3-dioxanes were reported by Juaristi et al.[6] (Table 1). Although $\Delta G°$ values for the sulfides are very similar, the difference in conformational behavior for the sulfones is quite dramatic: the large preference of the methyl analogue for the axial position (1.19 kcal/mol; Table 1) is reversed in the *tert*-butyl derivative, where the equatorial isomer is more stable by 1.14 kcal/mol.

A crystallographic X-ray diffraction study of *cis*-2-*tert*-butyl-5-(*tert*-butylsulfonyl)-1,3-dioxane reveals that this heterocycle exists in a chair conformation with the substituent at C(5) being axial. The sulfonyl *tert*-butyl group is outside the ring, suggesting that the steric congestion that would be present if the alkyl group was inside the ring is more severe than the electrostatic repulsion between the (negative) oxygens, $S^{+}–O^{-}/^{\delta-}O_{1,3}$. The most interesting feature of the crystallographic data was, however, that they correspond to a conformation with *eclipsed* S–O/C–C and C-*t*-Bu/C–H bonds[6] (Eq. (4)). This bond eclipsing seems to be necessary to mitigate *gauche* *t*-Bu/CH_2 steric interactions present in staggered rotamers.[7]



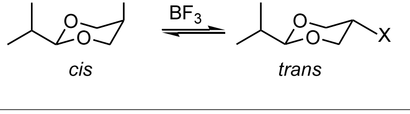
(4)

The difference in size, electronegativity, and bond polarities associated with oxygen and sulfur, as well as the availability of 3d orbitals in sulfur, are reflected in contrasting conformational behavior for oxygen-containing vis-a-vis sulfur-containing heterocycles.[3a,b,8] Thus, we deemed it important to examine the conformational preference of the methylsulfonyl group at C(5) in 1,3-dithiane. In this paper, we report the chemical equilibration of *cis*- and *trans*-2-*tert*-butyl-5-methylsulfonyl-1,3-dithiane (Eq. (5)). Two main questions are whether attractive $S^{\delta-}\cdots{}^{\delta+}SO_2CH_3$ interactions are reflected in an axial orientation of the 5-SO_2CH_3 group, and whether, by analogy with the 1,3-dioxane analog (see above), a methyl-inside rotamer is preferred.



(5)

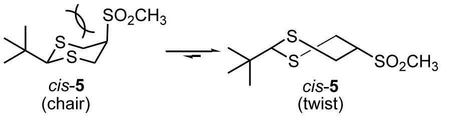
Table 1. Conformational free energy differences ($\Delta G°$ values) for several 5-substituted 2-isopropyl-1,3-dioxanes[4,6a]



Compd	X	$\Delta G°$, kcal/mol	Solvent
1	CH_3S	-1.82 ± 0.01	C_6H_{12}
2	CH_3SO_2	$+1.19\pm0.10$	$CHCl_3$
3	*t*-BuS	-1.90 ± 0.11	$CHCl_3$
4	*t*-BuSO$_2$	-1.14 ± 0.01	$CHCl_3$

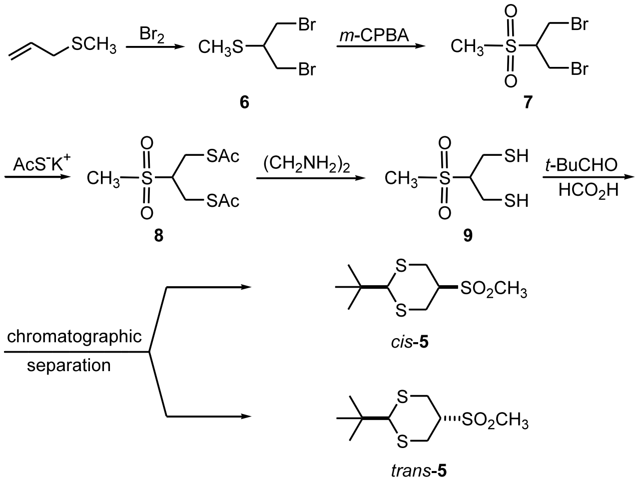
The synthesis of the desired diastereomeric 1,3-dithianes *cis*-**5** and *trans*-**5** was accomplished according to the route outlined in Scheme 1.[9] Allylmercaptan was methylated as described by Bland and Stammer,[10] and key dibromide **6** was obtained via the Knochel–Normant bromination–rearrangement protocol.[11] In situ oxidation with 2 equiv. of *m*-chloroperbenzoic acid afforded sulfone **7** as white needles, and in 85% yield (two steps). 1,3-Dithioacetate **8** was then obtained by displacement with freshly prepared, activated potassium thioacetate,[12] and aminolysis was achieved with ethylenediamine under a nitrogen atmosphere.[13] Finally, condensation of 2-methylsulfonyl-1,3-propanedithiol **9** with pivalaldehyde under acidic conditions[14] gave a mixture of *cis*-**5** and *trans*-**5**, that were separated and purified by chromatography.

^1H NMR spectroscopic analysis led to the assignment of both the configuration and conformation of *cis*- and *trans*-**5**. Indeed, the less polar component exhibited a proton coupling pattern that is only ascribable to *trans*-**5** in a chair conformation of the six-membered ring. In particular, $^2J_{gem}={}^3J_{anti}=12.6$ Hz for the axial hydrogens at C(4,6), that are coupled to the axial hydrogen at C(5). By contrast, *cis*-**5** (more polar isomer) presents a vicinal coupling constant between H(4,6) and H(5), $^3J_{vic}=6.0$ Hz, that is in line with a twist-boat conformation of the dithiane ring (Eq. (6)).



(6)

The fact that *cis*-**5** adopts a twist-boat conformation indicates that the steric and electrostatic repulsion suffered by an axial 5-methylsulfonyl group in the chair conformation of the 1,3-dithiane heterocycle is large enough to overcome the free energy difference between the chair and twist-boat forms of 1,3-dithiane. Support for the conclusion is gathered from the theoretical



Scheme 1.

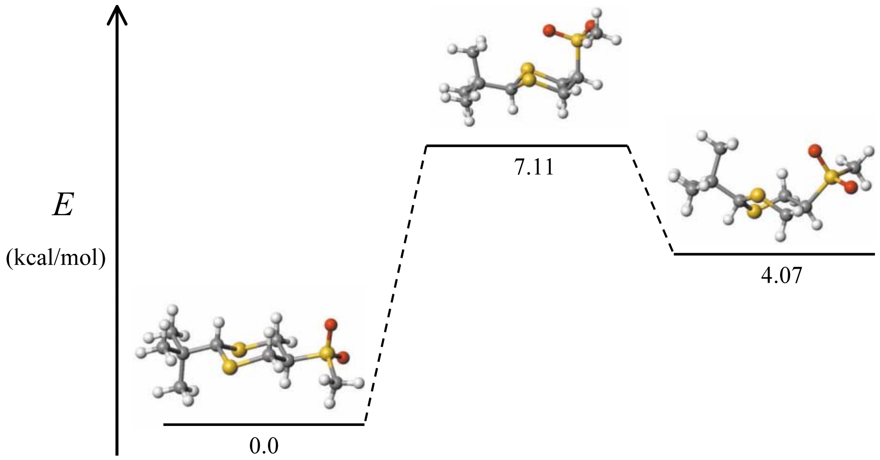
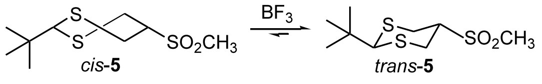


Figure 1. Calculated (DFT, B3LYP/6-311+G**//B3LYP/6-31G*) relative energies of the chair *trans*-**5** ($E_{\mathrm{rel}}=0.0$ kcal/mol), chair *cis*-**5** ($E_{\mathrm{rel}}=7.11$ kcal/mol), and 2,5-twist *cis*-**5** ($E_{\mathrm{rel}}=4.07$ kcal/mol).

(DFT, B3LYP/6-311+G**//B3LYP/6-31G*) estimation of the relative energies of the chair conformations for *trans*-**5** (relative $E=0.0$ kcal/mol) and *cis*-**5** (relative $E=7.11$ kcal/mol) (Fig. 1). By comparison, the 2,5-twist-boat conformation of *cis*-**5** is calculated to be nearly 3.0 kcal/mol lower in energy than the chair form (Fig. 1).[15]

Chemical equilibration of *cis*-**5** and *trans*-**5** was carried out in the presence of $BF_3\cdot OEt_2$, in chloroform solution and at 50°C. Equilibrium was reached from both sides and gave $\Delta G^{\circ}_{323\ \mathrm{K}}=-1.50\pm0.04$ kcal/mol in favor of *trans*-**5** (Eq. (7)).



(7)

It is then apparent that the attractive electrostatic interaction that stabilizes the axial form of 5-methylsulfonyl-1,3-dioxane ($O^{\delta-}\cdots{}^{\delta+}SO_2CH_3$; see entry 2 in Table 1) is not reproduced in the 1,3-dithiane analog; that is, $S^{\delta-}\cdots{}^{\delta+}SO_2CH_3$ electrostatic attraction is not appreciable in *cis*-**5**. As a consequence, the heterocyclic structure adopts a twist-boat conformation that minimizes the steric and electrostatic repulsions that an axial methylsulfonyl group generates, and that benefits from the increased entropy content of the flexible conformers in 1,3-dithiane derivatives.[16]

Acknowledgements

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15. In addition, the computed (DFT, B3LYP/6-311+G**// B3LYP/6-31G*) energy for the boat conformation of *cis*-**5** is 3.3 kcal/mol higher than that calculated for 2,5-twist conformation.
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